Initial Cutaneous Manifestations Consistent With Mononeuropathy Multiplex in Churg-Strauss Syndrome

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Background: Churg-Strauss syndrome (CSS), also known as allergic granulomatous angitis, is a rare entity that is characterized by systemic vasculitis in patients with a history of asthma. Patients with CSS show a marked peripheral blood eosinophilia, but the pathogenesis remains unknown.

Observations: A retrospective review was performed in 9 cases of CSS in whom cutaneous findings were present as an initial manifestation. All 9 patients had purpura and petechiae as well as severe pain and paresthesias of the lower extremities. Four patients (44%) used leukotriene receptor antagonists to treat their asthma, and 3 (75%) of them developed CSS within 3 months. Five patients (56%) were positive for perinuclear antineutrophil cytoplasmic antibodies before therapy, but in all 5 the levels of perinuclear antineutrophil cytoplasmic antibody normalized. Serum IgE levels were elevated in all patients before treatment but decreased after treatment. Histologically, all patients demonstrated leukocytoclastic vasculitis and eosinophilic infiltration. Eight biopsy specimens (73%) revealed marked eosinophilia around the nerve fibers in the dermis. Palisading granulomas in association with vessel-based changes were present in 4 (36%) of 11 biopsy specimens.

Conclusions: These characteristic cutaneous clinical patterns that are consistent with the presence of mononeuropathy multiplexes in the lower extremities may help physicians establish an earlier diagnosis. Both eosinophils and IgE, as well as perinuclear antineutrophil cytoplasmic antibodies to some degree, likely participate in skin lesion development in CSS. Furthermore, there appears to be a correlation between treatment with leukotriene receptor antagonists and the onset of CSS in some cases.

Arch Dermatol. 2005;141:873-878

The term Churg-Strauss syndrome (CSS) describes the clinical symptoms of allergic angiitis and granulomatosis. This disorder, which can present pathologically with necrotizing eosinophilic vasculitis involving nearly all major organs, represents a potentially fatal illness that is characterized by an initial history of asthma and rhinitis, followed by the precipitous development of vasculitis. Approximately 70% of patients with CSS have cutaneous involvement. The skin manifestations are typically overlapping vasculitic syndromes, such as palpable purpura, nodules, bullae, livedo, and urticaria. Churg and Strauss divided the clinical findings associated with allergic granulomatosis into 3 categories: (1) erythematous maculopapules resembling erythema multiforme; (2) hemorrhagic lesions ranging from petechiae to extensive ecchymosis, often associated with wheals; and (3) cutaneous and subcutaneous nodules. Tlacuilo-Parra et al similarly reported cutaneous manifestations, including palpable purpura, petechiae, nodules, maculopapules, and livedo reticularis, in approximately 51% of patients with CSS. Some reports have suggested that clinical papules and nodules on the elbows in patients with CSS are compatible with histologic palisading granulomas in association with vessel-based changes. Sangueza et al described the lesions as palisaded neutrophilic granulomatous dermatitis. Identification of such cutaneous findings, in addition to the histologic features of the disease, may lead to early diagnosis of CSS and prevent irreversible tissue damage with early treatment. Therefore, we propose that skin biopsies be performed earlier to confirm the features of vasculitis or palisading granulomas and to establish an earlier diagnosis of CSS.

A number of classification systems have been proposed, including the 1990 American College of Rheumatology (ACR) classification and that from an international
Table. Clinical and Histologic Features in 9 Cases of Churg-Strauss Syndrome With Initial Cutaneous Findings

<table>
<thead>
<tr>
<th>Patient No./Age, y/Sex</th>
<th>Asthma Duration</th>
<th>Pranlukast Therapy</th>
<th>Distribution</th>
<th>Cutaneous Findings</th>
<th>Other Examination Findings</th>
<th>Histologic Findings</th>
<th>Eosinophil Count, x10⁹/µL</th>
<th>MPO-ANCA, EU/mL</th>
<th>IgE, IU/mL</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/65/F 4 mo</td>
<td>No</td>
<td>Lower extremities and abdomen</td>
<td>Purpura and erythema</td>
<td>Mononeuritis</td>
<td>LV, eosinophilia, and nerve infiltration</td>
<td>11.3</td>
<td>375</td>
<td>1400</td>
<td>Prednisolone, 60 mg/d</td>
<td></td>
</tr>
<tr>
<td>2/59/M 14 y 1 mo</td>
<td></td>
<td>Lower extremities, sole, and fingers</td>
<td>Petechiae, papules, and livedo</td>
<td>Mononeuritis, arthralgia, and gastroenteritis</td>
<td>LV and eosinophila, acute and chronic inflammation, granulomas</td>
<td>1.3</td>
<td>Negative</td>
<td>600</td>
<td>Prednisolone, 25 mg/d</td>
<td></td>
</tr>
<tr>
<td>3/30/M 4 y No</td>
<td></td>
<td>Lower extremities and elbow</td>
<td>Purpura, papules, and erythroderma</td>
<td>Mononeuritis, myalgia, and gastroenteritis</td>
<td>LV, eosinophilia, acute and chronic inflammation, granulomas</td>
<td>7.1</td>
<td>216</td>
<td>610</td>
<td>Prednisolone, 60 mg/d</td>
<td></td>
</tr>
<tr>
<td>4/52/F 1.5 y 2-3 mo</td>
<td></td>
<td>Lower extremities, head, and palm</td>
<td>Petechiae, papules, and bullae</td>
<td>Mononeuritis and myalgia</td>
<td>LV and eosinophilia, acute and chronic inflammation, granulomas</td>
<td>2.8</td>
<td>195</td>
<td>1100</td>
<td>Prednisolone, 40 mg/d</td>
<td></td>
</tr>
<tr>
<td>5/72/F 2 y 2-3 mo</td>
<td></td>
<td>Lower extremities, head, and palm</td>
<td>Petechiae, papules, and bullae</td>
<td>Mononeuritis and myalgia</td>
<td>LV and eosinophilia, acute and chronic inflammation, granulomas</td>
<td>6.1</td>
<td>219</td>
<td>3400</td>
<td>Prednisolone, 50 mg/d; methylprednisolone, 1 g/d × 3 d</td>
<td></td>
</tr>
<tr>
<td>6/44/F 3 mo No</td>
<td></td>
<td>Lower extremities</td>
<td>Purpura, papules, and livedo</td>
<td>Mononeuritis, myalgia, and gastroenteritis</td>
<td>LV, eosinophilia, acute and chronic inflammation, granulomas</td>
<td>11.1</td>
<td>Negative</td>
<td>730</td>
<td>Prednisolone, 50 mg/d</td>
<td></td>
</tr>
<tr>
<td>7/21/F 6 y 1.5 y</td>
<td></td>
<td>Upper and lower extremities</td>
<td>Purpura, papules, and livedo</td>
<td>Mononeuritis, myalgia, and gastroenteritis</td>
<td>LV, eosinophilia, acute and chronic inflammation, granulomas</td>
<td>15.0</td>
<td>Negative</td>
<td>1700</td>
<td>Prednisolone, 60 mg/d</td>
<td></td>
</tr>
<tr>
<td>8/21/M 1 y No</td>
<td></td>
<td>Lower extremities, palm, finger, and sole</td>
<td>Purpura, erythroderma, and bullae</td>
<td>Mononeuritis, myalgia, and arthralgia</td>
<td>LV, eosinophilia, acute and chronic inflammation, granulomas</td>
<td>9.9</td>
<td>Negative</td>
<td>2100</td>
<td>Prednisolone, 60 mg/d; methylprednisolone, 1 g/d × 3 d</td>
<td></td>
</tr>
<tr>
<td>9/51/F 3 y No</td>
<td></td>
<td>Lower extremities, knee, elbow, and fingers</td>
<td>Purpura and papules</td>
<td>Mononeuritis and myalgia</td>
<td>LV, eosinophilia, acute and chronic inflammation, granulomas</td>
<td>24.0</td>
<td>129</td>
<td>900</td>
<td>Betamethasone, 7 mg/d</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: EU/mL, enzyme-linked immunosorbent assay units per milliliter; LV, leukocytoclastic vasculitis; MPO-ANCA, myeloperoxidase–antineutrophil cytoplasmic antibodies.

The ACR proposed the following 6 classification criteria, 4 of which must be present for the diagnosis of CSS: asthma, eosinophilia greater than 10%, paranasal sinusitis, pulmonary infiltration, histologic proof of vasculitis, and mononeuritis multiplex.10 These criteria have 85% sensitivity and 99.7% specificity. Herein, we describe 9 Japanese patients who came to our institution between 1997 and 2002, presented with cutaneous findings as the initial manifestation, and met both the criteria of the ACR and Chapel Hill consensus conference. We report their clinical and laboratory characteristics and outcomes.

Churg-Strauss syndrome is characterized by necrotizing vasculitis of small- to medium-sized blood vessels, which are associated with eosinophilic infiltration around the vessels and adjacent tissues according to the description agreed on at the Chapel Hill consensus conference.11 The term antineutrophil cytoplasmic antibody–associated vasculitis has been applied to small vessel vasculitides, including CSS, Wegener granulomatosis, and microscopic polyangiitis. Antineutrophil cytoplasmic antibody (ANCA) has been hypothesized to participate in the pathogenesis of leukocytoclastic vasculitis based on its association with small vessel vasculitides and the ability of these antibodies to activate neutrophils, monocytes, and endothelial cells in vitro.12 Up to 95% of patients with Wegener granulomatosis are positive for cytoplasmic pattern ANCs, which are less common in patients with limited or inactive disease. Most cytoplasmic ANCs react with proteinase 3.13 In contrast, the perinuclear fluorescence pattern (p-ANCA) is less disease specific. In general, p-ANCs directed against myeloperoxidase are thought to be highly specific for small vessel vasculitides. Guillemin et al14 reported the frequency of ANCs to be 50% to 78% in patients with CSS, similar to that in patients with microscopic polyangiitis.

There are still many aspects of the etiology and pathogenesis of CSS that remain unclear. To evaluate the typical clinical and pathologic findings in CSS, we recorded the clinical and histologic features of the initial cutaneous manifestations.

The study included 9 patients with CSS who presented to the Department of Dermatology at St Marianna University School of Medicine, Kawasaki, Japan, with initial cutaneous manifestations. The clinical characteristics of the patients are listed in the Table. All patients had CSS that was consistent with the definitions proposed by the Chapel Hill consensus conference and that fulfilled the criteria of the ACR. When ANCs were detected, their specificity was characterized by an enzyme-linked immunosorbent assay for reactivity with proteinase 3 or myeloperoxidase, using the technique recommended by the European ANCA Assay Standardization Group.15 All tissue specimens were obtained by skin biopsy, fixed in 10% formalin, step-sectioned, and stained with hematoxylin-eosin.
CASE 1

A 65-year-old woman first visited our hospital in February 1999 with a 1-week history of intensively painful purpuric lesions on the extensor surface of her legs. Also, she began to experience severe pain and paresthesias in her lower extremities, with sudden loss of sensation on the dorsum of her right foot. Her medical history was significant for asthma, which had been diagnosed 4 months earlier. One week after presentation, she developed purpuric lesions and an erythematous rash resembling erythema multiforme, which progressively involved her soles, thighs, and abdomen (Figure 1). She complained of bilateral ankle numbness, and a right foot drop was noted. Skin biopsy specimens of the purpura of the left lower extremity and the abdominal erythema demonstrated leukocytoclastic vasculitis. There was a predominant infiltration of eosinophils into the dermis around the vascular walls and nerve fibers (Figure 2). Laboratory tests revealed the following values: leukocytes, 21.1 x 10^3/μL; eosinophils, 11.3 x 10^3/μL; and IgE, 1400 IU/mL. The level of ANCAs with antibodies to myeloperoxidase (MPO-ANCA) was elevated (375 EU/mL [enzyme-linked immunosorbent assay units per milliliter]), and serologic tests were negative for rheumatoid factor. Findings consistent with mononeuritis multiplex symmetrically involving the peroneal and posterior tibial nerves were observed. An electromyogram revealed grossly abnormal findings, indicating loss of both motor and sensory function in the peripheral nerves of the legs. Ophthalmologic findings showed episcleritis. Radiography of the chest and paranasal sinuses revealed no abnormalities. The patient showed a good response to treatment with oral steroids, with total remission of symptoms and normalization of the eosinophil count and IgE levels within 2 months. She did not develop any additional skin lesions or systemic vasculitis during the 2-year follow-up. However, she continues to take low-dose prednisolone and has residual weakness in her left wrist and left foot.

CASE 2

A 59-year-old man presented with a long-standing history of severe asthma, which was generally managed with bronchodilators and the intermittent administration of steroids, including prednisone. He had been well until several months earlier, when he developed asthma. Treatment with 250 mg of pranlukast twice daily was begun. One month later, the patient presented with a 2-day history of palpable purpura, petechiae on his heels and fingers, and livedo reticularis on both legs. The rash began at his heels and progressed to his toes (Figure 3). He complained of recent arthralgia of his fingers and both ankles, without any sign of arthritis. A skin biopsy specimen from the petechiae on one of his toes demonstrated leukocytoclastic vasculitis with eosinophils and many granulomatous changes in the dermis. An infiltration of eosinophils was observed around the nerve fibers in the dermis (Figure 4). Laboratory analysis showed a white blood cell count of 9.4 x 10^3/μL, with 14% eosinophils, and an elevated IgE level (600 IU/mL), but serologic tests were negative for MPO-ANCA. Mononeuritis multiplex was diagnosed based on loss of dorsiflexion of the wrist and foot. After the patient was admitted to the hospital, the pranlukast therapy was discontinued. Oral predniso-
lone therapy led to a dramatic improvement, with resolution of the skin lesions, blood eosinophilia, and elevation of the serum IgE levels.

RESULTS

We examined 9 patients (3 men and 6 women) aged 21 to 72 years (mean age, 46 years) at the time of initial examination. The median time between the onset of asthma and CSS diagnosis was 43 months (interquartile range, 4 months to 14 years). Four patients (44%) received the leukotriene receptor antagonist (LRA) pranlukast before the onset of cutaneous symptoms. Three of the 4 patients (75%) developed cutaneous symptoms within 3 months; the other patient did not develop the symptoms for more than a year.

Nonthrombocytopenic palpable purpura on the lower extremities was the most common skin manifestation of CSS and was observed in all patients. Other symptoms included hemorrhagic lesions ranging from petechiae to extensive ecchymosis. Erythematous maculopapules, resembling erythema multiforme, were observed in 4 patients (44%). The clinical cutaneous features of the patients who were treated with pranlukast tended to be moderate petechiae but not ecchymosis. Involvement of the mononeuritis multiplex in the lower extremities was a consistent initial manifestation in all patients. However, the clinical severity of the cutaneous findings did not always seem to correlate with other indicators, such as myalgia and arthralgia.

A total of 11 biopsy specimens were obtained from the 9 patients with cutaneous findings: 6 from the lower extremities, 2 from the elbows, and 1 each from the fingers, abdomen, and soles. Histologically, small vessel vasculitides with a predominant infiltration of eosinophils was identified in all specimens. The papillary and middermal vessels were involved. Eosinophilic infiltration around the nerve fibers in the dermis was evident in 8 (73%) of the 11 biopsy specimens (Figure 2). Palisading granulomas were present in association with vessel-based changes in 4 specimens (36%).

Laboratory studies revealed hypereosinophilia and an extremely elevated serum level of IgE in all patients, together with an increased erythrocyte sedimentation rate and C-reactive protein level. The eosinophil count ranged from 1.3 to 24.0 x 10⁹/µL. The mean IgE level was 1393 IU/mL (range, 600-3400 IU/mL). Serologic tests for ANCA were performed in all patients. The results were positive for MPO-ANCA in 5 patients (56%) and negative for proteinase 3 ANCA in all patients. The MPO-ANCA levels were highest at the time of diagnosis and lowest during remission.

All 9 patients initially received high-dose oral steroid therapy, followed by an oral taper during remission. Dramatic improvement in the clinical cutaneous abnormalities and persistent peripheral neuropathy was noted in all patients except 2 after steroid treatment. The 2 unresponsive patients received high-dose oral prednisone therapy, without improvement, and continued to deteriorate neurologically. Additional pulsed doses of corticosteroids led to an improvement in their symptoms. Steroids were the cornerstone of treatment for CSS. Because they are usually sufficient for treating most patients who do not have severe organ involvement, they should be viewed as first-line therapy, without the addition of other immunosuppressive agents.

COMMENT

Diagnosis of CSS can be difficult because the syndrome may initially seem to represent a common association between asthma and allergic rhinitis. Because asthma it-
self might be associated with sinusitis, occasional pulmonary infiltration, and steroid dependency, a definitive diagnosis of CSS can be difficult to make until the abdominal viscera, heart, or nervous system becomes involved, which may be fatal in the latter 2 regions. Clinically, the diagnosis alone is difficult in the early stages of CSS because of the substantial overlap between the disorder and the typical symptoms of severe asthma. Also, the ACR criteria and Chapel Hill nomenclature are not designed to be diagnostic in individual cases, although they are often used for this purpose. In addition, both classification systems fail to provide clinicians with the ability to accurately establish a diagnosis. In the present study, we attempted to demonstrate that severe pain and parasthesias, purpura, and petechiae on the lower extremities occur concomitantly as the initial CSS manifestation. Histologically, almost all our patients showed a remarkable infiltration of eosinophils around the nerve fibers in the dermis. To our knowledge, this article represents the first time eosinophil infiltration around the nerves has been reported in CSS. Costello et al reported that eosinophils accumulated around airway nerve fibers and nerve bundles in patients with asthma. They suggested either that an eosinophilic chemoattractant substance was recruiting eosinophils to the nerves or that a specific eosinophilic adhesion molecule was expressed by the nerves. These findings indicate that the mononeuritis multiplex plays a primary role in various cutaneous manifestations of this disorder. Eosinophilic chemoattractant factors or adhesion molecules may be released from the nerves within these cutaneous manifestations. Therefore, we believe that the onset of cutaneous symptoms in the lower extremities associated with the mononeuritis multiplex should alert physicians to the possibility of CSS. Palisaded neutrophilic granulomatous dermatitis is an unusual entity that has not been completely defined, either clinically or histologically. Most cases have been associated with rheumatoid arthritis. We have observed that the cutaneous eruption can be seen in patients with CSS. Peripheral blood findings, as well as these initial cutaneous clinical and histologic findings, are hallmark manifestations of CSS, and their presence should prompt the clinician to consider this diagnosis. A careful balance between assessment of the clinical manifestations and the available pathophysiologic evidence can provide timely treatment of CSS, which may prevent serious morbidity or death. With the introduction of corticosteroid treatment, remission and survival in cases of CSS have greatly improved. Corticosteroid therapy is usually sufficient for treating most patients who do not have severe organ involvement. Patients with CSS who do not respond adequately to systemic corticosteroid therapy alone can be treated with additional immunosuppressive agents. Our patients responded very well to corticosteroid therapy and did not need additional immunosuppressive therapy. We believe that earlier diagnosis and institution of steroid therapy in cases of CSS may prevent irreversible tissue damage.

Little is known about the origin of vasculitis in CSS or about the cause of tissue eosinophilia. Recently, CSS has been described as “vasculitides strongly associated with atopic disorder,” or type 1 reactions in the classification of Gell and Coombs. Activated T lymphocytes play a central role through their production of cytokines, such as interleukins 4, 5, and 13, mediating the accumulation of mast cells, basophils, and, especially, eosinophils. Activation of eosinophils is a central feature of CSS, whereas eosinophilic cationic protein, eosinophil-derived neurotoxin, and lipid mediators seem to play a major role in the induction of eosinophilic vasculitis. In our study, increased concentrations of IgE were observed in all patients, and these levels showed a propensity to normalize during periods of disease remission. Our patients with CSS responded very well to steroid treatment, and the response was often dramatic. These findings, together with eosinophil counts and IgE measurements, may be useful in following disease activity and response to therapy. The findings of the present study, when considered in conjunction with those published by others, suggest that factors, including eosinophil counts and IgE levels, have a pathogenic central role in CSS.

We were interested to find out whether ANCA positivity correlated with more vasculitic features. Central nervous system involvement, one of the most severe disease manifestations associated with poor prognosis, is reportedly more common in p-ANCA–positive patients. Data from some series suggest that ANCA levels correlate with CSS disease activity. Peripheral ANCA were detected in only 5 (56%) of our patients, suggesting that these antibodies may play a role in the inflammatory diathesis that characterizes the disorder. The frequency of ANCA in the early phase was less than previously estimated and justifies the inclusion of CSS as an ANCA-associated vasculitis. Antineutrophil cytoplasmic antibodies can cause neutrophil activation and degranulation. However, despite their potential role in amplifying inflammation, their presence was not generally viewed as the primary cause of CSS; they are present in approximately only 50% of all patients with CSS. Therefore, patients with CSS that is associated with a prominent eosinophil inflammatory response may produce autoantibodies that react with eosinophil peroxidase but not with MPO.

Pranlukast offers a novel approach for the treatment of asthma. It is considered to be safe and effective, but several asthmatic patients who were treated with LRA have developed CSS. Thus, LRA therapy to treat asthma may be involved in the onset of CSS. This theory remains a controversial topic because it is unclear whether the concomitant reduction in corticosteroid dose during LRA therapy unmasks preexisting CSS or whether the LRA itself has a primary causative effect. In the present series, we described 4 patients (44%) treated with LRA who subsequently developed prominent skin lesions and neurologic findings associated with CSS; p-ANCA was detected in 2 of them (patients 4 and 5). We also found that the cutaneous manifestations seen within several months in patients 2, 4, and 5, all of whom received LRA, tended not to be as severe as those of other patients in our series. Thus, we did not find sufficient evidence to suggest that the disorder is triggered by an idiosyncratic or hypersensitivity reaction to LRA therapy. However, we believe that there may be a correlation in some cases of CSS based on eosinophil and IgE activity. More experimental work in combination with clinical observa-
tions is required to further elucidate these mechanisms. Because asthma generally remains persistent and difficult to manage, patients with CSS who receive pranlukast treatment might need continuous observation and further therapeutic intervention.

Accepted for Publication: December 27, 2004.

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Funding/Support: This work was supported by grants from the Scientific Research Fund of the Ministry of Education, Science, Sports, and Culture, Japan (Grant-in-Aid for Scientific Research No. 14570828).

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