# Current Opinion in Rheumatology

## Issue Table of Contents

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### Editorial introductions

1. **Editorial introductions.**

### Vasculitis syndromes

<table>
<thead>
<tr>
<th>Page</th>
<th>Title</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Major vessel involvement in Behcet disease.</td>
<td>Calamia, Kenneth T a; Schirmer, Michael b; Melikoglu, Melike c</td>
</tr>
<tr>
<td>9</td>
<td>Use of ultrasonography and positron emission tomography in the</td>
<td>Schmidt, Wolfgang A a; Blockmans, Daniel b</td>
</tr>
<tr>
<td></td>
<td>diagnosis and assessment of large- vessel vasculitis.</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>Advances in the medical and surgical treatment of Takayasu arteritis.</td>
<td>Liang, Patrick a; Hoffman, Gary S b</td>
</tr>
<tr>
<td>25</td>
<td>Ocular vasculitis: a multidisciplinary approach.</td>
<td>Herbort, Carl P a; Cimino, Luca b; El Asrar, Ahmed M. Abu c</td>
</tr>
<tr>
<td>34</td>
<td>Chronic periaortitis: a spectrum of diseases.</td>
<td>Vaglio, Augusto; Buzio, Carlo</td>
</tr>
<tr>
<td>41</td>
<td>Peripheral neuropathy in systemic vasculitides.</td>
<td>Pagnoux, Christian; Guillemin, Loic</td>
</tr>
<tr>
<td>49</td>
<td>Endothelial cell dysfunction in systemic vasculitis: new</td>
<td>Bacon, P A</td>
</tr>
<tr>
<td></td>
<td>developments and therapeutic prospects.</td>
<td></td>
</tr>
<tr>
<td>56</td>
<td>Clinical approach to cutaneous vasculitis.</td>
<td>Gonzalez-Gay, Miguel A a; Garcia-Porrua, Carlos a; Pujol, Ramon M b</td>
</tr>
</tbody>
</table>

### Systemic disorders with rheumatic manifestations

**EDITORIAL OVERVIEW**

<table>
<thead>
<tr>
<th>Page</th>
<th>Title</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>62</td>
<td>The musculoskeletal roads less traveled.</td>
<td>Erkan, Doruk; Paget, Stephen A</td>
</tr>
<tr>
<td>64</td>
<td>Musculoskeletal manifestations of endocrine disorders.</td>
<td>Jacobs-Kosmin, Dana a; DeHoratius, Raphael J b</td>
</tr>
<tr>
<td>70</td>
<td>Musculoskeletal complications associated with lysosomal storage</td>
<td>Pastores, Gregory M a; Meere, Patrick A b</td>
</tr>
<tr>
<td></td>
<td>disorders: Gaucher disease and Hurler-Scheie syndrome (mucopolysaccharidosis type II).</td>
<td></td>
</tr>
<tr>
<td>79</td>
<td>Advances that are changing the diagnosis and treatment of malignant</td>
<td>Casas-Ganem, Jorge; Healey, John H</td>
</tr>
<tr>
<td></td>
<td>bone tumors.</td>
<td></td>
</tr>
<tr>
<td>86</td>
<td>Microchimerism and systemic sclerosis.</td>
<td>Jimenez, Sergio A; Artlett, Carol M</td>
</tr>
<tr>
<td>91</td>
<td>Central nervous system manifestations of rheumatologic diseases.</td>
<td>Chin, Russell L; Latov, Norman</td>
</tr>
</tbody>
</table>

### Current World Literature

<table>
<thead>
<tr>
<th>Page</th>
<th>Title</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>Bibliography Current World Literature.</td>
<td></td>
</tr>
</tbody>
</table>

List of journals scanned

<table>
<thead>
<tr>
<th>Page</th>
<th>Title</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>List of journals scanned.</td>
</tr>
</tbody>
</table>
Editorial introductions

Current Opinion in Rheumatology was launched in 1989. It is one of a successful series of review journals whose unique format is designed to provide a systematic and critical assessment of the literature as presented in the many primary journals. The field of rheumatology is divided into 15 sections that are reviewed once a year. Each section is assigned a Section Editor, a leading authority in the area, who identifies the most important topics at that time. Here we are pleased to introduce the Journal’s Editor and the Section Editors for this issue.

Editor

Cornelia M. Weyand, MD, PhD

Cornelia M. Weyand is the Director of the Lowance Center for Human Immunology, at Emory University School of Medicine, Atlanta, Georgia. Dr. Weyand is known for her studies of the immune system in rheumatoid arthritis and inflammatory blood vessel diseases, particularly giant cell vasculitis and acute coronary syndromes. Her work has focused on defining mechanisms of breakdown in self-tolerance and the contribution of T lymphocytes to immune-mediated disease. Dr. Weyand and her colleagues have emphasized the translation of bench research to the patient, exploring the value of disease risk genes in identifying clinical phenotypes of rheumatoid arthritis and predicting disease outcome. In her recent work, Dr. Weyand has linked autoimmunity to the process of cellular senescence in the immune system and is currently investigating mechanisms of immunosenescence and their relevance to rheumatoid arthritis and vascular disease.

Dr. Weyand received her M.D. degree from the University of Aachen, her Dr. med. degree from the University in Bonn and her Dr. habil degree in Medical Sciences from the University of Heidelberg. She completed subspecialty training in Clinical Immunology and Rheumatology at Stanford University and served as the Chief of Rheumatology at the University Hospital in Heidelberg before she joined the faculty of the Mayo Medical School. She has authored over 200 peer-reviewed research publications and 29 book chapters and has edited several books, including a textbook on Inflammatory Blood Vessel Diseases and the Primer on the Rheumatic Diseases. She is a member of the American Society for Clinical Investigation and the Association of American Physicians, and the recipient of numerous national and international awards, including the Henry Kunkel Young Investigator Award of the American College of Rheumatology and the Carol Nachman Award.

Section Editors

Carlo Salvarani, MD

Dr. Salvarani is Chief of the Division of Rheumatology at Arcispedale S. Maria Nuova, Reggio Emilia, Italy. He qualified in Medicine from Parma University and Rheumatology from Ferrara University. He spent one year as visiting clinician at the Division of Rheumatology, Mayo Clinic, Rochester, Minnesota, where he worked on research projects on polymyalgia rheumatica and giant cell arteritis under the supervision of Dr. Gene Hunder and Dr. Sherine Gabriel.

His research interests include vasculitis (particularly giant cell arteritis, polymyalgia rheumatica, Takayasu arteritis, chronic periaortitis and Behçet disease) and psoriatic arthritis. His work has helped to define the clinical spectrum of polymyalgia rheumatica with particular emphasis on distal musculoskeletal manifestations and the relationship between polymyalgia rheumatica, RS3PE syndrome and elderly-onset rheumatoid arthritis.

Dr. Salvarani is member of the Editorial Board of Arthritis Care & Research and Current Opinion in Rheumatology.
Doruk Erkan, MD

Dr. Erkan received his medical degree at the Hacettepe University, School of Medicine in Ankara, Turkey. After his Internal Medicine residency at Beth Israel Medical Center in New York, he completed his Rheumatology fellowship at the Hospital for Special Surgery in New York. Dr. Erkan is currently an Assistant Attending Rheumatologist, Clinical Researcher, and the Clinical Director of the international Lupus Clinical Trials Consortium (LCTC) at the Hospital for Special Surgery, Weill Medical College of Cornell University in New York. Dr. Erkan has a long time research interest in the field of autoimmune diseases, with particular focus on the Antiphospholipid Syndrome (APS) and Systemic Lupus Erythematosus. He is the principal investigator of the Arthritis Foundation-funded international multi-center “APLASA study” that focuses on primary thrombosis prevention strategies in APS; he has received several honors and awards from the American College of Rheumatology and the Arthritis Foundation for his research. Dr. Erkan has published over 50 articles including research papers, reviews, and invited editorials, 10 book chapters, and has given over 60 presentations. He is the co-editor of the Neurology volume of the Handbook of the Systemic Autoimmune Disease.

Stephen A. Paget, MD

Early on in his medical career, Dr. Paget was attracted to the field of rheumatology not only in medical school at Downstate Medical Center through his close interactions with David Kaplan, MD, but later at The Johns Hopkins Hospital via Mary Betty Stevens, MD, and Larry Shulman, MD. After completing his internal medicine training at Hopkins, he spent two stimulating and formative years as a Clinical Associate at the National Institutes of Health under the guidance of John Decker, MD, and John van Boxel, MD. There his research focused on defining the character of the immune cells that infiltrated rheumatoid synovial membranes, eventuating in an important New England of Medicine paper that demonstrated that the T lymphocyte was the predominant cell type. Thereafter, Dr. Paget was a rheumatology fellow in Charles L. Christian’s program at Hospital For Special Surgery and since then he has remained on the faculty at that august institution for nearly thirty years. After his fellowship, Dr. Paget continued his basic research focused on characterizing the immunopathogenesis of rheumatoid arthritis, in collaboration with Dr. Paul Phillips. In the 1990s, he switched his focus to clinical research and was an Associate Director of the HSS/Cornell, NIH-funded Multipurpose Arthritis Center. In 1995, Dr. Paget succeeded his mentor Dr. Charles Christian as Physician-in-Chief, Chairman of the Division of Rheumatology and the Joseph P. Routh Professor of Medicine and Rheumatic Disease at the Weill Medical College of Cornell University. Under his direction, HSS has expanded its rheumatology staff to over 40, likely the largest rheumatology division in the world, has helped to carry on and expand the educational and investigative excellence initiated by Chuck Christian, and has supported a worldwide rheumatology outreach via the HSS website www.hss.edu.
Major vessel involvement in Behçet disease
Kenneth T. Calamia\textsuperscript{a}, Michael Schirmer\textsuperscript{b} and Melike Melikoglu\textsuperscript{c}

**Purpose of review**
Large vessel vasculitis occurs in a subgroup of patients with Behçet disease at high risk for disease-related morbidity and mortality. Recognition of patients at risk, early detection of vasculitis, and the need for aggressive treatment are essential for optimal care of these patients. The authors review the clinical spectrum and management of large vessel problems in Behçet disease, highlighting contributions over the past year.

**Recent findings**
Vasculo-Behçet patients are at risk for multiple vessel-related complications including thromboses, stenoses, occlusions, and aneurysms. A number of factors may contribute to thrombosis in individual cases, but the primary reason for clot seems to reside in the inflammatory process in the arterial wall, still incompletely understood. An appreciation for the challenges in the perioperative period requires the joint efforts of physicians and surgeons, and fuels the study of alternate, less invasive procedures for Behçet patients.

**Summary**
Because of earlier recognition, aggressive medical treatment, and novel surgical procedures, the morbidity and mortality of large vessel vasculitis in Behçet disease are beginning to change. In the absence of controlled treatment studies, reports of clinical experience remain an important source of information for clinicians. Identification of patients at risk for vascular complications remains a priority.

**Keywords**
Behçet disease, vasculitis, aneurysms, thrombosis

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**Introduction**
Vasculitis is thought to underlie the clinical manifestations of Behçet disease. The vasculitis of Behçet disease is distinctive because of involvement of both arteries and veins of all sizes, but different histologic features of various lesions evidence the heterogeneity of the condition. Perivascular mononuclear cell infiltration without vessel wall involvement itself is commonly seen in many locations. The small vessel is the predominant site of inflammation, but large vessel involvement in Behçet disease affects approximately one fourth to one third of patients, a prevalence similar across most geographic areas \[1\]. The concept of vasculo-Behçet has been adopted for cases in which vascular complications are present and often dominate the clinical features. After the first vascular lesion, the risks are increased for other vascular lesions, and the potential exists for progressive, multifocal vessel-related complications (Fig. 1). These patients are important to identify because their prognosis is less favorable \[2\] and they are candidates for more aggressive treatment. However, management decisions may be difficult because of the lack of controlled studies.

The clinical syndromes that may result from large vessel vasculitis have been well described over the years, with last review by Aydintug \[3\]. The relationships of complications that define vasculo-Behçet are becoming clearer. This review provides an overview and classification of large vessel vasculitis in Behçet disease. This picture is highlighted and extended by reports in the literature over the past year.

**Clinical aspects**
There are differences in the clinical behavior of thromboses and aneurysms in Behçet disease compared with similar lesions associated with atherosclerosis or other disorders. The inflammatory process at arterial sites is acute and destructive to the vessel wall, resulting in the rapid formation of true and/or false aneurysms with an increased incidence of rupture and bleeding. Vessel occlusion is marked by extensive adherent thrombus formation, without clinical evidence of thromboemboli. Deep venous thrombosis may progress despite anticoagulation. Clots, aneurysms, or pseudoaneurysms may complicate surgery or invasive procedures, reflecting a pathergy-like effect in the vessel wall. Large vessel disease is one of few manifestations of Behçet disease that is associated with systemic symptoms and laboratory evidence of an acute phase response. The vasculitis and its
Recent series of patients from Turkey and Lebanon confirm that males and patients with a younger age of onset are at higher risk for vascular involvement [4•,5••]. Large vessel involvement in Behçet disease can be arterial or, more commonly, venous [2,6], and may involve both systems in the same patient [7]. A classification of large vascular lesions in Behçet disease is shown in Table 1. The characteristics of the vessels and the distinctive presentation and course of pulmonary arterial vasculitis separate it from that in the systemic arterial circulation. In both circulations, thrombotic occlusions, stenoses, and aneurysms may result and frequently coexist. The unique individual syndromes associated with venous thrombosis in different sites are recognized in this scheme. Varices occur as a consequence of deep-seated venous thrombosis and may result in characteristic presentations and diagnostic findings. In Behçet disease, these may include inverted esophageal varices, cavernous transformation of the portal vein, and enlarged bronchial arteries. Despite the specificity of vascular lesions, these complications are not included in the diagnostic (classification) criteria for Behçet disease [8,9], but a course characteristic of vasculo-Behçet can support the clinical diagnosis of the disease.

### Venous occlusions
Superficial thrombophlebitis should raise the suspicion for Behçet disease in candidate patients, especially when it is migratory or recurrent. Thrombosis of superficial veins may occur after venipuncture and has been reported at sites of heparin infusions. It remains to be determined whether superficial thrombophlebitis should be considered as a risk factor for future vascular events and treated from this perspective. It is associated with deep venous thrombosis [10], and both conditions appear to be associated with caval thrombosis and for arterial disease. The spectrum of subcutaneous venous inflammation may be extended to include erythema nodosum-like lesions, in which the process is more vasculitic than panniculitic, involving the small vessels of the septa of subcutaneous fat [11,12].

Deep venous thrombosis occurs earlier in the course of disease than arterial disease, which was found to occur after a median of 7 years [2]. Associations have been reported with ocular involvement [13] and with pathergy. Deep venous thrombosis occurs primarily in the lower extremities, but involvement is possible at any site. Findings of chronic venous insufficiency in the lower
extremities are common in patients with Behçet disease from areas of high prevalence (Fig. 2). Arterial and venous clots were recognized as a cause of priapism in a Behçet patient with the factor V Leiden mutation [14].

Occlusions of the venae cavae are commonly recognized complications in Behçet disease, and Behçet disease is a common cause of vena cava syndromes in areas where the disease is prevalent. Thrombosis of the vena cava may begin in proximal large veins or in the cava itself. Radiologic studies are necessary to appreciate contributing causes of thrombosis in atypical cases. Superior vena cava syndrome was reported in association with mediastinal fibrosis in a 13-year-old boy with Behçet disease [15]. With adequate collateral vessels, patients may tolerate chronic caval occlusion for many years, but deaths have been reported as a result of extensive thrombosis, treatment, hemoptysis, or other vascular causes, including, rarely, pulmonary embolus.

Extension of inferior vena cava clot to the hepatic vein ostia may be the mechanism for Budd-Chiari syndrome in most patients with Behçet disease. Patients seek treatment with right upper quadrant pain, hepatosplenomegaly, and ascites [16]. The prognosis of hepatic vein thrombosis is poor, with a 1-year survival of approximately 50%. One third of these patients follow an acute course, often leading to death from hepatic failure within weeks [17]. Spontaneous improvement occurs in some patients, but most remain at risk for slowly progressive liver failure, elevated portal pressure, and esophageal varices. Portocaval shunting can be considered if the inferior vena cava is patent. Opening of obstructed veins has also been attempted [18], but active vasculitis in other locations has been a common complication in the surgical setting. There are no reports of liver transplant or transcutaneous intrahepatic portosystemic shunt in these patients.

Nine percent (six patients) of vasculo-Behçet patients from Turkey were found to have portal vein thrombosis, resulting in cavernous transformation [19]. Patients seek treatment with splenomegaly, but hepatomegaly and ascites are found in patients with coexisting Budd-Chiari syndrome, and those with inferior vena cava involvement have lower extremity edema. An obstructive pattern of liver enzymes may result from the compression of the biliary tree by the enlarged collaterals in portal tract or as a result of coexisting hepatic vein thrombosis. Death from vascular complications is common in these patients.

Right ventricular thrombi are found in patients with vasculo-Behçet, often associated with pulmonary aneurysms, thus complicating the treatment with anticoagulants. A case with clots in all four cardiac chambers, along with pericarditis, was treated with corticosteroids and cyclophosphamide with resolution of thrombi in 6 months [20]. Lysis of a large, mobile atrial thrombus was accomplished with streptokinase; anticoagulants were added to corticosteroids and colchicine for maintenance [21••]. A right ventricular thrombus and pulmonary embolus in a patient with Behçet disease with the factor V Leiden mutation improved with anticoagulants [22]. Endomyocardial fibrosis has been reported rarely in Behçet disease but should be considered in patients with a cardiac mass. Myocardial infarctions occur in Behçet disease with angiographically normal coronary arteries, thought caused by thrombosis or vasculitis [23].

Cerebral venous thrombosis (CVT) results in signs and symptoms of increased intracranial pressure. Cerebrospinal fluid pressures are elevated along with elevation of protein and pleocytosis. MRI and venous magnetic resonance angiography are the imaging procedures of choice for the diagnosis of CVT. Elevated intracranial pressure may be the presenting manifestation of Behçet disease, but other vascular manifestations of Behçet disease, particularly venous thromboses, may be present. The clinical features, course, and prognosis of patients with CVT in Behçet disease appear similar to those of patients without the disease. Neurologic symptoms frequently resolve in a matter of weeks, occasionally with mild residual focal deficits.

Therapeutic considerations
There is no consensus regarding the use of anticoagulants for treatment of venous thrombosis in Behçet disease [24,25]. The conspicuous rarity of pulmonary emboli in Behçet disease with venous thrombosis has long been noted, attributed to adherent clot formation on the inflamed vessel wall (vide infra). Pulmonary emboli do rarely occur in Behçet disease, however, often associated
with progressive venous thrombosis, unresponsive to anticoagulants. High intensity anticoagulation with both coumadin and heparin, in combination with antiaggregants when necessary, has been effective in some cases resistant to standard anticoagulants. The authors favor the use of immunosuppressive drugs in the setting of recurrent or progressive thrombosis [26]. In the treatment of each of the clinical syndromes associated with venous thrombosis, various combinations of anticoagulants, antiaggregants, colchicine [27], corticosteroids, and immunosuppressive agents have been used. Thrombolytic therapy has been used in these syndromes with mixed results but may be a better option if used early in acute cases.

Patients with CVT are often successfully treated with corticosteroids and anticoagulants. The benefit of heparin has been shown in patients with idiopathic CVT [28]. The value of anticoagulation in patients with Behçet disease with CVT is less certain, but the safety and efficacy of these agents are supported by clinical experience [29]. Immunosuppressive agents could be considered if the disease is recurrent or resistant to treatment. Optic nerve sheath fenestration has been reported in Behçet disease as a vision salvaging procedure in a patient who failed to respond to conservative treatment [30].

**Pathogenesis of thrombosis in Behçet disease**

It is unlikely that thrombophilia plays a role in the pathogenesis of thrombosis in most patients with Behçet disease, because there has been no consistent primary abnormality of the coagulation, antiocoagulation, or fibrinolytic systems yet identified. High concentrations of procoagulant factors VIII, IX, and fibrinogen in Behçet disease were reported in patients with ocular involvement, but the findings were variable in individual patients, and no distinct abnormality was found [31•]. Deficiencies of the naturally occurring anticoagulant proteins antithrombin, protein C, and protein S have been implicated in some individual patients with thrombosis. A Behçet patient with a pulmonary artery aneurysm was reported with low levels of both factor C and factor S, but without a certain history of clot [32]. The available data also do not support the evidence for the role of antiphospholipid antibodies in thrombosis of Behçet disease; and a recent publication failed to show increased levels of antibodies to the phospholipid annexin in patients with thrombosis compared with those without [33•].

Studies of the association of factor V Leiden mutation and thrombosis in Behçet disease have shown contradictory results. A high prevalence of factor V Leiden mutation (33%) was found in patients with Behçet disease and thrombosis from Turkey [34•]. However, a recent study of 118 consecutive patients with Behçet disease from Italy failed to find an association between factor V Leiden or the G20210A prothrombin mutation and the thrombosis of Behçet disease. A higher frequency of the prothrombin mutation was found in a subgroup of patients with posterior uveitis and retinal vasculitis [35••]. Factor V Leiden did not correlate with retinal vascular occlusion in 53 patients from the United Kingdom [36•] but was present in significantly more patients in Turkey with this complication than in controls with Behçet disease [37•].

There are significant differences in the epidemiology, genetics, and clinical manifestations of Behçet disease between ethnic groups and in different geographical locations. Reports of the positive association of factor V Leiden with thrombosis have primarily come out of Turkey, suggesting the possibility of a regional difference in the significance of this mutation. HLA-B5 (B51) has been found to be a significant risk for thrombophlebitis in certain ethnic groups, including Israelis, but not in others [7]. MEFV gene mutations were found in 26% of Turkish patients with Behçet disease, compared with 9.1% in healthy controls [38•]. There was a strong association of these mutations with large vessel disease, most prominently in females who are affected less often, reflecting the complexity of susceptibility factors for this complication.

Evidence for the role of hyperhomocysteinemia in thrombosis of Behçet disease remains unclear. In a study from Tunis [39], hyperhomocysteinemia was more common in Behçet patients compared with controls but was not found to differ between patients with and without clots. Canataroglu [40•] found no differences in patients versus controls but higher mean levels of homocysteine in patients with thrombosis. In a recent publication from Turkey, hyperhomocysteinemia was found to be associated with thrombosis and ocular manifestations of Behçet disease together with low plasma levels of vitamin B12 and folate [41•]. This observation suggested that the abnormalities were caused by increased inflammatory metabolic activity or the effect of immunosuppressive drugs.

In individual patients, it is expected that vascular thrombosis may be facilitated by any of a number of thrombophilic factors, if present, but the primary cause of clot is related to factors in the vessel wall itself. Increased serum levels of von Willebrand factor are found, reflecting endothelial cell activation [31•]. Elevated levels of thrombomodulin [42,43] in the serum of patients with Behçet disease likely reflect vascular cell injury [25]. If these levels reflect a loss of thrombomodulin in the vessel walls, then thrombosis would be favored because of the role of this molecule in the activation of protein C. Mural production of prostacyclin (PGI₂) or other eicosanoid products may be disordered, favoring thrombosis.
Recently, Turkish investigators detected high plasma levels of platelet activating factor and P-selectin (CD62P) activation markers on platelets in patients with thrombosis in Behçet disease, supporting the association of endothelial activation and thrombosis [44••]. The role of antiendothelial cell antibodies is unclear. Although detected in a number of vasculitides, these antibodies were found no more frequently in Behçet patients compared with controls in a recent study using three different assays [45•]. Variations in the assays used may be responsible for discrepant results.

**Systemic arterial vasculitis**

Arterial complications are less common than venous problems in Behçet disease, occurring in 1 to 7% of patients [46,47]. Males are much more likely to be affected with arterial disease than females. Cigarette smoking may be risk factor for arterial disease in patients with Behçet disease [26,48]. Elevated levels of endothelin-1 levels, a vasoconstrictor peptide, indicate the presence of arterial pathology in Behçet disease. Supporting earlier findings, reactive arterial wall flow-mediated dilatation after ischemia [49] and aortic elastic properties [50••] were found to be impaired in Behçet disease. The authors believe there is a common pathophysiologic link that might be identified as a risk factor for vascular disease in patients with Behçet disease.

In most reports, arterial lesions are isolated, but these may be multiple and frequently coexist with venous thromboses [51••]. Arterial occlusions or stenoses may be asymptomatic or associated with ischemic symptoms, depending on the adequacy of the collateral circulation. Like occlusive lesions, arterial aneurysms are caused by vasculitis that begins in the vasa vasorum. The aorta is the most common site of aneurysm formation. Acute arteritis or dilatation may lead to aortic valve dysfunction, necessitating repair [52]. The femoral artery is commonly involved, but any extremity or visceral vessel may be involved, including the coronary arteries [53], a recently reported renal artery stump after nephrectomy [54], and the inferior mesenteric artery, associated with multiple visceral artery occlusions [55]. Aneurysm formation in Behçet disease may follow arterial puncture [56] for blood gas determination or angiography, or may occur at the time of surgery. Less invasive PET scanning may be of value in the recognition of large artery disease [57], but experience is limited.

**Therapeutic considerations**

For occlusive or stenotic lesions, nonoperative treatment is elected in the absence of symptoms, but corticosteroids [58••], immunosuppressives, or surgery may be appropriate. Surgery is generally indicated for the treatment of systemic arterial aneurysms because of the risk of rupture [59], even recognized in childhood Behçet disease [60]. However, arterial repair may be complicated by recurrent disease, graft occlusion, and/or anastomotic aneurysms in a high percentage of patients [51••,58••]. An unusual case of intestinal obstruction caused by the migration of a synthetic aortofemoral graft into the jejunum was reported [61]. The unique challenges of surgical arterial repair in Behçet disease and the need for simultaneous medical management are increasingly recognized in the surgical literature [62••].

Endovascular repair techniques are increasingly being used in Behçet disease in attempt to reduce complications that may result from surgical trauma. Endovascular aortic repair in two patients was associated with fewer complications than open repair in three [63••]. Behçet patients may actually be better candidates for this less invasive procedure than those with atherosclerosis because they are younger and have better renal function, and aneurysms involve a shorter vessel segment [64•]. Dual aortic and celiac stent-grafts have been placed successfully [65]. Endovascular repair has been used to treat an aneurysm of the popliteal artery [66] and intracranial aneurysms in Behçet disease [67••]. Percutaneous injection of thrombin has been used to treat a pseudoaneurysm of the radial artery [56]. The long-term results of endovascular procedures in this vasculo-Behçet group remain uncertain, but proponents are cautiously optimistic.

Experience suggests that adjunctive treatment with corticosteroids and immunosuppressive agents, and possibly with anticoagulants or antiaggregants, may be effective in reducing postoperative recurrences or graft occlusions [47,51••,58••,68]. We believe that immunosuppressive treatment should be used together with any surgical repair method, including endovascular repair [69••].

**Pulmonary arterial vasculitis**

Pulmonary artery aneurysms (PAAs) are one of the life-threatening complications of Behçet disease that require prompt diagnosis and treatment. It affects almost exclusively males and has a strong association with the systemic pattern of vessel involvement at other sites. Patients often have deep venous thrombosis and may have intracardiac thrombus formation and systemic arterial aneurysms as well [70,71]. Evidence thus suggests that PAA may represent the culmination of multiple lesions in patients with vasculo-Behçet.

Histopathologically, the inflammatory process appears to be located primarily in the vasa vasorum. In vessels dependent on this diseased vascular supply, necrosis of the vessel wall occurs with the formation of true aneurysms, or detachment and hemorrhagic dissection of the layers resulting in the formation of false aneurysms [69a]. Thus, it is not uncommon to see true aneurysms and pseudoaneurysms side by side in Behçet disease [53]. These lesions erode into bronchi, leading to lethal bleeding. During the evolution of this process, the development of
adventitial fibrosis and thrombus formation may contribute to lower the risk of aneurysm rupture. The co-occurrence of PAA and deep venous thrombosis is referred to as the Hughes-Stovin syndrome [72], which may be a forme fruste of Behçet disease. Because PAA is associated with thrombophlebitis, because ventilation perfusion lung scans and angiography are consistent with emboli [73], and because pulmonary emboli may cause hemoptysis, anticoagulants may be initiated in these patients, leading to more bleeding and death. Considering the rarity of pulmonary emboli in Behçet disease, hemoptysis should be viewed with a very high index of suspicion for PAA.

Pulmonary artery aneurysms are typically confined to the main pulmonary arteries and their lobar branches. Perihilar or parenchymal nodular opacities occur, are frequently multiple and bilateral [32,74,75], and can usually be seen on chest radiograph. However, microscopic or small vessel disease may not be apparent on radiographs, or their appearance can be entirely nonspecific. CT scanning and MRI have largely replaced angiography as the initial diagnostic procedure of choice.

The short-term mortality associated with PAA has been reported to be 50% [76], and these lesions contribute to the overall mortality of Behçet disease [2]. In patients with ruptured pulmonary artery aneurysm, the diagnosis is often delayed or missed, and this may adversely affect survival. In a report on 26 cases with PAA diagnosed after 1992, Hamuryudan et al. [71] reported a more favorable survival rate of 80% at 5 years and found that improved outcome is mainly caused by earlier recognition and rapid treatment of this complication.

Therapeutic considerations
Emergency surgery for ruptured pulmonary aneurysms has an excessively high mortality rate. In a recent experience, three patients died after emergency surgery for hemoptysis as a result of ruptured aneurysms on the opposite side [58••]. Pulmonary artery repair with reimplantation of pulmonary arterial branch has been described as a technique to limit lung parenchymal loss [77]. The operated patient was later able to tolerate a lobectomy on the opposite side. Endovascular embolization techniques have been used successfully to thrombose bleeding PAA [69••,78], but aneurysm size or vena cava thrombosis may limit the use of this technique in some patients.

All attempts should be made to treat PAA with medical therapy, but no controlled studies are available regarding the optimal treatment of patients with Behçet disease. Spontaneous remissions have only very rarely been reported, but corticosteroids and immunosuppressive agents, particularly cyclophosphamide, have been used successfully in many [71,75], but not all, cases [58••,74]. In some cases, patients have developed PAA while taking cyclophosphamide for other indications [70]. Considering all experiences and the poor prognosis of patients with pulmonary vasculitis, aggressive treatment that includes immunosuppressive agents, probably cyclophosphamide, is warranted.

Conclusion
Vasculo-Behçet implies a high risk of progressive complications, morbidity, and mortality. Early detection of vasculitis and the need for aggressive treatment are essential for optimal care of these patients. The challenges remain to identify those patients at risk and to develop effective therapies to arrest or reverse the course of pulmonary arterial vasculitis in Behçet disease.

References and recommended reading
Papers of particular interest, published within the annual period of review, have been highlighted as:

• Of special interest
•• Of outstanding interest
8 Vasculitis syndromes


Use of ultrasonography and positron emission tomography in the diagnosis and assessment of large-vessel vasculitis
Wolfgang A. Schmidt and Daniel Blockmans

Purpose of review
Ultrasonography and positron emission tomography have been increasingly studied and, in part, introduced in clinical practice to diagnose large-vessel vasculitides, such as temporal arteritis, Takayasu arteritis, large-vessel giant cell arteritis, and isolated aortitis.

Recent findings
Ultrasonography reveals characteristic homogenous, concentric wall thickening in vasculitis, often combined with stenoses and, less frequently, with acute occlusions. Thirteen studies describe sensitivities of 40 to 100% (median, 86%) for temporal artery vessel wall edema compared with histology, and of 35 to 86% (median, 70%) compared with clinical diagnosis. If wall edema, stenoses, and occlusions are included, sensitivities increase to 91 to 100% (median, 95%) compared with histology, and to 83 to 100% (median, 88%) compared with clinical diagnosis. Specificities for wall edema are 68 to 100% (median, 93%) compared with histology, and 78 to 100% (median, 97%) compared with clinical diagnosis. One should be aware of large-vessel giant cell arteritis in all patients with temporal arteritis and polymyalgia rheumatica. Ultrasonography reveals characteristic wall thickening, particularly of the distal subclavian, axillary, and proximal brachial arteries. Findings in Takayasu arteritis are similar, but the vessel wall swelling is usually brighter. Positron emission tomography reveals vasculitis in arteries with a diameter of more than 4 mm. Ultrasonography and positron emission tomography agreed completely in the anatomic distribution of changes in patients with large-vessel giant cell arteritis. It reveals asymptomatic large-vessel vasculitis in giant cell arteritis and Takayasu arteritis. Positron emission tomography is not suitable for the assessment of temporal arteries.

Summary
Ultrasonography and positron emission tomography are new, promising techniques to assess large-vessel vasculitides.

Keywords
ultrasonography, positron emission tomography, temporal arteritis, aortitis, Takayasu arteritis

Introduction
The Chapel–Hill classification of primary vasculitides distinguishes two entities: temporal arteritis (giant cell arteritis [GCA]) and Takayasu arteritis (TAK) [1]. In addition, a subset of temporal arteritis patients present with involvement of larger vessels, such as the distal subclavian, axillary, and proximal brachial arteries. This newer entity is called “large-vessel GCA.” Large-vessel GCA may occur without involvement of the temporal arteries. Furthermore, an increasing number of patients who are not typical for either GCA or TAK, are diagnosed with isolated aortitis because of new imaging techniques. Isolated aortitis can appear as a primary autoimmune disease or in combination with bacterial [2] or mycotic [3] infections, rheumatoid arthritis, spondyloarthritides, systemic lupus erythematosus, Behçet disease [4•], or poly- chondritis.

Ultrasonography (US) and positron emission tomography (PET) have been investigated and, in many centers, introduced into clinical practice as diagnostic tools for large-vessel vasculitides within the last few years.

Ultrasonography
US can delineate both the temporal arteries and larger arteries like the common carotid and axillary arteries. Modern transducers provide a resolution of 0.1 mm. US cannot depict vessels that are localized behind bone or lungs, like the proximal left subclavian artery and the thoracic descending aorta. US is widely accessible. The investigation is relatively inexpensive. There is no radia-
tion. US can assess blood flow characteristics, wall elasticity, and plaques. It is performed in the diagnosis of temporal arteritis, large-vessel GCA, and TAK. Furthermore, transesophageal echocardiography can depict the thoracic aorta. In color Doppler US, the information from Doppler US on blood flow is integrated in the grayscale image as a color signal. Duplex US is the combination of real-time imaging and Doppler US.

**Ultrasonography in temporal arteritis**
The US image of an inflamed temporal artery is characterized by three typical findings (Fig. 1) [5]:

1. **Edema:** A dark, hyperechoic (not anechoic), circumferential wall thickening ("halo") appears around the lumen of the temporal artery. It disappears with corticosteroid treatment after a mean of 16 days [5–7].

2. **Stenosis:** The narrowing of the vessel lumen leads to increased blood flow velocities and turbulence. Color Doppler US shows a mixture of colors and persisting color signals in the diastole. Doppler curves confirm this finding if the blood flow velocity is more than twice the rate recorded in the area before the stenoses, perhaps with waveforms demonstrating turbulence and reduced velocity behind the area of stenosis.

3. **Occlusion:** The image delineates a temporal artery with absence of color signals in it.

**Figure 1. Color Doppler US of the temporal arteries**

![Image of normal and inflamed temporal arteries](attachment:temporalarteryUS.png)

(A, B) Normal temporal artery in the longitudinal (A) and transverse (B) planes. (C, D) Acute temporal arteritis with edematous wall swelling (arrows) in the longitudinal (C) and transverse (D) planes. (E) Stenosis with turbulent flow (asterisk). (F) Doppler curves show increased flow velocities of about 2.5 m/second in the stenosis and lower velocities outside the stenosis.

In addition, the pulsatility of an inflamed temporal artery is often reduced.

One needs high-quality color Doppler US equipment with a linear probe that exhibits a frequency of more than 8 MHz, experience with vascular US, knowledge of the US image of a normal temporal artery, and standardized US machine adjustments. The color signal should cover the artery lumen exactly. It must not extend over parts of the vessel wall. In this case, minor wall edema may be missed. On the other hand, if the color only covers the center of the lumen, false hypoechoic areas may appear [8•]. Anechogenicity represents fluid. Hypoechogeticity represents edematous tissue. The color sample steering should have an angle of 20 to 30°, as the parallelograms show in Figure 1. One small study described many false-positive findings, obviously the result of suboptimal investigation technique. The sonographer did not perform color sample steering [9•]. A sonographer should have investigated at least 50 persons without temporal arteritis to be sure about the appearance of a normal temporal artery before he starts to assess patients with suspected GCA. The superficial temporal artery with the parietal and longitudinal ramus should be investigated in two planes on both sides in full length.

Thirteen studies from different centers reported sensitivities and specificities of temporal artery US (Tables 1 and 2 [10•,11,12,13•,14•,15–17,18•,19–21]). Sensitivities for vessel wall edema ("halo") are 40 to 100% (median, 86%) compared with histology, and 35 to 86% (median, 70%) compared with clinical diagnosis. Specificities are 68 to 100% (median, 93%) compared with histology, and 78 to 100% (median, 97%) compared with clinical diagnosis. Five studies investigated both color Doppler and duplex US including the assessment of stenoses. The sensitivity of stenoses for the diagnosis of temporal arteritis is comparable with the sensitivity of wall edema. If both features are included, sensitivities increase to 91 to 100% (median, 95%) compared with histology, and to 83 to 100% (median, 88%) compared with clinical diagnosis. Specificities for histology compared with clinical diagnosis are similar. Most studies arrive at sensitivities of 80 to 90%, [10•,22]. We have seen several patients with typical clinical and US signs of temporal arteritis who were biopsy negative because of skip lesions. Sensitivities for occlusions are low. Sensitivity is 30% in our series of 101 patients [14•], and 16% and 5% in two other series with respect to diagnosis [13•,18•]. Specificity for occlusions is high. The three studies found specificities of 99.8%, 98%, and 100%, each, with respect to the clinical diagnosis [13•,14•,18•]. Temporal artery occlusion was recently described in a patient with juvenile temporal arteritis and activated protein C resistance. Histology disclosed an inflammatory infiltrate with mononuclear cells without giant cells or granuloma [23•]. Both negative US and negative histology do not exclude the presence of temporal arteritis. Thus, patients with negative
results should be treated if clinical suspicion of arteritis is strong.

We additionally apply temporal artery US to detect temporal arteritis in patients with polymyalgia rheumatica (PMR). We found halos and/or stenoses in 8 of 102 patients with “pure” PMR. Finally, four of these eight patients had a positive biopsy [22]. US is also used to determine the most appropriate artery for biopsy [24].

Histology is still the diagnostic gold standard for temporal arteritis [25••,26•]. Nevertheless, some centers start to rely on the US results if the sonographer is experienced, if earlier US investigations proofed to be specific in this center, and if clinical presentation and US findings are typical (“halo”).

One to 6% of patients with clinical features of temporal arteritis may have another form of systemic vasculitis. In these cases, temporal arteritis is generally associated with extracranial clinical features suggestive of systemic vasculitis, and even biopsy may exhibit a classic GCA histologic pattern [27]. The US image of temporal vasculitis cannot differentiate between GCA and other forms of vasculitis. Therefore, one has to be particularly aware of other systemic vasculitides if one only performs US without biopsy.

**Ultrasonography in Takayasu arteritis**

TAK predominantly occurs in young females. The subclavian arteries are most commonly involved (93%), followed by the aorta (65%), and the common carotid arteries (58%) [10•]. Vasculitis of the renal, vertebral, innominate, axillary, superior mesenteric, common iliac, and pulmonary arteries is also common. US reveals characteristic long segments of smooth, homogeneous, hypechoic, concentric wall thickening (Fig. 2) [3]••. The wall thickening is, in general, brighter than in temporal arteritis and in large-vessel GCA because the course of TAK is more chronic with less vessel wall edema [28,32]. Furthermore, the stiffness of the in-

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*This study was performed in patients who had corticosteroid treatment for 10 to 17 days at the time of US investigation.

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volved arteries is often increased, as in temporal arteritis. The US image of arteriosclerotic lesions is entirely different with a nonhomogenous, irregular vessel wall and calcifications.

Many patients with TAK have prestenotic disease for months or years. US of the common carotid and subclavian arteries can detect typical changes before hemodynamically relevant stenoses occur [32]. Homogenous wall thickening of more than 1.0 mm at the common carotid or subclavian arteries is suspicious for the presence of TAK. Stenoses and occlusions develop, in general, slowly. Therefore, many patients exhibit collaterals. In our experience, retrograde flow of the vertebral arteries with or without subclavian steal syndrome is common [33].

Echocardiography should be performed in all patients with TAK. There are four important possible findings: (1) aortic valve regurgitation, (2) characteristic motion limitation of the thickened aortic cusp with dilated and thickened aorta [34••], (3) left ventricular hypertrophy because of renal arterial hypertension, and (4) pulmonary hypertension because of pulmonary artery involvement.

US correlates well with angiography, MRI, and MR angiography [31••,35•]. MR angiography may overestimate stenoses. US found scarce flow in severe stenoses that had been diagnosed as occlusion by angiography. Minor wall thickening may be missed by angiography because it does not delineate the vessel wall [32].

### Positron emission tomography

PET with radioactive-labeled 18-fluorodeoxyglucose (FDG) makes in vivo measurements of metabolic processes possible. FDG is a glucose analog that is transported across the capillary and cellular membranes in proportion to the rate of glucose uptake. Before 1999, it was predominantly used in cancer patients (lymphoma, lung cancer, gastrointestinal malignancies) to show the extent and possible spread of the malignant process. Because not only malignant cells, but also inflammatory cells, have an increased glucose uptake, FDG PET has been used recently in infectious and inflammatory disorders as well. In 1999, the first use of FDG PET in GCA [36] and TAK [37] was reported.

#### Positron emission tomography in giant cell arteritis

The temporal arteries cannot be visualized because of their small diameter, their superficial localization (there is always an increased FDG signal at the transition between body and air), and the intense FDG signal of the brain. In a preliminary study of six patients with biopsy-proved GCA and five PMR patients, increased FDG uptake in the larger thoracic vessels (aorta, subclavian arteries, carotid arteries) seemed to be a specific finding for GCA and/or PMR [36] (Fig. 3). FDG uptake decreased with corticosteroid treatment, at a time when inflammatory parameters had normalized and patients had become asymptomatic.

In 2000, the same authors published a larger study of 69 patients, 25 of whom had GCA or PMR and 44 age-matched control subjects [38]. These control subjects were initially also thought to have GCA/PMR and all underwent a temporal artery biopsy, but finally another disease was held responsible for their complaints. Vascular FDG uptake in the large thoracic arteries was again significantly more common in patients with GCA/PMR (56%) than in control subjects (2%, P < 0.0001). Vascular uptake in the arteries of the legs was seen in 64% of patients with GCA/PMR and in 23% of control subjects (P < 0.001). Vascular FDG uptake in any location (thorax or legs) was seen in 76% of patients and in 23% of control subjects (P < 0.0001). Notably, patients with predominant systemic symptoms such as fever, malaise, and weight loss had increased FDG uptake in the thoracic vessels. Thoracic vascular FDG uptake had a positive predictive value of 93% and a negative predictive value of 80%.

These two studies show that vasculitis of larger arteries occurs much more frequently (probably in every other patient) than previously thought. In most cases, this large vessel involvement (entire aorta, subclavian, axillary, subclavian and even iliac and femoral arteries) remains clinically asymptomatic, and it subsides with corticosteroid treatment. FDG PET has the advantage of identifying all the sites of large-vessel inflammation within one...
examination. Furthermore, FDG uptake in the shoulders was increased in about half the GCA/PMR patients.

No other studies comparing FDG PET in GCA/PMR patients and in control subjects have been published. One might hypothesize, however, that arteriosclerosis might produce false-positive vascular FDG uptake because the cellular components of the arteriosclerotic plaque, such as macrophages, exhibit high glucose metabolic activity. Yun et al. [39] evaluated the presence of FDG uptake in the abdominal aorta, and the iliac and the proximal femoral arteries in 137 consecutive patients, age 20 to 80 years, who underwent a PET scan, most frequently for malignant tumors. Fifty percent showed FDG uptake in at least one vessel, with an increased prevalence in older patients. These figures (although higher) are in concordance with our findings (23% vascular uptake in the legs of control patients). The specificity of an increased vascular FDG uptake for true vasculitis in, for instance, the subclavian artery, which is less prone to atherosclerosis than lower limb arteries, is indeed higher. Therefore, we advise one to rely on thoracic vessel FDG uptake in the diagnosis of GCA.

Several case reports and small case series have been published recently that confirm the initial findings [40–46,47•]. Most patients presented with a history of fever of unknown origin, fatigue, and weight loss, for which an FDG PET scan was performed. The published images are dramatic, with very extensive FDG uptake, sometimes involving all major arteries. The diagnosis of GCA was then confirmed by temporal artery biopsy [40,43,45,46]. Control FDG PET studies after some weeks of corticosteroid therapy showed a marked reduction or even disappearance of the vascular uptake [40,41,43–45]. One has to keep in mind, however, that vascular FDG uptake is not always as extensive or intense as shown in these case reports.

Meller et al. [47•] compared FDG PET with MRI in 15 patients with early aortitis, 14 of which had features of GCA (no temporal artery biopsy performed) and one with TAK. In six patients, the PET scan was repeated during corticosteroid treatment. At baseline, abnormal FDG uptake was present in 56% of the vascular regions studied. On repeat PET scan, 80% of the initial regions with pathologic uptake had normalized. Of 76 vascular regions studied with PET and MRI, 47 were concordantly positive or negative on both modalities, 11 were positive on MRI only, and 18 were positive on PET only. The authors concluded that FDG PET is valuable in the diagnosis of early aortitis, that it identifies more regions with vasculitis than MRI, and that it is more reliable than MRI in monitoring disease activity during immunosuppressive therapy.

In 2004, a series of 22 consecutive GCA patients was published [48••]. All patients had a hypoechoic halo in duplex US. Temporal artery biopsies were not routinely performed (only 8 of 22). As judged by duplex US, six patients had GCA involving both the large arteries and the temporal arteries, five patients showed GCA only in the large arteries without concomitant involvement of the temporal arteries, and 11 patients showed only involvement of the temporal arteries. All patients with US signs of GCA (ie, a hypoechoic halo) in the aorta, the subclavian, axillary, and iliac arteries also showed elevated FDG uptake in the same vessels, with complete agreement in the anatomic distribution of the vasculitis. When the positive US was limited to the temporal arteries, FDG PET was completely negative in the temporal arteries and all other arterial locations. In conclusion, the correlation between US and PET with re-
gard to large-artery vasculitis is excellent, but PET is not yet suitable for the assessment of the temporal arteries.

We do not recommend FDG PET be performed in every patient with presumed GCA, but it is a valuable diagnostic procedure in patients with vague or atypical clinical pictures, when systemic complaints dominate in combination with unexplained inflammation. In patients with fever of unknown origin, FDG PET scan has replaced gallium scintigraphy in our center [49]. Besides these clinical uses, FDG PET is, in our center, mainly performed for scientific reasons in GCA/PMR.

**Positron emission tomography in Takayasu arteritis**

Until 2003, only single observations have been published [37,50–53]. All these cases confirm the increased FDG signal in the thoracic arteries.

Webb et al. [54•] reviewed 28 FDG PET scans performed on 18 patients suspected of having TAK. Sixteen of 18 satisfied the American College of Rheumatology criteria for this disease. When compared with the combined assessment of disease activity (based on a combination of constitutional symptoms, biochemical markers, and angiography), FDG PET correctly detected 11 of 12 patients with active disease and all six with inactive disease. There was one false-negative scan and no false positives. FDG PET had a sensitivity of 92%, a specificity of 100%, a positive predictive value of 100%, and a negative predictive value of 85%. Ten additional FDG PET scans were performed in the follow-up of eight patients. They showed universal agreement with the clinical assessment of the disease activity. It was the authors’ experience that FDG PET was able to detect inflammation in many more sites than those that were clinically active. If these findings are confirmed in a prospective study, FDG may become an elegant way to diagnose and monitor disease activity in TAK.

**Positron emission tomography in idiopathic aortitis**

Because this disease is relatively rare, no large series on the use of FDG PET in idiopathic (peri)aortitis has been published, but several case reports have demonstrated that the inflammatory process is easily visible on FDG PET scan and that FDG uptake disappears with treatment [51,55•,56•,57,58].

**Conclusion**

Sensitivities of temporal artery US are high for the clinical diagnosis of temporal arteritis, if edema, stenoses, and occlusions are assessed. Specificities are very high if sonographers are experienced with this method, if they use high-quality US equipment with correct machine adjustments, and if they know the occurrence of artifacts and the appearance of normal temporal arteries. All patients with temporal arteritis and PMR should be investigated for large-vessel GCA that predominantly occurs in the axillary region. Artery wall thickening is similar in TAK, but it is brighter in many cases. Complete agreement was found between US and PET with regard to the anatomic distribution in large-vessel GCA, but PET cannot assess the temporal arteries. On the other hand, PET reveals involvement of larger arteries such as the aorta, subclavian, and axillary arteries in every other patient with temporal arteritis and PMR. Monitoring of disease activity in patients with TAK and large-vessel GCA with FDG PET seems to be possible.

**References and recommended reading**

Papers of particular interest, published within the annual period of review, have been highlighted as:

- Of special interest
- Of outstanding interest


15. LeSar CJ, Meier GH, DeMasi RJ, et al.: The utility of color duplex ultrasono-
Echocardiographic and clinical characteristics of primary vasculitides, including small-, medium-, and large-vessel vasculitides. This study compares duplex US of the temporal arteries with clinical and histologic findings in patients with active temporal arteritis. This is a review of all important imaging techniques in the diagnosis of primary vasculitides, including small-, medium-, and large-vessel vasculitides. This study compares FDG PET and MRI in 14 patients with large-vessel GCA and one patient with TAK, including follow-up investigations in some patients. This study compares duplex US with PET in temporal arteritis and in large-vessel GCA with regard to the temporal arteries and larger arteries. This is the first study to compare duplex US with PET in temporal arteritis and in large-vessel GCA.

US and PET in large-vessel vasculitis

Schmidt and Blockmans


Meller J, Strutz F, Sieker U, et al.: Early diagnosis and follow-up of aortitis with • (18)FFDG PET and MRI. Eur J Nucl Med Mol Imaging 2003, 30:730–736. This study compares FDG PET and MRI in 14 patients with large-vessel GCA and one patient with TAK, including follow-up investigations in some patients.


This is a retrospective study of a large group of TAK patients that showed that FDG PET may be an elegant way to diagnose and monitor disease activity in TAK.


This is a case report of an 82-year-old man with pneumococcal aortitis, in whom FDG PET made an important contribution to the diagnosis.


This is a case report of a 62-year-old woman with an idiopathic inflammatory aortitis that compares the findings of CT, MRI, and FDG PET.


Advances in the medical and surgical treatment of Takayasu arteritis
Patrick Liang and Gary S. Hoffman

Purpose of review
Takayasu arteritis remains a therapeutic challenge. In spite of current treatments, progression of vascular lesions is observed frequently. The purpose of this article is to describe advances in therapeutic strategies for Takayasu arteritis.

Recent findings
Immunosuppressive agents including methotrexate, mycophenolate mofetil, and azathioprine added to corticosteroids can bring Takayasu arteritis into remission in many patients. Unfortunately, relapse is common when prednisone is tapered to dosages of 15 mg/day or less. A better understanding of pathogenesis has lead to trials with anti–tumor necrosis factor-α agents in patients with refractory disease. Preliminary results are encouraging. For patients who require revascularization intervention, both surgical and endovascular procedures can be performed that are safe, with low morbidity and mortality. The best long-term outcomes are achieved with conventional bypass grafts. Percutaneous transluminal angioplasty provides good results for short lesions. In contrast to the results in treating atherosclerosis, the use of conventional stents may not yield long-term vessel patency in Takayasu arteritis. Persistent inflammation and endothelial dysfunction may put patients with Takayasu arteritis at risk for premature atherosclerosis.

Summary
In the future, greater therapeutic success may be achieved by addressing both the inflammatory and the myointimal proliferative components of Takayasu arteritis. New drugs that target intimal hyperplasia, as well as drug-eluting stents, deserve to be studied for possible utility as adjuncts to present treatments.

Keywords
Takayasu arteritis, stents, anti–tumor necrosis factor-α, bypass grafting, percutaneous transluminal angioplasty, revascularization procedures
ment. Furthermore, serial angiographic studies show that new lesions can be found in 61% of patients even when the disease is thought to be in remission [1]. TA is thus challenging because disease activity may be inapparent but clinically significant, and available therapeutic agents are toxic and do not ensure remission.

Recent improved understanding of the pathogenesis of TA has brought hope of new therapeutic opportunities. Progress in the identification of better surrogate markers of ongoing inflammation may allow for more timely therapeutic interventions. The purpose of this article is to review recent advances in the medical and surgical management of TA.

**Traditional immunosuppressive agents**

Traditional immunosuppressive agents include corticosteroids, methotrexate, azathioprine, and various other agents such as mycophenolate mofetil and cyclophosphamide.

**Corticosteroids**

Corticosteroids constitute the first line of treatment for active inflammation, with suggested initial dosages of 0.5 to 1 mg/kg/day [1,2]. Although remission is achieved in as many as 60% of patients [1], relapses during corticosteroid tapering occur in more than 50% of patients. The development of new lesions at previously unaffected sites is common and represents the most convincing evidence of intervening active disease. Therefore, other immunosuppressive drugs are regularly added to corticosteroids with the aim of halting disease progression and reducing disease and corticosteroid-related morbidity.

**Methotrexate**

Methotrexate can improve the remission rate in patients with corticosteroid-resistant TA [1,3,4]. In the largest prospective study of the use of methotrexate for TA, remission, defined by the absence of clinical signs of active disease, and absence of new angiographic lesions could be achieved in 13 of 16 patients. Starting dosages of methotrexate were 0.3 mg/kg/week, up to 15 mg/week. Dosages could thereafter be increased up to 25 mg/week to achieve remission. Seven patients in whom remission had been achieved later experienced relapse as corticosteroids were tapered to the point where discontinuation was approached or achieved. Remission could again be induced with the same regimen. Overall, remission could be maintained in half of patients without corticosteroids during a follow-up period of approximately 1.5 year [5].

**Azathioprine**

Valsakumar et al. [6] recently published their experience with a combination of azathioprine and prednisolone for patients with newly diagnosed active TA who had not previously received any immunosuppressive drug treatment, including corticosteroids. From 1996 to 2001, 15 of 65 consecutive patients with TA were considered to have active disease based on the presence of two or more of the following: (1) constitutional features, (2) painful arteries, (3) elevated erythrocyte sedimentation rate, and (4) elevated C-reactive protein. Treatment consisted of azathioprine 2 mg/kg/day and prednisolone 1 mg/kg/day for 6 weeks, to be tapered to a maintenance dosage of 5 to 10 mg/day by 12 weeks. Angiograms were performed in all patients before treatment and at 1-year follow-up. All patients had complete resolution of systemic symptoms; and no progression (nor regression) of lesions was observed in any patient. Of note, new lesions were not identified on follow-up angiography.

Although this report suggests that the combination of azathioprine and prednisolone improves outcome and may prevent progression of the disease, it remains unclear whether these encouraging results would have been achieved with prednisolone alone. Controlled trials with longer follow-up times will be required to assess the value of this approach and determine the requirements for long-term therapy.

**Other immunosuppressive drugs**

Experience with other immunosuppressive drugs in the treatment of TA has been limited to case reports [7–9]. Mycophenolate mofetil at a dosage of 2 g/day has been reported by one group to be efficacious in three patients with refractory TA [8], but others have not found it to be useful [10].

The efficacy of cyclophosphamide at a dosage of 2 mg/kg/day when added to corticosteroids has been established in a study of seven patients with TA [11]. Cyclophosphamide enabled corticosteroid dosage to be tapered in all patients. Four of seven patients did not have progression of lesions on subsequent angiograms. Concerns about toxicity from chronic cyclophosphamide therapy, however, led the authors to recommend using this agent only for patients with severe TA refractory to other immunosuppressive agents.

**Therapeutic insights from improved comprehension of pathogenesis**

Despite treatment with corticosteroids and cytotoxic drugs, most patients still experience progressive vascular disease [1]. Recent progress in understanding the pathogenesis of TA has been achieved, and this may help in identifying new targets for treatment.

The outer layers of the walls of large elastic arteries are nourished by the vasa vasorum, a penetrating network of capillaries that enter the vessel in the adventitial layer. In the largest of elastic and muscular arteries, the vasa vasorum may enter the media as well. In TA, within injured and thickened vessels, the vasa vasorum proliferates and can penetrate as deep as the intima [12]. The inflammatory infiltrate, which is composed of dendritic cells, macrophages, various subsets of T cells (αβ, γδ, cytotoxic T cells), and natural killer cells enter the vessel...
Because TNF-α, a product of Th1 cells and macrophages, is an important mediator in the formation of granulomas, it represents an interesting target for the treatment of TA. Hoffman et al. [10] reported on their experience with anti-TNF agents in 15 patients with difficult-to-treat TA. Before treatment with anti-TNF agents, all patients required corticosteroids to maintain disease remission and had experienced multiple relapses, most of them (13/15) despite concomitant treatment with multiple other immunosuppressive drugs. Seven patients received etanercept, and 11 received infliximab (3 were switched from etanercept to infliximab). Ten of the 15 patients achieved sustained remission, defined as the absence of new vascular lesions, as determined by MRI/magnetic resonance angiography or invasive angiography, and the ability to discontinue corticosteroid therapy. The period of follow-up was 1 to 3.3 years. In addition, 4 other patients could reduce their corticosteroid requirements by at least 50%. All forms of therapy, including anti-TNF treatment, were unsuccessful in 1 patient. For all patients who responded to anti-TNF therapy, subjective and objective signs of improvement were apparent within 2 weeks to 2 months. Nine responders eventually required an increase in the dosage of anti-TNF agents to achieve a sustained remission. Although preliminary, these results suggest that anti-TNF agents may be a useful adjunct to corticosteroids in the treatment of TA patients.

**Interferon-γ**

Although no trial involving an IFN-γ inhibitor has been reported in TA, interesting data were published with regard to the use of aspirin in GCA [16]. As alluded to earlier, GCA and TA have similar histopathologic features and likely share common pathogenic pathways. In a mouse chimera model of GCA, aspirin, when given in dosages equivalent to 20 mg/kg, interfered with transcription of the IFN-γ gene and with production of the protein. It was shown that corticosteroids, though potent inhibitors of the inflammatory cytokines interleukin-1 and interleukin-6, had little effect on the production of IFN-γ. The authors proposed that aspirin may constitute a useful adjunct to corticosteroid therapy for GCA. Of note, Nesher et al. [17] showed, in a retrospective uncontrolled study of patients with GCA, that the use of low-dose aspirin in addition to corticosteroid therapy was associated with a fivefold reduction in the rate of ischemic complications in comparison with corticosteroid treatment alone. On the basis of their results, the authors suggested that aspirin should be prescribed as part of the standard treatment of GCA, with corticosteroids.

These findings are provocative and deserve to be evaluated in a controlled prospective study. However, they may not directly apply to TA. Many of the reported ischemic complications consisted of stroke and events that could have been due to age, preexisting hypertension, diabetes atherosclerosis, and other risk factors not accounted for, rather than to inflammation. In the age group of GCA patients, many people would likely benefit from aspirin treatment because of its antiplatelet activity. Thus, in TA, wherein patients are younger and have fewer atherosclerotic risk factors, it remains to be determined whether the hypothetical effects of low-dose aspirin inhibiting IFN-γ and reducing myointimal proliferation would be achieved and would prevent ischemic complications.

**Revascularization interventions**

The diagnosis of TA occurs at a stage when stenotic or occlusive lesions have already occurred. Such lesions are usually not reversible by medical treatment and, if they are hemodynamically significant, may require revascularization. Indications for revascularization include cerebrovascular disease due to cervicocranial vessel stenosis, coronary artery disease, moderate to severe aortic regurgitation, severe coarctation of the aorta, renovascular hypertension, limb claudication, and progressive aneurysm enlargement with risk of rupture or dissection.
For correction of stenoses and occlusions, the largest body of experience comes from bypass graft procedures, where good long-term outcomes have been achieved [1,18,19] (Table 1). On average, a 20 to 30% rate of restenosis or occlusion is reported on long-term follow-up. In the series from the National Institutes of Health by Kerr et al. [1], 50 bypass procedures were performed in 23 patients. Overall, 24% of procedures were followed by restenosis, which may or may not have been hemodynamically significant. Thirty-six percent of 39 procedures using synthetic grafts were complicated by subsequent restenosis. By contrast, only 1 of 11 procedures (9%) in which autologous vessel was used for bypass was associated with restenosis. The follow-up times for these patients were as long as 20 years (median 5.3 years), and surgical follow-up times were as long as 13.5 years.

A review of patients monitored at the Cleveland Clinic Foundation between 1979 and 2001 showed that out of 31 bypass graft procedures, restenosis, occlusion, or the need for revascularization occurred in 11 procedures after a median follow-up period of 11 months (1 day to 168 months) [20].

Weaver et al. [21•] recently reported their experience with renal revascularization procedures in TA-induced renal artery stenosis. Thirty-two aortorenal bypass procedures were performed. Of note, all patients had hypertension before surgery (mean: 167 ± 6/99 ± 5 mm Hg), 3 patients were dialysis dependent, and 2 had refractory congestive heart failure. Autologous bypass grafts were used in 20 patients and prosthetic materials in 12. No postoperative death was reported. Three graft stenoses (9%) and 3 graft occlusions (9%) were documented. Primary patency of the renal revascularization at 5 years was 79%. Importantly, mean blood pressure measurement decreased to 132 ± 4/79 ± 2 mm Hg, 2 patients no longer required dialysis, and congestive heart failure resolved in both patients who had this condition before surgery. In selection of the site for graft anastomosis, the authors mentioned the importance of finding an anatomic region without apparent inflammation, to prevent graft failure due to inflammation at the anastomotic site [21•]. This article also noted the importance of screening patients for renovascular hypertension, insofar as treating this condition is likely to reduce the occurrence of subsequent comorbid conditions such as renal insufficiency and congestive heart failure.

Miyata et al. [22] published a retrospective review of 106 consecutive patients who underwent surgical treatment from 1955 to 1995. There were 12 early hospital deaths. Thirty-one of the remaining 94 patients died after a mean follow-up period of 19.8 years. Congestive heart failure was the major cause of death, accounting for 45% of events. Interestingly, the authors divided the patients into two groups according to whether they were operated on before or after 1981. All 12 early hospital deaths occurred in patients operated on before 1981. The explanations offered for this finding included (1) better understanding of the pathophysiology of arterial reconstruction and improvement in operative techniques, (2) improved supportive care (eg, mechanical ventilation and hemodialysis), and (3) improved preoperative evaluation and planning.

Before surgical treatment, patients were also divided into three prognostic categories based on the criteria of Ishikawa [23] and Ishikawa and Shunzo [24]. This classification system relies on (1) the presence of complications (retinopathy, severe hypertension, grade 3 or 4 aortic regurgitation, aneurysms) and (2) clinical course (whether or not the disease progresses). The overall cumulative survival rate at 20 years was 73.5%, with no statistically significant difference between prognostic groups. However, patients with complications as defined above and/or a progressive disease course seemed to benefit the most from surgery, because their long-term survival

### Table 1. Selected studies of bypass grafting in Takayasu arteritis

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of patients/ no. of procedures</th>
<th>Length of follow-up (y)</th>
<th>Restenosis/occlusion (%)</th>
<th>Perioperative mortality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kerr et al. [1] (1970–1990)</td>
<td>23/50</td>
<td>Median: 5.3, Range: 0.5–20</td>
<td>24</td>
<td>0</td>
</tr>
<tr>
<td>Weaver et al. [18] (1963–1989)</td>
<td>10/13</td>
<td>Median: 6.25, Range: 0.5–15.4</td>
<td>31</td>
<td>0</td>
</tr>
<tr>
<td>Pajari et al. [48] (1960–1984)</td>
<td>18/36</td>
<td>Median: 4.8, Range: 0.1–14</td>
<td>31</td>
<td>7 (2/29)</td>
</tr>
<tr>
<td>Lagneau et al. [19] (1976–1984)</td>
<td>31/52</td>
<td>Mean: 3 years ±7 months</td>
<td>8</td>
<td>0b</td>
</tr>
<tr>
<td>Teoh [49]</td>
<td>11/18</td>
<td>Median: 0.6, Range: 0.1–6.7, 5.7 ± 0.75, Range: 0.25–13</td>
<td>18</td>
<td>0</td>
</tr>
<tr>
<td>Weaver et al. [21•]</td>
<td>32/32</td>
<td>Median: 2.16, Range: 0–14</td>
<td>35</td>
<td>0</td>
</tr>
<tr>
<td>Liang et al. [20]</td>
<td>15/31</td>
<td>Median: 0.25</td>
<td>0.1</td>
<td>0</td>
</tr>
</tbody>
</table>

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*a* The perioperative period is defined as the time from admission for surgery to hospital discharge. *b* Although no deaths occurred during the perioperative period, one patient died 2 months after operation as a result of graft infection. Adapted with permission [20].
Table 2. Outcomes of selected trials of percutaneous revascularization procedures in Takayasu arteritis

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of patients</th>
<th>No. of lesions available</th>
<th>Follow-up duration (mos)</th>
<th>Patency rate</th>
<th>Method for assessment of patency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tyagi et al. [36]</td>
<td>54</td>
<td>PTA renal: 52</td>
<td>Mean: 14.2</td>
<td>7/52 (86.5%)</td>
<td>Angiography</td>
</tr>
<tr>
<td>Tyagi et al. [50]</td>
<td>32</td>
<td>PTA: subclavian</td>
<td>43.4 ± 24</td>
<td>23/32 (72%)</td>
<td>Symptoms, pulse, blood pressure</td>
</tr>
<tr>
<td>Sharma et al. [51]</td>
<td>20</td>
<td>PTA: 12; Stent: 16</td>
<td>Median: 6</td>
<td>PTA: 12/12 (100%)</td>
<td>Angiography: 15</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Range: 4–10</td>
<td>Stent: 14–16 (88%)</td>
<td>Other: 13&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Rao et al. [52]</td>
<td>16</td>
<td>PTA: aorta (thoracic and abdominal): 16</td>
<td>Mean: 21.4 (range: 2–52)</td>
<td>10/16 (67.3%)</td>
<td>Angiography (only if symptoms occurred): 5 ABI: 14</td>
</tr>
<tr>
<td>Sharma et al. [53]</td>
<td>56</td>
<td>PTA: Renal: 77</td>
<td>Mean: 23 (range: 4–84)</td>
<td>62/77 (81%)</td>
<td>Angiography: 35</td>
</tr>
<tr>
<td>Fava et al. [35]</td>
<td>20</td>
<td>PTA: Renal: 12; Abdominal aorta: 3</td>
<td>All patients: 60</td>
<td>Renal: 4/12 (33%); Abdominal aorta: 1/3 Iliac: 3/5 (60%)</td>
<td>Unspecified</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sakaida et al. [54]</td>
<td>4</td>
<td>Stents: 14; Subclavian: 6</td>
<td>Mean: 12</td>
<td>10/11 (91%)</td>
<td>Symptoms</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Common carotid: 8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kerr et al. [1]</td>
<td>11</td>
<td>PTA: 20; Subclavian and renal arteries</td>
<td>Median: 12</td>
<td>56%</td>
<td>Angiography</td>
</tr>
<tr>
<td>Liang et al. [20]</td>
<td>Stents: 4</td>
<td>PTA: 7</td>
<td>Median: 13</td>
<td>4/7 (57%)</td>
<td>Angiography, MRI</td>
</tr>
<tr>
<td></td>
<td>Stents: 7</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tyagi et al. [55]</td>
<td>12</td>
<td>PTA: 7</td>
<td>Median: 11</td>
<td>2/7 (29%)</td>
<td>Blood pressure, symptoms, or angiography</td>
</tr>
<tr>
<td></td>
<td>Stents: thoracic and abdominal aorta</td>
<td>Mean: 26.8 ± 10.8</td>
<td></td>
<td>11/12 (91.6%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>Stents: Thoracic descending aorta</td>
<td>Mean: 26.9 ± 10.8</td>
<td>6/6 (100%)</td>
<td>Angiography</td>
</tr>
</tbody>
</table>

<sup>a</sup>Other: Symptoms, blood pressure, pulses, Doppler, requirement for increased number of antihypertensive drugs. ABI, Ankle-brachial index with Doppler ultrasound; BP, blood pressure; ΔRx: medication requirement; PTA, percutaneous transluminal angioplasty. Adapted with permission [20]
rate equaled that in patients with less severe disease. A 13.8% rate of anastomotic aneurysms at 20-year follow-up was reported and tended to occur mainly but not exclusively after operations for aneurysmal lesions [25]. This finding led the authors to recommend screening for anastomotic aneurysms by CT, MRI, or ultrasonography every several years, although the exact frequency was not specified.

To prevent the formation of aortic anastomotic aneurysms, it has recently been proposed that the aortic anastomotic suture line be reinforced with a polytetrafluoroethylene patch. This recommendation was based on successful interventions in only two patients [26]. The follow-up times were short (2 and 5 years), however. Thus, the true value of this procedure remains to be determined. In addition, it should be mentioned that anastomotic aneurysms have only infrequently been reported by other groups [1,17]. In the absence of clear recommendations with regard to the detection of anastomotic aneurysms, we believe that in most patients it is possible to screen for this complication at the time of imaging studies (CT or MRI) that are otherwise performed every year or two, or as dictated by symptoms, for the purpose of sequential assessment of disease activity or progression.

Bypass grafts for involved cervicobrachial vessels usually originate from the ascending aorta, inasmuch as this segment of the aorta seldom becomes stenotic or even, if diseased, essentially never becomes occluded. This is in marked contrast to the carotid or subclavian arteries. Because these latter vessels are frequently involved, they should not be considered as inflow sites for bypass grafts. However, in patients with severely reduced brain circulation, clamping or partial clamping of the ascending aorta at the time of surgical intervention may further compromise brain blood flow. To circumvent this potential risk, as reported in one case, the descending aorta may be used as an inflow site for a bypass graft [27].

Coronary artery involvement in TA may be found in 9 to 45% of cases [28,29]. Occlusive lesions are seen mostly around the coronary ostium [30]. They may result from inflammation, intimal proliferation, and/or fibrous contraction of the ascending aorta and coronary ostia. Endo et al. [31] reported their experience in 31 TA patients with coronary artery involvement. Their findings included stenotic lesions in 24 patients, aneurysms in 3, and coronary artery–bronchial artery fistula in 3. Of 16 patients who had bypass grafts, 2 required re-intervention after a mean follow-up period of 9.65 ± 6.9 years [31]. The same authors reported two successful transaortic endarterectomies and one patch angioplasty procedure with uneventful long-term postoperative courses. However, the role of endarterectomy and patch angioplasty in TA is unsettled. Although some reports suggest positive outcomes; others do not [32–34]. A limited experience with patch angioplasty procedures at the Cleveland Clinic Foundation was disappointing, with 4 of 6 procedures followed by restenosis, occlusion, or requirement for repeat surgery [20]. A possible explanation for these disappointing results may be that performance of a procedure on a vessel segment with active disease could enhance the inflammatory process. With regard to endarterectomy, because TA often involves the entire thickness of the vessel wall, achieving an adequate plane of cleavage to provide sustained patency may be technologically difficult or impossible.

Percutaneous transluminal angioplasty with or without a stent has been reported by some authors to have good to excellent short-term outcomes in TA (Table 2). However, our experience and that of others has been to the contrary [1,18,35]. Five of seven stents placed in our patients resulted in restenosis after a median follow-up period of 11 months. Such results could be explained by the very nature of vessel lesions in TA, which are usually long, fibrotic, and nearly or completely occluded. Thus, they may be less amenable to successful dilatation. Persistent inflammation in the TA vessel at the time of dilatation/stenting could also lead to enhanced myointimal proliferation. However, for short focal lesions, excellent results have been reported [36].

In summary, bypass graft surgery is the procedure with the best long-term patency rate. Furthermore, morbidity and mortality are low and comparable to other less invasive techniques. Endovascular procedures may provide good outcomes for lesions that are short and not already occluded. Conventional stents seem to be associated with a high failure rate in TA.

Detection of active disease

To improve treatment outcomes in TA, it is important to have more sensitive and specific measures of disease activity than those currently available. Active disease requires enhancement of immunosuppressive therapy, whereas such treatment provided during sustained remission for vague nonspecific symptoms would lack benefit and may as well be harmful. Improved imaging techniques such as CT, PET, and MRI/magnetic resonance angiography may detect inflammation before irreversible lesions develop [37].

Ideally, reliable hematologic surrogate markers would assist in determining the status of disease activity and aid in monitoring therapy. Until now, however, no single reliable marker has been identified [38]. Preliminary reports describing correlations with disease activity and circulating levels of matrix metalloproteinase-3, matrix metalloproteinase-9, and interleukin-6 deserve further study to more accurately determine performance characteristics [39,40].
Treatment of coexisting conditions

Intimal hyperplasia may occur in response to vessel wall injury or may be a consequence of ongoing active inflammation. In addition, persistent inflammation may be a risk factor for premature atherosclerosis in TA [41,42]. These observations encourage screening for and treating risk factors for atherosclerosis, as well treating active inflammation.

The future

Intimal hyperplasia is a constant finding in TA. It is a common response of blood vessels to injury, whether from inflammatory (TA, GCA, allograft vasculopathy) or mechanical (e.g., post-angioplasty or stents) sources. Corticosteroids and cytotoxic agents may control inflammation; however, they may not arrest intimal proliferation and the development of stenotic lesions. Treatment aimed specifically at myointimal proliferation could play a complementary role to immunosuppressive therapies in TA. Agents that have a modest effect in decreasing intimal hyperplasia include statins and sirolimus [43,44]. A recent study compared azathioprine with everolimus in their ability to diminish cardiac allograft vasculopathy, a condition characterized by intimal proliferation. Everolimus was used because of its known immunosuppressive and antiproliferative properties. It reduced allograft vasculopathy, raising questions about whether studies of such agents in TA might be worthy of consideration [45].

Stents, used in atherosclerotic disease, have also been used in TA. Restenosis, which occurs in as many as 20% of patients with atherosclerotic disease, is more likely to occur in TA. In an attempt to decrease intimal proliferation and restenosis, stents have been designed that are impregnated with immunosuppressive/antiproliferative medications that are slowly released over several weeks. Although intimal proliferation is inhibited, reendothelialization of the stent surface may occur. Sirolimus-eluting stents have demonstrated superiority to conventional stents in patients with coronary artery disease [46,47]. The development of similar devices fitted for larger vessels may improve the results and provide an important option for patients with TA. Platelet-derived growth factor and vascular endothelial growth factor, which contribute to intimal proliferation, may also be logical targets for inhibition in TA [15••]. Although our understanding of the pathogenesis of TA offers new investigative opportunities, these modalities should not be endorsed without proof of efficacy from formal well-designed trials.

Concluding remarks

We have witnessed in recent years an increasing appreciation for the inherent difficulties in recognizing disease activity and providing effective treatment for TA. Better imaging techniques may facilitate our understanding of disease activity and may help in guiding the proper timing of therapeutic interventions.

Corticosteroids remain the cornerstone of treatment. The adjunctive use of immunosuppressive agents is frequently required to induce and maintain remission. Cyclophosphamide should be reserved for patients with the most severe or refractory disease states. When cyclophosphamide is used, the duration of treatment should be limited to 3 to 6 months, if possible. If remission is achieved, cyclophosphamide should be replaced by methotrexate or azathioprine in an attempt to maintain remission. The ideal duration of therapy for any individual patient is uncertain and must be tailored to each patient’s unique circumstances.

Although preliminary results with anti-TNF therapy for TA are promising, these findings will have to be confirmed in randomized controlled trials before they can be generally endorsed. Acetylsalicylic acid may also represent an important adjunct, both for its antithrombotic effects and for its inhibitory actions on IFN-γ. The development of therapies designed to prevent fibrosis and intimal hyperplasia might have a favorable impact on the progression of stenotic lesions.

Fixed, irreversible lesions may be amenable to revascularization procedures that in experienced hands have low morbidity and mortality. Bypass grafts provide the longest-lasting patency rates. Percutaneous balloon angioplasty can provide good outcomes for short lesions. Conventional stents may be associated with a high rate of failure, as suggested by studies with long-term follow-up. Encouraging results have been reported with the use of antiproliferative/immunosuppressive agents (systemically or in drug-eluting stents) in atheromatous vascular disease. Whether their use for treatment of TA would be of benefit needs to be determined.

At least 40% of patients with TA experience hypertension. Whenever possible, surgical cure of hypertension should be pursued by anatomic correction of lesions such as renal artery stenosis. Atherosclerosis may become an important comorbidity in TA. It may be due in part to persistent inflammation and conventional risk factors that require identification and treatment. Sequential assessments of changes in large vessel anatomy and subsequent hemodynamic consequences are as important as managing complex medical regimens. The care of patients with TA requires a well-coordinated multidisciplinary team that includes rheumatology, imaging, cardiovascular, and surgical specialists.
References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

• Of special interest

** Of outstanding interest

16. A comprehensive review of the current understanding of pathogenesis of large vessel vasculitides.
38. The authors provide a good summary of new imaging modalities for diagnosis and follow-up of TA patients, emphasizing the strengths and weaknesses of each.
51. Tyagi S, Verma PK, Gambhir DS, et al.: Early and long-term results of subcla-
Vasculitis syndromes


Ocular vasculitis: a multidisciplinary approach
Carl P. Herborat
Luca Cimino and Ahmed M. Abu El Asrar

Purpose of review
The ophthalmologist has direct visual access to inflamed vessels when examining the retina, and "vasculitis" in ophthalmology has so far mainly referred to retinal vasculitis. In the past few years the means to explore vasculitis in the ocular sphere have improved. Indocyanine green angiography now enables the analysis of choroidal inflammatory vasculopathy as well as vasculitis of the sclera (scleritis) and episclera (episcleritis) in addition to retinal vasculitis. Because vasculitis detected by the ophthalmologist can be the presenting sign of a systemic disease and has to be approached in a multidisciplinary fashion, the emerging term "ocular vasculitis," instead of retinal vasculitis, should be used in the future. The term covers vasculitis affecting all structures of the eye and the periorcular tissues as detailed in this article. The ocular findings have to be integrated within the established and accepted classification of systemic vasculitis, which is divided into primary vasculitides, where the vessel itself is the target of the inflammatory reaction, and secondary vasculitides, caused by other inflammatory processes. This review will deal with recently published articles on ocular vasculitis, including its clinical aspects, its link with systemic diseases, and its investigation and management. The discussion will be conducted within the framework of the new classification put forward here.

Recent findings
Novel imaging techniques such as indocyanine green angiography have made it possible to explore inflammation of choroidal vessels and of scleral vasculitis in addition to retinal vasculitis, contributing to the global concept of ocular vasculitis. It has been shown, in particular, that the choriocapillaris, a vascular structure adjacent to the retina, can be the site of a primary inflammatory vasculopathy unrecognized so far. Most of the recent articles cited, however, deal not so much with new findings but with the integration of ocular pathologic changes into the systemic diseases they are part of. New knowledge about disease mechanisms and novel therapeutic modalities with biologic agents cited in this review are coming from other fields but have contributed to progress in the management of ocular vasculitis.

Summary
New investigational techniques of vasculitis in ocular structures other than the retina have contributed to the development of the global concept of ocular vasculitis. This review shows the importance of promoting a comprehensive and global classification of ocular vasculitis compatible with the concepts accepted for systemic vasculitis to contribute to its multidisciplinary approach.

Keywords
ocular vasculitis, choroidal vasculitis, classification of ocular vasculitis, indocyanine green angiography, tumor necrosis factor-α blocking agents

Current Opinion in Rheumatology 2005, 17:25–33
Abbreviation
ICGA indocyanine green angiography

Introduction
In the ophthalmic literature, the term “vasculitis” classically refers to retinal vasculitis, and most of the published work on vasculitis in the ocular field concerns retinal vasculitis. Classically, retinal vasculitis was divided into entities localized to the retina and into systemic diseases involving the eye. Vasculitis in the ocular sphere is, however, not limited to the retina, but can also touch the choroid, the sclera, the periocular tissue, and the ocular adnexa. Therefore, the more global concept of ocular vasculitis including retinal vasculitis should now be put forward as an emerging terminology because it is clinically more relevant for the appraisal of vasculitis in a multidisciplinary approach. Such a terminology is emerging presently because we now have the means to explore efficiently not only retinal vasculitis as was the case so far with fluorescein angiography but other vasculitic ocular involvement. Thanks to indocyanine green angiography (ICGA), we are now also able to explore choroidal inflammatory vasculopathy that was previously inaccessible [1]. ICGA also makes it possible to analyze more precisely the vasculitic process in anterior scleritis [2].
At the level of the choroid, this new technology has fundamentally changed our appraisal of intraocular inflammation and vasculitis because it allows us to have imaging access to the inflamed choroidal vessels. The technique allows differentiation between at least two choroidal inflammatory vasculopathies, the first involving the choriocapillary circulation at the origin of a group of diseases classified within the new concept of primary inflammatory choriocapillaropathies, and the second involving larger choroidal vessels defined as stromal choroidal inflammatory vasculopathies [3,4].

Because the ophthalmologist can detect retinal or choroidal vasculitis or other lesions caused by a vasculitic process such as episcleritis, scleritis, and orbital disease that may all be part of a systemic disease, it is important to classify and integrate ocular vasculitis within the accepted classification of systemic vasculitis.

In 1992, the Chapel Hill consensus conference on the nomenclature of systemic vasculitis generated a uniformly accepted classification of primary systemic vasculitides based on histopathologic changes showing that the vessel wall is the primary target. These entities were differentiated from secondary vasculitides in which vessel inflammation may be prominent but is a phenomenon secondary to other inflammatory processes. Primary systemic vasculitides were subdivided according to the size of the vessel principally involved into large, medium, and small vessel vasculitis.

The emerging term “ocular vasculitis” should encompass episcleritis, scleritis including peripheral ulcerative keratitis, retinal vasculitis, choroidal vasculitis, optic nerve vasculitis, and papillitis and should be extended to the orbit and adnexa because all these locations can produce vasculitis-induced ophthalmologic signs diagnosed by the ophthalmologist.

Such a global approach to the vasculitic process in the ocular field will surely be clinically more relevant to initiate a comprehensive multidisciplinary approach when this is necessary.

Ocular vasculitis following the accepted classification of systemic vasculitis should likewise be divided into lesions caused by primary systemic vasculitides and lesions caused by secondary systemic vasculitides. In addition to systemic vasculitides that involve the eye, there are entities wherein the vasculitic process or seems to be limited to the eye. The mechanism is suspected to be primary in some of these entities, and they can provisionally be classified into primary inflammatory vasculopathies limited to the eye, such as the primary choriocapillaropathies recently individualized [3]. However, the primary nature of the vascular insult has not yet been proved, as we do not have any histology, and therefore these diseases should be called inflammatory vasculopathies rather than vasculitides. In most of these “local entities” the inflammation of ocular vessels is, however, secondary to another inflammatory mechanism, such as in birdshot chorioretinopathy, wherein the primary immune-mediated mechanism is a granulomatous inflammatory reaction. Infections represent the other factors causing secondary inflammatory vasculopathy that may be limited to the eye, such as acute retinal necrosis caused by the ubiquitous herpesviruses but that occurs only in the eye.

Following this principle, we have come up with a detailed classification of ocular vasculitis that takes into account four main subclasses: (1) primary vasculitis or inflammatory vasculopathy limited to the eye, a group recently individualized with no histopathologic information yet; (2) systemic primary vasculitis involving the eye; (3) secondary vasculitis or inflammatory vasculopathy limited to the eye; and (4) the vast group of systemic secondary vasculitic entities involving the eye, whether immune-mediated, infectious, drug-induced, or neoplastic (Table 1). The entities from these four subclasses have been listed under the different ocular structures from front to back when they cause lesions in these structures (Table 1). Although this classification is as complete as possible, it is by far not exhaustive. As for ocular involvement of primary systemic vasculitides, the authors followed the classification described by Jennette and Falk [5] based on the Chapel Hill consensus conference on the nomenclature of systemic vasculitis and the ocular counterpart article that discussed the ocular manifestations of these primary systemic vasculitides [6••].

With this classification as a background, we reviewed the recent literature contributing to better knowledge of ocular vasculitis regarding its appraisal and management. The selection of articles is the result of the authors’ choice, is probably biased, and does not aim to be fully exhaustive but was nevertheless meant to be as complete as possible, taking into consideration the limited space provided for this review.

**Investigational and diagnostic methods of ocular vasculitis and disease mechanisms**

Significant progress in the investigation of ocular vasculitis is represented by the introduction of ICGA, which has been routinely, although not yet universally, used for the past few years [1]. In the ocular fundus, this technique uses the unique properties of the indocyanine green molecule, which, after being injected intravenously, causes an infrared fluorescence in the choroid that can be seen through the retinal pigment epithelium. Until ICGA was introduced, the choroidal vessels could not be analyzed because the choroidal fluorescence caused by the fluorescein molecule used for fluorescein angiography was blocked by the retinal pigment epithelium. Therefore, little was known about the inflammatory behavior of choroidal vessels. The technique showed that two main patterns of choroidal inflammatory
Table 1. Classification of ocular inflammatory vasculopathy or vasculitis

<table>
<thead>
<tr>
<th>Primary (ocular) inflammatory vasculopathy or vasculitis (the vessel is the primary target of the inflammatory process)</th>
</tr>
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<tbody>
<tr>
<td><strong>Localized to the eye and adnexa</strong></td>
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<tr>
<td>Episcleritis</td>
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<tr>
<td>Episcleritis without any systemic involvement, negative test results</td>
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<tr>
<td>Scleritis and peripheral ulcerative keratitis (PUK)</td>
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<tr>
<td>Scleritis without any systemic involvement negative test results</td>
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<tr>
<td>PUK due to a vasculitic process without any systemic involvement</td>
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<tr>
<td>Retinal inflammatory vasculopathy or vasculitis</td>
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<tr>
<td>Idiopathic retinal vasculitis</td>
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<tr>
<td>Intermediate uveitis of the pars planitis type</td>
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<tr>
<td>Frosted branch angiitis</td>
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<tr>
<td>Idiopathic retinal vasculitis, aneurysms, and neuroretinitis (IRVAN)</td>
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<tr>
<td>Acute multifocal hemorrhagic retinal vasculitis</td>
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<tr>
<td>Choroidal inflammatory vasculopathy or vasculitis</td>
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<tr>
<td>Primary inflammatory choriocapillaropathies*</td>
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<tr>
<td>Multiple evanescent white dot syndrome (MEWDS)</td>
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<tr>
<td>Acute posterior multifocal placoid pigment epitheliopathy (APMPPE)</td>
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<tr>
<td>Multifocal choroiditis (MFC)</td>
</tr>
<tr>
<td>Serpiginous choroiditis</td>
</tr>
<tr>
<td>Rare or unclassifiable primary inflammatory choriocapillaropathies</td>
</tr>
<tr>
<td>Vasculitic optic neuropathy or papillitis</td>
</tr>
<tr>
<td>Most conditions under rational inflammatory vasculopathy or vasculitis and choroidal inflammatory vasculopathy or vasculitides are associated with a papillitis indicating inflammation of optic disc vessels</td>
</tr>
<tr>
<td>Orbital, periorbital and neuro-ophthalmologic involvement</td>
</tr>
<tr>
<td>Inflammatory pseudotumor of the orbit without systemic involvement</td>
</tr>
<tr>
<td><strong>Involving the eye and other organs (primary systemic vasculitides)</strong></td>
</tr>
<tr>
<td>Episcleritis</td>
</tr>
<tr>
<td>Primary systemic vasculitides</td>
</tr>
<tr>
<td>Giant cell arteritis: anterior segment ischemia (uveitis &amp; episcleritis)</td>
</tr>
<tr>
<td>Polyarteritis nodosa: episcleritis, conjunctivitis, &amp; conjunctival vasculitis</td>
</tr>
<tr>
<td>Kawasaki disease: conjunctivitis &amp; punctate keratitis &amp; anterior uveitis</td>
</tr>
<tr>
<td>Wegener’s granulomatosis: episcleritis &amp; uveitis</td>
</tr>
<tr>
<td>Churg-Strauss syndrome: episcleritis &amp; panuveitis</td>
</tr>
<tr>
<td>Henoch-Schönlein purpura: recurrent episcleritis; anterior uveitis &amp; keratitis</td>
</tr>
<tr>
<td>Cutaneous leucocytoclastic angiitis: anterior granulomatous uveitis</td>
</tr>
<tr>
<td>Scleritis and peripheral ulcerative keratitis (PUK)</td>
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<tr>
<td>Primary systemic vasculitides</td>
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<tr>
<td>Giant cell arteritis: anterior segment ischemia (scleritis)</td>
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<tr>
<td>Polyarteritis nodosa: diffuse &amp; nodular scleritis, PUK resembling Mooren’s ulcer</td>
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<tr>
<td>Wegener’s granulomatosis: necrotizing scleritis, anterior &amp; posterior, PUK</td>
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<tr>
<td>Churg-Strauss syndrome: PUK</td>
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<tr>
<td>Microscopic polyangiitis: PUK resembling Mooren’s ulcer + conjunctival ulcerated nodules</td>
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<tr>
<td>Essential cryoglobulinemic vasculitis: cryoglobulin corneal deposits</td>
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<tr>
<td>Retinal inflammatory vasculopathy or vasculitis</td>
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<tr>
<td>Primary systemic vasculitides</td>
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<tr>
<td>Giant cell arteritis: central retinal artery occlusion</td>
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<tr>
<td>Takayasu arteritis: retinal vasculitis, ischemia, and neovessels</td>
</tr>
<tr>
<td>Polyarteritis nodosa: retinal vasculitis, macular star, cotton-wool spots, central retinal artery occlusion</td>
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<tr>
<td>Wegener’s granulomatosis: occlusive retinal vasculitis</td>
</tr>
<tr>
<td>Churg-Strauss syndrome: panuveitis &amp; retinal arterial occlusion and infarction</td>
</tr>
<tr>
<td>Essential cryoglobulinemic vasculitis: with retinal and RPE detachments, Purtscher-like retinopathy</td>
</tr>
<tr>
<td>Cutaneous leucocytoclastic angiitis: retinal vasculitis, multifocal retinitis and panuveitis</td>
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<tr>
<td>Choroidal inflammatory vasculopathy or vasculitis</td>
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<tr>
<td>Primary systemic vasculitides</td>
</tr>
<tr>
<td>Giant cell arteritis: posterior ciliary arteries, choroidal ischemia</td>
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<tr>
<td>Panarteritis nodosa: choroidal vasculitis most common ocular involvement (posterior ciliary arteries, large and small choroidal vessels, choroidal ischemia)</td>
</tr>
<tr>
<td>Wegener’s granulomatosis: choroiditis versus posterior scleritis</td>
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<tr>
<td>Primary inflammatory choriocapillaropathies</td>
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<tr>
<td>Acute posterior multifocal placoid pigment epitheliopathy (APMPPE) (systemic vasculitis can be associated with APMPPE in some cases)</td>
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<tr>
<td>Vasculitic optic neuropathy or papillitis</td>
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<tr>
<td>Primary systemic vasculitides</td>
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<tr>
<td>Giant cell arteritis: ischemic optic neuropathy</td>
</tr>
<tr>
<td>Panarteritis nodosa: vasculitis of optic nerve vessel supply, papilledema, ischemic optic neuropathy</td>
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<tr>
<td>Takayasu arteritis: anterior ischemic optic neuropathy</td>
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<tr>
<td>Wegener’s granulomatosis: ischemic optic neuropathy</td>
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<td>Churg-Strauss syndrome: ischemic optic neuropathy</td>
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</table>
Table 1. Classification of ocular inflammatory vasculopathy or vasculitis (continued)

### Orbital, periocular and neuro-ophthalmological involvement

#### Primary systemic vasculitides

- Giant cell arteritis: extracocular muscle palsies
- Panarteritis nodosa: orbital vasculitis & pseudotumor; neuro-ophtalmologic involvement [extraocular muscle palsies, amaurosis fugax, homonymous hemianopia]
- Kawasaki disease: orbital myositis & extracocular muscle palsy
- Wegener’s granulomatosis: orbital inflammation, periocular inflammation (dacryoadenitis, dacryocystitis, and periocular granuloma) and neuro-ophtalmologic involvement (ischemic optic neuritis, Horner’s syndrome, cranial nerve palsy, and cavernous sinus thrombosis)
- Churg-Strauss syndrome: orbital inflammatory tumor, periocular granuloma & neuro-ophtalmologic involvement (cranial nerve palsies)
- Microscopic polyangiitis: inflammatory ulcerated nodules in periocular location and conjunctiva

#### Secondary (ocular) inflammatory vasculopathy or vasculitis (vasculitis is a prominent feature but is secondary to an inflammatory process not primarily directed to the vessel)

### Localized to the eye or adnexa

- **Episcleritis, and scleritis and PUK**
  - Although immune or infection-induced lesions can be localized to the eye, but the mechanism is usually systemic (see Episcleritis, and scleritis and peripheral ulcerative keratitis)

- **Retinal inflammatory vasculopathy or vasculitis**
  - **Immune-mediated**
    - Birdshot choriotoretinopathy retinal vasculitis
    - (Ocular sarcoidosis)
  - **Infectious or parainfectious**
    - Necrotic herpetic retinopathies (herpes simplex virus, varicella zoster virus)
      - + acute retinal necrosis (ARN)
    - + progressive retinal necrosis (PRN)
    - Toxoplasmic retinochoroiditis
    - Tuberculous hypersensitivity vasculitis (also falsely called Eale vasculitis)
    - DUSN (Diffuse unilateral subacute neuroretinitis, due to parasites, Toxocara canis)

- **Neoplasms**
  - Primary ocular lymphoma

### Choroidal inflammatory vasculopathy or vasculitis

- **Secondary inflammatory choriocapillaropathy** (any severe intraocular inflammation can cause secondary choricapillaris inflammation adjacent to retinitis or choroiditis)

### Secondary stromal vasculitis

- **Immune-mediated**
  - Birdshot choriditis (choroidal disease of birdshot choriotoretinopathy)
  - Sympathetic ophthalmia
  - Toxoplasmic retinochoroiditis
  - (Vogt-Koyanagi-Harada disease)
  - Sarcoidosis (the eye can be the only organ involved, but the mechanism is systemic)
  - Infectious: any infectious agent localized to the choroid, producing exclusively choroidal disease and vasculitis

### Vasculitic optic neuropathy or papillitis

- **Toxoplasmic optic neuropathy** (Jensen papillitis)

### Any inflammatory disease causing retinal or choroidal vasculitis can cause an associated inflammation of the optic nerve vessels

### Orbital, periocular, and neuro-ophtalmological involvement

- **No specifically known entity; usually systemic involvement (see orbital, periocular, and neuro-ophtalmologic involvement)**

### Associated with systemic involvement

- **Episcleritis (rare causes) and scleritis and peripheral ulcerative keratitis**
  - **Immune mediated**
    - Rheumatoid arthritis
    - Sarcoidosis
    - Systemic lupus erythematosus
    - Ankylosing spondylitis
    - Inflammatory bowel diseases
    - Psoriatic arthritis
    - Relapsing polychondritis
    - Behcet disease
  - **Infectious** (rare cause; partial nonexhaustive list)
    - Mycobacteria
    - Spirochetes
    - Herpes zoster

- **Retinal vasculitis**
  - **Immune-mediated**
    - Multiple sclerosis
    - Behcet disease
    - Sarcoidosis
    - Systemic lupus erythematosus
    - Spondylarthritis with HLA-associated uveitis (posterior uveitis in ~15%)
<table>
<thead>
<tr>
<th>Classification of ocular inflammatory vasculopathy or vasculitis (continued)</th>
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<tbody>
<tr>
<td>Inflammatory bowel diseases</td>
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<tr>
<td>Relapsing polychondritis</td>
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<td>Susac syndrome</td>
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<tr>
<td>Sjögren syndrome (rare)</td>
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<tr>
<td>Rheumatoid arthritis (rare)</td>
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<tr>
<td>Juvenile idiopathic arthritis (JIA) (rare)</td>
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<tr>
<td>Infectious vasculitis (nonexhaustive list)</td>
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<tr>
<td>Bacteria</td>
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<td>Tuberculosis</td>
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<td>Syphilis</td>
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<td>Lyme disease</td>
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<tr>
<td>Bartonella henselae</td>
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<td>Whipple disease</td>
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<tr>
<td>Rickettsial diseases (Rocky mountain spotted fever, Mediterranean fever)</td>
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<tr>
<td>Viruses</td>
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<tr>
<td>Cytomegalovirus</td>
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<td>Human immunodeficiency virus</td>
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<td>HTLV vasculitis</td>
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<td>Hepatitis-related vasculitis</td>
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<td>West Nile virus</td>
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<td>Rift valley fever</td>
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<td>Parasites</td>
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<td>Toxocara canis</td>
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<tr>
<td>Drug induced retinal vasculitis</td>
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<td>in association with inhalation of methamphetamine</td>
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<tr>
<td>intravenous immunoglobulins</td>
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<tr>
<td>Bilateral optic neuritis complicating rabies vaccination</td>
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<tr>
<td>Retinal vasculitis secondary to malignancies</td>
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<tr>
<td>Cancer-associated retinopathy</td>
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<tr>
<td>Oculocerebral lymphoma</td>
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<tr>
<td>Choroidal inflammatory vasculopathy or vasculitis (stromal) (list is nonexhaustive; few conditions have been explored so far)</td>
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<tr>
<td>Immune-mediated</td>
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<tr>
<td>Behcet disease</td>
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<td>Sarcoidosis</td>
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<tr>
<td>Systemic lupus erythematosus</td>
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<tr>
<td>Relapsing polychondritis</td>
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<tr>
<td>Infectious choroidal vasculitis</td>
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<tr>
<td>Tuberculosis</td>
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<tr>
<td>Syphilis</td>
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<tr>
<td>Vasculitic optic neuropathy or papillitis</td>
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<tr>
<td>Immune mediated</td>
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<tr>
<td>IBD optic neuritis (retrobulbar and papillitis)</td>
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<td>Ocular sarcoidosis: papillitis due to sarcoidosis</td>
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<td>SLE (in ~1% of patients who have SLE)</td>
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<td>Multiple sclerosis (and Devic disease)</td>
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<td>Behcet disease</td>
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<tr>
<td>Reiter syndrome</td>
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<td>Sjögren syndrome</td>
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<tr>
<td>HLA-B27–related diseases</td>
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<tr>
<td>Infectious or parainfectious</td>
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<td>Syphilis</td>
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<td>Tuberculosis</td>
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<td>Lyme disease</td>
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<td>Whipple disease</td>
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<tr>
<td>Cat-scratch disease (Bartonellosis)</td>
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<tr>
<td>Human immunodeficiency virus</td>
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<tr>
<td>West Nile virus infection</td>
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<tr>
<td>Aspergillosis</td>
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<tr>
<td>Orbital, periocular and neuro-ophthalmologic involvement (Only immune-mediated causes cited)</td>
</tr>
<tr>
<td>Sarcoidosis (orbital, lacrimal and neuro-ophthalmological signs)</td>
</tr>
<tr>
<td>SLE: orbital involvement</td>
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<tr>
<td>IBD: orbital pseudotumor &amp; myositis</td>
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<tr>
<td>Rheumatoid arthritis: pseudotumor orbital apex syndrome</td>
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<tr>
<td>Zoster hypersensitivity arteritis: ocular nerve palsies after zoster opthalmicus</td>
</tr>
</tbody>
</table>

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*a* The primary nature of the inflammatory vasculopathy is not proved yet.

*b* The eye can be the only organ involved; however, the mechanism is systemic.

*c* Although herpes virus infections are systemic, the vasculitic process of NHVs is exclusively limited to the eye.

*d* Although toxoplasmosis is a systemic infection, retinal and choroidal vasculitis associated with toxoplasmic retinochoroiditis are limited to the eye.
Vasculitis syndromes

vasculopathy occur at the level of the choroid, namely, inflammation of the choriocapillaris and inflammation of the larger stromal vessels [4].

The protein-bound indocyanine green is a large molecule that impregnates tissues when it is extruding from inflamed vessels. This property also makes the method useful in evaluating the vasculitic process in episcleritis and scleritis, where it shows the extension of the inflamed vessels and seems to be useful for distinguishing between episcleritis, a more benign process, and scleritis, a more severe condition, especially in case of arteriolar closure [7]. Several publications on disease mechanisms deserve to be cited. A Dutch group found pathologic endothelial cell activation and a hypercoagulability state in ocular Behçet disease, possibly explaining occlusive disease in some patients, although the authors could not establish a correlation between disease pattern and hypercoagulability [8••]. The association of severe vaso-occlusive retinopathy in systematic lupus erythematosus with the presence of antiphospholipid antibodies was shown in a literature review that stressed the place of anticoagulation in addition to immunosuppression in these cases [9].

**Primary vasculitis or inflammatory vasculopathy limited to the eye**

The availability of ICGA made it possible to have new insights into choroidal inflammation. It allowed better classification of choroiditis and a better understanding of disease mechanisms. Diseases such as acute posterior multifocal placoid pigment epitheliopathy, multiple evanescent white dot syndrome, multifocal choroiditis, and serpiginous choroiditis, thought to be diseases of the retinal pigment epithelium, were shown to be due to inflammation of the choriocapillaris, and all these diseases could be regrouped under the term “inflammatory choriocapillaropathies” [3]. It is still unknown whether the mechanism is a primary inflammation of the choriocapillaris or whether choriocapillaris involvement is secondary. Furthermore, no histopathologic description of these diseases is available. ICGA has further identified the inflammatory eye diseases that cause inflammation to the choroidal stromal vessels in addition to retinal vasculitis. The new classification of choroiditis and choroidal inflammatory vasculopathies based on ICGA has been discussed in a recently published book on uveitis [10•–12•].

Idiopathic retinal vasculitis, aneurysms, and neuroretinitis (IRVIN) constitute a rare bilateral condition including retinal arteritis, aneurysmal dilatations of the retinal and optic nerve head arterioles, neuroretinitis, and uveitis that is limited to the eye. The association of this condition with allergic fungal sinusitis, recently reported, seems to indicate that a systemic hypersensitivity mechanism could be at the origin of idiopathic retinal vasculitis, aneurysms, and neuroretinitis, which would imply that the vasculitis is possibly secondary [13].

**Primary systemic vasculitides involving the eye and adnexa**

Recent publications in this field are mostly case reports or review articles on the involvement of the eye and adnexa in primary systemic vasculitides. A crucial article is the extensive review of the ocular lesions in primary systemic vasculitides that follows the Chapel Hill consensus conference classification [6••].

The authors realized the importance of integrating ocular vasculitis into this well-established classification. For each of the large, medium, and small vessel vasculitides, ocular manifestations have been compiled [6••]. McDonald et al. [14] describe a case of Takayasu arteritis in a child with bilateral uveitis and cystoid macular edema, an unusual ocular involvement, which responded well to the administration of corticosteroids and was not due to ocular ischemia. In their series of nine patients with Wegener granulomatosis, Biswas et al. [15] showed that scleritis with peripheral corneal ulceration was the most frequent ocular sign, in contrast to the predominant orbital involvement usually reported in the literature. Two case reports of ocular involvement in Churg-Strauss syndrome stress the two main types of ocular lesions: orbital involvement in the form of pseudotumors, presenting also rarely as a myositis that is usually antineutrophil cytoplasmic antibody (ANCA) negative, and the ischemic-vasculitic type, usually ANCA positive, with serious consequences on the retina and visual function [16,17].

**Secondary vasculitis or inflammatory vasculopathy limited to the eye**

Birdshot chorioretinopathy is an ocular vasculitis involving retinal, choroidal, and optic disc vessels for which no systemic involvement has been found so far, despite a very strong (nearly 100%) association with the HLA-A29 major histocompatibility antigen. Recently the first autopsy case showed that the choroidal inflammation is characterized by granulomatous foci and choroidal vasculitis, indicating that the vasculopathy in birdshot chorioretinopathy is secondary to a granulomatous inflammation [18].

An angiographic study using fluorescein and ICGA showed that retinal vasculitis and choroidal inflammation occur and develop independently from each other [19•]. Choroidal disease responds well to corticosteroid and immunosuppressive therapy, whereas retinal involvement is more resistant to therapy and is responsible for the severe functional impairment that occurs in some cases [19•]. Eale disease, often also called tuberculosis protein hypersensitivity vasculitis because of a hyperpositive tuberculin skin test present in these patients, includes peripheral retinal periphlebitis, nonperfusion, and recur-
Recent vitreous hemorrhages caused by neovascularization. A recent study showed that reactive nitrogen species and reactive oxygen species were elevated in Eale patients, indicating that free radicals are involved in mediating tissue damage [20]. Sympathetic ophthalmia is a bilateral granulomatous inflammation thought to be caused by sensitization of the immune system to secluded ocular antigens after a penetrating eye injury. The disease causes a granulomatous inflammation in the choroid and a secondary choroidal vasculitis and is limited to the eye. A recent report on sympathetic ophthalmia associated with cerebral vasculitis seems to indicate, if this is confirmed in future, that the inflammation can have a systemic expression in some cases [21].

**Secondary systemic vasculitides involving the eye and adnexa**

Susac syndrome is a microangiopathy involving the arterioles of the brain, the retina, and the cochlea and clinically presents with subacute encephalopathy, branch retinal artery occlusion, and sensorineural hearing loss. Primary vessel inflammation has not been proved and we have classified the disease in the secondary systemic vasculitides until another classification is demonstrated. A recent series of four patients with Susac syndrome, preceded by an editorial by Susac [22], gives a complete review of this underdiagnosed disease, with good MRI images and histopathology of arteriolar lesions [23].

A multitude of ocular sites can be involved by the vasculitis associated with inflammatory bowel diseases. Episcleritis and scleritis are associated with inflammatory bowel diseases in as many as 29% and 18% of patients, respectively. Uveitis is usually nongranulomatous and is mostly associated with the presence of the HLA-B27 major histocompatibility antigen. Peripheral ulcerative keratitis can be present alone but can also be seen with scleritis. Orbital pseudotumor and optic neuropathy have also been described, as has retinal vasculitis [24]. Ocular involvement in association with inflammatory bowel diseases has been reviewed exhaustively in a recent review [24]. Similar review work has been done to identify the lesions shared by the kidney and the eye in primary and secondary vasculitic processes [25•]. Numerous articles dealing with ocular vasculitis associated with infectious causes have been published, but we will cite only a few articles on emerging agents or newly recognized pathologic changes. Rickettsial diseases are known to cause retinal vasculitis. A recent series of 30 patients with Mediterranean spotted fever caused by *Rickettsia conorii* showed that approximately half of the patients had signs of retinal vasculitis on clinical examination or by fluorescein angiography, and this cause should be considered in endemic areas [26•].

Human T cell lymphotropic virus type 1 (HTLV-1), a RNA retrovirus endemic in Japan, the Caribbean islands, and parts of central Africa and South America, causes adult T cell lymphoma, HTLV-1 associated myelopathy, and tropical spastic paresis. Associated ocular inflammation, first described by Mochizuki *et al.* [27] in 1992, includes granulomatous and nongranulomatous anterior uveitis, intermediate uveitis, retinochoroidal lesions, and retinal vasculitis. Buggage [28•] recently published a very complete review article on the ocular involvement and ocular vasculitis in HTLV-1 infection.

The West Nile virus is one of the emerging infectious agents that cause retinal and choroidal vasculitis. It is a single-stranded RNA flavivirus belonging to the Japanese encephalitis virus serocomplex. It was first isolated in 1937 in the West Nile district of Uganda, is transmitted by a mosquito vector with wild birds serving as its reservoir, and is distributed extensively throughout Africa, Asia, the Middle East, Europe, and North America. Approximately 20% of infected persons are symptomatic and experience a flu-like illness, which develops into meningitis or encephalitis in 1% of cases. Almost 80% of patients have posterior segment involvement consisting of 20 to 50 roundish lesions per eye with a size from 100 µm to 1500 µm and a linear disposition. Associated retinal vascular changes include intraretinal hemorrhages, white-centered hemorrhages, focal vascular sheathing, and retinal vascular leakage. Thanks to the work of a Tunisian group that has published the largest series so far on ocular involvement due to West Nile virus infection and that performed a prospective study during the last outbreak in their country, the clinical picture has been well established [29••]. Occlusive retinal vasculitis has been described in association with West Nile virus infection [30].

**Progress in the management of vasculitis involving the eye**

Corticosteroid therapy of ocular inflammatory diseases and vasculitis has recently been rejuvenated because of new therapeutic modalities that allow the delivery of high-dose corticosteroids to the inside of the eye by the use of implanted slow-release devices or direct intraocular injections. Especially conditions localized to the eye or with predominant ocular involvement or with unilateral ocular disease will profit most from these potent local treatments, with consecutive reduction of systemic therapy. Ciulla *et al.* [31•] gave a detailed review of these new intraocular corticosteroid delivery techniques and reviewed present-day indications for corticosteroid use in ocular posterior segment disease, including inflammatory diseases and vasculitis. Several articles deal with the new therapeutic modalities applied to uveitis and vasculitis. A German group published an extensive review that included their own work on the use of interferon-α in Behçet vasculitis. They showed that interferon-α is effective in the treatment of ocular Behçet disease, including posterior uveitis and vasculitis resistant to other treat-
ments, and achieved preservation of visual function [32]. Infliximab, a tumor necrosis factor-α inhibitor, is increasingly used in the treatment of uveitis and ocular vasculitis. Murphy et al. [33] treated a heterogenous group patients with inflammatory conditions, of whom six of seven patients had ocular vasculitic disease, including two cases of retinal vasculitis and four cases of scleritis. In the six patients in whom treatment could be continued, infliximab showed a positive effect, inducing remission in five patients and allowing significant reduction of immunosuppression in all six. One group reported success in the treatment of ocular inflammation in Behçet disease [34]. Thereafter, a larger Japanese series showed the effectiveness of infliximab in the treatment of ocular involvement in Behçet disease [35]. Infliximab significantly reduced the mean numbers of ocular attacks compared with the pre-infliximab observation period, both in the group treated with 5 mg/kg and in the group treated with 10 mg/kg. The management of tuberculosis protein hypersensitivity vasculitis, sometimes called Eale disease, has not been well established and is often unsuccessful. El-Asrar and Al-Kharashi [36] published a series of 19 patients who were treated aggressively with systemic steroids, antituberculous therapy, full panretinal photocoagulation, and early vitrectomy if necessary.

Conclusion
Vasculitic involvement of the eye should no longer be reduced to retinal vasculitis alone. The emerging term “ocular vasculitis” should apply to all ocular and periocular lesions caused by a vasculitic process, including episcleritis, scleritis, peripheral ulcerative keratitis, retinal vasculitis, choroidal vasculitis, and optic nerve vasculitis as well as orbital and adnexal lesions. The ophthalmologist should try to classify ocular lesions suspected to be of vasculitic origin within the new classification presented here and derived from the universally accepted classification of systemic vasculitis. This will allow a multidisciplinary approach to the great proportion of cases of ocular vasculitis that are part of a systemic disease.

References and recommended reading
Papers of particular interest, published within the annual period of review, have been highlighted as:
• Of special interest
**Of outstanding interest

11. New classification of choroiditis and choroidal inflammatory vasculopathy is given, based on ICGA and not on clinical appearance as had been the case so far.
14. Primary inflammatory chorioropapathies result from inflammation of the chorioropapathies. Disease characteristics and physiopathology of the entities newly assembled in this group are discussed.
16. Primary inflammation of the choroidal stroma characterizes the diseases regrouped under the term “stromal choroiditis.” These are mostly granulomatous diseases that cause secondary stromal inflammatory vasculopathy.
25. On the basis of ICGA findings, the authors show that birdshot chorioretinopathy is an inflammatory disease limited to the eye that shows primary stromal disease associated with primary retinal disease, indicating that the inflammatory targets are both the retina and the choroidal stroma.
31. This is a detailed review of the ocular and renal pathologic changes caused by immune-mediated diseases, including primary and secondary systemic vasculitides.
This is one of the largest series describing ocular involvement, including vasculitis, in rickettsial infections


29 Khairallah M, Ben Yahia S, Ladjimi A, et al.: Chorioretinal involvement in patients with West Nile virus infection. Ophthalmology 2004, 111, in press. So far, this is the only large series and prospective study on ocular lesions associated with West Nile virus infection.


This is an essential review of new ocular delivery methods for corticosteroids that will determine new therapeutic attitudes in the management of intraocular inflammation.


This report of a multicenter trial details the results of the use of infliximab for ocular involvement in Behçet disease.

Chronic periaortitis: a spectrum of diseases
Augusto Vaglio and Carlo Buzio

Purpose of review
Chronic periaortitis includes idiopathic retroperitoneal fibrosis, perianeurysmal retroperitoneal fibrosis, and inflammatory abdominal aortic aneurysms. This review analyses the different aspects of the disease and highlights evolving concepts concerning its pathogenesis, diagnosis, and management.

Recent findings
It has recently been reported that asbestos exposure is a major risk factor for idiopathic retroperitoneal fibrosis. An increasing number of studies showing an association with autoimmune diseases clearly support the hypothesis of a close link between autoimmunity and chronic periaortitis. Furthermore, various findings (eg, constitutional symptoms, the involvement of other organs, high acute-phase reactant levels) support the hypothesis that chronic periaortitis may be a manifestation of a systemic disease and challenge the well-known theory of a local immune response to antigens in atherosclerotic plaque. In addition to CT and MRI, which are the diagnostic modalities of choice, positron emission tomography may be useful in monitoring disease activity and response to therapy. Although there is a lack of prospective randomized trials, recent studies have highlighted the role of steroids, immunosuppressive agents, and tamoxifen in the medical treatment of chronic periaortitis.

Summary
Chronic periaortitis is a rare disease with protean manifestations but, if correctly diagnosed, can be successfully managed. It should be approached in the setting of a systemic process, and clinicians must be aware that other organs may be affected. Its clinical course is chronic-relapsing, so a careful follow-up is essential. Further studies are needed to investigate the pathogenetic mechanisms and the most appropriate therapeutic options.

Keywords
chronic periaortitis, idiopathic retroperitoneal fibrosis, inflammatory abdominal aortic aneurysms, autoimmune disease, steroids

Introduction
The term chronic periaortitis refers to a spectrum of idiopathic diseases characterized by a fibroinflammatory reaction that extends from the adventitia of the abdominal aorta and the common iliac arteries into the retroperitoneum and often leads to the encasement of adjacent structures (eg, ureters, inferior vena cava) [1,2]. It includes three main entities: idiopathic retroperitoneal fibrosis (IRF), inflammatory abdominal aortic aneurysms (IAAAs), and perianeurysmal retroperitoneal fibrosis [2,3]. In IRF, the aorta is undilated, and the retroperitoneal fibroinflammatory tissue may or may not involve neighboring structures (Fig. 1); in IAAAs, the mass develops around a dilated aorta and usually does not cause obstructions (Fig. 2). Perianeurysmal retroperitoneal fibrosis, which represents a link between these two diagnoses, is an IAAA whose periaortic tissue involves adjacent organs [4]. These definitions may be somewhat confusing, and it would probably be more appropriate to distinguish aneurysmal from nonaneurysmal forms of chronic periaortitis.

Although most studies have considered these entities separately, they have common clinical and histopathological findings, and thus probably represent different manifestations of the same disease. This review outlines the clinical and histopathological characteristics and pathogenetic mechanisms of chronic periaortitis, concentrating particularly on their immune-mediated aspects and the associations between chronic periaortitis and systemic autoimmune diseases. The article discusses diagnostic strategies and the most feasible therapeutic options.

Epidemiology
The epidemiologic characteristics of chronic periaortitis are difficult to establish, but some data on IRF and...
IAAAs are now available. Reports from Duke University and the Mayo Clinic estimate that the incidence of IRF is less than 1 per 10,000 patients [5]. A study conducted in Finland showed an annual incidence of 0.1 per 100,000 people and a prevalence of 1.38 per 100,000 inhabitants [6••]. Data regarding the incidence of IAAAs in the whole population are lacking, but they represent 4 to 9% of all abdominal aortic aneurysms [6••,7].

Chronic periaortitis frequently occurs in middle-aged adults with a mean age of approximately 60 years, but it may also occur in older adults and children [3,5,6••,8,9•]. Men are more frequently affected (the male:female ratio is 2:1–3:1) [3,5,6••], a finding that is even more pronounced when only IAAAs are considered [10].

There is no ethnic predisposition or familial clustering; the disease has been described in only rare case reports of twins or siblings [11,12]. A few studies have addressed the question whether genetic factors may contribute to the development of chronic periaortitis: a case-control study of patients with IAAA and healthy subjects found that a genetic risk determinant mapped to the HLA-DR B1 locus, thus suggesting that congenital immune-system abnormalities are involved in the pathogenesis of the disease [13].

Among environmental and occupational agents, asbestos exposure has been associated with a markedly increased risk of developing the disease [6••], and smoking is also a significant risk factor [6••,14]. The previous use of ergot derivatives has been considered to be another risk factor [6••], but ergot-related retroperitoneal fibrosis should be included among the secondary forms of the disease [15].

Clinical manifestations
The clinical presentation of chronic periaortitis is insidious and vague. Pain occurs in approximately 80% of patients [3,8]; it is usually dull, poorly localized and, in most cases, originates in the lumbo-sacral region and then spreads to the abdomen. In the case of ureteral involvement, the pain may mimic that of ureteral colic [3,8,16]. Constitutional symptoms, particularly fatigue, anorexia, weight loss, and low-grade fever, are found in 40 to 80% of patients [3,8,16]. Constipation and claudication are less common; lower limb edema and/or deep venous thrombosis may occur, probably as a result of inferior vena cava and iliac vein involvement. Varicocele and hydrocele, sometimes associated with testicular pain, are not uncommon, and also probably develop because of compression of the gonadal vessels [3,8]. In cases of advanced bilateral ureteral obstruction, oligoanuria and symptoms secondary to uremic syndrome occur.

Physical examination usually reveals abdominal tenderness and, in some cases, a palpable, pulsatile, and tender abdominal mass; a periumbilical bruit may be heard in patients with IAAAs. The combination of abdominal pain, a pulsatile mass with overlying bruit, constitutional symptoms, and high levels of acute-phase reactants usually distinguish IAAAs from noninflammatory abdominal aortic aneurysms [14].

Laboratory findings
Laboratory examinations show a severe inflammatory reaction: the levels of acute-phase reactants, such as erythrocyte sedimentation rate and C-reactive protein, are strikingly high at onset in more than 80% of patients [3,17••]. Varying degrees of renal insufficiency may be found, but only a minor percentage of patients actually experiences end-stage renal failure. Anemia is often present as a result of ongoing inflammation or, if present, renal failure.

Figure 1. Abdominal CT in a patient with idiopathic retroperitoneal fibrosis
Figure shows a soft tissue mass (arrows) surrounding an undilated aorta and right hydronephrosis caused by ureteral involvement.

Figure 2. Abdominal CT in a patient with an inflammatory abdominal aortic aneurysm
Figure shows a retroperitoneal fibrous rind (arrows) surrounding a dilated aorta.
Immunologic and autoimmune tests should always be assessed in patients with chronic periaortitis. In most cases, positive results are nonspecific, but they may suggest the presence of an associated autoimmune or connective tissue disease; alternatively, they may be the earliest manifestation of a smoldering disorder that will clinically emerge late in the course of chronic periaortitis. Antinuclear antibodies have been reported in as many as 60% of patients [3], whereas anti-dsDNA and anti-extractable nuclear antigen antibodies are rare. Rheumatoid factor is not uncommon. P-antineutrophil and C-antineutrophil cytoplasmic antibodies have been detected in a few cases of chronic periaortitis associated with small vessel vasculitis [18–20]. When autoimmune thyroiditis coexists, antithyroglobulin and antithyroid microsome antibodies test positive [3].

Associations with autoimmune diseases
The association between chronic periaortitis and systemic autoimmune disorders has been acknowledged since the earliest descriptions of the disease [21] and is an intriguing aspect. Two recent studies have investigated this: a case-control study comparing IAAAs and noninflammatory abdominal aortic aneurysms showed a higher incidence of systemic autoimmune diseases in the former group [22], and in a study of 16 consecutive patients with chronic periaortitis, the authors found that three had antineutrophil cytoplasmic antibody-positive renal disease, three had autoimmune thyroiditis, and one had rheumatoid arthritis [3].

However, most of the evidence suggesting a link between autoimmune diseases and chronic periaortitis has come from case reports. In a number of cases, chronic periaortitis was associated with well-defined small and medium-sized vessel vasculitis (eg, Wegener granulomatosis, polyarteritis nodosa) [23–25] or unclassifiable systemic vasculitis [21,26]. Ankylosing spondylitis has also been reported frequently [26–28], whereas rheumatoid arthritis is rare [3,29]. The association with systemic lupus erythematosus is uncommon, but many patients with chronic periaortitis have a lupuslike syndrome [30,31]. Moreover, different types of immune-mediated glomerulonephritis (eg, membranous, membrano-proliferative, and rapidly progressive glomerulonephritis) can occur in chronic periaortitis [19,32], and in such cases, renal failure may be caused by glomerular disease rather than obstructive uropathy.

Chronic periaortitis (particularly IRF) may frequently be associated with fibroinflammatory disorders affecting other organs (eg, sclerosing cholangitis, mediastinal fibrosis, Riedel, and chronic autoimmune thyroiditis), most of which have an autoimmune origin [5,21,33].

Finally, other uncommon associations include inflammatory bowel diseases, primary biliary cirrhosis, systemic sclerosis, and uveitis [5,34,35].

Histopathological findings
Chronic periaortitis appears grossly as a whitish, hard periaortic mass which, in most cases, extends between the origin of the renal arteries and the bifurcation of the common iliac vessels. Histology shows signs of active mononuclear cell inflammation in a framework of fibrous tissue and fibroblasts [3,5]. The inflammatory infiltrate is often diffuse, although nodular aggregates of inflammatory cells, sometimes with a follicular appearance and germinal centers, are often found on small retroperitoneal vessels. In cases of severe inflammation, there may be focal infiltration of the small and medium-sized retroperitoneal vessels, with frank vasculitis and fibrinoid necrosis [3,36,37]. Immunohistochemistry reveals that the perivascular aggregates consist mainly of B lymphocytes and a smaller component of plasma cells, macrophages, and T lymphocytes, most of which are CD4+. On the other hand, the diffuse infiltrate has an equal percentage of T cells and B cells. Scattered eosinophils are common, whereas neutrophils are rare [3,36]. Giant multinucleated cells or granulomas have been found only in some anecdotal cases [38].

The background of chronic periaortitis consists of varying degrees of fibrosis, which is particularly abundant in the late stages when the tissue becomes relatively avascular and acellular; its distribution is usually diffuse, but sometimes perivascular and perineural. Some spindle-shaped cells may be found within the fibrous tissue; most authors have considered these to be fibroblasts, but they have been immunophenotypically characterized as tissue macrophages [39].

The aortic wall also shows particular changes, such as atherosclerotic degeneration of the intima, medial thinning, and marked adventitial inflammation and fibrosis [1–3,28,36]. The composition and distribution of the inflammatory infiltrate of the aortic adventitia are similar to those seen in the retroperitoneum: B cells outnumber T cells and macrophages and may be diffuse or arranged in a follicular pattern. The nodular aggregates of inflammatory cells are usually centered on the adventitial vasa vasorum, which may show signs of vasculitis with fibrinoid necrosis [3,37,40]. These aortic wall changes are found in all chronic periaortitis disease entities, regardless of the presence of aneurysmal dilatation. It is interesting to note that autopsy studies have shown that moderate adventitial inflammation and fibrosis may not be limited to the abdominal aorta, but may also involve its thoracic portion [41].

Pathogenesis
The pathogenesis of chronic periaortitis is still obscure. The time-honored leading theory is that proposed by Parums [2], Parums et al. [42], and Ramshaw and Parums [43], who suggested that it may be the result of a local immune response to atherosclerotic plaque antigens such
as oxidized low-density lipoproteins and ceroid [2,42,43]. Morphologic and experimental findings support this view: histologic examinations of aortic wall sections from patients with chronic periaortitis have revealed that, in cases of severe media thinning or breaching, some atheromatous debris ruptures into the adventitia; adventitial inflammation also seems to be more marked where the media is thinner [1,2,41]. IgG has been detected in close apposition to extracellular ceroid [42], and serum antibodies to oxidized low-density lipoprotein and ceroid were more common in patients with chronic periaortitis than in controls [44]. Furthermore, a wide spectrum of adhesion molecules and gene products for cytokines (eg, interleukin-1α, interleukin-2, interleukin-4, and interferon-γ) have been detected in the aortic adventitia, thus strengthening the hypothesis that chronic periaortitis is associated with active adventitial chronic inflammation [43,45]. According to this theory, advanced atherosclerosis is a sine qua non for the development of chronic periaortitis, which may be an exaggerated local immune response to plaque antigens.

However, the role of atherosclerosis in chronic periaortitis remains controversial, mainly because no substantial difference in the incidence of advanced atherosclerotic disease has been clearly demonstrated between patients with chronic periaortitis and healthy controls [6••,46]. Furthermore, a number of findings support the hypothesis that chronic periaortitis may be a manifestation of systemic disease rather than the result of a local reaction. These include its constitutional symptoms, the high acute-phase reactant levels, autoantibody positivity, and the frequent association with other autoimmune diseases [3,5,17,30]. Chronic periaortitis also has histologic similarities to large vessel vasculitis, such as prominent adventitial inflammation and the involvement of the vasa vasorum [47], and sometimes extends beyond the abdominal aorta [41,48••]. It cannot be excluded that it originates as a primary arteritis involving the aorta, which may in turn promote atherosclerosis and extend into the retroperitoneum, thus eliciting a fibroinflammatory reaction. Further studies are needed to investigate the potential immune-mediated mechanisms and the full extent and distribution of the disease.

**Diagnosis**

Diagnosis should start by excluding possible primary causes of retroperitoneal fibrosis, such as drugs (eg, ergot derivatives, β-blockers), infections (eg, tuberculosis, histoplasmosis), malignancies (primary retroperitoneal sarcoma/lymphoma or metastatic tumors from other sites), radiotherapy, trauma, or previous surgery [5].

Chronic periaortitis is diagnosed by means of imaging studies, such as sonography, urography, and particularly CT and MRI [49,50].

Sonography shows a retroperitoneal hypoechoic or isoechoic mass and can also reveal aneurysmal aortic dilatation and ureterohydronephrosis. Excretory urography usually demonstrates the triad of medial ureteral deviation, extrinsic compression, and hydronephrosis. Although rarely used, retrograde pyelography may be useful in patients with significantly impaired renal function in whom intravascular contrast medium is contraindicated [50].

CT and MRI are the choice modalities for the diagnosis and follow-up of chronic periaortitis. CT reveals a peri-aortic soft tissue mass that may extend laterally to entrap the ureters; unlike most retroperitoneal tumors, chronic periaortitis does not tend to displace the aorta anteriorly or the ureters laterally. In rare cases, it may have an unusual (eg, peripancreatic, periduodenal, pelvic) localization [50]. Chronic periaortitis has the attenuation of muscle on unenhanced images, and after contrast medium administration, enhancement is high in the early stages of the disease and low in the late, inactive stages [50].

MRI provides a more exact anatomic definition than CT because of its multiplanar capabilities. It also avoids the need for nephrotoxic contrast medium, but it is less sensitive to vascular calcifications [51•]. Chronic periaortitis is hypointense in T1-weighted images, but its intensity in T2-weighted images is usually high in the early stages because of abundant fluid content and hypercellularity, and low in the late stages [49,50]. Fat saturation images provide an excellent distinction between the mass and surrounding fatty tissue.

CT and MRI are both good diagnostic means, but when chronic periaortitis presents atypically, mass biopsy is recommended.

CT and MRI show the morphology of chronic periaortitis, but positron emission tomography with 18F-fluorodeoxyglucose is emerging as a useful functional imaging modality for assessing the metabolic activity of the mass. In the early stages of the disease, there is a strikingly higher periaortic uptake of fluorodeoxyglucose, which disappears after successful medical therapy [52,53]. In a recent study, the authors have also shown that this technique seems to be even more reliable than acute-phase reactant levels in monitoring disease activity, and that abnormal fluorodeoxyglucose uptake can also be seen at disease relapse [54]. Furthermore, positron emission tomography allows whole-body imaging and can thus reveal other diseased sites (eg, thyroid, mediastinum) [52] or detect an infectious or neoplastic processes to which chronic periaortitis may be secondary [55].
Treatment

The treatment can be surgical and/or medical, and may differ between the aneurysmal and nonaneurysmal forms mainly because the former have particular surgical indications.

Patients with IRF often undergo surgery to relieve ureteral obstruction, and in such cases, ureterolysis and wrapping the obstructed ureters with omentum is the primary mode of treatment [16]. However, both ipsilateral and contralateral progression have been described after surgical ureterolysis, thus underlining the need for adjuvant medical therapy [8,16]. An alternative to ureterolysis may be the placement of ureteral stents or nephrostomy followed by medical therapy. This can be considered the approach of choice because it is safe and, in most cases, effective [17].

There are no clear guidelines concerning medical treatment because most of the published studies were retrospective and uncontrolled and involved small numbers of patients. Steroids represent the mainstay of therapy; in most cases, they improve patients’ symptoms, switch off the acute-phase reaction, and relieve obstruction [8,16,24,51•]. There is no consensus regarding the optimal dose and duration of steroid therapy, but long treatment periods are recommended because of the high relapse rate. A recent study has found that a 2-year course of steroids (initial prednisolone dose, 60 mg on alternate days) combined with ureteral stents or nephrostomy is safe and effective [16], but treatment failures and recurrences during and after steroid therapy have often been reported [16,48••].

A number of immunosuppressive drugs, such as azathioprine, cyclophosphamide, and methotrexate, have been used as steroid-sparing agents or in patients not responding to steroids alone [17,56–58]. A recent retrospective analysis found that the combination of steroids and azathioprine was as effective as and safer than steroids plus cyclophosphamide [17]. However, the real need for immunosuppressive agents in IRF has yet to be elucidated.

Antiestrogen tamoxifen has also been proposed for IRF [59,60]. Its mechanism of action is unknown and is probably unrelated to its antiestrogenic properties; it probably modulates the synthesis of transforming growth factor-β, but there is no experimental evidence in IRF. Tamoxifen has been used alone or in combination with steroids and has also been successfully used in steroid-resistant patients [59,60,61•]. Although it is safe, its effectiveness is still uncertain because only case reports have been published; it therefore cannot be recommended as first-line therapy.

A combined surgical and medical approach must also be considered in the aneurysmal forms of chronic periaorti-

tis. Surgery aims at preventing the risk of rupture and is usually indicated when the aortic diameter exceeds 5 cm [48•]; open surgery with graft placement is widely performed, although endovascular repair has also been successfully tried [62]. In comparison with the noninflammatory type, the risk of IAAA rupture and operative mortality associated with ruptured IAAA surgery does not seem to be any different [63•]. Open surgery with grafting was once thought to resolve symptoms and inflammation, but many studies have shown that periarteric inflammation may persist and even progress after surgery [7,14]. This also indicates the need for medical therapy in the case of aneurysmal chronic periaortitis. There is a lack of reliable data, but steroids seem to be effective and, if used preoperatively, can reduce the mass and facilitate surgery; when used after surgery, they can prevent disease progression [64]. Finally, when the aneurysm is not large enough to require surgery, medical therapy may be used alone to improve symptoms.

Conclusion

Chronic periaortitis is a chronic disease characterized by a retroperitoneal fibroinflammatory reaction surrounding the abdominal aorta, which may or may not be dilated. Although it has been considered to be the result of a local reaction to advanced atherosclerosis, there is increasing evidence supporting the hypothesis of an underlying systemic autoimmune disease whose pathogenetic mechanisms need to be investigated. The diagnosis is suggested by CT and/or MRI, and positron emission tomography may be helpful in assessing disease activity. Steroids, alone or in combination with surgery, are usually effective, but prospective randomized trials are required to establish the best treatment approach.

Acknowledgments

The authors are indebted to all of their colleagues contributing to the study of chronic periaortitis.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

• Of special interest

•• Of outstanding interest


A very interesting case-control study that highlights the role of asbestos as a risk factor for retroperitoneal fibrosis and also provides important data on the epidemiology of the disease.


A good report of idiopathic retroperitoneal fibrosis in a child, and a comprehensive review of the published literature concerning the clinical aspects of the disease in the pediatric population.


Although retrospective, this is the first study of a large series of patients showing the clinical results of the use of immunosuppressive therapy in idiopathic retroperitoneal fibrosis.


This case-control study compares inflammatory and non-inflammatory abdominal aortic aneurysms and provides evidence that the former are more frequently associated with systemic autoimmune diseases.

De Roux-Serratrice C, Serratrice J, Granel B, et al.: Periaortitis heralding aortic aneurysms and provides evidence that the former are more frequently associated with systemic autoimmune diseases.

Comprehensive review of the whole spectrum of chronic periaortitis, enriched by the genetic, diagnostic, and therapeutic aspects of the disease.


A detailed description of MRI findings in patients with chronic periaortitis at disease onset and during follow-up.


An updated review of the whole spectrum of chronic periaortitis, enriched by the description of three intriguing case reports. The article focuses mainly on the pathogenetic, diagnostic, and therapeutic aspects of the disease.


A good report showing that tamoxifen alone may also be effective after the withdrawal of steroid therapy.


This study challenges the previous assumption that inflammatory abdominal aortic aneurysms are at lower risk for rupture than their noninflammatory counterparts, and provides useful data concerning the postoperative follow-up of ruptured inflammatory aortic aneurysms.

Purpose of review
Peripheral nervous system (PNS) involvement is of great diagnostic value in systemic vasculitides, because it occurs frequently and often early during the course of these diseases, despite the supposed blood–nerve barrier that should prevent or at least minimize PNS damage. However, it carries no poor prognostic value in vasculitides. Recent advances have been made in understanding the pathogenetic mechanisms of PNS involvement.

Recent findings
Vasculitic neuropathy may result from primary or secondary systemic vasculitides, or may be restricted to the PNS, in a form that is now also considered to be a systemic vasculitis. The blood–nerve barrier is not as efficient as the blood–brain barrier. Inflammatory cell infiltration into the vasa nervorum and epineurial arteries leads to ischemic axonal nerve injury and is facilitated by additional breaches in the blood–nerve barrier, induced by proinflammatory cytokines, oxidative stress-derived molecules, and matrix metalloproteinases. Although animal models of myeloperoxidase or, now, proteinase 3-antineutrophil cytoplasmic autoantibody–inducing vasculitis have been developed, they do not support a role for antineutrophil cytoplasmic autoantibodies in PNS involvement. Treatment should be chosen based on the other organ involvement and the patient’s general condition. When PNS involvement is isolated, corticosteroids alone should be used as first-line treatment.

Summary
Apart from the so-called nonsystemic nerve vasculitis, PNS involvement is rarely the sole clinical sign of systemic necrotizing vasculitides, and its association with other typical manifestations is often suggestive of the diagnosis of vasculitis. Herein are summarized recent advances that have clarified but not yet fully elucidated the pathogenesis of peripheral neuropathy in systemic vasculitides, together with the latest clinical findings and therapeutic strategies.

Keywords
systemic necrotizing vasculitis, ANCA-associated vasculitides, polyarteritis nodosa, peripheral nervous system involvement, peripheral neuropathy, mononeuritis multiplex, therapeutics

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Abbreviations
ANCA antineutrophil cytoplasmic autoantibody
CNS central nervous system
CSS Churg-Strauss syndrome
HBV hepatitis B virus
HCV hepatitis C virus
MMP matrix metalloproteinase
mPR3 murine proteinase 3
PNS peripheral nervous system
SLE systemic lupus erythematosus
SNV systemic necrotizing vasculitides
TNF tumor necrosis factor

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Introduction
Peripheral neuropathy is a major clinical feature of primary and secondary systemic vasculitides, often observed during the early phases of the disease and therefore carrying an important diagnostic value. The vasculitic processes defining these diseases may indeed affect the vasa nervorum and epineurial arteries and cause axonal neuropathy. According to previous published studies on primary systemic necrotizing vasculitides (SNV), peripheral nervous system (PNS) involvement occurs in 50 to 75% of the patients with polyarteritis nodosa (polyarteritis nodosa and hepatitis B virus (HBV)-related polyarteritis nodosa, although the latter has become rare nowadays) [1,2], 10.6 to 67% of those with Wegener granulomatosis [3,4], 50 to 78% of those with Churg–Strauss syndrome (CSS) [5,6], 10 to 58% of those with microscopic polyangiitis [7,8], and less frequently in other primary systemic vasculitides [9•,10,11•]. Systemic and/or PNS vasculitis can be paraneoplastic, especially in association with some lymphoproliferative disorders and small-cell lung cancer [12], or may be attributed to certain infections, such as HBV, HIV (with PNS vasculitis developing in 0.3–1% of HIV-infected subjects [13]), hepatitis C virus (HCV; with peripheral neuropathy developing in HCV-infected people with or without mixed cryoglobulinemia in 45% and 9–10% of the cases, respectively [14•,15•]), cytomegalovirus, human T cell leukemia/lymphoma virus (1 or 2), Herpesviridae, Epstein-Barr virus [16], tuberculosis, or Lyme disease [17,18]. Finally, vasculitis may also develop as a drug reaction, eg, after exposure to carbimazole [19], amiodarone, naproxen, allopurinol, hydralazine, or...
sulfasalazine [9•], or as a secondary phenomenon in other connective tissue diseases, like Behçet disease [20], rheumatoid arthritis [21], sarcoidosis [22], systemic sclerosis, Sjögren syndrome, or systemic lupus erythematosus (SLE), with peripheral neuropathy occurring in 10 to 20% and PNS vasculitis in 1% of the patients [9•,23,24•].

**Clinical manifestations**

Peripheral neuropathy reflecting PNS involvement is the initial symptom of SNV in 36.4% (8/22) [25] to 55.6% (15/27) [26] of these patients. Onset is usually acute but may be more progressive, particularly in the elderly. Sensory involvement is responsible for hypoesthesia or hyperesthesia, dysesthesia, or frank pain as the prominent and earliest features [27], reflecting the long lengths of these fibers and their smaller ramifications compared with the peripheral motor fibers. Usually, motor deficits start later and often abruptly, but they can sometimes precede the sensory loss. The first manifestations typically affect the lower limbs, with one particular nerve initially involved and other nerves becoming affected later; this pattern is referred to as mononeuritis multiplex. In its late stage, mononeuritis multiplex can be mistaken for a symmetric process because so many nerves can be involved.

Mononeuritis multiplex affects 56.5 to 61.5% of patients with polyarteritis nodosa, whereas 16.5% have mononeuritis (simplex) and 25% of them have distal, symmetrical, often patchy sensory or sensorimotor neuropathy [28,29]. The most frequently affected nerves are the sciatic nerve or its peroneal branch, unilaterally in 62.5 to 84% of the patients, and bilaterally but asynchronously in one third, followed by the tibial, ulnar, median, and/or radial nerves [23].

Peripheral neuropathy occurs in 10.6 to 67% of patients with Wegener granulomatosis [3,4] and develops early, with the first manifestations noted even before the Wegener granulomatosis diagnosis in 55.4% of the patients [30]. PNS involvement, electromyographically documented in 43.8% of the patients with Wegener granulomatosis, corresponded to mononeuritis multiplex in only 45% of the cases and symmetric polyneuropathy at an unexpectedly higher frequency in 55%, which might be explained by other contributing factors (age, medications, end-stage renal failure, diabetes mellitus) [30,31]. Indeed, PNS involvement was more frequent in patients with Wegener granulomatosis, with higher antineutrophil cytoplasmic autoantibodies (ANCAs) titers, but also in those older than 50 years at diagnosis and those with renal, skin, and/or cardiac involvement [32].

Peripheral neuropathy is one of the ACR classification criteria for CSS [33], with 60 to 71% of the patients having mononeuritis multiplex, 5 to 29% asymmetric polyneuropathy, and 0 to 35% symmetric polyneuropathy [6,34]. Acute fulminant involvement of peripheral nerves during the early phase of CSS has been reported [35], with demyelination, assessed electromyographically, that mimicked Guillain-Barré syndrome.

Radicular syndromes and plexopathies have also been described in polyarteritis nodosa [36]. Cutaneous scattered sensory neuropathies have occasionally been observed in CSS and polyarteritis nodosa; they reflect damage to the smaller sensory nerves of the skin that is histologically difficult to visualize by routine staining [37•]. Notably, in childhood SNV, symmetric polyneuropathy is the most frequent clinical manifestation of PNS involvement, whereas the frequencies of mononeuritis multiplex (and nonsystemic nerve vasculitis) are lower [38•].

Peripheral vasculitic neuropathies are not common in giant-cell arteritis (less than 14% of the patients) [10] and are very unusual in Takayasu arteritis, Kawasaki disease, and Henoch-Schönlein purpura [9•].

**Diagnostic investigations**

In the context of vasculitic PNS involvement, electromyography with nerve conduction studies typically reveals axonal neuropathy and may show extensive denervation. Amplitudes of motor and sensory nerve action potentials are markedly decreased, or may even be absent, in the most severely affected nerves, whereas motor nerve conduction velocities are normal or only slightly diminished. Subclinical PNS involvement is common [28] and is supported by the observation of more diffuse electrophysiological involvement than was clinically apparent in the 22 patients with SNV examined by Bouche et al. [25]. Electromyography can sometimes detect myopathy with fibrillation potentials resulting from severe neuropathy [39]. Conduction block, often transient, can be seen sporadically in association with axonal neuropathy as a consequence of ischemia-induced segmental demyelination [40].

In the context of neuropathy with suspected SNV, when the other investigations (eg, ANCA testing for ANCA-associated vasculitides, kidney biopsy for microscopic polyangiitis or Wegener granulomatosis with renal involvement, abdominal arteriography for polyarteritis nodosa, and so forth) fail to diagnose vasculitis, neuromuscular biopsy should be performed, but it can itself be responsible for disabling sensory and/or motor sequelae at the biopsy site, with persistent but usually mild and not bothersome pain in as many as 25% of the patients (21 months after sural nerve biopsy) [41•]. The specimen should ideally include a clinically and electromyographically affected sensory nerve. Whole nerve biopsy is preferable to fascicular biopsy. However, combined muscle–nerve biopsy (especially the superficial peroneal nerve–peroneus brevis muscle or sural nerve–gastro-
Nonsystemic nerve vasculitis is a clinical picture that raises some diagnostic and therapeutic difficulties, and is worth mentioning here. Indeed, in approximately one third of the patients who undergo muscle–nerve biopsy because of clinical neuropathy and who have histologically proven peripheral nerve vasculitis, the disease appears to be restricted to the PNS [50,51••]. In this setting, there is no clue to distinguish those who will later develop systemic vasculitis from those in whom vasculitis will remain limited to the PNS. Six percent [51•••] to 37% [23] of these patients will subsequently develop systemic manifestations of vasculitis, limited to the skin in almost all cases, whereas 24% [23] to 46% [51••] of them will experience neuropathy relapses. As many as 14% of these nonsystemic nerve vasculitides were reported to be paraneoplastic, mainly associated with small-cell lung cancer or a malignant hemophagocytic syndrome [12,52].

Leukocytoclastic vasculitis is another clinicopathological entity that usually remains limited to small skin vessels in connective tissue diseases or infections. Rare cases with clinical PNS involvement have been reported [16], but without histologic evidence of nerve vasculitis.

Other differential diagnoses of SNV peripheral neuropathy include subacute or acute multifocal diabetic neuropathy, in which histologic vasculitic features may occasionally be seen (in 27% of the nerve biopsies but with perivascular mononuclear cell infiltration in as many as 95% of the 22 cases studied by Said et al. [53]), and proximal diabetic amyotrophy, which is rare and is defined as a proximal inflammatory vasculitis that predominantly affects the lower limb nerves, with some signs of necrosis at histopathology [54].

Pathogenesis

Peripheral nervous system involvement in vasculitides typically results from focal or multifocal axonal ischemia caused by vasculitis of the vasa nervorum in the branches of small epineurial vessels. Under normal conditions, the nervous system is supposed to be protected from immunologic attack by the blood–brain and blood–nerve barriers. However, the peripheral nerves are affected frequently and early in vasculitides, which might be explained by the breakdown of the blood–nerve barrier at the precise level of epineurial vessels, in contrast with endoneurial vessels [11•,55]. Central nervous system (CNS) vasculitis is less common, except in association with infections, and mostly occurs later during the course of SNV. Pertinently, PNS endothelial cells are physically and biochemically distinct from those of the CNS. Moreover, antigen presentation in the PNS mainly involves endothelial cells, unlike in the CNS, in which the less accessible microglial cells are implicated.

T-lymphocyte and macrophage infiltration of nerve tissue may be furthermore enhanced by dysfunction of this blood–nerve barrier, induced by some effector molecules. In peripheral neuropathy in SNV and SLE (but also in chronic inflammatory demyelinating polyneuropathies), it has been shown that some endopeptidases directed against extracellular matrix components, such as zinc-dependent matrix metalloproteinases (MMPs), are able to degrade the subendothelial basement membrane, resulting in vessel destruction [24•]. MMP-1 (collage-
nase 1) was overexpressed by macrophages in the endoneurium [56], and excess MMP-2 (gelatinase A) was localized in the endothelium and perineurial stroma in the sural biopsies of patients with vasculitic neuropathies [57•,58••]. In contrast, MMP-9 (gelatinase B) was overexpressed in blood vessel walls, in perivascular inflammatory infiltrates (mainly CD8+ T lymphocytes), and in epineurium and endoneurium in nerve tissue biopsies from patients with SLE vasculitic neuropathy [24], and it was shown that MMP-9 could be induced by tumor necrosis factor (TNF)-α [58••]. The altered expression of these MMPs in vessel walls may contribute to their subsequent destruction, followed by immune cell infiltration, but might also directly participate in ischemic nerve injury.

Proinflammatory cytokines and oxidative stress-derived molecules may also play a role in the development of vasculitic peripheral neuropathy, at least during the early phases, concomitant with or just after the onset of blood–nerve barrier dysfunction [9•]. Interleukin-1β, interleukin-6, and TNF-α are overexpressed in nerve specimens from SNV patients with PNS involvement, mostly by endoneurial CD68+ macrophages and epineurial T cells [59,60•]. In addition to their proinflammatory role in PNS vasculitis, relatively high cytokine levels are associated with the neuropathic pain [60••]. The cyclooxygenase isoform cyclo-oxygenase–2 (inducible by proinflammatory cytokines and activated nuclear factor κB) is overexpressed in the sera and sural nerve biopsies of patients with vasculitic neuropathy, and might thereafter be responsible for the enhanced macrophage synthesis of prostaglandins [61•]. PNS involvement in SNV would thus result from blood–nerve barrier permeability, associated with and followed by an abnormally upregulated immune response with inflammatory cell infiltration, then vessel destruction and subsequent ischemic neuropathy. However, the primary triggering factors of vasculitic neuropathy and SNV itself remain to be identified.

The pathogenetic mechanisms may differ according to the type of SNV. Higher levels of antineuronal IgG (anti-GM1 and antisulfatidate) have been detected in patients with ANCA-associated SNV (compared with cryoglobulinemic patients) and were associated with electrophysiologically demonstrated PNS involvement. However, no relation could be established between these antibodies and ANCA titers or other clinical symptoms of vasculitis, and they might simply be an epiphrenomenon caused by vasculitic nerve injury [62]. In CSS, axonal neuropathy would result from immune-mediated ischemia rather than from eosinophil degranulation products, like major basic protein, whose roles have been demonstrated in cardiac or splenic lesions of CSS [63]. Indeed, eosinophil invasion was seen in 25% of the 28 patients with CSS with neuropathy, without marked IgE deposition, and less than 14% of them had granulomas [64], but, above all, with CD4+ as often as CD8+ T-lymphocyte invasion [34]. Notably, epineurial necrotizing vasculitis was seen in 53% of their sural nerve biopsies. However, in CSS, other mechanisms may be at work, such as immune complex deposits, with IgM [65] but also IgA and C3 [66]. In a preliminary analysis of 112 patients with CSS, we found peripheral neuropathy, unlike heart involvement, to be significantly associated with a higher frequency of ANCA positivity [67], but the overall frequencies of PNS involvement in each ANCA-associated SNV is quite similar. In experimental murine models of ANCA-induced vasculitides, no patent clinical signs of neurologic involvement were reported, even though ANCA may directly induce and/or enhance inflammation and endothelial cell injury, at least in skin (intravenous injection of antimouse proteinase 3 antibodies into wild-type mice primed by intradermal injection of TNF-α enhanced local cutaneous inflammation) [68••] or in kidney and lung vessels (intravenous injection of antymyeloperoxidase antibodies induced vasculitis in kidneys and lungs) [69].

Cranial neuropathies

In Wegener granulomatosis, cranial nerve involvement mostly results from extension of sinus, orbital, or paranasal granulomas, with nerve compression against the external wall of the cavernous sinus, or from inflammatory pachymeningitis with cranial nerve engulfment, rather than from real cranial nerve vasculitis, which may nonetheless also develop. Cranial neuropathies occur in 4.7 to 13.5% of patients with Wegener granulomatosis [30,32], most often unilateral but also bilateral, in less than 2% of patients with polyarteritis nodosa [70], and in some patients with CSS and microscopic polyangiitis [6], supporting that a cranial nerve vasculitic process may be seen in SNV. Oculomotor (III), abducens (VI), facial (VII), trochlear (IV), and/or acoustic (VIII) nerves are the most affected [70], followed by the trigeminal (V), then cranial nerves XII, IX, and X. Ischemic vasculitis of the optic nerve, optic chiasm, and/or occipital cortex has also been well described in polyarteritis nodosa [71] and CSS [6], but mostly in Wegener granulomatosis [72]. Neuroimaging may be crucial in this setting to distinguish between visual loss secondary to a compressing granuloma and ischemia of the ophthalmic artery.

Prognosis and management

Peripheral neuropathy does not worsen the prognosis and survival of patients with SNV, even though possible neurologic sequelae may be severely incapacitating. Moreover, peripheral neurologic relapses occurred in 31% of the 41 patients with SNV [50], whereas neurologic sequelae have been reported in 5.2% of the patients with polyarteritis nodosa, microscopic polyangiitis, or CSS who were still alive after a mean follow-up of 7.3 years [73]. Sensory symptoms persisted longer than motor deficits and could remain indefinitely [74]. Even in
patients with complete motor deficit at the time of diagnosis, its regression can be seen, albeit slowly, under treatment, and it is not unusual to wait as long as a year after disease onset and effective treatment to see improvement. However, today, despite improved therapeutic management, overall mortality remains higher for patients with SNV (12–17%) and those with nonsystemic nerve vasculitis (10%) than in the general population [9•,51].

Decisions to treat and with which agents should rely on the presence or absence of factors of poor prognosis according to the five-factor score (which includes creatininemia > 140 µmol/L, proteinuria > 1 g/24 hours, specific CNS, gastrointestinal tract, and/or cardiac involvements) [75]. The therapeutic armamentarium for primary SNV essentially is composed of corticosteroids and immunosuppressants, mainly cyclophosphamide. However, immunosuppressants should be added only for patients with severe forms of polyarteritis nodosa, microscopic polyangiitis, or CSS. When factors of poor prognosis are absent, corticosteroids alone can be prescribed (at least 1 mg/kg/d, usually preceded by a daily methylprednisolone pulses for 1–3 days to control rapidly the more disabling symptoms, then gradually tapered over a period of 12–18 months). In the case of corticosteroids resistance or dependence, for systemic Wegener granulomatosis, or when the patient with SNV has one or more factors of poor prognosis, the combination of corticosteroids and cyclophosphamide, oral (2 mg/kg/d), or intravenous pulses (0.5–0.7 g/m² every 15 days for the first three doses, then every 3 weeks for Wegener granulomatosis and microscopic polyangiitis, or monthly for polyarteritis nodosa and CSS) is mandatory for 10 months (12 pulses) in CSS, microscopic polyangiitis, and polyarteritis nodosa [76,77•] or until clinical remission has been achieved in Wegener granulomatosis, usually within 3 to 6 months (at least six pulses) [78,79]. Thereafter, maintenance therapy with azathioprine or methotrexate is recommended for Wegener granulomatosis for at least 1 year. This latter therapeutic regimen, validated for Wegener granulomatosis, is probably also applicable to the other primary SNV (ie, CSS, polyarteritis nodosa, microscopic polyangiitis) to reduce the cumulative cyclophosphamide dose and, hence, toxicity.

In secondary vasculitides, especially in HIV-related or HBV-related polyarteritis nodosa and in HCV-associated mixed cryoglobulinemia, an etiologic approach to treatment is essential. Initial but short-term corticosteroid therapy may be used to control rapidly the common, severely disabling, or life-threatening manifestations of these vasculitides, possibly in association with plasma exchanges to clear circulating immune complexes rapidly; antiviral agents should be prescribed as soon as possible after diagnosis (lamivudine or interferon–α-2b for HBV-related polyarteritis nodosa; interferon–α-2b and ribavirin for HCV-related mixed cryoglobulinemia; specific antiretroviral therapy for HIV infection) [80].

Alternatively, other immunosuppressants or immunomodulating agents can be prescribed for relapses or patients who fail to respond to conventional regimens. The efficacy of intravenous immunoglobulins (2 g/kg delivered in 2 to 5 days and then every month) has been demonstrated in Guillaum-Barre syndrome, multifocal motor neuropathy, and chronic inflammatory demyelinating polyradiculopathy, and was reported for some vasculitic peripheral neuropathies resistant to corticosteroids [81••,82]. Even though intravenous immunoglobulins appear to be an effective adjuvant therapy in prospective studies on SNV, their beneficial effect is often only transient. Plasma exchanges have also been used with some good results to treat peripheral neuropathies resistant to conventional therapies in Sjogren syndrome, HBV-related polyarteritis nodosa, and HCV-mixed cryoglobulinemia [83•,84]. Other treatments are being evaluated in ongoing therapeutic trials in primary SNV (anti-TNF-α, anti-CD20 monoclonal antibodies) or merit closer attention in vasculitic peripheral neuropathies (eg, MMPs inhibitors like interferon-β, cyclo-oxygenase–2 inhibitors).

Management of nonsystemic peripheral neuropathy has been extrapolated from that of SNV and primarily relies on corticosteroids. However, initial and systematic combination of corticosteroids and cyclophosphamide has been advocated by some authors, because it increased the long-term response rate and achieved greater attenuation of the neurologic disability, with no significant increase of adverse effects [51••,74], but this latter conclusion might be too premature. Other immunosuppressants, recognized as being less toxic than cyclophosphamide, for example azathioprine or methotrexate, may represent other options when a steroid-sparing regimen is needed [9•].

Conclusion
Peripheral neuropathy is a frequent clinical feature in SNV. Its most characteristic clinical manifestation is mononeuritis multiplex, whereas electromyographic and histologic studies demonstrate axonal neuropathy, usually with marked fiber loss. Although PNS involvement can cause, and leave, severe disabling symptoms, it does not worsen the overall prognosis of patients with SNV. Treatment should rely primarily on corticosteroids, with immunosuppressants and other immunomodulating therapies reserved for resistant or very severe disease. However, in light of the many therapeutics that are now available to treat vasculitides, it must be kept in mind that treatment modalities have to be adapted to the patient’s age and general condition.
References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:
• Of special interest
**Of outstanding interest

A good review on vasculitic peripheral neuropathy.
An excellent review on nervous system involvement in vasculitides.
Study on 51 HCV-infected patients, 78% of whom had mixed cryoglobulinemia, showed that peripheral neuropathy is more frequent in patients with mixed cryoglobulinemia than in those without (45 vs 9%, respectively; P = 0.01).
Study on 30 HCV-infected patients with peripheral neuropathy, 63% with mixed cryoglobulinemia, showed that peripheral neuropathy in these patients is mainly represented by distal axonal polyneuropathy and that inflammatory vascular infiltrates are present in 87% of the muscle–nerve biopsies, whereas genomic HCV RNA was detected in only 33% of the biopsies. The authors concluded that HCV neuropathy preferentially results from virus-triggered immune mechanisms rather than direct nerve infection.
Matrix metalloproteinases MMP-3 and MMP-9 are upregulated in vessel wall of patients with SLE and may be responsible for vascular damage and axonal and demyelinating neuropathy.
The authors report three illustrative cases, followed by a comprehensive review on cutaneous sensory neuropathy, which usually manifests as multiple, sharply demarcated areas of hypesthesia with varying degrees of pain. This entity has mainly been described in leprosy, and sometimes develops in polymyositis nodosa and Churg-Strauss syndrome.
Three cases are reported followed by a comprehensive review on peripheral neuropathies, especially monoclonal neuropilx, in childhood systemic vasculitides.
The authors report preliminary results in three patients of their strategy of microsurgical repair of the sural nerve after nerve biopsy. Their technique combined excision of a shorter nerve biopsy (10 mm) that still assured enough material for conclusive pathological diagnosis, with sectioned nerve repair that prevented sensory disturbances. However, their results remain to be confirmed in more patients.
phases in sural nerve biopsies of patients with systemic vasculitic neuropathy, and was associated with increased serum levels of prostatlandins PGE2 and PGF2α.


69 An animal model was lacking to support a pathogenic role of antiproteinase 3 in ANCA-associated vasculitides, mainly Wegener granulomatosis. Immunorelevant antimeuse-proteinase 3 autoantibodies were generated by immunizing mice-proteinase 3/mice-estrophilic deficient knockout mice with recombinant murine proteinase 3 (mMP3) and adjuvant. Local inflammation induced in wild-type female mice after intradermal injection of TNF-α was increased after systemic passive transfer of anti-mP3R. However, no inflammatory changes or vasculitic manifestations (in kidneys or lungs) were noted after intravenous injection of anti-mMP3 into wild-type male mice primed intraperitoneally with LPS before passive anti-mMP3R transfer, or in the absence of previously induced local inflammation.


79 Patients with polyarteritis nodosa or microscopic polyangitis and one or more poor prognosis factors according to the five-factor score had a higher event-free survival rate when treated with 12 cyclophosphamide pulses compared with six pulses (and no maintenance treatment).


Vasculitic peripheral neuropathy resolved after intravenous immunoglobulin administration in four of six patients who had previously failed to respond to steroid therapy.


A comprehensive review of immunotherapy in inflammatory neuropathies, including vasculitides.

Endothelial cell dysfunction in systemic vasculitis: new developments and therapeutic prospects
P.A. Bacon

Purpose of review
The role of the endothelium as an active player rather than a passive victim of inflammation has received considerable interest in atherosclerosis, but less so in systemic vasculitis (SV). However, the accumulating multi-organ damage seen in SV probably includes the endothelium. Assessment of endothelial function is now a standard clinical research tool in cardio-vascular departments. The exciting insights provided by their application to SV, in both primary disease and connective tissue diseases (CTD), is reviewed here.

Recent findings
Diffuse endothelial cell dysfunction (ECD) documented by several techniques occurs commonly in adult and childhood SV. Similar ECD is also seen in CTD. The mechanisms probably relate to inflammatory cytokines such as TNF. The particular role of vasculitic, as opposed to synovial or internal organ inflammation, may be release of secondary mediators directly into the blood stream—whence they can reach distant endothelial beds to induce this diffuse ECD.

Summary
Endothelial injury is the first step in atherosclerosis, where peripheral abnormalities correlate with coronary artery responses. The diffuse ECD in CTD suggests that vascular inflammation may initiate the accelerated CVS disease there. The new findings of similar ECD in primary SV predicts enhanced atherosclerosis here too. In Kawasaki syndrome, persistent late ECD correlates with abnormal coronary responses. In adult SV, initial data also suggests increased subclinical atherosclerosis. The role of endothelial function in the clinical outcome of SV deserves more attention. Research to pinpoint the mechanisms of ECD should lead to more specific therapies that may ameliorate the continuing late morbidity and mortality of SV.

Keywords
systemic vasculitis, endothelial cell dysfunction

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Abbreviations
AA.SV antineutrophil cytoplasmic antibody–associated systemic vasculitis
ANCA antineutrophil cytoplasmic antibody
CAD coronary artery disease
CHD coronary heart disease
CTD connective tissue disorders
EC endothelial cells
ECD endothelial cell dysfunction
1°SV primary systemic vasculitis
RA rheumatoid arthritis
SLE systemic lupus erythematosus
SV systemic vasculitis
TNF tumor necrosis factor

Introduction
The longer-term outcome in vasculitis is receiving increasing focus now that the ability to control acute flares has improved markedly. However, vasculitis still presents serious problems, both when it complicates connective tissue disorders (CTD) and as a primary condition. Indeed, primary systemic vasculitis (1°SV) continues to show high residual morbidity and longer-term mortality. The latter is multifactorial, but relapse and accumulating scars are clearly major factors. Organ damage from such scars occurs early and makes an important contribution to the severity of 1°SV [1]. However, the long-term effects on the endothelial lining of the blood vessels themselves were largely ignored for a long time, even though endothelial cells (EC) seem to be the primary site of the acute inflammation. In atherosclerosis, another more common disease of blood vessels, EC injury is viewed as the first stage in the complex process of atherogenesis according to the “response to injury” paradigm [2]. As a consequence, widespread EC dysfunction (ECD) occurs, which seems to be persistent and a major contributor to the disease process. Thus, it is relevant to ask whether similar EC injury occurs in 1°SV. This is predicted to occur at the focus of the primary vasculitic inflammation. The important question is whether diffuse ECD, distant from inflammatory vasculitic sites, also develops in 1°SV (Fig. 1). That could influence acute-stage recovery and also have late effects. The persistence of EC aberrations in 1°SV needs exploring, together with its potential to progress to atheroma, although there has been little to suggest that phenomenon as a late complication in 1°SV. However, in other systemic CTD such as rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE), coronary artery dis-
Endothelial cell dysfunction: what it is and how it is measured

In this context, ECD basically reflects depressed release or increased breakdown of nitric oxide, with consequent loss or diminution of the ability to produce vasodilatation in response to stimuli such as flow. ECD when it is observed at one site is often assumed to occur consistently across a range of vessels. Indeed, studies in classic CAD have shown a close correlation between induced coronary responses and peripheral arteries such as the brachial artery. This is the basis for the clinical research use of brachial flow-mediated dilatation to gather pathophysiologic data from larger groups of at-risk populations than could be measured by use of invasive cardiac procedures. However, ECD may be patchy in distribution. Certainly in systemic CTD, the assumed correlation between peripheral artery and coronary responses has not specifically tested. Experimental physiologists and cardiologists interested in this area have developed several tools to assess ECD, which are now sufficiently flexible to be applied in the clinical arena. However, they assess different aspects and may not all provide the same answer, complicating comparisons. This is illustrated by the disparity between two tests used in one study in RA [4]. Although all the tests used reflect the effects of nitric oxide, the degree to which each test is dependent on nitric oxide alone is variable. Thus, the specific test is mentioned for the studies discussed here.

Endothelial cell dysfunction in primary systemic vasculitis in adults: patterns and frequency

The occurrence of ECD in adult 1°SV was first established by the Birmingham group in a cross-sectional clinic survey that aimed to establish whether ECD occurs as part of the frequent organ damage [6]. EC function, tested by flow-mediated dilatation using brachial artery ultrasonography, was significantly impaired. Some patients showed little or no physiologic response to the transient ischemia, in comparison with the positive vasodilatation seen in all matched control participants, whereas a few actually showed a paradoxical vasoconstriction. There was no clear relation between flow responses and disease severity. However, a subgroup tested during an acute flare showed a return of EC function to the normal range when retested after the induction of remission. Subsequent examination of a larger group of patients asked whether impaired EC function related to any particular syndrome within 1°SV [6•]. This study demonstrated ECD in both small and medium vessel vasculitis, virtually ruling out any contribution from undetected primary vasculitic inflammation in the brachial artery. Examination of dermal microvasculature, using laser Doppler flowmetry responses to acetylcholine, showed that this vascular bed was also significantly impaired. This important paper suggested that ECD may be a consequence of vascular inflammation of any type, because ECD occurred commonly across all groups with either antineutrophil cytoplasmic antibody (ANCA)-associated systemic vasculitis (AA.SV) or polyarteritis nodosa. Significant impairment was demonstrated across both vascular beds, irrespective of the size of vessel targeted in the primary disease. The ECD occurred in the absence of any evidence of local vasculitis and was independent of renal involvement or ANCA status. Thus, the mechanisms seem to be distinct from the primary vasculitis.

A recent paper from a nephrology group has essentially confirmed the link between vascular inflammation and 1°SV, but importantly it did this using a different test system [7•]. These authors used forearm blood flow, measured by plethysmography after intraradial infusion of acetylcholine in a clinical physiology laboratory, and looked at a more homogenous group of patients with active AA.SV before and after the addition of new therapy. That study did show an inverse correlation between EC function and disease activity, as assessed by either the Birmingham Vascular Activity Score or C-reactive protein. It also confirmed that ECD improves after therapy-induced suppression of the inflammation related to the primary vasculitis. The same group also looked at arterial stiffness as another measure of the relation between inflammation and cardiovascular risk [8••]. Arterial stiffness is increasingly recognized as an important determinant of cardiovascular risk that may even contribute directly to atherogenesis. The Booth data indicate that AA.SV is also associated with increased arterial stiffness that correlates with the degree of inflammation. Significant differences were found between the active AA.SV group and patients in remission; these differences were not due to disease duration, given that the remission group actually had longer disease duration.
These data are interesting because arterial stiffness reflects not only structural components of the vessel wall (such as collagen and elastin) but also smooth muscle tone regulatable by endothelial-derived nitric oxide. Arterial stiffness may thus be a modifiable parameter, related at least in part to current inflammation even in chronic disease.

These four studies have clearly established ECD as a major new aspect of vasculitis. The first three studies used response to nitrate as a positive control to establish that the test vessels were capable of responding to an endothelial-independent stimulus similarly to the normal group, establishing that the abnormality was indeed at the EC level. The last two clarified the relation to inflammation as assessed both by a disease activity index and by C-reactive protein. The overall conclusion was that circulating inflammatory mediators can influence endothelial function in vessels distant from the primary vasculitic disease process. The ECD observed is potentially reversible with remission-induction, so it does not represent fixed damage. It is not due to factors that have been established to cause ECD, such as renal failure. It does relate to disease activity, but not to well-studied mechanisms of vascular inflammation such as ANCA. Thus, the authors raise many new questions about the mechanisms of ECD, its persistence, and its effect on long-term outcome in 1°SV. Indeed, both groups, pointing to the current interest in inflammatory mechanisms in coronary heart disease (CHD) and the role of EC injury in the complex process of atherogenesis, suggested vasculitis as a model to study the interaction of inflammation and atherosclerosis. The best place to start looking at long-term follow-up data is frequently childhood rheumatic disease, which has an excellent tradition of extended studies.

Endothelial cell dysfunction in childhood vasculitis

Kawasaki disease is a childhood vasculitis complicated by coronary artery aneurysms in severe cases. Follow-up of these patients into adult life in several centers has established an association with late morbidity, despite resolution of the acute lesions. The outcome in cases without evidence of early coronary involvement was less clear. However, the Great Ormond Street group previously reported that EC function assessed by brachial artery ultrasonography was abnormal in early adult life, for as long as 17 years after the acute stage of the disease [9]. Importantly, this was seen even in the absence of detectable coronary artery involvement in the acute stage. These patients had not been tested for EC function at that stage; however, given the new data on ECD 1°SV, it is tempting to speculate that the abnormalities found were a consequence of persistent EC dysfunction rather than subclinical structural disease of the coronary arteries at the acute stage. Preclinical testing of subjects at high risk for CHD, such as familial hypercholesterolemia or smoking, has shown that ECD may be present years before clinical disease [10]. It may also be very persistent in adult disease, when it is a risk factor for subsequent clinical events, making it all the more relevant to perform longer-term follow-up studies in adult 1°SV to look at outcome in terms of EC function and CHD [11].

Evidence of impaired EC function late after recovery from Kawasaki disease is accumulating from various sources. A series from Canada showed significantly decreased fibrinolytic responses to venous occlusion stress testing [12]. That has also been considered as a marker of endothelial dysfunction and was associated with increased plasma concentrations of clotting factors that, again, are risk factors for CHD. This ties more closely the relation of late Kawasaki disease with atherosclerosis and CHD. Interestingly, these abnormalities were again seen in individuals without, as well as those with, evidence of previous coronary lesions in the acute stage, adding weight to the suggestion that the underlying problem was ECD rather than coronary aneurysms. Another hint to support this comes from a Japanese case report of a young woman with coronary spasm presenting nearly 20 years after Kawasaki disease without clinical or echocardiographic evidence of coronary involvement [13]. Despite normal coronary angiograms, she experienced coronary spasm in response to local intraarterial acetylcholine infusion. This was also attributed to persistent subclinical ECD.

The persistence of endothelial impairment and the relation of this to previous coronary aneurysms have been investigated in some detail in two important papers from the Far East, where Kawasaki disease is commoner. In the first, from China, the presence and persistence of ECD was examined by the use of brachial artery ultrasonography in 39 individuals [14••]. This showed marked impairment of responses to reactive hyperemia when studied between 1 and 10 years after the acute syndrome. The impairment was equally present in patients treated during the acute stage with intravenous γ-globulin. Interestingly, the impairment was not a fixed one, despite its persistence, because the infusion of ascorbate significantly restored the response. A similar rapid improvement in flow responses after vitamin C has been shown in idiopathic atherosclerotic disease. A study from Japan of the late effects of Kawasaki disease, at a mean of 17 years after the acute stage, has considerably furthered our understanding of the relation of ECD to coronary disease [15••]. These authors directly correlated EC function in the coronary vessels—by blood flow in response to cold pressor testing—with myocardial flow reserve estimated after adenosine infusion, in each of the three coronary territories by positron emission tomography. The detailed results of both tests showed significant impairment. This was detected in 30 regions with
regressed coronary aneurysms as well as stenotic regions, although all showed similar myocardial blood flow at rest. The most relevant finding was of similar impairment in 21 regions with no evidence of past or present abnormality of coronary anatomy. The authors concluded that endothelial function (assessed in the most relevant vascular bed) is impaired after Kawasaki disease regardless of acute-stage coronary aneurysms and that this has direct correlations with myocardial flow reserve. This is consistent with the concept of a risk for CAD late after Kawasaki disease in all cases, not limited to patients with coronary involvement in the acute stage.

**Endothelial cell function in connective tissue diseases with secondary vasculitis**

The systemic CTD frequently manifest vascular inflammation, including overt clinical vasculitis that seems to be essentially similar to 1°SV, as well as more common subclinical involvement. Evidence to support that this is also associated with widespread ECD, and may thus be a major factor in the CAD well documented in CTD, has been assembled for RA [16]. Evidence for excess CAD in RA is extensive, but the link to vasculitis is less so [17]. However, the RA groups at risk are those with seropositive disease and extraarticular features—exactly the severe RA that shows frequent evidence of vascular inflammation when examined in detail [18,19]. Evidence for impaired EC function is also accumulating. It was first described in a small series of active RA that improved after therapy [20]. This may have been related directly to tumor necrosis factor (TNF-α) blockade, as the authors suggested, or to the marked clinical improvement. A subsequent study of the effect of TNF-α blockade showed active but transient improvement of EC function in RA [21–•]. The same group looked for ECD in a much larger series and related it to HLA-DRB1 status rather than therapy [22–•]. This is consistent with the concept that ECD occurs in severe RA, which also has more evidence of vascular inflammation. The patients studied had severe disease and were taking a range of disease-modifying drugs, including methotrexate. No relation was found to disease duration. ECD was reported to be common in relatively early RA despite low disease activity [23]. However, an Australian group found little evidence of ECD in late RA, using the same brachial artery flow test [4]. Interestingly, that study did find evidence for altered arterial compliance and suggested that it may be a more sensitive test for vascular function in RA. Such arterial stiffness reflects connective tissue changes in the vessel wall (as discussed above), and in this late disease it may be this that has altered. In support of this, a correlation was noted with radiographic progression seen on the Sharp score. Another Australian group independently reported altered arterial elasticity in RA with an inverse correlation with disease activity, using C-reactive protein, SAA, and s-vascular cell adhesion molecule-1 levels. Most recently, impaired EC flow responses have been reported in a large group of Italian patients and related to the percentage of CD28- T cells [24•]. The ECD was particularly marked in the subgroup of patients with persistent elevations of this T cell subset. However, this patient group already showed subclinical atherosclerosis, evidenced on carotid ultrasonography. It is probable that these T cells are more involved in the perpetuation of ECD seen in established coronary atherosclerosis than in its initiation. They are not a feature of the early RA with low disease activity with ECD reported by Vaudo et al. [23]. However, they are common in the blood and unstable plaque of late symptomatic CAD [25]. They are also a feature of the type of severe RA with vascular inflammation as well as primary vasculitis such as Wegener granulomatosis [26,27]. Expansion of such cells is particularly seen in generalized Wegener granulomatosis, with extensive vasculitic lesions [28]. These cells are a major source of the cytokine TNF-α, and the suggestion has been made that EC dysfunction in SV may be a consequence of this TNF-α production [29,30].

Systemic lupus erythematosus is a CTD with extensive evidence of vascular inflammation involving multiple territories. There is also widespread evidence for clinical and subclinical atherosclerosis [31,32–•]. An important study that compared well-matched control participants has shown that in SLE the premature atherosclerosis occurs independently of classic risk factors, suggesting a major role for disease-related factors [33•]. One obvious factor would be ECD, but surprisingly few data have been collected on EC function in SLE. A preliminary study in the United Kingdom showed impaired brachial artery responses to reactive hyperemia, and this was confirmed from Brazil in a large group of premenopausal women with SLE [34,35]. This was not related to either classic cardiovascular risk factors or to disease activity or duration. Similar ECD was not found in childhood SLE [36]. However, more studies have confirmed endothelial impairment in adults. In a cross-sectional study, the Pittsburgh group examined for subclinical vascular disease in a large group of women without overt cardiovascular disease and found increased aortic stiffness as well as subclinical atheroma [37–•]. The determinants for the former included SLE-related variables, such as complement aberrations. This contrasted with carotid atheroma, where the determinants were largely classic risk factors such as hypertension and age. In another major study of young women in the United States, brachial artery flow-mediated dilatation was depressed in SLE patients, as in CAD patients, compared with healthy control participants [38••]. This important study correlated this with elevated levels of circulating apoptotic EC. Similar circulating EC or EC debris has been described as a marker of disease activity in both adult vasculitis and Kawasaki disease [39•,40•,41]. They have also been adduced as further evidence for vascular inflammation in SLE and
In secondary vasculitis, several other potential mechanisms have the ability to induce EC injury and apoptosis with disease activity [39•,40•,41]. Such EC microparticles have been reported in Behçet syndrome [51,52]. Another potential factor is endothelial microparticles, which are elevated in both childhood and adult 1°SV, correlating with disease activity [39•,40•,41]. Such EC microparticles have the ability to induce EC injury and apoptosis [53,54].

Behçet syndrome is another CTD with extensive evidence of vascular inflammation. Indeed, it is sometimes regarded as a primary vasculitis. There seems to have been no detailed attempt to look for evidence of excess CAD risk. However, impaired EC function has been reported and related to oxidative stress [43]. It improved with vitamin C treatment. Circulating factors may be important here, as suggested in 1°SV, because sera from patients with Behçet syndrome in both active and inactive states have been reported to depress nitric oxide production in EC in culture [44]. Patients with Behçet syndrome may also show evidence of EC activation and hypercoagulability [45]. It is far from clear what influences the occurrence of these two seemingly contradictory EC states in this disease.

Mechanisms of endothelial cell dysfunction induction in disease

In 1°SV, the correlation of ECD with the disease activity was noted above. One key inflammatory cytokine here is TNF-α, and there is experimental evidence to link this to induction of ECD [46]. The improvement noted in EC function after TNF blockade supports the relevance of this in 1°SV [7•]. However, similar improvement in EC function was previously recorded after conventional therapy, suggesting that suppression of inflammation is more relevant than the particular agent used [5]. Serial observations of the short-term effects of TNF blockade have demonstrated a transient improvement that reverts to marked impairment of EC function while the vasculitis is still active [47]. This may relate to the persistence of the CD28− T cells that are major producers of TNF-α in active vasculitis [27]. Similar observations on the transient nature of the effects of TNF blockade on ECD have been reported in RA [21••]. There may be relevant genetic influences on EC function, also. A link has been shown between endothelial nitric oxide haplotype and giant cell arteritis in two independent series [48,49]. Nitric oxide is well established as a key molecule in the regulation of arterial tone and physiologic responses to flow. It has recently been shown to be an important influence on arterial stiffness as well [50]. The relevance of endothelial nitric oxide synthase polymorphisms may be greater in some vasculitides than others. No link was detected in Henoch-Schönlein purpura, but a link has been reported in Behçet syndrome [51,52]. Another potential factor is endothelial microparticles, which are elevated in both childhood and adult 1°SV, correlating with disease activity [39•,40•,41]. Such EC microparticles have the ability to induce EC injury and apoptosis [53,54].

In secondary vasculitis, several other potential mechanisms were recently reviewed [31]. These include immune complexes, which can trigger adhesion molecule expression in EC; complement activation, where complement products have been found in early vessel wall lesions; CD40L, which may react with the upregulated CD40 expression on EC in SLE; and finally C-reactive protein, which can promote complement activation, induce ECD by spreading adhesion molecules and chemokines, and modulate uptake of low-density lipoprotein. These seem to be more relevant to secondary vasculitis, such as that seen in SLE, than to 1°SV, where there is little evidence for complement-related events.

The simplest conclusion to be drawn from this confusing mass of potential mechanisms is that multiple facets of the inflammatory process can induce EC dysfunction, suggesting that it must have a physiologic role. However, inflammatory lesions in blood vessels may have a particular role in the induction of ECD because of the ability of soluble mediators released here to immediately access the blood stream and reach distant EC beds at effective concentrations. This would explain why both the various types of 1° SV as well as secondary vasculitis are associated with ECD despite rather different causes. The key task now is to identify the nature of such secondary mediators. EC microparticles are clearly one potential candidate.

Significance of endothelial cell dysfunction in systemic vasculitis

Part of the rationale for the initial study of EC function was that poor health status persisting after acute SV could relate to altered blood flow responses and poor tissue perfusion consequent on ECD. Patient self-assessment of function using the SF36 shows that poor quality of life in 1°SV is not just anxiety or depression related to a life-threatening disease, because low scores relate to physical health as much as to mental health. The frequent ECD in 1°SV can have many physical effects and contribute to both poor healing and scar development. There is new evidence that endothelial nitric oxide synthase has an important role in neovascularization in response to tissue injury, which is a major factor in the healing of ischemic lesions such as those occurring in active vasculitis. Improvement of this healing is seen as an important therapeutic goal after limb ischemia or myocardial infarction [55]. Studies in mice deficient in endothelial nitric oxide synthase have demonstrated significantly reduced limb perfusion after femoral blockage compared with wild-type animals [56]. The depressed nitric oxide responses in active SV may be predicted to similarly retard neovascularization in ischemic tissue. In the longer term, depressed EC function is a major risk factor for clinical events in CAD [57]. Indeed, EC function has been described as a barometer for cardiovascular risk, whereas dysfunctional EC are the basis for the initiation of atheroma development and plaque formation [58].
Evidence for atherosclerosis in 1°SV is currently scanty compared with the well-developed literature on CTD, but that may be because it has not previously been looked for. There have been odd case reports of particularly extensive disease, and preliminary epidemiologic evidence for enhanced cardiac lesions detected during follow-up using damage scores [59]. The only objective evidence for subclinical atherosclerosis to date comes from a survey of patients with Wegener granulomatosis in whom carotid artery ultrasonography was used [60].

**Conclusion**

Clearly, ECD in SV is not a new phenomenon, but only recently has it been looked for. It is thus a classic example of Voltaire’s dictum that a man sees what he knows. Once seen, it has been confirmed in multiple vasculitic syndromes by a variety of tests in several centers. Currently, the significance of this remains speculative. A chain of events seems to link ECD, the first step in atherogenesis, with the accelerated CHD seen in systemic CTD such as RA and SLE. This supports the hypothesis that vascular inflammation in the CTD is a major event in the development of such CHD, through the induction of ECD. It also predicts that enhanced rates of atherosclerosis will be seen in 1°SV as well. Currently, CHD has not been observed extensively in any adult 1°SV syndrome, but maybe now that we know what to look for, it will be seen as commonly as ECD. This will have important implications for the therapy of 1°SV. Control of disease activity seems to improve EC dysfunction in due course, but more rapid improvement probably occurs with the addition of TNF blockade to the remission-induction regimen. The addition of further agents to specifically improve EC dysfunction, such as statins, needs proper assessment. This is already under trial in CTD like RA and SLE. The established risk of CHD in these conditions has not been clearly linked to secondary vascular inflammation, although this is commonly seen. Thus, there remain many important questions to address, but it is clear that research is moving fast in this clinically relevant area.

**Acknowledgments**

The author thanks Dr. Michael Frennaux for helpful discussions.

**References and recommended reading**

Papers of particular interest, published within the annual period of review, have been highlighted as:

- Of special interest
- Of outstanding interest


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21. Gonzalez-Juanatey C, Testa A, Garcia-Castelo A, et al.: Active but transient improvement of endothelial function in rheumatoid arthritis patients undergoing long-term treatment with anti-tumor necrosis factor alpha antibody. Arthritis Rheum 2004, 51:447–450. The effects of TNF blockade on EC function are relevant both to understanding the mechanisms of EG dysfunction and to controlling it. This paper suggests a complex response variable with time, as was also noted in an earlier abstract on 1°SV (see
This paper established that circulating EC particles (and precursors to replace damaged endothelium) are common in diseases with vascular inflammation and that the particles in turn affect endothelial function. Similar EC particles have been reported in acute coronary syndromes. See [54].


Clinical approach to cutaneous vasculitis
Miguel A. Gonzalez-Gay, Carlos Garcia-Porrúa, and Ramon M. Pujol

Purpose of review
This review provides the readers with an update on the clinical approach of a patient seeking treatment with cutaneous vasculitis. It outlines the work-up for assessing patients with cutaneous vasculitis and discusses the essential features of the main conditions included within this category.

Recent findings
Recent works on genetic and infectious factors implicated in the pathogenesis of Henoch-Schönlein purpura are discussed. Special attention is given to the prognosis and response to treatment. Also, recent reports on cutaneous vasculitis secondary to connective tissue diseases are reviewed.

Summary
With this review, the reader will be able to establish the steps to be followed in the clinical approach to a patient seeking treatment with cutaneous vasculitis.

Keywords
cutaneous vasculitis, skin vasculitis, leukocytoclastic vasculitis, purpura, diagnostic approach

Introduction
Cutaneous vasculitis is composed of a wide spectrum of diseases characterized by predominant skin involvement and a different grade of systemic manifestations [1••]. In this regard, the distinction between small blood vessel cutaneous vasculitides mainly restricted to arterioles, capillaries, and postcapillary venules and those that also involve medium-sized arteries is often difficult [2,3].

Pathologic considerations
Small-sized blood vessel cutaneous vasculitis generally includes capillaries, postcapillary venules, and nonmuscular arterioles (<50 µm in diameter) that are found mainly within the superficial papillary dermis. In contrast, medium-sized blood vessels (between 50 and 150 µm in diameter) have muscular walls and are found principally in the deep reticular dermis, near the junction of the dermis and subcutaneous tissue. Larger vessels are not found within the skin.

Most authors include within the group of cutaneous vasculitis those conditions characterized by leukocytoclastic changes [4]. Their histology shows infiltration of neutrophils within and around blood vessel walls; leukocytoclasis (degranulation and fragmentation of neutrophils leading to the production of nuclear dust); fibrinoid necrosis of the damaged vessel walls; and necrosis, swelling, and proliferation of the endothelial cells (Fig. 1). However, the presence of leukocytoclasis is merely an expression of a significant neutrophilic infiltrate, which may also be found in nonvasculitic conditions involving the skin, such as in cutaneous infections or in Sweet syndrome. Also, some authors accept a wider definition for small vessel vasculitis, without the requirement for evidence of leukocytoclastic vasculitis, if an inflammatory infiltration within the vessel walls is observed along with at least one of the features described [5].

Clinical considerations
Cutaneous involvement is the typical finding in patients with cutaneous vasculitis. The pattern of skin involvement is initially a maculopapular rash that may be followed by other skin lesions, in particular by palpable purpura (Fig. 2). This is a result of extravasation of erythrocytes through damaged blood vessel walls into the dermis. Other skin lesions such as nonpalpable macules and patches, urticaria, bullous lesions, vesicles, splinter hemorrhages, ulcers, or nonspecific changes may also be observed. A combination of different lesions is
common (Fig. 3). Because of increased hydrostatic pressure, skin lesions are more common on the legs and buttocks [1••].

Cutaneous vasculitis as the clinical expression of small-sized blood vessel vasculitis may be limited to skin, and in this case, the outcome is good. However, small-sized blood vessel cutaneous vasculitis may involve other organs, eg, Henoch-Schönlein purpura (HSP) [1••].

Cutaneous vasculitis may be the presenting manifestation of a vasculitides with frequent overlap of small and medium-sized blood vessel involvement, eg, microscopic polyangiitis [6]. In these cases, the outcome depends on the type and severity of visceral involvement.

In the presence of typical palpable purpura, a diagnosis of cutaneous vasculitis can be made in a straightforward fashion. However, a skin biopsy to confirm the presence of leukocytoclastic vasculitis is always required because other conditions, eg, pigmented purpuric eruptions or scurvy, may mimic cutaneous vasculitis [7]. Because cutaneous vasculitis is a dynamic process, it is more convenient to perform a biopsy from a lesion of a duration of 18 to 24 hours, because this will show the most diagnostic features.

Because of the lack of specific diagnostic tests, the clinician should remain alert to the possibility that a disease other than a primary vasculitis may be present, eg, a hematologic disorder or severe infection [8–10].

Main clinical syndromes associated with small-sized blood vessel cutaneous vasculitis

Only the group of vasculitides involving exclusively small blood vessels is discussed here.

Primary cutaneous vasculitides

Cutaneous leukocytoclastic angiitis

Cutaneous leukocytoclastic angiitis defines an isolated cutaneous leukocytoclastic vasculitis limited to skin, generally precipitated by the use of drugs [11]. This definition encompasses most cases considered hypersensitivity vasculitis [12]. Lesions tend to develop and be approximately the same age, occurring at approximately the same time and evolving simultaneously. Deep ulceration is uncommon. A diagnosis of cutaneous leukocytoclastic angiitis is one of exclusion, because other features of systemic vasculitides must be absent [3].

Joint symptoms usually respond to nonsteroidal anti-inflammatory drugs. Colchicine and dapsone have also

Figure 1. Leukocytoclastic cutaneous vasculitis

Presence of fibrinoid necrosis, neutrophilic infiltration of vessel wall with leukocytoclasia (hematoxylin and eosin ×200).

Figure 2. Purpuric papular rash involving the lower parts of the legs in a child with Henoch-Schönlein purpura

Palpable purpura as the best clinical expression of small vessel vasculitis.
been used [13•]. Nonresponders have been treated with a short course of corticosteroids or azathioprine. However, no clear evidence exists about the benefit of these more aggressive therapies.

Henoch-Schönlein purpura
Henoch-Schönlein purpura is the most common vasculitis in children and an infrequent condition in adults [14•]. It is characterized by purpuric rash; arthralgia/arthritis; gastrointestinal manifestations, in particular abdominal pain; and nephritis. The diagnosis is confirmed by the demonstration of IgA deposition in and around blood vessel walls on direct immunofluorescence. Besides genetic [15•,16•] and environmental factors [17], many antigens, including bacterial, viral, and food-related components, have been considered to play a role in its pathogenesis. It is preceded by upper respiratory tract infection in 30 to 50% of the cases. Mesangial deposition of nephritis-associated plasmin receptor, a group A streptococcal antigen, has been detected in the glomeruli of children with HSP who developed nephritis [18]. *Helicobacter pylori* has also recently been implicated in the gastrointestinal and the extragastrointestinal manifestations [19•].

In a series of 114 children, Kawasaki *et al.* [20•] found that nephrotic syndrome, decreased factor XIII activity, hypertension, and renal failure at onset were more frequent in those with unfavorable prognosis (N = 20). The rate of glomeruli with crescents, macrophage infiltrations, tubulointerstitial changes, and acute exacerbation in these patients was higher than in those with good outcome.

The question of whether early treatment with corticosteroids reduces the risk of subsequent renal involvement in HSP remains unsettled. Huber *et al.* [21•] performed a randomized, placebo-controlled project investigating whether early corticosteroid administration could reduce the rate of renal or gastrointestinal complications in children with HSP. The treatment group (N = 21) received oral prednisone, 2 mg/kg/d for 1 week, with weaning over the period of a second week, whereas 19 received placebo. At 1 year, there was no difference in the rate of renal involvement and acute gastrointestinal complications.

Patients with severe nephritis have been treated with various therapeutic modalities, including corticosteroids alone or in combination with immunosuppressive agents, plasmapheresis, high-dose intravenous immunoglobulin therapy, and danazol. Fifty-six patients with histopathologically severe HSP nephritis were randomized to receive supportive therapy with or without cyclophosphamide, 90 mg/m²/d for 42 days. However, there were no differences in outcome between the two trial groups [22•].

In general, HSP is benign and self-limited in children and more severe in adults [23]. A minority of patients, more commonly adults, may progress to end-stage renal insufficiency.

Urticarial vasculitis
Unlike in common urticaria, the skin lesions of urticarial vasculitis persist for more than 48 hours and resolve with purpura and hyperpigmentation. Hypocomplementemia is observed in 35 to 64% of the patients with urticarial vasculitis, and systemic manifestations (pulmonary) are more common in these patients [24]. It has been associated with systemic lupus erythematosus [25], complement deficiencies, viral infections, serum sickness, drug reactions, and hematologic disorders, and more rarely with solid tumors, sun exposure, or cold. In general, patients with urticarial vasculitis have a chronic but benign course.

Cryoglobulinemic vasculitis
Cryoglobulins are cold-precipitating immunoglobulins. Three subtypes can be distinguished based on the pres-
ence of rheumatoid factor, activity, and monoclonality. In type I, the cryoglobulin fraction is a single monoclonal immunoglobulin; type II has mixed cryoglobulins with monoclonal component (usually IgM rheumatoid factor-like) combined with polyclonal component (generally IgG); and type III has mixed polyclonal cryoglobulins (with one or more components) [26]. Type I is observed in lymphomyproliferative disorders, and it may be associated with hyperviscosity symptoms rather than with vasculitis. Although types II and III are associated with immune complex vasculitides and predominantly affect small vessels, medium-sized or sometimes large vessels may also be involved [6]. Lymphoproliferative or autoimmune diseases and viral (mainly hepatitis C virus) and bacterial infections may be associated with type II and III cryoglobulins. Mixed cryoglobulinemia may be found in more than 50% of patients with hepatitis C virus infection. However, the frequency of vasculitis in these patients is much lower [27].

The definition of essential mixed cryoglobulinemic vasculitis has been recently reconsidered. Only those cases in which clinical signs of infections or autoimmune or lymphoproliferative diseases are absent will fall into this category.

In patients with cryoglobulinemic vasculitis, recurrent palpable purpura generally involving the lower extremities, arthralgias or arthritis, and weakness are almost invariably present. Peripheral neuropathy and subclinical lymphocytic alveolitis are observed in 40 to 70% of the cases. Renal complications, manifested as nephritic or nephrotic syndrome, secondary Sjögren syndrome, Raynaud phenomenon, and central nervous system, gastrointestinal, cardiac, and retinal involvement have been described in less than 40% of the cases [26]. Low serum C4 levels are generally observed. High titers of rheumatoid factor are found in most patients.

Erythema elevatum diutinum

Erythema elevatum diutinum is an uncommon disease characterized by nonpurpuric prominent and persistent edematous erythematous papules and plaques on the extensor surface of the extremities (backs of hands, elbows, or knees) that heal over a period of months or years with fibrosis. Treatment with dapsone has yielded good results [5].

Secondary leukocytoclastic vasculitis

Lymphoproliferative disorders, leukemia, or even solid tumors must be suspected in patients with an unexplained chronic relapsing course of skin purpura [8].

**Figure 4. Work-up in a patient with cutaneous vasculitis**

*Hematologic cytopenias, immature blood cells or monoclonal peak of gammaglobulin.*

ACA= Anti-cardiolipin antibodies. ANA= Antinuclear antibodies.

ANCA= antineutrophil cytoplasmatic antibodies. C= Complement.

CMV= Cytomegalovirus. CSS= Churg-Strauss syndrome.

HIV= Human immunodeficiency virus. MPA= Microscopic polyangiitis.

RF= Rheumatoid Factor. WG= Wegener's granulomatosis.
In some patients, a small-sized cutaneous vasculitis may be the presenting sign of a concealed life-threatening bacterial infection [10].

Small-vessel cutaneous vasculitis is not uncommon in the context of connective tissue diseases. Ramos-Casals et al. [28••] assessed the frequency of cutaneous vasculitis in a series of 558 patients with primary Sjögren syndrome. Fourteen presented with cryoglobulinemic vasculitis, 11 with urticarial vasculitis, and 26 with cutaneous purpura not associated with cryoglobulins. Most patients with primary Sjögren syndrome associated with cutaneous vasculitis had small-sized blood vessel leukocytoclastic vasculitis, with a higher prevalence of extraglandular and immunologic features. Cutaneous vasculitis has been associated with secondary Sjögren syndrome [29•]. Also, new drugs have been associated with cutaneous vasculitis [30,31].

Clinical approach to a patient with cutaneous vasculitis

A purpuric lesion does not always indicate the diagnosis of small-sized blood vessel cutaneous vasculitis as a heterogeneous group of conditions (atheroembolic disease, thrombotic disorders such as the antiphospholipid antibody syndrome, thromboembolism, neoplasms such as the cardiac myxoma or scurry) may also cause purpuric cutaneous lesions and mimic cutaneous vasculitis.

In the study of a patient with palpable purpura or with other cutaneous lesions suggestive of vasculitis skin biopsy, specimens for routine microscopy and direct immunofluorescence are recommended, particularly in adult patients.

A careful clinical history should search for data regarding ingestion of drugs, presence of preexisting symptoms suggestive of chronic or acute disorders, autoimmune diseases, and history of a recent or chronic infection.

Physical examination, routine laboratory tests (blood and urine), and chest radiograph should be performed in all the cases.

If specific symptoms or signs of an underlying systemic disorder are present, further studies should be considered [1••] (Fig. 4).

Conclusion

Cutaneous vasculitis includes a wide spectrum of conditions with predominant skin involvement and different degrees of systemic manifestations. Frequent overlap among these conditions is observed. However, a systematic clinical approach of a patient seeking treatment with cutaneous vasculitis will help the clinician establish adequate and cost-effective management of this condition.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- Of special interest
- Of outstanding interest


Prospective study on 40 children with HSP. Early prednisone therapy in HSP did not reduce the risk of renal involvement at 1 year or the risk of acute gastrointestinal complications.


The authors did not find a beneficial effect of short-term cyclophosphamide therapy in severe HSP nephritis.


Large series of patients with primary Sjögren syndrome. The main characteristics of Sjögren syndrome associated with cutaneous vasculitis were the predominance of small leukocytoclastic vasculitis, with a higher prevalence of extraglandular and immunologic features.


Retrospective review of 93 patients with Sjögren syndrome (31 of them with secondary). Cutaneous vasculitis was present in 29% of patients with secondary Sjögren syndrome.


EDITORIAL OVERVIEW

The musculoskeletal roads less traveled
Doruk Erkan and Stephen A. Paget

This section of the Current Opinion in Rheumatology will be about “the musculoskeletal roads less traveled” by rheumatologists, but also ones that are having profound effects on our knowledge about and treatment of the disorders that plague our patients. We are currently appropriately fixated on and frankly amazed by the advances in biologic treatment for rheumatoid arthritis and other systemic disorders. However, the disorders that we shall speak about in this section are no less deserving of our awe, and thus they should not be relegated to chapters designated as “systemic disease with musculoskeletal manifestations” or the oftentimes stated “miscellaneous disorders.” They are front and center in modern science and give us extraordinary and broader views into the medical world of today and tomorrow. Lessons learned here will not simply help us to avoid missing and optimally treating the rare disorders such as lysosomal storage, but they will broaden our investigative and therapeutic horizons.

Although musculoskeletal signs and symptoms usually point toward a mechanical injury, arthritis, or a rheumatologic autoimmune disorder, it is not uncommon for patients to present with musculoskeletal complaints that are secondary to systemic nonrheumatologic disorders. In the clinical setting, these disorders can create a diagnostic challenge for rheumatologists and possibly delay diagnosis and eventually affect patient outcomes. Thus, rheumatologists should be familiar with the clinical manifestations as well as diagnostic and therapeutic modalities of these rare disorders. In the research setting, these diseases may help us better understand and treat those more common and debilitating diseases.

Musculoskeletal manifestations of endocrine disorders range from arthralgia, myalgia, or bone pain to joint destruction, muscle infarction, or osteonecrosis. Drs. Jacobs–Kosmin and DeHoratius (pp. 64–69) discuss the new developments regarding the musculoskeletal manifestations of endocrine disorders including diabetes mellitus, hyper- and hypothyroidism, hyperparathyroidism, acromegaly, and hypercortisolism. Although the mechanisms remain to be clarified and treatment options are still limited, prevention and identification of the musculoskeletal manifestations and complications of endocrine disorders are essential for rheumatologists.

Lysosomal storage disorders, mainly Gaucher disease and the Hurler–Scheie syndrome (mucopolysaccharidosis type I) can be associated with profound and life-altering musculoskeletal complications such as bone pain, osteopenia, osteonecrosis, secondary osteoarthritis, or hip dysplasia. As discussed by Drs. Pastores and Meere (pp. 70–78), trailblazers in this field, enzyme therapy to correct the underlying cause represents the most significant recent advance in the management of lysosomal storage disorders. This medical story reads like a Conan Doyle detective story and is a must for all physicians who love when the “investigative game is afoot” and how we make quantum medical and scientific leaps. Lessons learned here should “make all the difference” in the progress of research and ultimately in patient outcomes.

Drs. Casas–Ganem and Healey (pp. 79–85) discuss the advances in the diagnosis and treatment of malignant bone tumors, which can present as local bone pain, arthralgia, or arthritis. Nowhere in medicine has our understanding of the molecular and genetic mechanisms of disease been more ideally and innovatively employed. Although we in rheumatology are still trying to make sense out of the pathogenetic, diagnostic, and therapeutic impact of knowing whether our patients are HLA B27 or DR4 positive, these scientists are typing tumors and being guided therapeutically by the results. In the near future, as a result of our increased understanding of the molecular mechanisms of primary bone tumors such as osteogenic or Ewing sarcoma, new medications (bisphos-
phonates, cyclooxygenase-2 inhibitors, and statins) will be incorporated into treatment options. Forward-thinking advances in the surgical management of bone tumors (such as expandable prostheses for growing children that allow limb lengthening without surgery) are also discussed.

This next story can be entitled the “gift that keeps on giving.” The presence of cells in one individual transferred from another genetically distinct individual is defined as microchimerism. Fetal microchimerism can persist for many years in maternal blood and has been investigated in the development of autoimmune diseases such as systemic sclerosis, systemic lupus erythematosus, and dermatomyositis. Drs. Jimenez and Artlett (pp. 86–90) discuss the role of microchimeric cells in the pathogenesis of systemic sclerosis and explore the hypothesis that microchimeric cells may be mediating a graft-versus-host disease-like reaction in systemic sclerosis patients.

Another diagnostic challenge for a rheumatologist is atypical presentations of rheumatologic disorders, especially when connective tissue disorders present solely with central nervous system involvement. Drs. Chin and Latov (pp. 91–99) discuss recent advances in the diagnosis and treatment (including tumor necrosis factor-α blockers) of central nervous system manifestations of vasculitides and other connective tissue disorders. Early diagnosis, especially in the presence of better diagnostic techniques, and aggressive treatment of these diseases are crucial to improve patient outcomes.

The road of rapid identification of the genetic and molecular mechanisms of systemic diseases is crucial for the expansion of medical science and patient care. This road will help us elucidate target-specific treatments such as enzyme therapies, biologic agents, or gene therapy. An additional branch of the road not yet fully explored but likely to become a major path is that of individualized treatments based on a patient’s biomarker profile (eg, cytokine panel) and therapeutic genetic profile (ie, pharmacogenetics), whereby patients would receive optimized treatments based on their ability to process those agents. We look forward to traveling this exciting but predictably bumpy road.
Musculoskeletal manifestations of endocrine disorders
Dana Jacobs-Kosmin and Raphael J. DeHoratius

Purpose of review
Much of our education about endocrine disorders focuses on their diagnosis and treatment. Although the musculoskeletal manifestations of endocrine disorders are well documented, they are often overlooked. This review will discuss new developments regarding those rheumatic manifestations.

Recent findings
Diabetic research is investigating connective tissue alterations in hand syndromes. A recent review elucidated the natural history of diabetic muscle infarction. Research has identified factors that stimulate osteoblast activity in diffuse idiopathic skeletal hyperostosis and bone loss in diabetics. Accumulating evidence documents thyroid disease coexisting with connective tissue disorders. Reports document cases of vasculitis occurring after propylthiouracil treatment. Finally, data clarifies the effects of thyroid dysfunction, hyperparathyroidism, acromegaly and hypercortisolism on bone.

Summary
Current research mainly relates to the effects of endocrine disorders on bone. As we advance our understanding of mechanisms that lead to rheumatic disorders in endocrine disease, we will improve our ability to treat them.

Keywords
rheumatic manifestations, diabetes mellitus, thyroid disease, hyperparathyroidism, acromegaly, hypercortisolism

Introduction
Many patients with endocrine disorders develop rheumatic conditions overshadowed by the primary disease. The clinical importance of the rheumatic disorders, particularly osteopenia, cannot be overemphasized. New developments regarding the musculoskeletal manifestations of endocrine disorders including diabetes mellitus, hyper- and hypothyroidism, hyperparathyroidism, acromegaly and hypercortisolism will be discussed herein.

Diabetes mellitus
The rheumatic disorders associated with diabetes mellitus (Table 1) are generally not unique to diabetics. They do, however, occur at a higher prevalence in diabetics than the general population. Hand and shoulder syndromes occur similarly in type 1 and 2 diabetes. Diffuse idiopathic skeletal hyperostosis (DISH) develops more commonly in type 2 diabetics while osteopenia, Charcot joints, and possibly diabetic muscle infarction, are more prevalent in type 1 disease. Research suggests that patient age, as well as the duration of diabetes, affect the development of the musculoskeletal manifestations associated with this disease. However, studies have not consistently shown that metabolic control of diabetes can prevent the development of those rheumatic disorders [1].

Hand and shoulder syndromes
Over 30% of diabetics have potentially disabling hand or shoulder disorders including Dupuytren disease, limited joint mobility (LJM), flexor tenosynovitis, carpal tunnel syndrome and shoulder capsulitis [2]. In a recent study, Dupuytren disease was the most frequent musculoskeletal complication, present in 21.8% of type 2 diabetics [3•].

Altersations in connective tissue may contribute to hand syndromes. LJM is often accompanied by skin changes similar to those seen in scleroderma [2] and must be distinguished from that disease as well as other diabetic hand syndromes and reflex sympathetic dystrophy. Biopsy findings include excessive fibrosis with increased deposition of dermal collagen. Data suggest that diminished collagen breakdown occurs in LJM due to increased tissue glycation [2]. To further explore this, researchers studied patients with type 1 diabetes with and without LJM. They could not demonstrate a significant difference between serum markers of type I and III collagen metabolism in these subjects [4]. Future studies
exploring tissue markers may be more informative. Corticosteroid injections have been used with good response in diabetic adults with LJM and flexor tenosynovitis [5]. Additionally, an aldose reductase inhibitor was used with success in 2 diabetic patients with LJM, offering further insight into the molecular basis for the disorder [6].

**Diabetic muscle infarction**
Diabetic muscle infarction is rare. Of the 116 patients in one literature review, 74 patients had type 1 diabetes, and nearly all had thigh involvement [7•]. Magnetic resonance imaging characteristically reveals increased T2-weighted signal of involved muscles as well as muscle enlargement, subcutaneous edema and subfascial edema. Biopsies show myofiber necrosis, inflammation, and microvasculopathy. Following resolution, the disease recurs in many patients [7•]. Widespread muscle infarction, as in a patient with bilateral thigh and calf muscle involvement, is unusual [8].

**Diffuse idiopathic skeletal hyperostosis**
DISH has been associated with the metabolic derangements of type 2 diabetes. Its pathogenesis is complex. The production of insulin like growth factor-1 (IGF-1) may be induced by elevated insulin and growth hormone, in addition to platelet aggregation in the setting of atherosclerosis. IGF-1 stimulates osteoblast proliferation. The pathogenesis of DISH may also include nuclear factor kB, prostaglandin I2 and matrix Gla protein (MGP). Alteration or deficiency of MGP appears to increase activity of bone morphogenetic protein-2 (BMP-2), a potent osteogenic factor [9•].

**Charcot joints**
Diabetes is the major cause of Charcot joints. The disorder typically occurs as a neuropathic foot or ankle. Joint destruction results from inflammation and bone resorption either due to repetitive mechanical trauma or altered sympathetic tone and ensuing hyperemia [10]. Regardless, the outcome is weakened bone. Osteopenic bone, particularly the metaphysis, is susceptible to subchondral bone collapse [11] and intra-articular fractures. An association has been found between fracture in the Charcot joint and low bone mineral density (BMD) in the contralateral femoral neck or distal radius. Dislocation in the joint, though, was associated with normal BMD [12•].

**Osteopenia**
Patients with type 1 diabetes are at risk for osteopenia, and all diabetics have increased likelihood of fracture, especially in the hip. Mechanisms contributing to poor bone health in diabetes include: elevated urinary excretion of calcium coupled with lower intestinal absorption, altered parathyroid hormone and vitamin D regulation, decreased insulin and IGF-1, and accumulated glycation end products [13••,14••]. Damaging effects on the bone of diabetics can develop at an early age. One study revealed that diabetic adolescents had lower whole body mineral content and lower whole body, tibia trabecular, and femoral neck density than controls [15]. In a separate study, female diabetics aged 20 to 36 had significantly lower femoral neck and lateral spine BMD thanagematched controls. Notably, N-telopeptides, osteocalcin, IGF-1 and IGF binding protein-3 levels were not significantly different between groups [16]. The inconsistent relation between BMD and bone biomarkers is not unique to this study [14••]. The identification of other specific markers may clarify this disparity.

Although patients with type 2 diabetes have increased fracture risk, they generally have normal or high BMD on dual energy X-ray absorptiometry (DXA). The cause for this discrepancy is unclear. Normal BMD may be promoted by high body mass index along with elevated insulin, estrogen and leptin; fractures may thus be due to more frequent falls [14••,17]. However, as DXA does not measure volumetric BMD, bone quality could be poor despite normal DXA results. Studies using peripheral quantitative computed tomography (pQCT) on animal models support this notion [11,14••].

### Table 1. Musculoskeletal manifestations of diabetes

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Manifestation</th>
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<tr>
<td>Limited joint mobility (diabetic cheiroarthropathy or diabetic hand syndrome)</td>
<td>Painless limitation of hands begins in the 5th finger and proceeds radially +/- thickened waxy skin on dorsum of hand</td>
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<tr>
<td>Dupuytren’s disease (Dupuytren’s contracture)</td>
<td>Chronic thickening of palmar aponeurosis leads to flexion deformities involving 3rd and 4th digits</td>
</tr>
<tr>
<td>Shoulder capsulitis (adhesive capsulitis or frozen shoulder)</td>
<td>Thicken joint capsule adhering to the humeral head results in pain and stiffness in the shoulder followed by full recovery</td>
</tr>
<tr>
<td>Flexor tenosynovitis (trigger finger)</td>
<td>Proliferation of fibrous tissue in the tendon sheath leads to limited movement</td>
</tr>
<tr>
<td>Carpal tunnel syndrome</td>
<td>Paresthesia over the median nerve distribution</td>
</tr>
<tr>
<td>Charcot joint (neuropathic arthropathy)</td>
<td>Painless joint swelling, laxity, subluxation and bone resorption</td>
</tr>
<tr>
<td>Diffuse idiopathic skeletal hyperostosis (Forestier’s disease)</td>
<td>Osteophytes along anterolateral surface of vertebral bodies may lead to back pain, mild stiffness and loss of motion</td>
</tr>
<tr>
<td>Diabetic muscle infarction</td>
<td>Swelling and pain usually affecting the lower extremities. Can spontaneously resolve but tends to recur</td>
</tr>
<tr>
<td>Osteopenia</td>
<td>Increased fracture risk</td>
</tr>
</tbody>
</table>
Periodontal disease in animals was used as a model for bone loss. Periodontitis led to decreased osteoclastogenesis and bone resorption. In diabetic animals, however, bone formation was also suppressed, and apoptosis of bone-lining cells continued after it had declined in controls. The authors suggest that net loss of bone was due to this prolonged apoptosis [18]. Perhaps osteopenia in human diabetics, too, is fostered by inhibition of bone formation through apoptosis of bone-lining cells.

Rosiglitazone, an oral agent used to treat diabetes, has deleterious effects on bone. Rosiglitazone activates a nuclear receptor expressed in bone that regulates osteoblast and adipocyte differentiation from common progenitors. Animals given rosiglitazone exhibited reduction of osteoblast formation, increased adipocyte formation and significant bone loss [19••].

Thyroid disease
Hypo- and hyperthyroidism are commonly linked to rheumatic syndromes (Table 2). Patients often present with myalgia, muscle weakness, and arthralgia. In one study, patients with hypothyroidism had carpal tunnel syndrome significantly more often than other hand syndromes. Trigger finger was significantly more common in patients positive for thyroperoxidase antibody [20].

Links between autoimmune thyroid disease, thyroid autoantibodies and systemic connective tissue disorders such as Sjögren syndrome, systemic sclerosis, rheumatoid arthritis and Wegener granulomatosis, have been suggested [21•,22,23]. Thyroid glands in autoimmune thyroid disease are histopathologically similar to exocrine glands in primary Sjögren syndrome [21•]. Overlap between the diseases may be explained by shared susceptibility alleles [23].

Hyperthyroidism
Patients with hyperthyroidism can have significant osteopenia and increased fracture risk. Animal studies indicate that some of thyroid hormone’s effect may be mediated by interleukin-6 stimulation of osteoclastic activity [24•]. Some of the effects of hyperthyroidism on bone are reversible. In a meta-analysis of patients with untreated hyperthyroidism, BMD normalized following correction of hyperthyroidism [25]. Quantitative ultrasound evaluation of the calcaneus in women with Graves’ thyrotoxicosis revealed decreased stiffness, broadband ultrasound attenuation and speed of sound. The parameters increased after 2 years of treatment. BMD of the lumbar spine, total skeleton and femoral neck improved significantly after therapy, as well [26]. Despite the rise of BMD after treatment, lifetime fracture risk remains high in patients with hyperthyroidism. This may be explained by changes in bone quality unaffected by therapy [27•].

Table 2. Musculoskeletal manifestations of other endocrine disorders

<table>
<thead>
<tr>
<th>Endocrine disorder</th>
<th>Bone</th>
<th>Joint</th>
<th>Neuromuscular</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperparathyroidism</td>
<td>Bone pain</td>
<td>Arthralgia</td>
<td>Myalgia</td>
</tr>
<tr>
<td></td>
<td>Osteoporosis</td>
<td>(Pseudogout and chondrocalcinosis)</td>
<td>Proximal muscle weakness with normal creatine kinase</td>
</tr>
<tr>
<td></td>
<td>Fractures</td>
<td>Arthritis</td>
<td>Resting tremor</td>
</tr>
<tr>
<td></td>
<td>Osteitis fibrosa cystica (rare)</td>
<td>Chondrocalcinosis</td>
<td>Hyperreflexia</td>
</tr>
<tr>
<td></td>
<td>Increased BMD</td>
<td>Degenerative arthritis</td>
<td>Hypokalemic periodic paralysis</td>
</tr>
<tr>
<td>Hypercortisolism</td>
<td>Pain osteosarcoma</td>
<td>Joint laxity</td>
<td>Myalgia</td>
</tr>
<tr>
<td></td>
<td>Osteoporosis</td>
<td>Chondrocalcinosis</td>
<td>Proximal muscle weakness with normal creatine kinase</td>
</tr>
<tr>
<td></td>
<td>Fractures</td>
<td>Diffuse idiopathic skeletal hyperostosis</td>
<td>Carpal tunnel syndrome</td>
</tr>
<tr>
<td>Acromegaly</td>
<td>Acral &amp; soft tissue overgrowth</td>
<td>Arthralgia</td>
<td>Proximal muscle weakness with normal creatine kinase</td>
</tr>
<tr>
<td></td>
<td>Osteoporosis</td>
<td>Degenerative arthritis</td>
<td>Myalgia</td>
</tr>
<tr>
<td></td>
<td>Growth retardation in children</td>
<td>Joint laxity</td>
<td>Proximal muscle weakness with normal creatine kinase</td>
</tr>
<tr>
<td></td>
<td>Osteonecrosis (more common with exogenous steroids)</td>
<td>Chondrocalcinosis</td>
<td>Carpal tunnel syndrome</td>
</tr>
<tr>
<td></td>
<td>Osteoporosis</td>
<td>Myalgia</td>
<td>Proximal muscle weakness with normal creatine kinase</td>
</tr>
<tr>
<td></td>
<td>Fractures</td>
<td>Proximal muscle weakness with normal creatine kinase</td>
<td>Muscle atrophy</td>
</tr>
</tbody>
</table>
Associations between propylthiouracil and antineutrophil cytoplasmic antibody (ANCA)-positive vasculitis have been described. Two cases were recently reported in which patients on propylthiouracil developed both anti-myeloperoxidase and anti-proteinase 3 antibody positive vasculitis [28, 29]. One patient exhibited purpuric skin lesions, the other, diffuse alveolar hemorrhage. Though these patients recovered after discontinuing the drug, the mechanism by which PTU stimulated development of vasculitis remains unknown.

**Hypothyroidism**

Like hyperthyroidism, hypothyroidism is linked to increased fractures. Notably, patients with hypothyroidism tend to have higher BMD than normal and, like type 2 diabetics, increased fractures may be attributable to increased falls or changes in bone quality that aren’t evaluated by DXA [26]. Whether thyroid hormone therapy also has injurious effects on bone still remains controversial. A review of 63 studies could not settle the debate. Authors concluded the studies are of moderate quality and not readily comparable; therefore, there is insufficient evidence about levothyroxine’s effect on BMD [30]. One cohort of patients with subclinical hypothyroidism had significantly higher bone turnover (indicated by bone biomarker levels) than controls, but minimal loss of BMD. The authors suggest that rather than being an adverse effect of thyroid hormone, increased turnover could be a short-term adaptive response to low turnover in the pre-existent hypothyroid state [31]. Long-term studies may help resolve this issue.

**Hyperparathyroidism**

Hyperparathyroid patients may experience muscle weakness, arthralgia and bone pain (Table 2). An association between crystal arthropathies and hyperparathyroidism has been inconsistently supported [32]. Type 2 muscle fiber atrophy and osteitis fibrosa cystica, once characteristic of hyperparathyroidism, now rarely occur due to early diagnosis.

Even without overt skeletal manifestations, hyperparathyroidism still impacts bone. Epidemiological studies suggest hyperparathyroid patients have an increase in fracture rate at all sites [30]. Parathyroid hormone increases bone resorption and turnover, especially at cortical sites. Although cortical thinning occurs, there is also evidence for maintenance of bone architecture. An increase in the number and connectivity of trabecular plates is observed [33].

Most patients with asymptomatic or mild primary hyperparathyroidism have diminished but stable BMD and biochemical indices for years after diagnosis. This indicates there is a period prior to discovery of disease when hyperparathyroid-induced bone loss occurs [34]. In an attempt to examine this, investigators studied normocalcemic patients with elevated parathyroid hormone. Of the patients with osteoporosis, more had bone loss at the spine and hip than distal radius. These patients, therefore, did not exhibit preferential cortical bone loss as would be expected if induced by hyperparathyroidism [34]. Nevertheless, data support an increased fracture risk in asymptomatic hyperparathyroid patients [35]. The exact derangements of bone in these patients need to be elucidated.

Parathyroidectomy patients exhibit rapid improvement in BMD after surgery, particularly in the spine and hip [35]. The bone changes in patients with secondary hyperparathyroidism were examined one week after parathyroid removal; the number of osteoclasts and bone resorption decreased. Bone formation markers, elevated prior to surgery, increased further. Active osteoblasts and lamellar osteoid increased [36]. Patients with primary hyperparathyroidism showed an 11.5 to 13% improvement in BMD of the lumbar spine 2 years after parathyroidectomy. Premenopausal women had a significantly greater increase than postmenopausal women, suggesting an additive role for estrogen [37].

**Acromegaly**

Musculoskeletal manifestations of acromegaly include joint pain, stiffness, swelling, and hypermobility (Table 2). Limited movement occurs in advanced disease. Carpal tunnel is prevalent as well [38]. The impact on bone in acromegalic patients may depend on whether deficiencies of other hormones are present. One study demonstrated a significant decrease in fracture risk in patients with acromegaly. Researchers felt this decrease likely reflected the anabolic effects of growth hormone on bone [39].

**Hypercortisolism**

Adults and children have distinct manifestations of hypercortisolism. Adult Cushing syndrome (CS) typically includes muscle atrophy. Severe myopathy has been reported as an atypical presentation of Cushing disease macroadenoma [40]. Approximately 50% of adult CS patients are osteoporotic [41]. On the other hand, children with CS frequently demonstrate growth retardation, reduced peak bone mass and probable increase in long-term osteoporosis risk.

Overall, 30 to 50% of patients with CS experience pathologic fractures, predominantly involving the spine [41]. Measures of BMD in patients with CS reflect greater detriment to trabecular bone as well: the lumbar spine and distal radius are most affected with less effect occurring at the hip [42]. The mechanisms by which glucocorticoids influence bone metabolism may include: hypogonadism, inhibition of growth hormone, decreased intestinal calcium absorption and renal calcium reabsorption. Additionally, loss of cortical osteocytes and decrease in osteo-
blast number and function are involved. Finally, a decrease in the synthesis and increase in degradation of bone collagenous matrix occur [40].

Recently, it was reported that patients with adrenal CS exhibit greater bone loss at the lumbar spine than those with pituitary-derived Cushing disease. Reduced dehydroepiandrosterone sulfate levels were noted in adrenal CS patients, and the authors postulated that this could account for the difference in BMD between patients [42]. The effect of sex steroids was also reported in a study of pre- and postmenopausal women. Distal forearm BMD was reduced in postmenopausal women but not in premenopausal women with CS. Results of QUS of the heel, however, showed no difference between pre- and postmenopausal women [43]. The studies illustrate that the osteopenic effects of hypercortisolism could be opposed by anabolic effects of sex steroids.

Remission of hypercortisolism may lead to reversal of bone loss. Two years after the surgical removal of pituitary adenomas and normalization of cortisol, adolescents and adults demonstrated improvement in severely altered bone mass and turnover, but not to pre-disease states [44]. Full recovery of BMD may occur, but this can take up to 10 years, and increased fracture risk may persist during that time. Despite trabecular thinning induced by hypercortisolism, preservation of trabecular architecture may allow for reversal of bone loss [40].

**Conclusion**

Endocrine disorders have a variety of associated rheumatic manifestations. The exact mechanisms leading to musculoskeletal manifestations need to be elucidated. Understanding the limitations of our knowledge allows us to highlight areas that need further study and will ultimately improve the prevention and treatment of these disorders.

**References and recommended reading**

Papers of particular interest, published within the annual period of review, have been highlighted as:

- Of special interest
- Of outstanding interest


A controlled study revealed the presence of hand syndromes in a significant proportion of diabetics.


A valuable retrospective review combines data from 116 patients.


Clinically oriented and comprehensive review focusing on the pathogenesis of DISH.


Interesting study identifies subgroups of diabetics with Charcot joint disease by pattern, joint and BMD.


A critical analysis of recent data on bone involvement in diabetes considers the pathophysiological aspects, biochemical markers of bone turnover and histomorphometry, BMD and fracture risk.


Comprehensive review of the pathways through which diabetes affects bone and the controversies associated with current evidence.


Noteworthy study of one agent in the newest class of oral antidiabetic drugs illustrates the adverse effects of rosiglitazone on bone and has important implications for diabetes management.


Patients with primary Sjogren syndrome were followed for 1-16 years in this study. Findings highlight the relevance of thyroid autoantibodies in Sjogren patients.


The role of interleukin-6 and associated cytokines in hyperthyroidism is investigated.


27 Lakatos P: Thyroid hormones: beneficial or deleterious for bone? Calcif Tissue Int 2003, 73:205–209. Thorough reviews discusses the effects of thyroid disorders and controversy of thyroid treatment on bone in patients with overt and subclinical thyroid disease.


39 Vestergaard P, Mosekilde L: Fracture risk is decreased in acromegaly—a potential beneficial effect of growth hormone. Osteoporos Int 2004, 15:155–159. First study of this kind to include a large sample of acromegalic patients.


Musculoskeletal complications associated with lysosomal storage disorders: Gaucher disease and Hurler–Scheie syndrome (mucopolysaccharidosis type I)
Gregory M. Pastores \textsuperscript{a} and Patrick A. Meere \textsuperscript{b}

**Purpose of review**
Enzyme therapy for lysosomal storage disorders directed at correcting the underlying cause of disease represents the most significant recent advance in patient management. This review focuses on two disease groups: glycosphingolipidoses and mucopolysaccharidoses. Specifically, Gaucher disease and Hurler–Scheie syndrome have been selected as the prototypical disorder for each respective class.

**Recent findings**
Musculoskeletal complications are encountered in several of the lysosomal storage disorders and often represent a major source of extraneurologic morbidity, particularly in the subacute or chronic variants. Enzyme therapy has led to improvements in physical and functional well-being. However, bone involvement remains a recalcitrant feature, especially among patients with established disease before institution of therapy.

**Summary**
Early diagnosis and appropriate timely intervention are critical in achieving the best therapeutic results. A better understanding of the fundamental mechanisms of bone pathology may enable the identification of complementary approaches (e.g., the use of bisphosphonates for severe osteopenia) for optimized outcomes. Symptomatic care and rigorous physical and occupational therapy remain critical components of a comprehensive management approach.

**Keywords**
enzyme therapy, lysosomal storage disorders, Gaucher disease, mucopolysaccharidosis, Hurler–Scheie syndrome

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**Abbreviations**
- BMT: bone marrow transplantation
- ERT: enzyme replacement therapy
- GAG: glycosaminoglycan
- GD: Gaucher disease
- LSD: lysosomal storage disease
- MPS: mucopolysaccharidosis

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**Introduction**
The lysosome is a subcellular organelle that represents the main site of intracellular degradation for a variety of macromolecules (including the glycosphingolipids and mucopoly-/oligosaccharides). Specific membrane-delimited substrates, which are the by-product of cellular turnover, accumulate in several tissues/organs of affected individuals as a result of gene defects that lead to a deficiency of the responsible hydrolytic enzyme or its cofactor, or the synthesis of an aberrant transport protein normally involved in facilitation of the various relevant metabolic pathways. The corresponding clinical manifestations constitute diagnostic entities that often bear eponymous designations in recognition of the seminal contributions made by physicians, often before delineation of the underlying biochemical and molecular basis. Gaucher disease (GD) and the Hurler–Scheie syndrome represent two conditions that belong to the group of disorders referred to as the lysosomal storage diseases (LSD) (Table 1). As a group, the LSDs include rare to infrequent single-gene disorders with a combined prevalence ranging from 8 to 14 per 100,000 live births (see review [1]).

**Historical annotations, nomenclature, and developments related to therapy**

**Gaucher disease**
Gaucher (1854–1918) was a French dermatologist who in 1882 described a patient with splenomegaly (resulting from the presence of atypical histiocytes now recognized to be lipid-engorged macrophages). There are several clinical GD subtypes associated with either acute or chronic neurologic involvement or the absence of primary central nervous system disease (referred to as type I GD, which also represents the most common variant).
These distinctions are artificial because the various presentations have since been recognized to represent the spectrum of clinical disease associated with deficiency of the lysosomal enzyme glucocerebrosidase. The cause of GD was defined by Brady [2] in 1965. His team (which then included Barton) at the National Institutes of Health (NIH, Bethesda, MD) was instrumental in the development of enzyme replacement therapy for this disorder.

In 1991, a placental-derived product (alg-glucerase, Cerezyme; Genzyme Corporation, Cambridge, MA) was shown to be safe and effective in reversing the hematologic and visceral manifestations of GD (in a 12-patient study). Subsequently, in 1994, a recombinant formulation of the human enzyme (imiglucerase, Cerazyme; Genzyme Corporation) was introduced, shortly after clinical trials involving 30 patients in a collaborative effort between the NIH group and physicians at Mount Sinai Medical Center in New York led by Grabowski and one of the authors (G.M.P.). Studies have shown the two enzyme preparations are equivalent, but only imiglucerase is currently available commercially (see review [3]). Both protein therapies are administered as an intravenous infusion over approximately 1 to 2 hours, typically using doses ranging from 30 to 60 U/kg body weight and given at 2-week intervals. The significant clinical benefits derived from enzyme replacement therapy (ERT; given to more than 3000 patients worldwide) and its outstanding safety profile have led to the recognition of this approach as the standard of care for symptomatic GD patients [4]. The clinical effectiveness of enzyme therapy for GD is dependent on targeted delivery to cellular sites of tissue metabolite (substrate) storage.

In 2002, regulatory approval was granted in Europe for an oral agent (miglustat, Zavesca; Actelion Pharmaceutical Ltd, Basil, Switzerland) for symptomatic patients with GD in whom ERT is inappropriate (eg, because of an allergic reaction to the infused protein or the inability to establish intravenous access). In contrast to ERT, which involves the provision of functional enzyme to deficient cells as a means of achieving metabolic correction, the use of miglustat constitutes substrate (synthesis) reduction therapy. Essentially, substrate reduction therapy is a means of achieving metabolic homeostasis within diseased cells by restricting the amount of substrate that is synthesized (and that subsequently requires degradation) to a level that can be sufficiently hydrolyzed by a mutant enzyme that exhibits residual activity (see review [5]). The rationale for the use of substrate reduction therapy in lysosomal disorders was supported by preclinical studies performed in mouse models for several glycosphingolipidoses (such as Tay–Sachs and Sandhoff disease), principally conducted by Platt et al. at the Glycobiology Institute (Oxford University, UK). Clinical proof of concept was subsequently demonstrated in a multicenter clinical trial led by Cox at Addenbrooke’s Hospital (Cambridge University, UK) and Zimran at Sha’are Zedek Hospital (Jerusalem, Israel). In the

This strategy required the sequential deglycosylation of the outer carbohydrate (sugar) side chains of the mature recombinant protein to expose the mannose residues that represent the appropriate signal for the predominant cells (derived from monocyte/macrophage lineage) that are affected in GD. The insights for this approach were gleaned from experiments conducted by Barranger and Furbish, then affiliated with Brady.

### Table 1. Representative LSDs

<table>
<thead>
<tr>
<th>Disease, incidencea</th>
<th>Biochemical, molecular basis</th>
<th>Cellular sites of pathology, key clinical features</th>
<th>Directed treatments,b therapeutic responses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gaucher (GD) 1 in 57,000 LBa</td>
<td>β-glucosidase; encoded by gene on 1q21</td>
<td>-Cells of monocyte/macrophage lineage (reticuloendothelial tissues); -Anemia, thrombocytopenia, hepatosplenomegaly, osteopenia, osteonecrosis, pulmonary hypertension, in severe neurologic forms (type 2 and 3 GD): spasticity, myoclonic seizures</td>
<td>-ERT, HSCT/BMT (in severe type 3 GD); -Improved blood counts; reduction of hepatosplenomegaly; stabilization of bone disease</td>
</tr>
<tr>
<td>Hurler/Scheie (MPS-I) 1 in 88,000 LBa</td>
<td>α-L-iduronidase; encoded by gene on 4p16.3</td>
<td>-Meninges, perivascular spaces, neurons; connective tissue, endocardium, and heart valves; -Obstructive airway disease, valvular heart disease, progressive limitation in range of joint motion, short stature, dysostosis multiplex, hip dysplasia, corneal opacity, retinal degeneration, deafness, hepatomegaly; neurologic deficits secondary to spinal cord compression from focal soft tissue deposits, hydrocephalus, mental retardation</td>
<td>-ERT, HSCT/BMT (in severe MPS-IH [Hurler syndrome]); -Improvement in measures of obstructive airway disease; enhanced endurance (based on distance walked over 6-min period); increased range of joint motion; reduction in apneic/hypopneic episodes</td>
</tr>
</tbody>
</table>

*aEstimated, data from Meikle et al. [9].

bERT, enzyme replacement therapy; HSCT/BMT, hematopoietic stem cell transplantation/bone marrow transplantation; LB, live births. ERT is not anticipated to alter the ultimate neurologic prognosis in neuropsychiatric forms of the disease, whereas HSCT/BMT may enable stabilization or some improvement. Please refer to the text for details.
United States, approval for the use of miglustat in patients with GD was granted by the Food and Drug Administration in 2003. At this time, the reported experience with the use of miglustat in GD patients is limited (approximately 100 patients), and when compared with ERT, the rate and magnitude of the extraskeletal (non-neurologic) response appears less. The nonspecific inhibition of several other enzymes that occur with this approach also necessitates the careful monitoring of patients on miglustat for potential adverse events (eg, neuropathy, gastrointestinal problems such as diarrhea, and weight loss).

**Hurler–Scheie syndrome**

Hurler (1889–1965) was a German pediatrician who, in 1919, described two infants with corneal clouding, dwarfing skeletal dysplasia, spinal malalignment, and mental retardation. The condition was subsequently recognized to be associated with increased urinary excretion of the mucopolysaccharides (or glycosaminoglycans [GAGs]) dermatan and heparan sulfate. As the first entity described for what was subsequently recognized as a group of disorders with significant overlap in clinical features, the condition has also been designated as mucopolysaccharidosis (MPS) type I disease.

Sheie (1909–1990) was an American ophthalmologist who, in 1962, described a patient with progressive corneal clouding, coarsening of the facial features, and skeletal dysplasia. The condition was initially referred to as MPS type V, until further studies revealed that both MPS types I and V are the result of a deficiency of the same lysosomal enzyme α-L-iduronidase. Today, Scheie syndrome is used when referring to an attenuated form of MPS type I, and Hurler–Scheie syndrome is used to refer to the intermediate form of the disorder. Assignment of MPS I subtype is made clinically, based on age at onset and rate of disease progression (see review [6]).

The development of enzyme therapy for MPS-I, using the recombinant enzyme laronidase (Aldurazyme; Biomarin–Genzyme, LLC), was spearheaded by Kakkis and Neufeld at the Harbor–University of California at Los Angeles Medical Center in California. The clinical trials that immediately preceded regulatory approval were an international multicenter endeavor led by Muenzer (University of North Carolina, Chapel Hill, NC) and Wraith (Manchester, UK), and involved one of the authors (G.M.P.) at New York University Medical Center in New York. In contrast to the experience with the development of treatment for GD, the rationale for enzyme therapy in MPS was supported by preclinical studies in the mouse and canine models, and was based on cellular delivery of the intravenously administered protein through mannose-6-phosphate (the traditional route used by the endogenously synthesized enzyme; see review [7]). Additionally, the clinical trials involved a larger number of patients (n = 45) with MPS-I (primarily patients with Hurler–Scheie syndrome), half of whom were on placebo (or no active medication) for the initial 6-month period of observation [8].

The brief account of the development of treatment for the two LSDs described can be viewed as representative of the fruitful outcome of collaborative efforts between industry and academia, and is a by-product of the Orphan Drug Act (1983) in the United States. The Orphan Drug Act provides incentives, including fast-track approval and marketing exclusivity, to stimulate industrial development of medical drugs and devices for rare disorders. (Rare disorders are defined as affecting individuals numbering less than 200,000 in the United State or no more than 5 in 10,000 people in Europe.)

**General comments on disease incidence, diagnostic confirmation, and molecular genetic aspects**

**Gaucher disease**

This disorder is panethnic, with an estimated incidence of 1 in 57,000 [9]. However, type 1 GD (the nonneurologic form) is prevalent among individuals of Ashkenazi Jewish ancestry (with an estimated carrier frequency of 1 in 20). The high occurrence of GD among the Ashkenazim has been attributed to a founder effect (ie, a common ancestry by descent following a reduction of the gene pool).

The diagnosis of GD is confirmed based on demonstration of decreased glucocerebrosidase (acid β-glucosidase) activity in peripheral blood leukocytes or cultured skin fibroblasts. This diagnostic approach obviates the need for a bone marrow biopsy. There are patients with neurologic signs (eg, oculomotor apraxia), mild splenomegaly, and evidence of glucocerebrosidase storage but normal glucocerebrosidase (enzyme) activity in vitro. These rare cases have been attributed to saposin C deficiency. Saposin C is a nonenzymatic protein encoded by a gene on chromosome 10 (q21) that serves as a cofactor for glucocerebrosidase and is required for the in vivo hydrolysis of glucocerebrosidase.

The glucocerebrosidase gene has been mapped to chromosome 1 (q21), and more than 200 disease mutations have been described. Mutations analysis has revealed the relatively common frequency of several gene defects, including N370S, L444P, 84insG, and IVS2+1. In the Ashkenazi Jewish people, this accounts for about 90% of disease alleles, but only for 40 to 60% of mutations in individuals of non-Jewish ancestry. The high frequency of the N370S mutation (approximately 70%) in the Ashkenazim also explains the occurrence primarily of type 1 GD, because this particular mutation is associated with residual activity, and its presence among affected individuals precludes development of primary central ner-
Musculoskeletal complications and lysosomal storage disorders Pastores and Meere 73

vorous system involvement (typical of types 2 or 3 GD). The L444P mutation is a deleterious allele, often associated with visceral, skeletal, and nervous system involvement. Thus, the variability in clinical GD expression (ie, phenotype) is partly explained by the underlying mutations (ie, genotype).

Hurler–Scheie syndrome
This condition is panethnic, with an estimated incidence of 1 in 88,000 [9]. It is likely that this figure is an underestimate because the disorder may be missed among patients with the attenuated Scheie form of MPS-I(S), which has milder symptoms such as corneal clouding and hearing loss, and with normal intelligence and life span. In the Hurler (MPS-IH) and Hurler–Scheie (MPS-IHS) variants, additional manifestations include coarse facies (with depressed nasal bridge and frontal bossing), upper airway obstruction (complicated by sleep apnea), cardiac valve disease, and hepatosplenomegaly. MPS-IH is also associated with mental retardation, and a proportion of patients with MPS-IHS also experience mental subnormality.

The diagnosis of MPS-I is confirmed based on demonstration of decreased α-L-iduronidase activity in peripheral blood leukocytes or cultured skin fibroblasts. Urine analysis reveals excessive dermatan and heparin sulfate.

The α-L-iduronidase gene has been mapped to chromosome 4 (p16.3), with more than 70 mutations described [10]. Molecular characterization of MPS-I patients has indicated that to a certain extent the wide variability in clinical presentation is a reflection of the high degree of genetic heterogeneity. Two mutations, W402X and Q70X, that are prevalent among individuals of European extraction (accounting for up to 70% of MPS I disease alleles) tend to be associated with severe MPS-IH when found in homozygosity or in combination with another deleterious allele. On the other hand, two other less common mutations (R89Q and R89W) tend to be found in patients with the attenuated phenotypes: MPS-IHS and MPS-IS.

Gaucher disease and Hurler–Scheie syndrome are autosomal recessive disorders, and siblings of an affected individual have a 25% risk of being similarly affected (essentially the reproductive risk counseling given to carrier couples). These disorders can be diagnosed prenatally, by chronic villus sampling or amniocentesis, through application of relevant biochemical and/or molecular testing.

Musculoskeletal complications
Gaucher disease
Clinical or radiographic evidence of bone disease occurs in 70 to 100% of patients with types 1 and 3 GD. The bone findings in these patients, which tend to be age dependent, range from asymptomatic osteopenia to focal lytic or sclerotic lesions and osteonecrosis [11]. It is important to recognize that GD bone involvement may not correlate with the severity of hematologic or visceral problems, and significant complications can be encountered even during childhood in some patients. However, the insidious and chronic nature of the problem may explain why significant bone disease is usually not appreciated in severely involved patients with type 2 GD, which is associated with significant neurologic involvement and death by 2 to 3 years of age.

Bone involvement may lead to acute or chronic bone pain, pathologic fractures, and subchondral bone collapse resulting from osteonecrosis and secondary degenerative arthritis. These complications likely have a multifactorial basis, including microcirculatory disease from a combination of intrinsic and extrinsic causes consequent to the progressive marrow infiltration by lipid-engorged macrophages (Gaucher cells; Fig. 1). Upregulation of cysteine proteinases including osteoclast cathepsin K has been described [12]. Significant decrease of both osteocalcin and type I collagen C-terminal telopeptide levels in type 1 GD has also been reported (n = 16 patients) [13], whereas another study (n = 10) noted no significant difference in osteocalcin and alkaline phosphatase levels [14]. The failure to demonstrate consistent abnormalities in the levels found in serum and urine of markers of bone turnover suggests the dominance of local rather than systemic events. A recent study (n = 60) reported significantly elevated concentrations of fibrinogen and accelerated erythrocyte sedimentation rates, accompanied by a significantly enhanced degree of erythrocyte and leukocyte adhesiveness/aggregation [15•]. Furthermore, assay of D-dimers (a marker of cross-linked fibrin) in 118 unselected adult type 1 GD patients revealed significant correlations between D-dimers and osteonecrosis (n = 29) [16]. These observations suggest that thrombosis in situ may play a contributory role, and explain the often asymmetric pattern of involvement and the regional occurrence of bone infarcts. During a bone crisis there can be periosteal elevation (“pseudo osteomyelitis”), presumably from microscopic fluid egress through the Hassian and Volkmann canals persisting in the devitalized cortex.

Severe osteopenia among GD patients may reflect “chronic macrophage activation,” and the induction and promotion of increased bone turnover. Patients with type 1 GD have demonstrated elevated plasma interleukin-6 levels [17], which have also been implicated in localized osteolysis in multiple myeloma. Severe osteopenia involving the spine has been reported to result in secondary neurologic complications among patients with types 1 and 3 GD, as a result of spinal cord or nerve root compression [18].
Conventional radiographs may reveal undertubulation (ie, Erlenmeyer flask configuration) of the distal femur and endosteal scalloping as a sign of bone marrow infiltration (Fig. 2). MRI reveals the extent of marrow involvement and the presence of fibrosis and/or infarction. In general, marrow infiltration extends from the axial to the appendicular skeleton, and greater involvement is often seen in the lower extremities and proximal sites of an affected bone [11]. The epiphyses are usually spared, except in advanced cases. In our series, osteonecrosis (primarily of the femoral head) has been observed in 41% of patients (mainly adults) [11].

Different approaches have been proposed for the assessment of bone marrow burden or stage of bone disease, including the application of MRI-based quantitative chemical shift imaging [19••]. These methods are based on measuring the extent of displacement of the hematopoietic elements and the adipocytes (predominantly composed of triglycerides) by Gaucher cells, and the associated cellular response (resulting in the transformation of yellow to red marrow signal on T2-weighted MRI). In one study, a low “fat fraction” was found to correlate with liver volume and the incidence of bony complication among GD patients [20,21]. Because pediatric patients (younger than 15 years) have a predominantly cellular marrow in the healthy state, the use of MRI for quantification of bone disease in these individuals does not appear to be as useful as when testing adults [22]. Because quantitative chemical shift imaging can be cumbersome and not generally available, one practical strategy that has been proposed involves assessment of the vertebra-to-disc ratio [21]. The vertebra-to-disc ratio is determined based on the MRI bone marrow signal of the region of interest (ie, the Gaucher cell-infiltrated vertebral bone marrow, which gives a reduced T1-weighted signal) divided by the signal of the healthy adjacent intervertebral disc (used as an internal reference signal).

Bone marrow scintigraphy (Tc-99m sulfur colloid) may demonstrate peripheral expansion and abnormalities of central marrow activity, with patchy areas of infarction showing a lack of signal uptake (Fig. 3). Other techniques have involved bone scans with Tc-99m methylene diphosphonate and the lipophilic cationic complex Tc-99m sestamibi or Tc-99m hexametazime [23•,24]. Although of great interest, nuclear scans have limited practical application because of scant information regard-
ing histopathologic correlation and the lack of the superior spatial resolution of the MR image. Bone densitometry enables quantitative assessment of the degree of osteopenia.

**Hurler-Scheie syndrome**

Glycosaminoglycans are complex molecules usually found on the surface of cells and in the extracellular matrix, and are believed to have major roles in maintaining the structural integrity of various organs. Cellular turnover necessitates the sequential degradation of GAGs. The specific substrates (e.g., dermatan, heparan and keratan sulfate) found in the tissues and excreted in excessive amounts in the urine of patients with MPS are determined by the particular enzyme deficiency. In certain subtypes there is secondary storage of gangliosides in the central nervous system possibly as a result of the inhibition (by the accumulating GAGs) of the activity of the primary hydrolases responsible for their degradation [25]. This central nervous system accumulation of gangliosides may explain, in part, the development of mental retardation associated with severe forms of MPS-I (and also with MPS types II and IIIA, B, and C).

There is significant overlap in the clinical features noted among the various MPS subtypes, most of which are characterized by abnormal cartilage and bone development, leading to short stature, dysostosis multiplex, and degenerative joint disease. These abnormalities arise from a lack of skeletal remodeling, disordered endochondral and intramembranous ossification, and the infiltration by GAGs of the ligaments, tendons, joint capsules, and other soft tissue structures [26]. Recently, it has been shown that dermatan sulfate-bearing moieties bind to and cause functional inactivation of the elastin-binding protein [27], a molecular chaperone for tropoelastin, which normally facilitates its secretion and assembly into elastic fibers. These observations may contribute to the observed skin, bone, and joint alterations seen in these patients. Added insights into the mechanisms of bone disease in MPS have come from investigations involving the mouse model of disease [28]. Although the skeletal and joint complications associated with MPS represent major sources of morbidity, death in these patients is usually related to cardiac involvement and upper airway obstruction. In MPS-IH, death often ensues between the ages of 5 years and 15 years. Life expectancy in MPS-IHS and MPS-IS can extend into the third and fifth decades.

Dysostosis multiplex (Fig. 4) is the term used to describe the constellation of radiographic skeletal findings encountered in the MPS. These bone abnormalities include a large skull with a thickened calvarium and J-shaped sella turcica, paddle (or oar)-like ribs, and anterior inferior beaking (with a hooklike appearance) of the lower thoracic and upper lumbar vertebral bodies that are hypoplastic (i.e., platyspondyl) [29,30]. The gibbus deformity of the upper lumbar spine, typically seen in severe MPS-IH patients, is hypothesized to develop from a combination of factors such as poor truncal muscle tone, weight-bearing forces, growth disturbance, and anterior disc herniation [31]. The vertebral anomalies result

![Figure 3. Scintiscan images of the pelvis and femurs obtained from a 52-year-old woman who presented with severe bone crises in the left pelvic area](image)

(A) There is absence of sulfur colloid signal uptake in the left hemipelvis, indicative of marrow infarction (arrow). (B) On the bone scan taken a month later, there is increased signal over the left anterior iliac wing (arrow) and pubic ramus, suggestive of a persistent active bone disease process.

![Figure 4. Dysostosis multiplex](image)

(A) Lateral view of the lower thoracic and lumbar spine in a pediatric patient with MPS-IHS, which reveals anteroinferior beaking of the vertebral bodies. (B) View of the left hand reveals broadening of the metacarpals. The phalanges are characteristically short and thick (or "bullet shaped").
in disproportionate short-trunk dwarfism or short stature. These findings can be demonstrated on selected examinations, such as lateral spine films and radiographs of the left hand and wrist (to include an assessment of bone age) and anteroposterior views of the entire femur bilaterally.

Craniofacial abnormalities include mandibular condylar hypoplasia, retarded tooth eruption, and cystic jaw radiolucencies (particularly about the molars) [32]. The typical corneal opacities have been closely examined in at least two patients with MPS-IS. Transmission electron microscopy and synchrotron X-ray diffraction studies revealed abnormally large stromal collagen and stromal disruption [33].

There is also flaring of the iliac wings, constrictive iliac bodies, diaphyseal expansion of the long bones, central pointing of proximal metacarpals, and bulletlike proximal phalanges [29,30]. The femoral head is usually small and there is coxa valga.

These skeletal changes may have neurologic and orthopedic implications. In the hands, MPS-I is associated with prominent joint involvement and ulnar nerve entrapment leading to the “claw hand” deformity, which can be aggravated by the potential loss of thumb function resulting from carpal tunnel syndrome (CTS) [34]. Most patients with MPS and carpal tunnel syndrome lack the typical symptoms of pain, tingling, or numbness until severe compression has developed. These observations necessitate routine electromyographic/nerve conduction velocity testing to identify patients who may require surgical intervention.

In addition, MPS-IH syndrome can be complicated by hydrocephalus. Pachymeningitis cervicalis, that is, compression of the cervical spinal cord resulting from the accumulation of GAGs in the dura, and spondylolisthesis of the lower spine leading to spinal cord compression, can occur in MPS-I H/S as well as in MPS-IS patients. The best long-term outcomes (with minimal neurologic sequelae) are achieved with early detection and appropriate timely intervention. Thus, ongoing patient evaluations should include a thorough neurologic examination.

Several approaches have been proposed as a means of measuring the limitations in physical performance resulting from bone and joint involvement in patients with MPS [35]. These methods will be increasingly important in staging the disease and assessing the potential benefits resulting from treatment.

Management
Before ERT, patients received palliative care or were subjected to bone marrow transplantation (BMT) in the most severe of cases (i.e., in patients with type 3 GD and MPS-IH). In GD, symptomatic approaches for extraskeletal problems included splenectomy and blood transfusions for severe anemia or bleeding complications. In patients with MPS-I, tonsillectomy, adenoidectomy, and tracheostomy are usually performed to provide symptomatic relief of upper airway obstruction, and continuous positive airway pressure is given to patients with sleep apnea [36]. Appropriate precautions are also undertaken in patients with MPS-I who required anesthesia for diagnostic or surgical procedures.

BMT is effective in alleviating most of the manifestations of GD, including arresting further neuropsychological deterioration in type 3 disease and greatly reducing skeletal problems in severe early-onset type I disease (see review [37]). However, BMT regimen-related toxicities (e.g., threat of serious and often fatal infections from pancytopenia with myeloablation) and other potentially limiting factors (e.g., availability of a histocompatible donor) preclude its general recommendation for this indication. Currently, even among patients with type 3 GD and most symptomatic patients with type 1 GD, ERT has become the preferred initial approach to treatment. In MPS-IH, BMT (ideally before 18 months of age) leads to several positive changes, including dramatic reduction of obstructive airway symptoms, hepatosplenomegaly, and corneal clouding (see review [37]). Furthermore, hydrocephalus is either prevented or stabilized, and hearing improves in many transplanted children. Heart failure and tachyarrhythmias are also eliminated by 1 year after transplantation. However, some MPS-I disease features, including the skeletal problems (discussed later), show much poorer response, likely because of poor penetration of donor cells/enzyme into the relevant tissue. Intellectual and developmental deterioration may also occur, especially during the first year after transplant (possibly aggravated when donor enzyme levels are low, as seen with carrier or heterozygote tissue donors). Cardiac valvular deformities also persist and can progress, and there is also a relatively high incidence of primary and secondary graft failure. These observations have generated interest in the potential use of ERT even among patients who may be ultimately candidates for BMT.

Recent therapeutic advances
Gaucher disease
Enzyme therapy for bone-related manifestations of GD has resulted in the resolution of bone pain in 50% of symptomatic patients within the first 2 years of therapy, and 80 to 90% of patients with prior bone crises reported no recurrent episode [4]. Treatment also appears to have reduced the incidence of new bone lesions, and “catch-up” growth in pediatric patients with delayed bone age has been demonstrated. These clinical findings are associated with improvements in vertebral fat fraction (as shown by MRI–quantitative chemical shift imaging and other methods) [20,38], and in isolated cases there has
been resolution of lytic bone lesions. However, improvements in bone density among GD patients with significant osteopenia are slow to occur with ERT alone, necessitating the added use of bisphosphonates in those with a high risk for fracture [39••]. Furthermore, in patients with advanced bone disease such as osteonecrosis of the femoral head, orthopedic intervention is often necessary to obtain relief from pain, restore functional joint movement, and improve gait [40]. Improvements in surgical technique and the design of prosthetic devices, together with the availability of enzyme therapy, appear to have improved the postoperative results and have reduced the incidence of previous complications from aseptic loosening. Pain management and physical therapy may also result in significant gain of function and relief from pain or discomfort.

Hurler–Scheie syndrome

The skeletal problems associated with MPS-IH is not significantly modified by BMT, and transplanted children often require major orthopedic surgery for genu valgum, acetabular hip dysplasia, kyphoscoliosis, carpal tunnel syndrome, and trigger digits [41••,42]. Ongoing intensive physical and occupational therapy are essential to optimizing physical and functional well-being in all patients with MPS-I (including all variants) regardless of whether they have been subjected to BMT. Improved surgical containment procedures such as the Ganz acetabular osteotomy now consistently provide superior femoral head coverage, while providing excellent range of motion, patient satisfaction, and potential deferment of secondary arthritis.

Enzyme therapy in patients with MPS-I, primarily for those with the MPS-IHS phenotype, has been shown to reduce GAGs storage significantly, leading to improvements in respiratory function (based on forced vital capacity testing and the apnea/hypopnea index) and physical ability and endurance (as assessed by the 6-minute walk test and range of shoulder flexion), the two primary clinical trials outcome [8]. Of note, clinical and pathophysiologic improvements occurred despite long-standing disease in most patients. However, the long-term impact of ERT on musculoskeletal disease resulting from MPS-I, and the extent to which treatment may enable achievement and maintenance of full independence in the performance of routine activities of daily living remains to be established.

Enzyme therapy in patients with either GD or MPS-I is relatively well tolerated, despite the development of antibodies to the enzyme in a proportion of treated individuals. More importantly, the presence of antibodies has not been shown to reduce or eliminate therapeutic gains, perhaps because most patients show a decline in the titers with ongoing therapy. However, the experience with the use of ERT in MPS-I is more limited, and additional follow-up data are necessary, not only with clarifying the issue of antibody formation but also with development of guidelines on the optimal enzyme dose–frequency schedule. The need for and appropriate timing of ERT introduction in patients with severe MPS-IH, in relation to BMT, needs to be addressed as well.

Conclusion

Gaucher disease and MPS-I are autosomal recessive LSDs that are associated with musculoskeletal complications that can be a significant cause of morbidity, and compromise the physical and functional well-being of affected individuals. Although each of these diseases is the result of distinct enzyme deficiencies, and the resultant storage of its incompletely metabolized substrate represents the primary cellular insult, the consequent musculoskeletal problems likely have a multifactorial basis. Symptomatic care and rigorous physical and occupational therapy are critical components of a comprehensive approach to patient management. The introduction of directed therapies in the form of enzyme replacement has modified the natural history of these otherwise progressive disorders. However, patients with advanced musculoskeletal disease and irreversible fibrotic or necrotic changes may have a suboptimal response to an approach directed primarily at promoting the clearance of tissue deposits. Key factors in achieving the most favorable outcomes include early diagnosis and timely intervention. Further studies are necessary to address several issues, such as the selection of appropriate imaging modalities and clinical methods for assignment of disease stage, the monitoring of clinical progression and/or assessment of treatment response, if any. The relatively rare incidence of these conditions, coupled with some of the recognized challenges in diagnosis, has limited the ability to investigate carefully the most cost-effective ERT regimens. Further investigations may lead to identification of potential adjunctive treatments or more efficient means of drug delivery to achieve full control, if not reversal of the disease process.

Acknowledgment

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41 Weisstein JS, Delgado E, Steinbach LS, et al.: Musculoskeletal manifesta-
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Advances that are changing the diagnosis and treatment of malignant bone tumors
Jorge Casas-Ganem and John H. Healey

Purpose of review
Several neoplastic conditions may affect bone. These include primary bone tumors as well as metastatic disease from distant primary sites. Often, these entities produce symptoms that may be difficult to distinguish from those of various rheumatologic entities. The purpose of this review is to discuss recent developments in orthopedic oncology, with special attention given to advances that are changing the diagnosis and treatment of bone sarcomas and carcinomas metastatic to bone.

Recent findings
Much effort in the field of musculoskeletal oncology has been dedicated to the elucidation of the molecular mechanisms underlying bone sarcomas, especially in the case of osteogenic sarcoma and Ewing family tumor. Telomere maintenance mechanisms are emerging as potential targets for anticancer therapy. The most exciting advances have been in the development of novel treatments for cancers affecting bone. The anticancer effects of bisphosphonates, cyclooxygenase-2 inhibitors, and statins may expand their indications to the treatment of primary bone tumors. Finally, new expandable implants have been developed for the treatment of bone tumors in growing children. These devices may help solve some of the problems encountered with reconstruction of the growing skeleton.

Summary
Recent discoveries in the molecular mechanisms of bone sarcomas may help to elucidate the pathogenesis of these rare diseases. This, combined with the recent findings of the anticancer effects of bisphosphonates, cyclooxygenase-2 inhibitors, and statins, may lead to the development of novel treatments for sarcomas of bone and of carcinomas metastatic to bone.

Keywords
sarcoma, bone, bisphosphonates, angiogenesis, apoptosis
mic hybridization to screen OS patient samples. They found that gains were more common than losses, with the most frequently amplified clones mapping to six chromosomal regions. Further investigations into the molecular mechanisms of OS have led to examination of the wingless-type (Wnt) family of proteins and its co-receptor, low-density lipoprotein receptor–related protein 5 (LRP5). They play an important role in human skeletal development by modulation of cell proliferation during embryogenesis [6]. In a series of experiments using patient tumor samples, Hoang et al. [7•] showed that LRP5 is commonly expressed in OS. In vitro, blockade of the LRP5 receptor reduced OS cell invasion and motility. It also induced changes in β-catenin localization consistent with an increase in cell-to-cell adhesion [8••]. These findings suggest a role for Wnt signaling in the pathobiology of OS.

Ewing family tumor is a malignant, small, blue, round cell tumor belonging to the family of primitive neuroectodermal tumors [3]. It is the second most common malignant bone tumor of late childhood and early adulthood. Although the cause of Ewing family tumor is unknown, the reciprocal chromosomal translocation t(11;22)(q24;q12) is present in at least 85% of cases [9,10•]. This translocation results in the chimeric transcript EWS–FLI1. Detection of this chimeric transcript in bone marrow or peripheral blood is prognostic and can be used to detect occult residual disease [9,11•]. The outcome is strongly correlated with which translocation breakpoint (type I versus non–type I) occurs [9].

There has been a recent interest in telomere maintenance mechanisms in sarcomas. Telomeres are the repetitive sequences at the ends of chromosomes that shorten with each cell division. Critical telomere shortening leads to cell senescence. Cancer cells avoid senescence by maintaining telomere length by one of two mechanisms: telomerase activity and alternative lengthening of telomeres. Screening of patient tumor samples has shown that alternative lengthening of telomeres predominates in OS, whereas telomerase activation is more common in Ewing family tumor [12••]. Furthermore, the absence of any detectable telomere maintenance mechanism may identify a subset of OS patients with a more favorable prognosis [13•]. Refinement of the molecular mechanisms underlying bone sarcomas may result in earlier identification of patients unlikely to respond to traditional cytotoxic therapies as well as in the development of novel therapies for these patients.

**Treatment of malignant bone tumors**

Osteogenic sarcoma is a systemic disease, with most patients having micrometastases at diagnosis. The current treatment paradigm for OS consists of induction chemotherapy and surgical resection and limb reconstruction, or amputation (if limb salvage is not possible). Chemotherapy regimens vary but usually consist of doxorubicin, cisplatin, and high-dose methotrexate, with or without other chemotherapeutic agents. The 5-year event-free survival is approximately 70%. For patients with pulmonary metastasis, nodules can be removed successfully [14•]. Attempts to improve survival have shown that there is no statistically significant difference in event-free survival with preoperative chemotherapy in comparison with postoperative chemotherapy [15•]. Furthermore, a trial adjusting the dosing of doxorubicin and cisplatin did not improve outcome in comparison with previous trials of the same agents [16•]. However, pegylated liposomal doxorubicin, a unique form of doxorubicin in which liposomes are coated with ethylene glycol, has shown activity in various sarcoma patients, including OS, Ewing, and soft tissue sarcoma, with modest toxicity, and may be included in future clinical trials [17]. A trial of the novel alkaloid ecteinascidin 743 was performed in OS patients who had been previously heavily treated with standard chemotherapeutic agents. Ecteinascidin 743 was well tolerated but had limited antitumor effects when used as a single agent [18•].

Like OS, Ewing family tumor is a systemic disease, with 90% of patients having micrometastatic disease at presentation. The 5-year event-free survival for Ewing family tumor is 65 to 70% for patients with localized disease at presentation, but only 25 to 30% for patients with metastatic disease [19•]. Clinical trials have shown two groups of Ewing family tumor patients [20••,21••]. In one group, event-free survival and overall survival can be achieved with traditional therapies; these are usually the patients with localized disease. The other group consists of patients with metastatic disease at presentation. These patients typically do not benefit from traditional therapies and require novel treatment strategies. Misér et al. [22] found that adding ifosfamide and etoposide to standard therapy does not improve outcomes of patients with metastases at presentation. However, in vitro studies have found that the combination of gemcitabine and docetaxel is active against a variety of sarcomas, suggesting a role for these agents in the treatment of sarcoma [23•]. Because the EWS–FLI1 fusion transcript is so common and the different translocation breakpoints impart different transforming ability in vitro and prognosis in vivo, research in this area may reveal potential targets for molecularly based therapy in Ewing family tumor [24•].

**Secondary cancers**

Chemotherapy for OS and Ewing family tumor is associated with an increased risk of long-term morbidity. Secondary acute leukemia and myelodysplastic syndrome may follow treatment for OS. Alkylating agents, etoposide, and topoisomerase II inhibitors such as doxorubicin have been implicated [25•]. Le Deley et al. [26•] reported on the increased risk of leukemia in OS patients...
treated with epipodophyllotoxins and anthracyclines. The risk that Ewing family tumor patients will experience a secondary malignancy is low: approximately 7% [27•]. However, Ewing family tumor patients who do experience secondary hematopoietic malignancies or secondary sarcomas (radiotherapy) have a poor prognosis [27•]. In the long term, the incidence of complications in Ewing patients is approximately 60%. These complications include local recurrence, metastasis, pathologic fracture, and chemotherapy-associated and radiotherapy-associated complications [28•]. Survivors should be monitored for life for these late complications.

**Metastatic disease**

Metastasis to bone is frequent in carcinoma and hematologic malignancies, although the exact incidence is unknown [29••]. Although almost any carcinoma may metastasize to bone, the most common include carcinomas of the breast, lung, prostate, kidney, and thyroid. Bone metastases occur most commonly in the axial skeleton and proximal limb girdles but are uncommon distal to the knee or elbow joints. The mechanism of metastasis to bone is incompletely understood. Recent work by Kang *et al.* [30••] has shown that certain genes are overexpressed in breast cancer cell lines with elevated metastatic activity. A profile of genes encoding cell surface proteins, an osteotropic promoter (osteopontin), an osteoclastic promoter (osteoprotegerin), and matrix-depending metalloproteinases seems to characterize the metastatic phenotype. *In vitro* experiments have also implicated bone sialoprotein in bone metastasis [31].

**Bisphosphonates**

The use of bisphosphonates has become routine in the treatment of patients with myeloma and carcinoma metastatic to bone, because they prevent fractures by inhibiting osteoclastic resorption of bone and because they are effective in the treatment of the hypercalcemia associated with bony metastases [32•]. Currently, there are various biochemical markers that may be used to assess patient response to bisphosphonates, although it is unclear which marker is the best [33•]. Markers include tartrate-resistant acid phosphatase, which is secreted by osteoclasts, N-terminal and C-terminal crosslinking telopeptide of type I collagen, which measure type I collagen degradation by cathepsin K, and pyridinoline cross-linked carboxyl-terminal telopeptides of type I collagen, which measure type I collagen degradation by matrix metalloproteinases [34•]. Bisphosphonates have also been found to have anticancer effects, with minimal toxicity. Nitrogen-containing bisphosphonates, such as pamidronate and zoledronate, exert their effects by inhibiting protein prenylation, which is required by all cells for normal function and survival. Upon administration, bisphosphonates are rapidly accumulated in bone, resulting in a short plasma half-life and low exposure of visceral tissues. However, upon release of osteolytic mediators by metastatic carcinoma, bisphosphonates bound to bone are released and may exert effects on adjacent tumor cells *via* inhibition of osteoclasts or by alterations in the bone microenvironment [35••]. It is believed that bisphosphonates may inhibit cancer by inducing apoptosis through antiangiogenic effects as well as by other mechanisms [36•]. Pamidronate has been found to significantly reduce circulating levels of vascular endothelial growth factor in patients with bone metastases [37]. Pamidronate is also effective in reducing tumor burden in breast cancer metastatic to bone in mice and in inhibiting Ewing family tumor cell line growth *in vitro* [38•,39]. Bisphosphonates are currently not recommended as a preventive treatment for patients with visceral metastases but no bony involvement [40•]. This may change, however, because zoledronate has recently been shown to inhibit visceral metastases in a mouse model of breast cancer [41••]. Furthermore, zoledronate sensitizes endothelial cells to tumor necrosis factor—induced, caspase-independent apoptosis *in vitro* [42•]. Because zoledronate is the only bisphosphate to demonstrate efficacy in various tumor types, it has been approved by the United States Food and Drug Administration for the treatment of myeloma and documented bone metastases from solid tumors when used in conjunction with standard cancer therapy [43•]. Healey *et al.* [44•] have evaluated the elution of pamidronate from polymethylmethacrylate (bone cement). This *in vitro* study showed that pamidronate elutes rapidly from cement, potentially delivering high doses locally to prevent tumor progression and implant failure after surgically stabilizing metastatic bone disease.

**Cyclooxygenase-2 inhibitors**

Cyclooxygenase-1 and -2 (COX-1 and COX-2) are important enzymes in the synthesis of prostaglandins from arachidonic acid (Fig. 1). Unlike COX-1, COX-2 is expressed in various neoplasms, endothelial cells, immune cells, and stromal fibroblasts, and there is evidence suggesting that COX-2 plays a role in the development of malignancy [45•,46••,47•]. COX-2 mediates angiogenesis through the action of three products of arachidonic acid metabolism: thromboxane A2, prostaglandins E2, and prostaglandins I2. The downstream angiogenic effects of these products include VEGF production, promotion of vascular sprouting, migration, and tube formation, enhanced endothelial cell survival, induction of matrix metalloproteinases, among others [45•]. Dickens *et al.* [49•] found that approximately 82% of OS, Ewing family tumor, and rhabdomyosarcoma patient samples expressed COX-2. COX-2 has also been found in chondrosarcoma patient samples [49•]. Given the implication of COX-2 in various malignancies, it is evident why COX-2 inhibitors are being used as anticancer agents, although at doses several times higher than those used in the treatment of degenerative arthritis. In gastric cancer in mice,
Sulindac and celecoxib have been found to induce apoptosis, suppress proliferation, reduce angiogenesis, and decrease invasiveness [50]. In humans, epidemiologic evidence suggests a decreased incidence of breast, lung, and colon cancers in patients who use aspirin and other nonsteroidal antiinflammatory drugs [47•]. Furthermore, celecoxib has been found to decrease the prostaglandin-mediated accumulation of wild-type p53 in the cytosol, where it is inactive, thus protecting p53 tumor suppressor function [51•]. Interestingly, sulindac has been shown to inhibit Wnt-signaling in human colorectal adenomas as well as in human colorectal cell lines, suggesting a mechanism of chemoprevention by nonsteroidal antiinflammatory drugs, although it is unclear whether this is dependent on COX-2 [52•].

**Paraneoplastic syndromes**

The incidence of paraneoplastic syndromes in the setting of primary bone sarcomas is extremely rare. The reason for this, though unknown, may be that sarcomas arise from mesenchymal tissue, unlike carcinomas, which arise from epithelial tissue. Paraneoplastic phenomena are quite common in the setting of carcinoma. In addition, there are multiple paraneoplastic syndromes associated with carcinomas that are known to mimic rheumatoid arthritis. Explosive onset of symptoms, older age at presentation, and absence of response to conventional therapies all suggest a paraneoplastic process [58•,59,60]. In cases of carcinoma metastatic to bone, it is quite common for patients to have hypercalcemia. This may be due to the presence of parathyroid hormone–related peptide, especially in cases of small-cell lung cancer. More commonly, however, hypercalcemia is secondary to stimulation of osteoclasts by metastatic disease. The resultant bone resorption that causes hypercalcemia and compromised skeletal integrity may be mitigated by bisphosphonates.

**Statins**

The statins are inhibitors of HMG-CoA reductase, an important enzyme in the mevalonate synthesis pathway, which results in the synthesis of cholesterol (Fig. 2). They have been found to demonstrate anticancer effects, although some studies have shown an elevated risk of cancer after cholesterol-lowering therapy [53••,54,55]. *In vitro*, inhibition of the enzyme geranylgeranyltransferase has been shown to decrease cancer cell invasion [56•]. In a series of experiments using a murine lung cancer cell line, Andela *et al.* [57••] found a dose-dependent inhibition of tumor cell proliferation, adhesion, and invasiveness after treatment with mevastatin, as well as with the bisphosphonate alendronate. These effects were reversible with geranylgeranyl pyrophosphates; however, the addition of farnesyl phosphate had no effect. These findings suggest a role for geranylgeranylated proteins in the development of cancer and highlight the mevalonate synthesis pathway as a potential target for anticancer therapies.

**Figure 1. Synthesis of prostaglandins from arachidonic acid**

Cyclooxygenase-2 (COX-2) converts arachidonic acid to prostaglandin H2 (PGH₂), which is then converted to one of three prostaglandins, which mediate angiogenesis.

**Figure 2. Mevalonate synthesis pathway**

The activity of HMG-CoA reductase is the critical step in cholesterol synthesis. Statins inhibit HMG-CoA reductase.
Sarcomas in growing children

After surgical resection of an extremity sarcoma in a young child, the subsequent reconstruction must take into account the remaining growth in the limb. To solve this problem, various expandable implants have been developed, each with its associated difficulties. A main drawback of these expandable implants is that surgical exposure of the prosthesis is required for each lengthening. To avoid multiple surgical procedures for limb lengthening, an extensible prosthesis (Fig. 3) has been developed that allows for implant lengthening without surgical intervention, by application of an electromagnetic field on the outside of the extremity [61]. An early multicenter trial of 15 of these implants has resulted in 8 revisions and 1 amputation (resulting from postoperative arterial thrombosis) at an average follow-up time of 21.5 months [62]. These results are promising, although long-term function must still be assessed.

Conclusion

Study of the molecular mechanisms of malignant bone tumors is helping to elucidate the pathology of both primary bone sarcomas and metastatic bone disease. As these mechanisms are further refined the treatment strategies may shift from cytotoxic therapies to treatments targeting specific molecules. The mevalonate synthesis pathway is a potential target for anticancer therapy, but further research is necessary to avoid potential toxicities or secondary cancers. Bisphosphonates and COX-2 inhibitors will likely be incorporated into the treatment paradigms for primary as well as metastatic cancer.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- Of special interest
- Of outstanding interest

Systemic disorders with rheumatic manifestations


Large, single-institution retrospective study of Ewing family tumor patients. This study points out the need for novel therapies for patients with metastatic disease.


This prospective, single-institution study found that current cytotoxic therapies are effective in treating young patients with localized disease. However, these treatments are relatively ineffective in patients with metastatic Ewing family tumors.


A brief review of leukemia associated with the treatment of OS.


This study implicates epipodophyllotoxins and anthracyclines in secondary leukemias.


Although the risk of treatment-induced secondary malignancy is low, this retrospective study from the Mayo Clinic found that these patients have a poor prognosis.


A comprehensive review of the current understanding regarding the anticancer effects of bisphosphonates.


This study examines the use of both bisphosphonates and statins in the treatment of cancer. The mevalonate synthesis pathway is identified as a potential target.


This mouse study found that bisphosphonates are most effective when given closest to the time of implantation of tumor cells. The question arises whether bisphosphonates should be used in cancer patients to prevent bone metastases before they arise.


A review of the antiangiogenic mechanisms of COX-2 inhibitors.


A thorough review of the mechanisms of COX-2 inhibitors in the treatment of cancer.
This study links prostaglandins synthesis and the Wnt signaling pathway. However, it is unclear whether this is COX-2 specific.

A detailed review of the biochemical pathways of the antitumor actions of statins.


This in vitro study implicates the mevalonate synthesis pathway in the invasiveness of cancer.


This elegant in vitro study examines the role of the mevalonate synthesis pathway in the behavior of cancer cells. Alendronate and mevastatin decreased cancer cell invasiveness, adhesion, and proliferation. This study highlights the mevalonate synthesis pathway as a potential target of anticancer treatment.

This good review of the associations between rheumatoid arthritis and cancer gives special attention to paraneoplastic syndromes.


This paper discusses a novel orthopedic implant for pediatric patients with significant residual growth who have undergone tumor resections about the knee.

This multicenter trial examined the outcome of a novel orthopedic implant in pediatric patients. These early results are promising.
Microchimerism and systemic sclerosis
Sergio A. Jimenez and Carol M. Artlett

Purpose of review
Although 6 years have elapsed since the initial report describing the presence of microchimeric cells in affected tissues from patients with systemic sclerosis, a mechanism by which these cells might contribute to the pathogenesis of the disease is still unknown. This article reviews the published literature related to the possible role of microchimeric cells in the pathogenesis of systemic sclerosis.

Recent findings
Numerous studies have reported the identification or quantification of microchimeric cells in the peripheral blood or tissues from systemic sclerosis patients; however, only one study to date has investigated their function. Recent investigations have demonstrated microchimeric cells in the clinically uninvolved tissues from patients with systemic sclerosis, suggesting that these cells are present in early disease. However, after the identification of microchimeric cells in blood and tissues of patients with systemic sclerosis, these cells have been found in organs affected by nonautoimmune conditions. These cells are also commonly detected in the peripheral blood of healthy people.

Summary
These observations have raised questions about whether microchimeric cells are responsible for the pathologic events in systemic sclerosis or are merely remnants of a pregnancy remote in time, and it has been suggested that they might also have beneficial effects for the host.

Keywords
microchimerism, systemic sclerosis, graft-versus-host disease

Introduction
Microchimerism has been implicated in the pathogenesis of certain autoimmune diseases because of numerous similarities that exist between these diseases and graft-versus-host disease (GVHD). However, it has not yet been determined whether microchimeric cells are integral involved in the pathogenesis of these diseases, or whether they are innocent bystanders or simply markers of an ongoing inflammatory process.

Scleroderma and graft-versus-host disease
Graft-versus-host disease occurs when foreign immunocompetent cells present in transplanted donor bone marrow or other tissues or in transfused blood react with the recipient’s cell surface antigens. HLA disparities, the immunologic competence of the host, and the numbers and characteristics of the T cells in the graft are factors that contribute to the development of GVHD [1]. The essential requirements for the induction of GVHD are (1) the graft must contain immunologically competent cells, (2) the host must appear foreign to these cells, and (3) the host must be incapable of mounting an effective immune response against the immunocompetent cells in the graft. Certainly, in the case of systemic sclerosis, microchimeric cells are immunologically competent, because they express CD3 [2] and CD4 [3], the host appears foreign to these cells in HLA class I [4,5], and the host is incapable of mounting an immune response to these cells, most likely because of tolerance established during gestation.

The hypothesis involving microchimerism in systemic sclerosis was first proposed by Scott Pereira in 1989 [6]. In the original publication, the authors stated, “Scleroderma has been postulated as a type of chronic GVHD resulting from transplacental transfer of cells between mother and fetus ...” [6], and in a companion article, they stated that “... this could lead to a state of microchimerism and activation of such [microchimeric] cells to cause a chronic GVHD-type of disease” [7]. Subsequently, other investigators [8] proposed and presented some evidence suggesting the involvement of fetal cells in the pathogenesis of systemic sclerosis. However, it was not until the discovery of the presence of male fetal cells in a normal woman 27 years after the birth of her infant [9] that the involvement of fetal cells in the pathogenesis of systemic sclerosis was given credence [10].

Systemic sclerosis is a complex disease characterized by humoral and cell-mediated immune abnormalities with...
n numerous clinical and histopathological features similar to those of chronic GVHD [11–13]. The incidence of systemic sclerosis in females is in great excess compared with its incidence in males, with a female to male ratio of 8:1 [14], and systemic sclerosis frequently manifests after the childbearing years [14,15].

Systemic sclerosis and chronic GVHD closely resemble each other, and it has been suggested that systemic sclerosis may be a form of chronic GVHD [2,5–7,11,12,16,17]. Skin, lung, and esophageal involvement are prominent features of both diseases [18–20], and both display lymphocytic infiltration in affected tissues [18,21–23], cytokine abnormalities [24–27], and prominent tissue fibrosis, particularly in the dermis and lungs [28]. Chronic inflammatory cell infiltrates are one of the earliest events in both systemic sclerosis and GVHD, and T cells are central to the development of tissue damage, because they are the most abundant cell in systemic sclerosis inflammatory infiltrates [29,30]. Furthermore, a recent analysis of antinuclear antibodies identified the systemic sclerosis-associated antibodies Scl-70 and Pm-Scl in 32% of patients with chronic GVHD who sought treatment with clinical symptoms similar to those of patients with diffuse systemic sclerosis [31].

Microchimeric cells in systemic sclerosis peripheral blood

Microchimeric cells have been identified in the peripheral blood of patients with systemic sclerosis [2,5]. However, if microchimeric cells are involved in the disease process, it would be important to demonstrate the presence of these cells in the lesions [2]. Indeed, microchimeric cells were found in the lesions of patients with systemic sclerosis, suggesting that nonautologous cells may be mediating a GVHD-like reaction in these patients. Although some studies have failed to show an association between microchimeric cells and systemic sclerosis [32–34], these negative observations may be a result of the cell selection strategy used. The optimal detection of microchimeric cells in pregnant women uses magnetic cell separation of peripheral blood for the enrichment of fetal cells before analysis; therefore, the analysis of whole peripheral blood may be suboptimal for the detection of microchimeric cells. Studies showing a lack of association between peripheral blood microchimerism and systemic sclerosis analyzed whole peripheral blood, whereas studies showing a positive correlation analyzed magnetically sorted peripheral blood cells [2,3,5]. In a direct comparison between polymerase chain reaction (PCR) of whole peripheral blood DNA and PCR of DNA from magnetically sorted cells for the detection of microchimeric cells, it was found that magnetic cell sorting before PCR increased the sensitivity of detection of male fetal cells by 200-fold [35•]. In the 60 samples analyzed by both methods, microchimeric cells were detected in the magnetically sorted cells in 49 of 60 (81.6%) samples, whereas PCR of whole peripheral blood DNA detected microchimerism in only 14 of 60 (23.3%) samples (P < 0.0001). In magnetically sorted cells, the median number of microchimeric cells was 13 (IQR 1–77.8)/500,000 autologous cells, whereas in whole peripheral blood DNA, it was 0 (IQR 0–0)/500,000 autologous cells (P < 0.0001). These results indicate that whole peripheral blood DNA may not be useful for the reliable detection of microchimeric cells, possibly because of the high background of autologous cells.

In women with systemic sclerosis, microchimeric cells were identified in the CD3+ T population from peripheral blood [2]. Furthermore, microchimeric cells were also found in the CD4+ and CD8+ T-cell populations, and patients with systemic sclerosis had significantly more microchimeric CD4+ T cells but not CD8+ T cells [3]. If the microchimeric cells were activated and expressing CD25, it was anticipated that they would have undergone clonal expansion and would have a limited T-cell receptor (TCR) repertoire. A recent study in systemic sclerosis has demonstrated a limited TCR repertoire compared with healthy controls, suggesting that systemic sclerosis is antigen-driven [36]. Studies investigating the TCR repertoire of microchimeric cells in comparison with the TCR repertoire of autologous cells will need to be performed to determine whether these cells are expanded in response to the same stimuli that cause oligoclonal T-cell expansion in systemic sclerosis.

Microchimeric cells in systemic sclerosis lesions

Studies have also demonstrated that microchimeric CD4+ and CD8+ cells are involved in GVHD responses [37,38]. Furthermore, these cells have been found in skin lesions from people who developed GVHD after bone marrow transplantation [39–41]. The presence of microchimerism in these functionally different cell populations supports the hypothesis that systemic sclerosis may represent a GVHD-like response mediated by activated microchimeric T cells. Recently, Scaletti et al. [42] demonstrated that microchimeric Y chromosome positive T-cell clones originating from a male fetus could be isolated from an active lesion from a patient with systemic sclerosis and that T-cell clones were primarily T112 in origin and reacted with maternal HLA antigens.

The demonstration of microchimeric cells in the peripheral blood of normal people indicates that the mere presence of these cells is not sufficient to cause systemic sclerosis. Therefore, the authors have postulated that the microchimeric cells must have become activated by a subsequent event, such as an environmental exposure (viral, chemical, or other). In a permissive host, these foreign cells would become activated and traffic to the skin or to other organs and initiate a cascade of
events, including the recruitment of autologous cells through the secretion of proinflammatory cytokines, resulting in the fibroproliferative and vascular alterations typical of systemic sclerosis. A diagram of this possible pathogenetic mechanism for systemic sclerosis is shown in Figure 1 [43•].

Recently, the authors performed a quantitative study comparing the numbers of microchimeric cells in affected and nonaffected skin from patients with systemic sclerosis [44••]. In this study, the authors demonstrated that microchimeric cells are present in the clinically uninvolved skin in patients with systemic sclerosis and that there are higher numbers of microchimeric cells than in involved skin [44••]. Based on the results of this study, we suggested that the influx of microchimeric cells into the uninvolved skin may precede the development of fibrosis. It is not possible to conclude whether microchimeric cells are involved in the early events that cause disease merely by their presence in the unaffected skin; however, the absence of microchimeric cells in tissues from healthy people gives support to the possible role they have in the development of disease [44••].

**Microchimeric cells and systemic sclerosis**

**mouse models**

To elucidate the correlation between systemic sclerosis and microchimeric cells, a mouse model for systemic sclerosis that integrally involved the presence of microchimeric cells was developed [44••]. Mice that harbored microchimeric cells from previous pregnancies were injected with vinyl chloride, an agent known to induce systemic sclerosis-like alterations. Subsequent PCR analysis demonstrated a 48-fold increase in the number of microchimeric cells in the peripheral blood after this treatment [45]. Associated with the increase in fetal cells, remarkable histopathological changes were found in several tissues, indicating cutaneous inflammatory changes, severe fibrosis, and marked splenomegaly with fibrotic tissue accumulation in the spleen. These histopathological changes were absent in virgin mice injected with vinyl chloride [45].

More recently, another mouse model for systemic sclerosis was described using the immunodeficient RAG-2KO mouse strain transplanted with B10.D2 spleen cells [46••]. This model closely mimicked systemic sclerosis in all clinical, histopathological, and immunologic aspects. The animals showed fibrosis of the skin, gastrointestinal tract, heart, lung, and kidney; immune activation; and typical systemic sclerosis-like vascular changes. Furthermore, the expression of TGF-β, a growth factor indicated in the pathogenesis of fibrosis in systemic sclerosis, was found to be elevated in affected tissues [46••]. Antinuclear antibodies were present in most mice and displayed the Scl-70–specific profile. This mouse model, in which there is replacement of T and B cells with chimeric cells, suggests that microchimeric cells may indeed contribute to the pathogenesis of systemic sclerosis by establishing an immune activation against the host. However, in contrast with the RAG-2KO mice, which are deficient in T and B cells, patients with systemic sclerosis have both T and B cells, and the proportion of microchimeric cells is extremely low. Whether such a small population of foreign cells can mediate a systemic disease in an immunocompetent host has yet to be determined.

The consequences of the combination of maternal microchimeric cells allogeneic to the child on the immune system are unknown but are most likely dependent on the alloantigens they express, on the antigen-presenting capacity of the cells, and on the response of the neonatal immune system to their presence. Tolerance to noninherited maternal antigens has been reported in approximately 50% of people undergoing kidney transplants, and it has been suggested that maternal cells entering the bloodstream of the fetus might be responsible for the induction of nonresponsiveness [47]. GVHD rarely occurs after organ transplantation. It may be that to produce GVHD, these passenger leukocytes must be unable to be primed adequately. It is possible that maternal cells may undergo selection in the peripheral circulation and become tolerant to fetal antigens; alternatively, they may act as vetoing cells, inactivating host T cells that recognize them.

**Figure 1. Pathway of the hypothesis of microchimeric cell involvement in the pathogenesis of systemic sclerosis**

- Maternal Cell Transfer During Pregnancy
- Engraftment of Microchimeric Cells
  - Activation of Microchimeric Cells by Vitox, Chemotherapeutic Exposure or Other Mechanism
  - Graft-versus-Host-like Disease
    - Endothelial Cells
    - Activation of Immune Cells
    - Fibroblasts
      - Increased Extracellular Matrix Gene Expression
      - Tissue Fibrosis
    - Platelets
      - PDGF (+)
      - P-selectin aggregation (+)
      - TGF-β (+)
      - CTGF (+)
      - Nitric Oxide (+)
    - Increased Extracellular Matrix Gene Expression
      - Tissue Fibrosis

CTGF, connective tissue growth factor; IFN, interferon; IL, interleukin; PDGF, platelet derived growth factor; TGF, transforming growth factor; TNF, tumor necrosis factor. Adapted with permission [43•].
Conclusion
The role that microchimeric cells may play in the pathogenesis of systemic sclerosis has yet to be fully elucidated. The studies on microchimerism in systemic sclerosis coupled with the clinical similarities of systemic sclerosis to chronic GVHD provide a strong rationale for the hypothesis that microchimeric cells may be mediating a GVHD-like reaction in these patients. Moreover, the observed association between systemic sclerosis and HLA class II compatibility between female patients and their offspring suggests that in these instances, fetal cells that gain access to maternal circulation would not be recognized as foreign by the maternal immune system. These findings suggest that the immunopathogenesis of systemic sclerosis may involve differentiation and activation of foreign cells from a pregnancy remote in time and that these cells are then able to initiate a chronic GVHD. The breakdown of tolerance of the microchimeric cell toward the recipient, caused by an undetermined event, probably of environmental origin, could result in the activation of these cells to cause an allograft reaction, which manifests clinically as systemic sclerosis or another autoimmune disease. Currently, it is not known whether the increased frequency of microchimeric cells in patients with systemic sclerosis is a result of the increased expression of proinflammatory cytokines that drive a generalized inflammatory response in those patients or whether these cells are elevated because of their specific activation recognizing recipient HLA antigens. Although the hypothesis that microchimeric cells from previous pregnancies or from maternal origin in the case of nulliparous women or male patients with systemic sclerosis is quite compelling and provocative, further studies are necessary to clarify the role of these cells in the pathogenesis of systemic sclerosis.

References and recommended reading
Papers of particular interest, published within the annual period of review, have been highlighted as:
• Of special interest
**Of outstanding interest

This article compares the detection of microchimeric cells in peripheral blood that
has been magnetically sorted for specific cell populations and in whole peripheral blood. It reports that whole peripheral blood is inadequate for detecting microchimeric cells.


This article discusses numerous pathogenic mechanisms that may be involved in the onset of systemic sclerosis.


This article reports, for the first time, microchimeric cells in the clinically affected and unaffected skin from patients with systemic sclerosis. It suggests that microchimeric cells are present in the lesions very early in disease, before any clinical manifestation.


This article reports a new mouse model for systemic sclerosis that exhibits all the major pathological features of the disease. Not only is there fibrosis of the skin and internal organ involvement, but the autoantibody Scl-70 is also produced.

Central nervous system manifestations of rheumatologic diseases
Russell L. Chin and Norman Latov

Purpose of review
To summarize the current literature on central nervous system manifestations of vasculitides and connective tissue diseases.

Recent findings
There have been advances in understanding the mechanisms behind the initiation and perpetuation of inflammatory processes in vasculitic neuropathy. Clinically relevant data have been obtained on the predictive criteria for a positive biopsy result in giant cell arteritis, the imaging characteristics of primary angiitis of the central nervous system, and Behçet disease, and the clinical and radiologic features of neuro–Behçet disease. There is more clarity about the central nervous system syndromes attributable to systemic lupus erythematosus and new insights into the central mechanisms involved in the manifestations of Sjögren syndrome and rheumatoid arthritis. Novel immunomodulatory agents, such as infliximab, have shown some benefit in rheumatoid vasculitis and Sjögren syndrome.

Summary
A better understanding of the clinical, radiographic, and serologic characteristics of various central nervous system complications of rheumatologic diseases has been gained in the past year. Recent advances in understanding the pathophysiology of peripheral nervous system complications and their treatment may affect the management of the central nervous system complications.

Keywords
vasculitis, Behçet disease, rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis, primary angiitis of the central nervous system, Sjögren syndrome, connective tissue disease, central nervous system, neurologic complications

Abbreviations
aPL antiphospholipid antibodies
CNS central nervous system
GCA giant cell arteritis
NPSLE neuropsychiatric systemic lupus erythematosus
PAN polyarteritis nodosa
PNS peripheral nervous system
RA rheumatoid arthritis
SLE systemic lupus erythematosus

Introduction
Vasculitides and connective tissue diseases, including rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), progressive systemic sclerosis, and Sjögren syndrome, are characterized by pathologic changes in systemic organs. However, involvement of the nervous system may be a striking early or presenting feature with a wide variety of manifestations (Table 1).

The central nervous system (CNS) may be affected by a focal or generalized vasculopathy or as a secondary consequence of the primary disease (eg, cranial neuropathies due to compression by granulomatous lesions). A focal cerebral vasculitic event may result in (1) a stroke-like presentation with an acute neurologic deficit, (2) a severe headache due to hemorrhage (eg, subarachnoid hemorrhage in vasculitis), (3) focal seizures, or (4) optic neuropathy. A generalized vasculitic event may result in diffuse cognitive changes, headaches, or seizures. The spinal cord may also be the target of an immune-mediated reaction with resulting paraparesis, bowel or bladder dysfunction, or sensory disturbances.

The most common complication of peripheral nervous system (PNS) involvement is peripheral neuropathy, with symptoms of numbness, sensory paresthesias, weakness, or gait imbalance. The neuropathy may be multifocal and asymmetric or, less frequently, distal and symmetric.

This paper will focus on the most recent work on CNS manifestations of rheumatologic conditions. The PNS complications of connective tissue diseases have been well reviewed elsewhere [1].
Vasculitis

Vasculitis refers to disorders defined by inflammation of the blood vessels (including arteries and veins of varying caliber) resulting in a wide variety of neurologic manifestations due to ischemic injury [2]. Vasculitis may occur as a hypersensitivity reaction to foreign proteins, drugs, infectious agents, or malignant processes; however, we will focus on the systemic vasculitides. These may be classified into the following categories:

1. Systemic necrotizing vasculitis: polyarteritis nodosa (PAN), Churg-Strauss syndrome, microscopic polyangiitis syndrome, Kawasaki disease
2. Wegener granulomatosis, a systemic granulomatous disorder
3. Giant cell arteritis (GCA), including Takayasu arteritis, or aortoarteritis
4. Primary angiitis of the nervous system
5. Behçet disease

Systemic necrotizing vasculitis

Polyarteritis nodosa, the prototypic disorder of this group, involves small and medium-sized muscular arteries, particularly of the kidney and viscera, whereas microscopic polyangiitis affects arterioles, capillaries, and venules and rarely affects medium-sized arteries. Churg-Strauss syndrome, or allergic angiitis and granulomatosis, affects small and medium-sized muscular arteries like classic PAN; however, arterioles, capillaries, and venules (particularly of the lung and kidney) are affected, and asthma, peripheral eosinophilia, and extravascular granulomas (epithelioid and giant cell infiltrates) are usually present.

The CNS may be affected in 20 to 40% of patients with systemic vasculitis, resulting in stroke, cerebral hemorrhage (intraparenchymal or subarachnoid), encephalopathy, seizures, or a meningitis or meningoencephalitis picture [3–6]. Global dysfunction may also result from metabolic dysfunction secondary to multisystem organ failure in terminal stages of the disease. In Churg-Strauss syndrome, granulomatous disease may erode through the nasopharynx and lead to basilar meningitis, dural venous thrombosis, or optic neuropathy due to compression. Asymptomatic anterior ischemic optic neuropathy in the setting of systemic disease has also been reported [7]. Acute myelopathy with paraparesis has been reported in association with PAN [8].

In general, CNS manifestations are believed to occur later in the disease course as a result of the accumulation of inflammatory changes [9]. However, lacunar stroke syndromes (including pure sensory, sensorimotor, or ataxic hemiparetic presentations) have been reported to be the most common stroke subtype in patients with PAN, and they may occur within 8 months of disease onset. These were postulated to be secondary to thrombotic microangiopathy rather than to active vasculitis causing occlusion. Corticosteroids may have induced a prothrombotic state through inhibition of phospholipase A2, and the concomitant use of antiplatelet drugs was a suggested method of reducing the risk of arterial occlusion [10].

The angiographic finding of “beading” (alternating areas of stenosis and ectasia) in multiple vessels in multiple vascular beds has diagnostic specificity; however, the cerebral angiogram may be normal in as many as 40% of biopsy-proven cases [11].

Insights into the mechanisms behind the initiation and perpetuation of inflammatory reactions have been gained from the study of vasculitic neuropathy, the most common peripheral manifestation of systemic necrotizing vasculitis, seen in as many as 60% of patients [12]. Increased expression of the matrix metalloproteinase MMP-9, an endopeptidase that degrades components of the extracellular matrix, may play a pathogenic role in the development of vasculitic neuropathy [13•]. Mononuclear cells in the perivascular infiltrate express granzymes and T cell–restricted intracellular antigen, which seem to induce apoptosis of other inflammatory mononuclear cells and may affect recovery [14]. Cyclooxygenase-2 mRNA is upregulated in endoneurial macrophages, resulting in an increased production of prostaglandins. Cyclooxygenase-2 might be a potential target for therapy, particularly early in the disease process [15•].

Increased cytokine expression in vasculitic neuropathy
has been found to positively correlate with neuropathic pain [16•]. Pain in vasculitic neuropathy may also be influenced by a differential expression of pain-related neurotrophic factors and their concomitant soluble receptors [17]. Binding of the ligand Nε-(carboxymethyl)lysine (CML) to the receptor for advanced glycation end-products results in activation of the proinflammatory transcription factor nuclear factor-κB (NF-κB) and subsequent expression of NF-κB–regulated cytokines. This pathway may play a role in the initiation and maintenance of inflammation during the course of vasculitic neuropathy. The potential therapeutic benefit of antioxidants, which reduce intracellular oxidative stress and CML formation (such as vitamin E, α-lipoic acid, or benfotiamine), has not yet been evaluated in vasculitic neuropathy [18•].

Wegener granulomatosis

Wegener granulomatosis is a rare systemic disease of unknown cause, characterized by necrotizing granulomatous inflammation and vasculitis that typically affects the upper and lower respiratory tracts and kidney. In its limited form, there may be an absence of renal disease and a relatively benign, protracted clinical course [19]. Neurologic involvement occurs in approximately 34% of patients with Wegener granulomatosis, with mononeuropathy multiplex and cranial neuropathies being the most common manifestations [6,20]. These complications may result from compression or infarction due to granulomatous invasion or as a result of focal vasculitis [21,22]. Sural nerve biopsy specimens have shown findings consistent with vasculitis or axonopathy [6].

The CNS may be involved in 2 to 8% of patients [6,23]. Stroke and seizures due to cerebral vasculitis are the most frequent clinical manifestations. Other manifestations of cerebral vasculitis include headaches, confusion, or transient neurologic events, such as paresthesia, blackouts, or visual loss [24]. Radiologically confirmed vasculitis of the CNS in Wegener granulomatosis is rare, because the small vessels (50–300 μm in diameter) are typically below the sensitivity of routine angiography [6]. Lesions arising within the brain parenchyma itself are rare [24,25]. However, granulomatous disease may infiltrate the dura of the brain and spinal cord, resulting in contrast-enhancing lesions by MRI [20]. This clinical picture of pachymeningitis may occur in the setting of early active, limited disease and can respond favorably to corticosteroids and cytotoxic drugs, such as cyclophosphamide, methotrexate, or azathioprine [21].

Cytoplasmic antineutrophil cytoplasmic antibodies are found in more than 90% of patients with Wegener granulomatosis involving the kidneys. The disease activity of patients with pachymeningitis may be monitored by the cytoplasmic antineutrophil cytoplasmic antibody titers in the cerebrospinal fluid (CSF), which may disappear after intrathecal methotrexate and steroid treatment [26].

Giant cell arteritis

Giant cell arteritis is typified by vasculitis of the extracranial branches of the aorta, with rare involvement of the intracranial vessels. It is the most common vasculitis affecting people over 50 years of age. Transmural inflammation of the arteries induces luminal occlusion through intimal hyperplasia [27].

The most dreaded complication of end-organ ischemia is vision loss due to central retinal artery occlusion. This has been reported in 6 to 49% of cases, depending on the source of the data, with greater numbers coming from ophthalmologic centers [28••]. The clinical picture of a vasculitic anterior ischemic optic neuropathy includes disc pallor and swelling, cotton wool spots, and a normal optic cup size [29••]. Systemic symptoms (such as fatigue, malaise, weight loss) and signs (particularly fever and an elevated erythrocyte sedimentation rate) seem to be associated with a lower incidence of cranial ischemic complications, possibly because such patients seek medical attention and treatment earlier or have increased angiogenic activity in comparison with patients who lack such a strong systemic inflammatory response [28••, 29••,30].

Glucocorticoid therapy is frequently begun when the disease is initially suspected, and short-term use does not seem to significantly alter the outcome of the biopsy [31,32]. The result of a temporal artery biopsy is more likely to be positive in patients with an elevated erythrocyte sedimentation rate (> 50 mm/h), temporal headache, and temporal artery tenderness. When jaw claudication alone or in combination with scalp tenderness and new headache is present, a patient’s chances of a positive biopsy result are even higher [33]. The application of these diagnostic criteria may help the clinician decide who should receive a biopsy and avoid prolonged courses of unnecessary steroids [34••].

The temporal artery may also be involved in systemic necrotizing vasculitis, which may be differentiated from GCA by the presence of clinical manifestations of PAN or antineutrophil cytoplasmic antibodies, especially the anti–proteinase-3 antibodies of Wegener granulomatosis, which are generally absent in GCA [35].

The extracranial complications of GCA include aortic arch syndrome, aortic aneurysm or dissection, and subclavian or brachial arteritis [35]. Involvement of the vertebral arteries may result in a clinical picture of vertebral artery dissection [36]. Aortic aneurysm and aortic dissection in GCA are associated with hyperlipidemia and coronary artery disease [37•]. Stroke has been reported to occur in 3 to 4% of patients, often within days of steroid
therapy initiation [38,39]. The addition of low-dose aspirin may be helpful in preventing ischemic complications [28••].

Takayasu arteritis, also known as aortoarteritis, affects primarily the large elastic arteries, such as the aorta and its main proximal branches. The mechanisms behind the arterial damage in this disorder have recently been reviewed [27]. Ischemic optic neuropathy and other isolated cranial nerve palsies due to involvement of the internal carotid artery or its branching vessels have been reported. Similar isolated cranial neuropathies have been reported in Behçet disease and GCA [40].

Primary angiitis of the central nervous system

Primary angiitis of the CNS is an idiopathic, recurrent vasculitis confined to the CNS, which involves small and medium-sized blood vessels. The prognosis is potentially fatal; however, it may be altered by aggressive immunosuppressive therapy with prednisone and cyclophosphamide.

Diffusion-weighted MRI of two patients with primary angiitis of the CNS showed heterogeneous signal intensities, most likely reflective of the various stages of the inflammatory process (edema, demyelination, hemorrhage, and ischemia) in primary angiitis [41•]. Of patients with vasculitis, 15% have been reported to have masslike lesions that may mimic infection or tumor [42].

Because of the focal and segmental distribution of primary angiitis, the sensitivity of meningeal and brain biopsy may not be greater than 65% [43]. In a small retrospective case series, the prognosis in patients with suspected primary angiitis of the CNS and negative biopsy results who then received immunomodulatory therapy did not vary significantly from the outcome in patients who did not receive immunomodulatory therapy, suggesting that this subset of patients had conditions other than primary angiitis of the CNS [44•].

Behçet disease

Behçet disease is an inflammatory multisystem disorder of unknown cause involving arteries and veins of all sizes, characterized by uveitis, erythema nodosum, skin lesions, and recurrent oral and genital ulcers. An association with HLA-B51 has been reported in severe cases [45]. The CNS may be affected in 10 to 49% of patients with Behçet disease, resulting either from primary inflammation of CNS tissue or from vasculitis with a venous predominance: changes leading to ischemic stroke [4,46,47].

The most common presentation of parenchymal CNS involvement is a subacute brainstem syndrome with cranial nerve findings, dysarthria, and cerebellar or corticospinal tract signs. More infrequent presentations include a strokelike presentation (with the acute onset of unilateral neurologic findings and signs of cortical involvement including seizures) and psychiatric features, such as psychosis. Sinus venous thrombosis may evolve relatively slowly and result in intracranial hypertension and resulting headache, vomiting, and bilateral papilledema [4,47]. Impaired memory (long-term verbal and nonverbal) and visuospatial skills occur frequently in patients with active disease who are taking large doses of steroids [48•]. Pure spinal cord or PNS involvement is rarely reported [46].

In addition to secondary headaches (due to ocular inflammation, meningoencephalitis, or dural sinus thromboses), nonstructural recurrent, bifrontal, vascular-type headaches are the most frequent neurologic symptom in Behçet disease [49••]. The latter headaches may be treated with tricyclic antidepressants or valproic acid, with triptans reserved for the most refractory patients [50]. Topiramate, a carbonic anhydrase inhibitor that may reduce CSF production, has been effective in a case of intracranial hypertension associated with Behçet disease [51].

Magnetic resonance imaging may show focal or more extensive lesions. Diffuse lesions in the brainstem or basal ganglia, extending to the diencephalon, are the most common parenchymal findings [52••]. The MRI findings and clinical course in Behçet disease (ie, primary progressive, relapsing-remitting, or secondary progressive) may mimic multiple sclerosis. Active and chronic neuro-Behçet lesions have increased diffusivity in a pattern that differs from the pattern of ischemic infarcts, so that analysis of the apparent diffusion coefficient may help differentiate these conditions [53]. Furthermore, patients with Behçet disease may have a serum and CSF cytokine and chemokine profile that differs from the profile seen in multiple sclerosis [54••].

Therapy of CNS lesions includes high-dose corticosteroid pulse therapy followed by long-term immunosuppression. Cyclophosphamide is reserved for severe cases [45].

Systemic lupus erythematosus

The term “neuropsychiatric systemic lupus erythematosus” (NPSLE) has been used to describe patients with cerebral involvement by SLE [55]. A review of the 30 CNS syndromes described in the literature found only 16 to be convincingly attributable to SLE. These included stroke, transient ischemic attacks, epileptic seizures, psychosis, cognitive disorder and dementia, and delirium [56]. The incidence of headache was not found to be clearly higher in patients with SLE than in the general population [57••]. Stroke accounts for approximately 20% of neurologic events in SLE and is often secondary to an antibody-associated hypercoagulable state or cardiogenic embolism. Hemorrhage (intracerebral or sub-
arachnoid) may also occur as a result of arterial dissection [58]. Others have found behavioral disturbances, occurring within the first year of the disease, to be most common symptoms of cerebral pathology [59].

Abnormalities on MRI (including cerebral atrophy, infarcts, or subcortical hyperintensity) in patients with NPSLE were found to be associated with antiphospholipid antibodies (aPL) [60]. Fluid-attenuated inversion recovery imaging in NPSLE has obvious advantages and is more sensitive than routine MRI in diagnosing cerebral lesions [61].

Antibodies to microtubule-associated protein 2 were found to be associated with NPSLE [62••]. Patients with NPSLE showed significantly higher levels of aPL (particularly anticardiolipin antibodies) than SLE patients who lacked neuropsychiatric symptoms [63,64]. β2-glycoprotein-I is the main target for aPL that can be responsible for small-vessel thrombosis, vasculopathy, or antibody-mediated damage [65,66]. The focal symptoms in NPSLE may be directly related to vascular lesions, whereas the more global manifestations may be related to autoantibody-mediated or cytokine-mediated impairment of the neuronal function [65].

Guidelines for primary stroke prevention of patients with aPL are not available, because the literature on asymptomatic (no history of thrombotic events) aPL-positive patients is limited. Furthermore, recent studies report that aPL do not seem to be a strong risk factor for recurrent stroke or transient ischemic attack, nor do they predict a differential response to aspirin or warfarin therapy [67,68••]. Secondary prevention with high-level oral anticoagulation is still the most commonly used treatment for aPL-positive patients who have experienced strokes, particularly those with left-sided cardiac valve lesions and persistent high titers of IgG antcardiolipin antibodies [69•].

The management of CNS lupus has been reviewed recently [70]. Intravenous cyclophosphamide may be required in severe acute nonthrombotic CNS manifestations. Plasmapheresis may be added for patients with severe illness refractory to conventional treatment. Intrathecal methotrexate and dexamethasone have been also reported to be beneficial in these patients [71,72]).

**Rheumatoid arthritis**

Neurologic complications occur in moderate to severe RA either as a result of the disease’s erosive effects on joints and bones or caused by the disease itself (e.g., compressive rheumatoid nodules, rheumatoid vasculitis).

The cervical spine is frequently involved in RA, and atlantoaxial subluxation is the most common type of instability [73]. In older studies it was present in as many as 70% of patients with advanced RA. Those with disease duration of more than 10 years and onset before the age of 50 were particularly at risk [74]. Atlantoaxial subluxation occurs when rheumatoid changes affect the synovial joints between the dens and the atlas anteriorly and the dens and transverse ligament posteriorly, resulting in spinal cord compression in the most severe cases. The patient may report neck pain and paresthesias and exhibit the myelopathic findings of hyperreflexia, weakness, gait abnormalities, flexor spasms, sphincter disturbances, or sensory changes. Occipital headache and obstructive hydrocephalus have also been reported [9]. Myelopathy may also result from compression by extradural rheumatoid nodules or by epidural lipomatosis, which frequently occurs as a result of long-term steroid administration [75,76].

The degenerative changes in the cervical spine may also compress the vertebral arteries, resulting in vertebrobasilar insufficiency, manifested by nausea, vertigo, diplopia, and dysphasia [73]. Laminoplasty may be benefit these patients [77]. However, proper bony fusion may not be possible because of the fragility of the vertebral bodies or the significantly altered anatomy.

Rheumatoid vasculitis affecting the CNS is rare and may present with seizures, dementia, hemiparesis, cranial nerve palsy, blindness, hemispheric dysfunction, cerebellar ataxia, or dysphasia [78,79].

The perception of joint stiffness may be maintained by secondary plastic changes in the CNS, as illustrated by the report of patients who experienced persistent joint stiffness after limb amputation [80].

The management of extraarticular disease manifestations in RA has recently been reviewed [81]. Cyclophosphamide is favored; however, tumor necrosis factor inhibitors such as infliximab may be successful in treatment-resistant vasculitis [82•].

**Progressive systemic sclerosis (scleroderma)**

Progressive systemic sclerosis is a disorder of excessive collagen deposition in the skin, blood vessels, and other organs. Neurologic involvement is rare, with myopathy and cranial neuropathies being the most frequently reported manifestations. Brachial plexopathy, lumbosacral radiculopathy, and polyneuropathy have also been reported [83]. CNS manifestations are even more rare and may be due to hypertension, renal or pulmonary dysfunction caused by scleroderma, or primary vascular changes. These manifestations include encephalopathy, aphasia, dementia, psychosis, anxiety disorder, grand mal seizures, and transient ischemic attacks [84]. Spontaneous intracerebral hemorrhages have been rarely reported [85]. A case of noncompressive transverse myelopathy was recently reported [86].
Linear scleroderma en coup de sabre, a localized form of scleroderma occurring on the face, is associated with changes in the underlying subcutaneous tissue and bony structures. A recent case report, however, described a child with lesions on his left arm and leg, but not on his face or scalp, who experienced atrophy of the ipsilateral cerebral hemisphere leading to severe neurologic dysfunction, including epilepsy and behavioral and intellectual deterioration [87].

Antinuclear antibodies are commonly found, usually in a nucleolar pattern. Subgroups of patients with certain antibodies (ie, anti-U1RNP and possibly anti–Scl-70 antibodies) may be more prone to neurologic manifestations [88]. Calcification due to primary vascular changes in the brain may be detected by CT [89]. CNS vasculitis and transverse myelitis associated with progressive systemic sclerosis may respond to cyclophosphamide [86,90].

Sjögren syndrome
Sjögren syndrome is a generalized autoimmune exocrinopathy resulting in keratoconjunctivitis sicca and xerostomia resulting from lymphocytic infiltration of the lacrimal and salivary glands [91]. It may occur as a primary disorder or as a secondary disorder in association with connective tissue disorders, such as RA and SLE.

The reported prevalence of CNS involvement varies widely; however, it is generally regarded to be less frequently involved than the PNS [92,93]. A pure sensory neuropathy is the most frequently PNS manifestation; a long-term, insidious course is typically observed [94•]. Anti-Ro (SS-A) antibody positivity has been associated with more severe CNS disease and abnormal angiographic findings [95].

Affective and personality disorders, memory disturbances with frontal lobe abnormalities, mild cognitive dysfunction, and aseptic meningitis have been reported [92,96,97]. CNS Sjögren syndrome, like Behçet disease, may mimic multiple sclerosis and present as a relapsing-remitting or primary progressive syndrome with increased IgG synthesis and oligoclonal bands in the CSF [98,99]. An increased incidence of affective disturbances and fatigue, associated with large ventricular volumes, were noted in patients with Sjögren syndrome when they were compared with control individuals [100•]. Patients with Sjögren syndrome may also have an increased number of abnormal findings by single photon emission CT and MRI [101,102].

Spinal cord involvement is rare. Patients have experienced subacute or acute transverse myelopathic processes, thought to be due to an inflammatory ischemic vasculopathy with small vessel angiitis [92,103,104]. Presenting symptoms include severe neck or interscapular pain followed by sensorimotor deficits distal to a spinal cord level.

As in RA, the CNS itself may play a role in the mechanisms of eye dryness in Sjögren syndrome. Active inhibition of the parasympathetic system at the periaqueductal gray area of the limbic system has been postulated to explain the reduction in lacrimation and alteration in pain sensations in Sjögren syndrome [105•].

Treatment of the CNS complications of myelopathy has recently been reviewed. Cyclophosphamide is the immunomodulatory agent of choice if treatment with steroids is not successful [106•]. Intravenous immunoglobulin, reported to be an effective treatment for Sjögren syndrome–related ataxic sensory neuronopathy, may be considered in the setting of acutely worsening CNS symptoms [107•,108]. Infliximab (chimeric human–mouse anti—tumor necrosis factor-α antibodies), reported to be beneficial in the treatment of sensory neuronopathy, may be of utility in CNS disease [109].

Conclusion
The entire neuraxis may be affected by rheumatologic conditions. CNS manifestations vary according to the location of the lesion and range from focal findings (eg, stroke-like presentations) to global dysfunction (eg, encephalopathy or psychiatric symptoms). Although most CNS complications may be secondary to vasculopathic changes causing ischemia, other mechanisms (eg, thrombotic microangiopathy in PAN) or compression due to inflammatory or erosive disease should be considered.

Insights into the inflammatory mechanisms behind the CNS complications of vasculitic neuropathy may have important implications for the treatment of CNS complications. Current treatments include standard immunosuppressive agents, such as corticosteroids and cyclophosphamide, which may hold promise.

References and recommended reading
Papers of particular interest, published within the annual period of review, have been highlighted as:
• Of particular interest
• Of outstanding interest

This retrospective review of 175 patients with GCA found that transient cerebro-ophthalmic ischemic episodes and male sex were risk factors for ischemic complications, whereas the presence of systemic symptoms was “protective.”


This excellent two-part report on vasculitis focuses on common questions that confront physicians regarding the diagnosis and treatment of these conditions.


Of 1113 patients who underwent temporal artery biopsy in a 10-year period, 34% were found to have GCA. The presence of jaw claudication, new headache, scalp tenderness, and decreased vision had positive predictive values.


In this retrospective review, 27% of 188 patients with GCA experienced large artery complications. Hyperlipidemia and coronary artery disease were associated risk factors. Cranial symptoms and a higher erythrocyte sedimentation rate were negatively associated with large artery stenosis.


The heterogenous MR findings in two patients likely reflect the various stages of the disease.


This case series of 25 patients found a lack of treatment effect in patients with suspected primary CNS and nondiagnostic brain biopsy results who received immunosuppressive drugs.


Impaired memory (long-term verbal and nonverbal) and visuospatial skills were evaluated in patients with Behçet disease, and noninflammatory neurologic diseases. The profile in patients with Behçet disease resembled nonspecific inflammation more than autoimmune disorders such as multiple sclerosis.


In this detailed study, the serum and CSF levels of various cytokines and chemokines were evaluated in patients with Behçet disease, multiple sclerosis, inflammatory neurologic disease, and noninflammatory neurologic diseases. The profile in patients with Behçet disease resembled nonspecific inflammation more than autoimmune disorders such as multiple sclerosis.


This excellent review highlights the current understanding of the clinical spectrum of the disease.


In this paper, 17% of 128 patients aged 18 to 45 years with recent ischemic attack or ischemic stroke had aPL, which did not seem to be a strong risk factor for recurrent stroke or transient ischemic attack.


In this review, high-level oral anticoagulation is the preferred treatment for patients who have experienced strokes, particularly those with left-sided cardiac valve lesions and persistent high titers of immunoglobulin G antiphospholipid antibodies.


Central nervous system in rheumatologic diseases


In this comprehensive report, a purely sensory neuropathy was the most frequently seen PNS complication. A prolonged insidious course, sometimes with periods of stability, was typically observed.


An increased incidence of affective disturbances and fatigue, associated with large ventricular volumes, was noted in patients with Sjögren syndrome versus control participants.


The discrepancies between clinical observations and disease severity are addressed by this interesting theory of the role of the CNS in Sjögren syndrome.


This is a comprehensive review of the nonsteroidal treatments of Sjögren syndrome.


The findings of a benefit in a chronic peripheral manifestation may have implications for the treatment of CNS manifestations.


This bibliography is compiled by clinicians from the journals listed at the end of this publication. It is based on literature entered into our database between September 1, 2003 and August 31, 2004 (articles are generally added to the database about two and a half months after publication). In addition, the bibliography contains every paper annotated by reviewers; these references were obtained from a variety of bibliographic databases and published between the beginning of the review period and the time of going to press. The bibliography has been grouped into topics that relate to the reviews in this issue.

- Papers considered by the reviewers to be of special interest.
- Papers considered by the reviewers to be of outstanding interest.

The number in square brackets following a selected paper, for example [7], refers to its number in the annotated references of the corresponding review.

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Contents

Vasculitic syndrome

100 Major vessel involvement in Behcet disease and other aspects of Behcet

101 The use of ultrasound and positron emission tomography in the diagnosis and assessment of large vessel vasculitis

102 Medical and surgical treatment of Takayasu arteritis

103 Ocular vasculitis: a multidisciplinary approach

103 The spectrum of chronic periarthritis and large vessel vasculitis

104 Peripheral neuropathy in systemic vasculitis

105 Endothelial cell dysfunction in systemic vasculitis: new developments and therapeutic prospects

106 A clinical approach to cutaneous vasculitis

107 Wegner granulomatosis, Churg-Strauss syndrome and ANCA, cryoglobulinemia

108 Childhood vasculitides

109 Miscellaneous

Systemic disorders with rheumatic manifestation

110 Musculoskeletal manifestations of endocrine disorders

110 Musculoskeletal manifestations of Gaucher disease and other mucopolysaccharidoses and hemoglobinopathies

111 Bone malignancies and paraneoplastic syndromes

111 Microchimerism

112 Central nervous system disorders with rheumatic manifestations

112 Musculoskeletal manifestations of hepatitis and other disease

113 Musculoskeletal manifestations of endocrine disorders

113 Musculoskeletal manifestations and autoimmune diseases related to new biologic agents

113 Familial Mediterranean fever and other periodic fever syndromes

114 Sarcoidosis

114 Therapeutic options in systemic disease

114 Mechanisms of autoimmune systemic disease

115 Miscellaneous

Vasculitis syndrome

Major vessel involvement in Behcet disease and other aspects of Behcet

Review (pp 1–8)


Vasculitis syndrome: Medical and surgical treatment of Takayasu arteritis


Medical and surgical treatment of Takayasu arteritis

Review (pp 16–24)
Feist E, Hermann KGA, Filimonow S, et al.: Benefit of immunosuppression for severe Takayasu’s
Ocular vasculitis: a multidisciplinary approach

Review (pp 25–33)


The spectrum of chronic periarteritis and large vessel vasculitis

Review (pp 34–40)


LopezHoyos M, BartolomePacheco MJ, Blanco R et al.: Selective T cell receptor decrease in
Peripheral neuropathy in systemic vasculitis

Review (pp 41-48)


Vasculitis syndrome: Endothelial cell dysfunction in systemic vasculitides: new developments and therapeutic prospects

Review (pp 49–55)


Schleinitz MD, Weiss JP, Owens DK: Clopodigrel versus aspirin for secondary prophylaxis of
Kuipers TW, Biezevedel M, Achterhuis A, et al.:
Vasculitis syndrome: Wegener granulomatosis, Churg-Strauss syndrome and ANCA, cryoglobulinemia

Wegener granulomatosis, Churg-Strauss syndrome and ANCA, cryoglobulinemia


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metabolism, and leukotriene receptor an-

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granulomatosis and intraventricular hemor-

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screening for acute pauci-immune crescentic glomerulonephritis. Nephrol Dial Transplant

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Strauss syndrome after pranlukast treatment in

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granulomatosis and intraventricular hemor-

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screening for acute pauci-immune crescentic glomerulonephritis. Nephrol Dial Transplant

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Strauss syndrome after pranlukast treatment in

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tic antibodies, and leukotriene receptor an-

Kohmoto M, Arakawa KC: A patient with Wegener
granulomatosis and intraventricular hemor-

Kitching AR, Hutchinson P, Atkins RC, et al.: The role of flow cytometric ANCA detection in
screening for acute pauci-immune crescentic glomerulonephritis. Nephrol Dial Transplant

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Koizumi A, Suga Y, Takezawa Y, et al.: The Churg-
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tic antibodies, and leukotriene receptor an-

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granulomatosis and intraventricular hemor-

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screening for acute pauci-immune crescentic glomerulonephritis. Nephrol Dial Transplant

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Strauss syndrome after pranlukast treatment in

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tic antibodies, and leukotriene receptor an-

Kohmoto M, Arakawa KC: A patient with Wegener
granulomatosis and intraventricular hemor-

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screening for acute pauci-immune crescentic glomerulonephritis. Nephrol Dial Transplant

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Vasculitis syndrome: Musculoskeletal manifestations of endocrine disorders

Systemic disorders with rheumatic manifestation

Musculoskeletal manifestations of endocrine disorders

Review (pp 64–69)


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Musculoskeletal manifestations of Gaucher disease and other mucopolysaccharidoses and hemoglobinopathies

Review (pp 70–78)


Bone malignancies and paraneoplastic syndromes

Review (pp 79–85)


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Fuchs B, Valenzuela RG, Inwards C, et al.: Compli-

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Review (pp 86–90)
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gative frontier in autoimmunity and transplanta-

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pects of the human disease. Arthritis 

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microchimerism in neonatal lupus congential 

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3466.

Central nervous system disorders with rheumatic manifestations
Review (pp 91–99)
MRI in Behcet’s disease - 134 examinations of 
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Systemic disorders with rheumatic manifestation: Musculoskeletal manifestations of hepatitis and other diseases


Systemic disorders with rheumatic manifestation: Musculoskeletal manifestations of endocrine disorders


**Familial Mediterranean fever and other periodic fever syndromes**


- **Musculoskeletal manifestations and autoimmune diseases related to new biologic agents**


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Current Opinion in Rheumatology

List of journals scanned

The Index Medicus abbreviation is given in parentheses.

Acta Orthopaedica Scandinavica (Acta Orthop Scand)
American Journal of Human Genetics (Am J Hum Genet)
American Journal of Medicine (Am J Med)
American Journal of Nephrology (Am J Nephrol)
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Annals of Internal Medicine (Ann Intern Med)
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Annual Review of Immunology (Annu Rev Immunol)
Archives of Disease in Childhood (Arch Dis Child)
Archives of Internal Medicine (Arch Intern Med)
Archives of Physical Medicine and Rehabilitation (Arch Phys Med Rehabil)
Arthritis and Rheumatism (Arthritis Rheum)
Arthritis and Rheumatism Arthritis Care and Research (Arthritis Rheum Arthritis Care Res)
Arthritis Research (Arthritis Res)
Arthritis Research and Therapy (Arthritis Res Ther)
Autoimmunity (Autoimmunity)

Baillieres Clinical Rheumatology (Baillieres Clin Rheumatol)
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Blood (Blood)
Bone (Bone)
Brain (Brain)
British Medical Journal (BMJ)
Bulletin on the Rheumatic Diseases (Bull Rheum Dis)
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Clinical and Experimental Immunology (Clin Exp Immunol)
Clinical and Experimental Rheumatology (Clin Exp Rheumatol)
Clinical Immunology (Clin Immunol)
Clinical Infectious Diseases (Clin Infect Dis)
Clinical Orthopaedics and Related Research (Clin Orthop)
Clinical Rheumatology (Clin Rheumatol)
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Digestive Diseases and Sciences (Dig Dis Sci)
European Journal of Immunology (Eur J Immunol)
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JAMA Journal of the American Medical Association (JAMA)
Journal of Arthroplasty (J Am Pathol)
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Journal of Clinical Immunology (J Clin Immunol)
Journal of Clinical Investigation (J Clin Invest)
Journal of Hand Surgery American Volume (J Hand Surg [Am])
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Journal of Immunology (J Immunol)
Journal of Infectious Diseases (J Infect Dis)
Journal of Investigative Dermatology (J Invest Dermatol)
Journal of Magnetic Resonance Imaging (J Magn Reson Imaging)
Journal of Medical Genetics (J Med Genet)
Journal of Musculoskeletal Pain (J Musculoskeletal Pain)
Journal of Neuroupathology and Experimental Neurology (J Neuropathol Exp Neurol)
Journal of Pediatric Orthopedics (J Pediatr Orthop)
Journal of Pediatrics (J Pediatr)
Journal of Rheumatology (J Rheumatol)
Journal of Spinal Disorders and Techniques (J Spinal Disord Tech)
Journal of the American Society of Nephrology (J Am Soc Nephrol)
Journal of the Royal Society of Medicine (J R Soc Med)
Kidney International (Kidney Int)
Lancet (Lancet)
Lupus (Lupus)
Medical Care (Med Care)
Medicine (Medicine)
Micros Res Tech (Micros Res Tech)
Nature (Nature)
Nature Medicine (Nat Med)
Nephrology, Dialysis, and Transplantation (Nephrol Dial Transplant)
Neurology (Neurology)
Neuroscience Letters (Neurosci Lett)
Occupational Medicine Oxford (Occup Med – Oxford)
Osteoarthritis and Cartilage (Osteoarth Cartilage)
Osteoarthritis Cartilage (Osteoarth Cartilage)
Osteoporosis International (Osteoporosis Int)
Pain (Pain)
Pediatrics (Pediatrics)
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Radiology (Radiology)
Rheumatic Disease Clinics of North America (Rheum Dis Clin North Am)
Rheumatology (Rheumatology)
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Science (Science)
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Spine (Spine)
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