This Month in Archives of Dermatology
Arch Dermatol. 2007;143:837.

Studies

Use of Biological Agents in Patients With Moderate to Severe Psoriasis: A Cohort-Based Perspective
María Jones-Caballero; Jane Unaeze; Pablo F. Peñas; Robert S. Stern

Vincent D. Criscione; Martin A. Weinstock
Arch Dermatol. 2007;143:854-859.

Sun-Related Factors, Betapapillomavirus, and Actinic Keratoses: A Prospective Study
Penelope McBride; Rachel Neale; Nirmala Pandeya; Adèle Green
Arch Dermatol. 2007;143:862-868.

Breaking Strength of Barbed Polypropylene Sutures: Rater-Blinded, Controlled Comparison With Nonbarbed Sutures of Various Calibers
Rashid Rashid; Mark Sartori; Lucile E. White; Mark T. Villa; Simon S. Yoo; Murad Alam
Arch Dermatol. 2007;143:869-872.

Observations

Efalizumab in the Treatment of Discoid Lupus Erythematosus
Naila Usmani; Mark Goodfield
Arch Dermatol. 2007;143:873-877.

Dendritic Cells in Pigmented Basal Cell Carcinoma: A Relevant Finding by Reflectance-Mode Confocal Microscopy
Sonia Segura; Susana Puig; Cristina Carrera; Josep Palou; Josep Malvehy

Treatment of Recurrent Squamous Cell Carcinoma of the Skin With Cetuximab
Julie E. Bauman; Keith D. Eaton; Renato G. Martins
Arch Dermatol. 2007;143:889-892.

Endemic Pemphigus Vulgaris
Rocielar Rocha-Alvarez; Alex G. Ortega-Loayza; Horacio Friedman; Iphis Campbell; Valeria Aoki; Evandro A. Rivitti; David Dasher; Ning Li; Luis A. Diaz; for the Cooperative Group on Fogo Selvagem Research
Arch Dermatol. 2007;143:895-899.
Efalizumab-Associated Papular Psoriasis
Akmal S. Hassan; Dagmar Simon; Hans-Uwe Simon; Lasse R. Braathen; Nikhil Yawalkar
Arch Dermatol. 2007;143:900-906.

Childhood Flexural Comedones: A New Entity
Margarita Larralde; María Eugenia Abad; Andrea Santos Muñoz; Paula Luna
Arch Dermatol. 2007;143:909-911.

Editorials
Poor Adherence to Treatments: A Fundamental Principle of Dermatology
Saba M. Ali; Robert T. Brodell; Rajesh Balkrishnan; Steven R. Feldman
Arch Dermatol. 2007;143:912-915.

Cutaneous T-Cell Lymphoma Epidemiology: Patients Providing the Power
Stuart R. Lessin
Arch Dermatol. 2007;143:916-918.

The Off-Center Fold
Michael E. Ming
Arch Dermatol. 2007;143:935-936.

Special Articles
Cutaneous T-Cell Lymphoid Dyscrasia: A Unifying Term for Idiopathic Chronic Dermatoses With Persistent T-Cell Clones
Joan Guitart; Cynthia Magro
Arch Dermatol. 2007;143:921-932.

skINsight
Dermoscopy of Port-Wine Stains
Francisco Vázquez-López; Pablo Coto-Segura; Alejandro Fueyo-Casado; Narciso Pérez-Oliva
Arch Dermatol. 2007;143:962.

Off-Center Fold
Acute Blue Patch on the Forearm—Quiz Case
Vera M. R. Heydendael; Rick Hoekzema
Arch Dermatol. 2007;143:937-942.

Acute Blue Patch on the Forearm—Diagnosis
Arch Dermatol. 2007;143:937-942.

Painful Nodule on the Knee—Quiz Case
Michael P. Heffernan; Danette D. Bentley; Beatriz Tapia; Paul Klekotka
Arch Dermatol. 2007;143:937-942.

Painful Nodule on the Knee—Diagnosis
Arch Dermatol. 2007;143:937-942.

Diffuse Cutaneous Nodules—Quiz Case
Mark Abdelmalek; Jennifer Han; Herbert Allen
Arch Dermatol. 2007;143:937-942.
Diffuse Cutaneous Nodules—Diagnosis
Arch Dermatol. 2007;143:937-942.

A Blue-Gray Subungual Discoloration—Quiz Case
Stéphane Dalle; Sandra Ronger-Savle; Lorenza Cicale; Brigitte Balme; Luc Thomas
Arch Dermatol. 2007;143:937-942.

A Blue-Gray Subungual Discoloration—Diagnosis
Arch Dermatol. 2007;143:937-942.

The Cutting Edge
Intralesional Bleomycin for Angiolymphoid Hyperplasia
Necmettin Akdeniz; Mustafa Kösem; Ömer Çalka; Serap Günes Bilgili; Ahmet Metin; Ibrahim Gelincik
Arch Dermatol. 2007;143:841-844.

Archives a Century Ago
Hydroa Pruriginosum.
Arch Dermatol. 2007;143:838.

Research Letters
Virologic Safety of Polyvinyl Chloride Film in Dermoscopic Analysis of Mucosal Areas
Maria Rosaria Zampino; Alessandro Borghi; Elisabetta Caselli; Monica Galvan; Monica Corazza; Enzo Cassai; Annarosa Virgili
Arch Dermatol. 2007;143:945-946.

Granuloma Annulare: Long-term Follow-up
Mark V. Dahl
Arch Dermatol. 2007;143:946-947.

Overexpression of Matrix Metalloproteinases, Chemokines, and Chemokine Receptors Relevant for Metastasis in Experimental Models Not an Indication of Lymph Node Metastases in Human Melanoma
Kerstin Otto; Hans Starz; Juergen C. Becker; David Schrama
Arch Dermatol. 2007;143:947-948.

Leadership Workforce in Academic Dermatology
Elissa Turner; Jane Yoo; Sharon Salter; Alexa B. Kimball
Arch Dermatol. 2007;143:948-949.

Correspondence
Paraneoplastic Relapsing Polychondritis
Philip R. Cohen
Arch Dermatol. 2007;143:949-950.

Success of Goeckerman Treatment in 2 Patients With Psoriasis Not Responding to Biological Drugs
Temitope F. Soares; Mark D. P. Davis
Arch Dermatol. 2007;143:950-951.
Dissemination of a Localized Cutaneous Infection With *Mycobacterium chelonae* Under Immunosuppressive Treatment
Wolfram Hoetzenecker; Anja Ulmer; Karin Klingel; Volkhard A. J. Kempf; Stefan Schanz; Gisela Metzler; Gerhard Fierlbeck
*Arch Dermatol.* 2007;143:951-952.

Verruca Plana–Like Papules as a New Manifestation of Erdheim-Chester Disease
Teruki Yanagi; Naoko Kato; Naoko Yamane; Rinko Osawa; Hiroaki Hiraga
*Arch Dermatol.* 2007;143:952-953.

Blaschko Linear Nodular Morphea With Dermal Mucinosis
Kapil Jain; Surabhi Dayal; Vijay Kumar Jain; Kamal Aggarwal; Anu Bansal
*Arch Dermatol.* 2007;143:953-955.

An Unusual Presentation of Cutaneous Larva Migrans
Pichaya A. Sarasombath; Priya K. Young
*Arch Dermatol.* 2007;143:955.

**Corrections**

Errors in Author Contributions in: Store-and-Forward Teledermatology in Skin Cancer Triage: Experience and Evaluation of 2009 Teleconsultations
*Arch Dermatol.* 2007;143:886.

Incorrect Dose in: Randomized Double-blind Trial of Treatment of Vitiligo: Efficacy of Psoralen–UV-A Therapy vs Narrowband–UV-B Therapy
*Arch Dermatol.* 2007;143:906.

**Archives Web Quiz Winner**

April 2007 Web Quiz Winner
*Arch Dermatol.* 2007;143:918

**Announcement**

Archives Feature
*Arch Dermatol.* 2007;143:932.

**Editor’s Note**
*Arch Dermatol.* 2007;143:936.

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Treatment of Recurrent SCC of the Skin With Cetuximab

Squamous cell carcinoma (SCC) represents approximately 15% of all nonmelanoma skin cancers. Few therapeutic options exist for patients with advanced SCCs, and progressive disease leads to substantial morbidity and mortality. Cetuximab is a recombinant, human-mouse chimeric antibody that competitively inhibits epidermal growth factor, a tyrosine-kinase receptor richly expressed by SCCs. In this case series, Bauman et al describe 2 elderly patients with extensive, in-transit recurrence of SCC following surgery and irradiation who demonstrated excellent responses to cetuximab. The drug was well tolerated with the exception of an acneiform rash requiring dose reduction in 1 patient.

See page 889

Sun-Related Factors, Betapapillomavirus, and Actinic Keratoses

Actinic keratoses (AKs) are sun-induced skin tumors that are strongly associated with squamous cell carcinomas (SCCs). In addition to solar radiation, epidemiologic and molecular data support the causative role of Betapapillomavirus in AKs. In this prospective, community-based cohort study, McBride et al measured the prevalence of Betapapillomavirus DNA in eyebrow hair follicle cells at baseline, documented subsequent sun exposure over the next 7 years, and then measured the prevalence of AKs. These data lend further support to the concept that Betapapillomavirus enhances the effects of increasing age, sun-sensitive phenotypes, and high-dose UV radiation to further increase the risk of developing AKs.

See page 862

Breaking Strength of Barbed Polypropylene Sutures

Barbed sutures have been approved by the US Food and Drug Administration for facial lifting procedures. Polypropylene is the most commonly used substrate from which barbs are shaved to extend outward in a helical array. The process of creating these barbs decreases the effective diameter of the suture and thus its strength. In this rater-blinded controlled trial, Rashid et al compared the fiber strength of barbed and nonbarbed suture, demonstrating that the breaking strength of barbed 2.0 polypropylene suture was intermediate between that of 2.0 and 3.0 nonbarbed suture. These data suggest that manufacturers of barbed suture are conservative in their estimate that the strength of 2.0 polypropylene is comparable to that of 4.0 nonbarbed suture. Surgeons may be reassured that rupture is unlikely, even with inadvertent application of excessive force.

See page 869


The incidence of cutaneous T-cell lymphoma (CTCL) was last examined extensively using data for 1973 through 1992 and including only cases of mycosis fungoides and Sézary syndrome. In this study from 13 population-based cancer registries of the Surveillance Epidemiology and End Results Program of the National Cancer Institute, Criscione and Weinstock investigated incidence trends for the entire group of diseases classified as CTCL from 1973 to 2002. These data may be useful in planning public health strategies, identifying risk factors, and understanding the causes of CTCL.

See page 854

Endemic Pemphigus Vulgaris

Pemphigus vulgaris, pemphigus foliaceus, and its endemic form, fogo selvagem, each possess distinct clinical, histologic, epidemiologic, and serologic features. Pemphigus foliaceus and fogo selvagem are identical clinically, histologically, and serologically, but the epidemiologic features of fogo selvagem are distinctive. In this case series, Rocha-Alvarez et al describe 8 patients with a mucocutaneous disease that clinically and histologically was consistent with pemphigus vulgaris, but with the epidemiologic features of fogo selvagem. Serologic evaluation of these patients revealed autoantibodies against desmoglein 3 and desmoglein 1, providing serologic evidence of a new endemic variant of pemphigus vulgaris.

See page 895
Hydroa Pruriginosum. By Dr. R. Abrahams.

In the discussion of the case the opinion was general that it was to be regarded rather as a bullous urticaria, since plain urticarial lesions were also present on various portions of the body. Dr. Parounagian believed, since all the bullous lesions were on the elbow and thighs, some external irritant was the cause of the urticarial efflorescences. Dr. Gottheil recognized the case as one that had been under his care at Lebanon Hospital for a general and violent seborrhoeal eczema and commented on the absolute worthlessness of the histories in the great majority of these cases.

Intralesional Bleomycin for Angiolymphoid Hyperplasia

Necmettin Akdeniz, MD; Mustafa Kösem, MD; Ömer Çağka, MD; Serap Günsel Bilgili, MD; Ahmet Metin, MD; İbrahim Gelincik, MD; Yüzyüncü Yıl University Faculty of Medicine, Van (Drs Akdeniz, Kösem, Çağka, Bilgili, and Gelincik), and S. B. Atatürk Education and Research Hospital, Ankara (Dr Metin), Turkey

REPORT OF CASES

CASE 1

A 51-year-old woman presented with a 4-year history of slightly pruritic, bleeding papules on her right ear. Approximately 2 years earlier, the lesions had been excised, but they had recurred the following year and had increased in number within the past 3 months. The dermatologic examination revealed 5 violaceous, erythematous soft papules ranging from 3 mm to 1 cm in diameter in the helix and on the upper lateral postauricular region of the right ear (Figure 1). The results of the systemic examination were normal, without evidence of lymphadenopathy. Routine laboratory tests, including a complete blood cell count, erythrocyte sedimentation rate, routine blood biochemical profile, complete urinalysis, IgE level, antistreptolysin-O and C-reactive protein assessments, and x-ray imaging of the chest, demonstrated no abnormalities. Histopathologic examination of a punch biopsy specimen revealed angiolymphoid hyperplasia with eosinophilia (ALHE) (Figure 2).

CASE 2

A 28-year-old woman presented with a 1-year history of generalized pruritic hemorrhagic papules on her right ear. The papules, which initially were small, itchy, and acneiform, had extended to the posterior auricular region during the last 3 months. The patient also had small, itchy, pimplelike lesions on her body, which had appeared almost simultaneously. There was no history of insect bite or trauma. On dermatologic examination, the helix of the right ear was erythematous and swollen, and there were a number of purple, erythematous, soft papules and nodules ranging from 0.5 to 3 cm in diameter on the helix and postauricular region (Figure 3). On the abdomen, midline of the back, extensor aspects of both forearms,
and bilateral pretibial regions, there were numerous erythematous, excoriated papules with hemorrhagic crusting. Three lymph nodes, approximately 1 cm in diameter, were palpable on the right postauricular and cervical region ipsilateral to the ear lesions. The results of the systemic examination were normal. Routine laboratory tests revealed an elevated level of IgE (1150 IU/mL) and eosinophilia (7.4%). The histopathologic diagnosis was reported as ALHE (Figure 4).

**THERAPEUTIC CHALLENGE**

Angiolymphoid hyperplasia with eosinophilia is a proliferative vascular lesion of skin and mucosa membrane.\(^1\)\(^-\)\(^5\) The most common treatments are local surgical excision, intralesional corticosteroid therapy, and laser ablation with continuous-wave carbon dioxide, argon laser, or 585-nm pulsed-dye laser.\(^7\) The rate of recurrence after surgical excision is as high as 33% to 50%.\(^7\) In case 1, the lesions recurred and increased in number after surgical excision. Because surgical excision was not successful, we prescribed bleomycin sulfate therapy, which had been locally used, with success, in proliferative lesions of skin such as verruca and lymphangioma. The exceptionally promising therapeutic response in case 1 prompted us to use bleomycin in the second case, in which the lesions were widespread and unsuitable for surgical excision.

**SOLUTION**

In case 1, intralesional bleomycin sulfate therapy was initiated at a dosage of 0.2 U (0.1 mg) once a month. The dose of the second injection was increased to 0.4 U. No systemic or local adverse effects, such as swelling, Raynaud phenomenon, scarring, or pigment alteration, were observed. The pain was mild to moderate but always tolerable and subsided within 30 minutes after the injection. The lesions completely disappeared at the end of the fifth month, and therapy was discontinued. After 9 months of follow-up, the patient still had no recurrence.

In case 2, intralesional bleomycin therapy was used in the same way as in case 1. All the lesions were injected with bleomycin, and the therapy was repeated once a month for 5 months. The protocol was interrupted because of pregnancy after the fifth injection. In both cases, all the lesions completely disappeared (Figure 5 and Figure 6). During the follow-up, no new lesions occurred.

**COMMENT**

Angiolymphoid hyperplasia with eosinophilia is a rare vasoproliferative disease with a benign nature.\(^1\)\(^-\)\(^6\) It occurs in the third to fourth decades of life, with a higher incidence in women. The etiology is unknown.\(^1\)\(^-\)\(^6\) The most common sites are the head and neck, particularly the region around the ears and external ear canals. Single or multiple, grouped, and dome-shaped red papules, nodules, or plaques, which are located in the subcutaneous tissue and dermis, are the most characteristic features.\(^1\)\(^-\)\(^6\) The condition was first described by Wells and Whimster in 1969. It is defined as a proliferation of skin and mucous membranes in the dermis and subcutaneous tissue that is known as to originate from the vascu-
lature. It mostly occurs among Asian women aged 20 to 50 years. The median age at presentation is 30 to 33 years. Our patients were 28- and 51-year-old women.

Clinically, dome-shaped papules and nodules with a relatively regular surface are the main features of the disease. They may be variable in color (red to brown) and either eroded or crusted. In approximately 85% of patients, skin lesions are located on the head and neck, particularly on the scalp, forehead, and area around the ears. They usually measure 0.5 to 2 cm in diameter, extend over an area of 0.2 to 8 cm², and may be painful and itchy. Spontaneous bleeding and pulsation are rare findings. Local lymphadenopathy is found in 5% to 20% of the cases, while peripheral eosinophilia is found in 20%. Although the pathogenesis is still unclear, it has been suggested that there may be some predisposing factors such as trauma, arteriovenous shunts, high blood levels of estrogens, atopic reactions, infections, and reactive hyperplasia or benign neoplasia of the vasculature.

The clinical differential diagnosis of ALHE includes Kimura disease, Kaposi sarcoma, salivary gland tumors, squamous cell carcinoma, pyogenic granuloma, angiomomas, cavernous hemangioma, granuloma faciale, periarthritis nodosa, sarcoidosis, lymphocytoma cutis, skin metastases, and enlarged lymph nodes. Kimura disease, hemangioendothelioma, angiosarcoma, and arthropod or insect bites should be considered in the histopathologic differential diagnosis. In past years, Kimura disease was classified as a variant of ALHE, but today it is considered a different entity. Complications are rare. In severe cases, obstruction of auditory tract may result in conductive hearing loss. Orbital involvement resulting in diplopia and proptosis was reported in 1 case.

Generally, surgical excision is the preferred treatment; however, about one-third of lesions recur after excision. Other treatment choices are Mohs microsurgery, diathermy, cryotherapy, cautery, laser therapy (carbon dioxide laser, argon laser, and 585-nm pulsed-dye laser), radiotherapy, cessation of estrogen replacement therapy, and therapy with corticosteroids (oral, topical, or intralesional), indomethacin, imiquimod, interferon alfa, oral retinoids, pentoxifylline, intravenous vinblastine sulfate, and intralesional chemotherapeutics (vinblastine and fluorouracil).

Bleomycin is a cytotoxic agent with antitumoral, antibacterial, and antiviral activity. The drug is available as a powder. It should be reconstituted with 0.9% sodium chloride into a 1-U/mL solution. It binds to DNA, causing strand scission and elimination of pyrimidine and purine bases. At 48 hours after injection, apoptotic keratinocytes are seen in the epidermis. Possible systemic toxic effects from bleomycin therapy include myelosuppression, hyperpigmentation, hyperkeratosis, ulceration, pulmonary fibrosis, headache, nausea, vomiting, hyperthermia, and hypotension. The small volumes used in local therapy, however, do not cause systemic toxic effects. Local adverse effects such as pain, swelling, and Raynaud phenomenon have been reported. Intralional bleomycin has been used in the treatment of recalcitrant warts, lymphangiomas, and hemangiomas.
Patient 1 had a recurrence and an increase in the number of lesions after surgical excision. To our knowledge, there is only 1 previous report mentioning the use of intralesional bleomycin for the treatment of ALHE in the current literature. We report complete responses in our 2 cases. There were no recurrences during 9 months of follow-up in either patient. This positive outcome suggests that intralesional bleomycin prescribed in the indicated dosages is an effective and safe mode of therapy for ALHE.

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Study supervision: Akdeniz.

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REFERENCES

Use of Biological Agents in Patients With Moderate to Severe Psoriasis

A Cohort-Based Perspective

Maria Jones-Caballero, MD, PhD; Jane Unaeze, MD; Pablo F. Peñas, MD, PhD; Robert S. Stern, MD

Objective: To compare characteristics of patients enrolled in a long-term multicenter cohort trial who had used biological therapies for treatment of psoriasis with those who had not used these agents.

Design: Retrospective analysis of users vs nonusers of biological therapies.

Setting: Database from the PUVA Follow-up Study, a multicenter, 30-year study of patients originally treated with psoralen UV-A (PUVA) for moderate to severe psoriasis.

Patients: A total of 521 patients who completed the last cycle of follow-up of the PUVA Follow-up Study.

Main Outcome Measures: Demographic data, severity data (physician global assessment), type of biological therapy used, patients’ opinions about their therapy, and their best treatment.

Results: Seventy-four of 521 patients (14%) used biological therapies: 65% etanercept (n=48), 22% infliximab (n=16), 11% efalizumab (n=8), and 8% alefacept (n=6). Users of biological therapies were younger, had more formal education, and were more likely to have had a greater extent of psoriasis at entry than the other cohort members. In 1998, those who used biological treatments were more likely than other cohort members to have been assessed as having severe psoriasis. In 2004, no significant difference was noted. Users of etanercept considered this agent to be as effective as methotrexate and more effective in clearing their skin and having fewer adverse effects than PUVA or UV-B. The proportion of patients originally enrolled in the 16 centers who had used biological agents varied greatly (0%-33%).

Conclusion: After short durations of therapy, patients’ opinions about biological agents tended to be positive.

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Since 2003, multiple biological therapies have been approved for treatment of moderate to severe psoriasis. Nearly all public data about those agents comes from company-sponsored studies, and most only assess response over a 3- to 6-month period of standardized doses. A recent report suggests that efficacy observed in clinical practice is less than that observed in clinical trials.

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See also pages 912 and 950

The PUVA Study was originally organized as a prospective study of the short-term efficacy and safety of oral psoralens and UV-A (PUVA) for the treatment of moderate and severe psoriasis. Organized in the 1975-1976 period at 16 academic centers, the study recruited 1450 patients, 65% men (mean age at enrollment, 44 years). In 1977, the PUVA Follow-up Study was reorganized as a long-term safety and efficacy study and enrolled 1380 of the 1450 patients treated under the initial protocol of the PUVA Study. For 30 years, the PUVA Follow-up Study has documented health events, treatments, adverse effects, quality of life, and severity of the psoriasis. The study includes 22 cycles of patient interviews, 9 cycles of standardized, study-sponsored dermatologic examinations, and periodic eye examinations. Patients were observed regardless of their continued use of PUVA or continuing care for their psoriasis at the original center. Data collection for the cohort ended in the spring of 2005.

This cohort experience provides an opportunity to study the use of biological agents among a diverse spectrum of patients ascertained at many academic practices independent of enrollment in company-sponsored clinical trials. In the last decade, use of PUVA in this cohort...
has become infrequent. Cohort patients have used a wide range of therapies, including systemic agents. We determined the frequency of the use of biological agents, compared the characteristics of cohort patients who used and did not use biological agents, and quantified the patients’ opinions about these new therapies.

### METHODS

Detailed descriptions of the methods of the PUVA Follow-up Study and the composition of the cohort have been previously published. The current report includes all data collected through the 22nd and final cycle of the follow-up (FY-22) as of May 2005.

We compared the disease and demographic characteristics for patients who reported use of any biological treatments for psoriasis (biological group) with other cohort patients who had never used these therapies and were interviewed during FY-22. We also compared physicians’ global assessments (PGAs) of patients in 1998, when no biological treatments were available, with those made in 2005, about 2 years after the first licensing of these agents. The PGAs of severity were completed as part of the standardized dermatologic examination (rated clear, mild, moderate, or severe). In addition, during FY-22, we asked all participants to answer the following question: “Over the 28 years of the PUVA study, is there one treatment that has been most beneficial? If yes, specify which treatment.”

We asked only the biological group to rate the biological treatments and other therapies they had ever used on a Likert scale (1, best; 5, worst) with respect to the following questions: (1) “How well did your skin clear?” (2) “How long did your skin stay clear after stopping treatment?” (3) “How easy was the treatment to use?” and (4) “The side effects you may have experienced?” We calculated the percentage of patients who responded 1 or 2 (best or near best) to determine the percentage of patients with a positive opinion. Any evaluation including fewer than 13 patients was excluded from the analysis.

Statistical analysis was performed with SPSS, version 11 for Mac OS (SPSS Inc, Chicago, Illinois), using the t test, Fisher exact test, Mann-Whitney test, and Wilcoxon signed rank test, depending on the characteristics of variables.

### RESULTS

As of May 2005, 521 patients had completed FY-22. Of the original cohort of 1380 patients, 617 had died, 127 had resigned, and 115 were otherwise lost. There were 74 patients (14% of those interviewed in FY-22) reporting use of biological agents, of whom 4 had used multiple agents (3 had used both etanercept and infliximab, and 1 had used infliximab and efalizumab). Overall, 48 patients had used etanercept (Enbrel; Amgen, Thousand Oaks, California) (65% of all users of biological agents), 16 infliximab (Remicade; Centocor, Malvern, Pennsylvania) (22%), 8 efalizumab (Raptiva; Genentech, South San Francisco, California) (11%), and 6 alefacept (Amevive; Biogen-Idec, Cambridge, Massachusetts) (8%). Because some patients used multiple treatments, these percentage add to more than 100.

Members of the biological group were not different from other cohort members in sex distribution, but the biological group was younger and had more formal education (Table 1). There were no statistically significant differences between groups with regard to job, marital status, or general health. The percentage of patients reporting a diagnosis of psoriatic arthritis was also comparable (data not shown).

In 1998, the time of the most recent study-sponsored dermatologic examination prior to the availability of biological therapies, eventual users of biological agents were significantly more likely than nonusers to have moderate to severe PGAs (Table 2). When FY-22 PGA scores for biological users were compared with 1998 scores, a significant increase in the proportion of patients rated as having clear skin or mild psoriasis was observed (57.7% vs 33.3%) (P = .01). Among cohort members who had not used biological agents, the distribution of PGA scores in 1998 and FY-22 was remarkably similar (Table 3).

A higher proportion of patients in the biological agent group than other study participants interviewed during FY-22 previously used methotrexate, retinoids, and cyclosporine. Both total lifetime PUVA treatments and months of use of methotrexate were significantly higher in the biological agent group (Table 3).

In response to the question about their most beneficial treatment over the 28 years of the PUVA study (Table 4), 74% of patients who had not used biological agents and who indicated a single most beneficial therapy chose PUVA as their most beneficial treat-
ments. Nearly half of all users of tumor necrosis factor α inhibitor gave comparable positive statements about these agents. In Table 5 we summarize the results of pairwise comparisons of opinions of etanercept users about effectiveness and safety of etanercept compared with PUVA, UV-B, and methotrexate in the categories of clearing the skin, durability of remission, ease of use, and tolerability so far experienced. Etanercept was considered more effective in clearing the skin than PUVA or UV-B, and in short-term use appeared to be better tolerated than the 3 drugs with which patients had long-term experience. The number of users of other biological agents was too small for meaningful comparisons. The proportion of patients at the 16 centers who reported using biological agents varied substantially, from 0% to 33% of those interviewed.

### Table 2. Psoriasis PGAs by Use of Biological Agents and Year of Assessment

<table>
<thead>
<tr>
<th>PGA</th>
<th>Biological Agent Users</th>
<th>Other Cohort Members</th>
<th>All Cohort Patients</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1998</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clear</td>
<td>0</td>
<td>22 (6)</td>
<td>22 (5)</td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>21 (33)</td>
<td>191 (52)</td>
<td>212 (49)</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>27 (43)</td>
<td>120 (33)</td>
<td>147 (34)</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>15 (24)</td>
<td>36 (10)</td>
<td>51 (12)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>63 (100)</td>
<td>369 (100)</td>
<td>432 (100)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>2004</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clear</td>
<td>9 (15)</td>
<td>30 (9)</td>
<td>39 (10)</td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>25 (42)</td>
<td>154 (47)</td>
<td>179 (46)</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>16 (27)</td>
<td>106 (33)</td>
<td>122 (32)</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>9 (15)</td>
<td>36 (11)</td>
<td>45 (12)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>59 (100)</td>
<td>326 (100)</td>
<td>385 (100)</td>
<td>.35</td>
</tr>
<tr>
<td>P value</td>
<td>.01</td>
<td>.08</td>
<td>.06</td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations: ND, not determined; NS, not significant; PGA, physician global assessment.**

a Unless otherwise indicated, data are reported as number (percentage) of patients.

b Test for biological agent users vs nonusers.

c May not sum to 100% due to rounding.

d Wilcoxon signed rank test for 1998 vs 2004 data.

### Table 3. Comparison of Other Treatments Used by Biological Agent Users and Other Cohort Members

<table>
<thead>
<tr>
<th>Other Treatment</th>
<th>Biological Agent Users (n = 74)</th>
<th>Other Cohort Members (n = 447)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PUVA</td>
<td>Patients</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>Total treatments, No.</td>
<td>275 (160-459)</td>
<td>181 (96-312)</td>
</tr>
<tr>
<td>UV-B</td>
<td>Patients</td>
<td>91.9</td>
<td>90.6</td>
</tr>
<tr>
<td></td>
<td>Total treatments, No.</td>
<td>277 (132-775)</td>
<td>250 (73-579)</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>Patients</td>
<td>78.4</td>
<td>55.9</td>
</tr>
<tr>
<td></td>
<td>Total treatment duration, mo</td>
<td>60 (25-102)</td>
<td>24 (9-68)</td>
</tr>
<tr>
<td>Oral retinoids</td>
<td>Patients</td>
<td>29.7</td>
<td>15.7</td>
</tr>
<tr>
<td></td>
<td>Total treatment duration, mo</td>
<td>49 (19-63)</td>
<td>36 (14-96)</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>Patients</td>
<td>17.6</td>
<td>4.2</td>
</tr>
<tr>
<td></td>
<td>Total treatment duration, mo</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

**Abbreviations: NA, not available; NS, not significant; PUVA, psoralen UV-A.**

d Data are presented as percentage of patients and median number (25th-75th percentile range) of treatment sessions or months.

By mid 2005, biological therapies for psoriasis had been used by about 1 in 7 members of the PUVA cohort. Most of these patients (82%) used tumor necrosis factor α inhibitors, and most of these used etanercept. Although alefacept and efalizumab were the first to receive US Food and Drug Administration approval for treatment of psoriasis, they were much less frequently used than etanercept. Some of our patients might have been treated as participants in clinical trials, and others might have received the drug by off-label prescription. The limited experience of dermatologists with these drugs might have affected the opinions of users about biological treatments, and some of our cohort might have been treated at doses lower than those currently advocated for etanercept.

In the present study, users of biological agents were younger and more educated than the other cohort members. Younger and more educated persons might be more likely to be early adopters of new therapies. Among the reasons for this might be greater awareness of new drugs, less resistance to new therapies, or better insurance coverage. Also, physicians might be more hesitant to use systemic immunosuppressive agents in older patients, which is supported by our findings that methotrexate users were significantly younger than nonusers (P < .05; data not shown).

Users of biological treatments had used other systemic therapies for treatment of psoriasis more often and for a longer time than other cohort members, including PUVA, methotrexate, oral retinoids, and cyclosporin. For example, the proportion of biological agent users who had also used cyclosporine was more than 3 times that...
of other cohort patients. In addition to being early adopters, users of biological agents might prefer a more aggressive approach to treatment or have better access to new treatments.

Dermatologists in this study assessed a higher proportion of biological agent users as having moderate or severe disease on a standardized examination performed about 5 years before biological agents became available. This finding suggests those who eventually used biological agents had more severe or treatment-refractory disease than other cohort members.

Our data suggest that use of biological agents in our cohort had a modest but significant beneficial effect on the severity of psoriasis. Among users of biological agents, there was a significant improvement in the distribution of PGA scores from 1998 to 2004-2005 (ie, from the era before the introduction of biological agents to roughly 2 years after they were approved). Most of the improvement in PGA scores occurred in the moderate-severity group. The proportion with severe disease did not decrease significantly. At the time of the final assessment, nearly half of biological agent users still had moderate or severe disease.

Patients’ opinions about biological agents were generally positive. Nearly half of the patients who used alefacept, etanercept, or infliximab considered those treatments to be the best they had ever used. In 7 of 10 comparisons to the 3 other systemic therapies most often used by the cohort (PUVA, UV-B, and methotrexate), users of etanercept were significantly more likely to rate this therapy more favorably with respect to clearing, remission, ease of use, and adverse effects than the other treatments they had used. However, this finding should be interpreted with caution. Experience with etanercept spanned at most a few years compared with decades of use for some patients with methotrexate, UV-B, and PUVA. Experience with etanercept was so limited that fewer than 50% of patients answered the questions concerning remission. Given the limited time these agents have been available, patients’ indications of safety at this point are most likely statements about tolerability rather than long-term safety.11,12

Recent analyses have raised concern about the safety of some of these agents in moderate to long-term use for other indications.13 Higher doses of some biological agents are used for psoriasis than for other indications. Robust long-term safety data for biological agents used to treat patients with psoriasis are still lacking.14 Although the manufacturers of these products are committed to long-term safety studies, a recent review of the status of such

### Table 4. Treatments Evaluated by Biological Agent Users and Other Cohort Members as Most Beneficial in Treating Psoriasis

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Biological Agent Users</th>
<th>Other Cohort Members</th>
<th>All Cohort Members</th>
<th>P Valueb</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ever Used</td>
<td>Thought It Best</td>
<td>Ever Used</td>
<td>Thought It Best</td>
</tr>
<tr>
<td>PUVA</td>
<td>70</td>
<td>14 (20)</td>
<td>352</td>
<td>259 (74)</td>
</tr>
<tr>
<td>UV-B</td>
<td>64</td>
<td>1 (2)</td>
<td>351</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>55</td>
<td>17 (31)</td>
<td>211</td>
<td>41 (19)</td>
</tr>
<tr>
<td>Retinoid</td>
<td>22</td>
<td>0</td>
<td>57</td>
<td>13 (23)</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>11</td>
<td>0</td>
<td>19</td>
<td>4 (21)</td>
</tr>
<tr>
<td>Alefacept</td>
<td>6</td>
<td>3 (50)</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>Etanercept</td>
<td>44</td>
<td>21 (48)</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>Infliximab</td>
<td>13</td>
<td>6 (46)</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>Efalizumab</td>
<td>7</td>
<td>2 (29)</td>
<td>0</td>
<td>NA</td>
</tr>
</tbody>
</table>

Abbreviations: NA, not available; ND, not determined; NS, not significant; PUVA, psoralen UV-A.

a Data are reported as number of patients who indicated that they had ever used the treatment and number (percentage) of patients who thought that treatment was the most beneficial for treating their psoriasis. Only patients who reported actual use of a therapy were asked to assess whether it was most beneficial. This was an optional section of the interview, and 99 patients chose not to complete this section.

b \( \chi^2 \) Test for biological agent users vs other cohort members who reported use of that therapy.

### Table 5. Pairwise Comparisons of Opinions of Etanercept Users About Effectiveness and Safety of Etanercept Compared With PUVA, UV-B, and Methotrexate

<table>
<thead>
<tr>
<th>Treatment Characteristic</th>
<th>PUVA</th>
<th>UV-B</th>
<th>Methotrexate</th>
<th>S E I P Value</th>
<th>S E I P Value</th>
<th>S E I P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clearing</td>
<td>13</td>
<td>22</td>
<td>4</td>
<td>.03</td>
<td>9</td>
<td>7</td>
</tr>
<tr>
<td>Stay clear</td>
<td>10</td>
<td>7</td>
<td>0</td>
<td>&lt;.002</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Easy to use</td>
<td>27</td>
<td>14</td>
<td>5</td>
<td>.01</td>
<td>5</td>
<td>11</td>
</tr>
<tr>
<td>Adverse effects</td>
<td>24</td>
<td>15</td>
<td>0</td>
<td>&lt;.001</td>
<td>6</td>
<td>11</td>
</tr>
</tbody>
</table>

Abbreviations: E, etanercept equal to other treatment; I, etanercept inferior to the other treatment; PUVA, psoralen UV-A; S, etanercept superior to the other treatment.

a Unless otherwise indicated, data are reported as number of patients who have used the 2 drugs in the pairwise comparison and have answered the questionnaire. Comparisons with fewer than 15 patients were excluded from the analysis.

b Wilcoxon signed rank test.
commitments suggests that it may be many years before
this key issue is resolved.15

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Author Contributions: Dr Stern had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Jones-Caballero and Stern. Acquisition of data: Unaeze and Stern. Analysis and interpretation of data: Jones-Caballero, Unaeze, Peñas, and Stern. Drafting of the manuscript: Jones-Caballero and Peñas. Critical revision of the manuscript for important intellectual content: Jones-Caballero, Unaeze, Peñas, and Stern. Statistical analysis: Peñas and Stern. Obtained funding: Stern. Administrative, technical, and material support: Stern. Study supervision: Unaeze and Stern.

Financial Disclosure: Dr Stern has served or is currently serving as a consultant for the following companies: Nucrst Pharmaceuticals, Wyeth, Johnson & Johnson, BASF, GSK, Pfizer, Oscient, Cephalon, and Bristol-Meyers Squibb.

Funding/Support: This study was supported in part by the Beth Israel Dermatology Foundation and National Institutes of Health contract NO1-AR-0-2246 (Dr Stern).

Role of the Sponsors: The sponsors had no role in the design and conduct of the study, in the collection, analysis, and interpretation of data, or in the preparation, review, or approval of the manuscript.

Additional Information: Dr Stern has been involved in the PUVA cohort study for more than 30 years and has relationships with manufacturers of phototherapy units. However, he has not had financial support from these manufacturers.

REFERENCES

Objective: To describe incidence trends for cutaneous T-cell lymphoma (CTCL) in the United States.

Design: Population-based study.

Setting: Data were obtained from 13 population-based cancer registries of the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute from 1973 through 2002.

Participants: A total of 4783 cases of CTCL were identified for the period 1973 through 2002.

Main Outcome Measure: Diagnosis of CTCL.

Results: The overall annual age-adjusted incidence of CTCL was 6.4 per million persons. Annual incidence increased by $2.9 \times 10^{-6}$ per decade over the study period. Incidence was higher among blacks ($9.0 \times 10^{-6}$) than among whites ($6.1 \times 10^{-6}$) and was higher among men ($8.7 \times 10^{-6}$) than among women ($4.6 \times 10^{-6}$). The racial differences in incidence decreased with age, while the sex differences increased with age and decreased over time. Substantial geographic variation in incidence was found. Incidence was correlated with high physician density, high family income, high percentage of population with a bachelor’s degree or higher, and high home values. Changes in International Classification of Diseases for Oncology (ICD-O) morphologic definitions have resulted in the redistribution of the cases of CTCL among specific subclassifications.

Conclusions: The continued rise in incidence of CTCL is substantial, and the cause of this increase is unknown. The racial, ethnic, sex, and geographic differences in incidence may be of etiologic importance. Changes in ICD-O definitions have made it difficult to evaluate incidence trends for subclassifications of CTCL such as mycosis fungoides. In addition, these changes resulted in the creation of ambiguous histologic codes, which may have caused coding errors. These errors along with the lack of independent verification are limitations of our study. An epidemiological investigation using population-based data is important to better understand this disorder.

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ous CD30+ lymphoproliferative disorder (code 9718). Race was classified by the registries as white, black, or “other.” The data were analyzed using Stata SE version 8 (StataCorp, College Station, Texas) and SEER*Stat version 6.1.4 (National Cancer Institute, Bethesda, Maryland) statistical software. Time trends were evaluated by linear regression of year as a predictor of incidence rate. Confidence intervals (CIs) of rates were calculated using 1- and 2-sample proportion tests in Stata SE, and incidence rate ratios (IRRs) were calculated using the IRR calculator function of Stata SE. P values were calculated conventionally and are 2-tailed. Incidence rates were age-adjusted to the 2000 US standard million population unless otherwise indicated.

RESULTS

A total of 4783 cases of CTCL were identified for the period 1973 through 2002 among all 13 SEER registries. Of these cases, 97% were histologically confirmed and most (87%) were reported by hospitals and clinics. Most cases (n=3430 [72%]) were histologically classified as MF. Other CTCL diagnoses included Sézary syndrome (n=120 [2.5%]), primary cutaneous CD30+ lymphoproliferative disorder (n=73 [1.5%]), subcutaneous panniculitis-like T-cell lymphoma (n=10 [<1%]), angioimmunoblastic T-cell lymphoma (n=1 [<1%]), mature T-cell lymphoma NOS (n=172 [3.6%]), and CTCL NOS (n=977 [20%]).

The overall annual age-adjusted incidence of CTCL for the original 9 SEER registries from 1973 through 2002 was 0.4 per million persons, representing 0.14% of all cancers other than keratinocyte carcinomas and 3.9% of all non-Hodgkin lymphomas in these registries.

Incidence increased by 2.9 × 10⁻⁶ (95% CI, 2.6-3.1 × 10⁻⁶) per decade (Table 1). This increase occurred at similar rates for all age groups and races. The increase was greater among men (3.5 × 10⁻⁶ [95% CI, 3.1-3.9 × 10⁻⁶] per decade) than among women (2.4 × 10⁻⁶ [95% CI, 2.1-2.7 × 10⁻⁶] per decade) and also varied by geographic location and period (Table 2).

Incidence was higher among blacks than among whites and lower among other racial groups (Table 1). The black-white IRR (1.5 [95% CI, 1.4-1.6]) did not vary significantly by sex, year or registry, but the ratio decreased by age (Table 3). The “other”-white ratio was 0.8 (95% CI, 0.7-0.9). Among the 13 SEER registries from 1992 through 2002, incidence was higher for non-Hispanics (8.3 [95% CI, 8.0-8.6]) per million persons) than for Hispanics (5.8 [95% CI, 5.0-6.0]) per million persons). This was true among both whites and nonwhites.

Men had significantly higher rates compared with women. The male-female IRR (1.9 [95% CI, 1.8-2.0]) increased with age from a low of 1.1 for individuals diagnosed before age 30 years to 2.1 for those diagnosed after age 60 years (Figure). The male-female IRR was lowest among blacks (1.3) and highest among the other racial groups (2.7). This ratio has decreased over time from 2.5 in the period 1973 through 1982 to 1.7 in 1993 through 2002 (Table 3).

There was a steep increase in incidence with age from 0.1 per million persons (0- to 9-year-olds) to 24.6 per million persons (70- to 79-year-olds) (Table 1). This increase with age was consistent over time.

Of all cases classified as CTCL, 4% (201 cases) were coded as having B-cell lineage on a separate variable that subclassified lymphomas by cell type (an apparent inconsistency in the SEER database), and 86% (172 cases) of those inconsistently classified cases were classified as CTCL NOS. The remainder of these cases were MF (17 cases) or another CTCL subcategory (12 cases). A similar proportion of cases were inconsistently classified for each of the 13 registries. Responses from 3 SEER registries to our specific inquiry about these inconsistencies indicate that many of these inconsistent cases may have been cutaneous B-cell lymphomas that were incorrectly categorized histologically owing to ambiguities in the second edition of the ICD-O (ICD-O-2) (see the “Comment” section). However, it is unclear from our data which of these cases were incorrectly coded by histologic type and which were coded incorrectly as having B-cell lineage.

Considerable variation in incidence exists across registries. Annual incidence was highest in San Francisco, Cali-
fornia (9.7 per million persons among whites and 10.8 per million persons among blacks) and lowest in Iowa (3.7 per million persons among whites and 5.8 per million persons among blacks) (Table 2). Incidence in San Francisco was also highest among the 13 SEER registries for the period 1992 through 2002 (14.9 per million persons).

We looked at correlations between demographic characteristics of each of the 13 registries (Table 4) and the incidence among whites for the period 1992 through 2002.

### Table 2. Annual Incidence of Cutaneous T-Cell Lymphoma by Year, Race, and Registry

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rate (95% CI)</td>
<td>No.</td>
<td>Rate (95% CI)</td>
</tr>
<tr>
<td>Whites</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>San Francisco, California</td>
<td>4.7 (3.9-5.6)</td>
<td>116</td>
<td>8.0 (6.9-9.1)</td>
</tr>
<tr>
<td>Connecticut</td>
<td>2.7 (2.1-3.3)</td>
<td>78</td>
<td>75 (65.6-8.5)</td>
</tr>
<tr>
<td>Seattle, Washington</td>
<td>3.5 (2.7-4.3)</td>
<td>68</td>
<td>4.9 (4.1-5.8)</td>
</tr>
<tr>
<td>Detroit, Michigan</td>
<td>3.1 (2.5-3.7)</td>
<td>86</td>
<td>5.5 (4.7-6.4)</td>
</tr>
<tr>
<td>Atlanta, Georgia</td>
<td>3.0 (1.9-4.1)</td>
<td>22</td>
<td>4.7 (3.6-5.8)</td>
</tr>
<tr>
<td>Hawaii</td>
<td>3.1 (1.1-1.5)</td>
<td>5</td>
<td>2.3 (0.6-4.1)</td>
</tr>
<tr>
<td>New Mexico</td>
<td>2.5 (1.6-3.3)</td>
<td>21</td>
<td>3.5 (2.5-4.5)</td>
</tr>
<tr>
<td>Utah</td>
<td>2.5 (1.6-3.3)</td>
<td>22</td>
<td>4.8 (3.7-5.9)</td>
</tr>
<tr>
<td>Iowa</td>
<td>2.2 (1.6-2.7)</td>
<td>58</td>
<td>3.7 (3.0-4.4)</td>
</tr>
<tr>
<td>San Jose, California</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Los Angeles, California</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Rural Georgia</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Blacks</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>San Francisco</td>
<td>8.4 (5.5-11.4)</td>
<td>24</td>
<td>8.7 (5.9-11.5)</td>
</tr>
<tr>
<td>Connecticut</td>
<td>80 (6.5-8.5)</td>
<td>11</td>
<td>103 (6.3-13.9)</td>
</tr>
<tr>
<td>Detroit</td>
<td>5.2 (3.7-6.7)</td>
<td>32</td>
<td>10.0 (8.0-12.1)</td>
</tr>
<tr>
<td>Seattle</td>
<td>10.8 (3.2-17.4)</td>
<td>4</td>
<td>4.8 (0.9-8.6)</td>
</tr>
<tr>
<td>Atlanta</td>
<td>1.3 (0.2-2.6)</td>
<td>2</td>
<td>4.9 (3.2-6.7)</td>
</tr>
<tr>
<td>Los Angeles</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; NR, not reported.

The rates and number of cases shown are based on data from the Surveillance, Epidemiology, and End Results Program (http://www.seer.cancer.gov) Public Use Data (1973-2002), National Cancer Institute, Division of Cancer Control and Population Sciences, Surveillance Research Program, Cancer Statistics Branch, released April 2005, based on the November 2004 submission.

All incidence rates are age adjusted to the 2000 US standard million population. Incidence rates are calculated per 1 million person-years. Data for the Alaska registry were only available for native Alaskans, who were included under the “other” racial category.

### Table 3. Black-White and Male-Female Incidence Rate Ratios (IRRs)

<table>
<thead>
<tr>
<th>Variable</th>
<th>IRR (95% Confidence Interval)</th>
<th>P Value (for Difference in IRR With Baseline IRR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Black-white</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-29</td>
<td>2.2 (1.5-3.1)</td>
<td>.12</td>
</tr>
<tr>
<td>30-59</td>
<td>1.8 (1.6-2.0)</td>
<td>.03</td>
</tr>
<tr>
<td>≥60</td>
<td>1.1 (1.0-1.3)</td>
<td>Baseline</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>1.3 (1.2-1.5)</td>
<td>.17</td>
</tr>
<tr>
<td>Women</td>
<td>1.7 (1.5-1.9)</td>
<td>Baseline</td>
</tr>
<tr>
<td>Year</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1973-1982</td>
<td>1.8 (1.4-2.2)</td>
<td>.19</td>
</tr>
<tr>
<td>1983-1992</td>
<td>1.5 (1.3-1.8)</td>
<td>.40</td>
</tr>
<tr>
<td>1993-2002</td>
<td>1.3 (1.2-1.5)</td>
<td>Baseline</td>
</tr>
<tr>
<td>Male-female</td>
<td></td>
<td></td>
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<tr>
<td>Age, y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-29</td>
<td>1.1 (0.8-1.4)</td>
<td>.03</td>
</tr>
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<td>30-59</td>
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<td>2.1 (1.9-2.3)</td>
<td>Baseline</td>
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<td>Race</td>
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<tr>
<td>White</td>
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<td>.20</td>
</tr>
<tr>
<td>Other</td>
<td>2.7 (2.1-3.6)</td>
<td>.06</td>
</tr>
<tr>
<td>Black</td>
<td>1.9 (1.3-1.8)</td>
<td>Baseline</td>
</tr>
<tr>
<td>Year</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1973-1982</td>
<td>2.5 (2.1-2.9)</td>
<td>.04</td>
</tr>
<tr>
<td>1983-1992</td>
<td>2.1 (1.9-2.3)</td>
<td>.23</td>
</tr>
<tr>
<td>1993-2002</td>
<td>1.7 (1.6-1.8)</td>
<td>Baseline</td>
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Figure. Age-specific incidence of cutaneous T-cell lymphoma by sex (United States, 1973-2002).
The overall incidence of Sézary syndrome was 0.3 per million persons. Men had significantly higher rates than women (0.07 [95% CI, 0.04-0.11] vs 0.06 [95% CI, 0.04-0.09]), and incidence among whites (0.07 [95% CI, 0.05-0.09]) was substantially lower than among blacks (0.03 [95% CI, 0.02-0.04]) per million persons. All but 2 cases occurred in adults 30 years and older.

Coping for cutaneous lymphoma morphology has changed several times throughout the history of the SEER program (Table 5). For cases diagnosed between 1973 and 1985, histologic types are defined in the morphology section of the ICD-O (1976). These definitions changed in 1986, 1992, and 2001 with the introductions of ICD-O Field Trial Edition, ICD-O-2, and ICD-O-3, respectively. Each new ICD-O edition contained either additional histologic classifications or revisions to previous classifications for CTCLs (ICD-O code 970). These new classifications resulted in the redistribution of broadly defined cases of CTCL (code 970) among the more specific subclassifications (codes 9700-9709 and 9718). For example, the incidence of MF in Connecticut dropped from 6.7 per million persons in the period 1981 through 1991 to 1.0 per million persons in 1992 through 2002 after the adoption of ICD-O-2, which included the subclassification cutaneous lymphoma NOS (code 9709). The incidence of cutaneous lymphoma NOS in this registry over the same 2 periods was 0.2 and 8.5 per million persons, respectively.

We used recent and comprehensive data from the SEER program to update the epidemiological features of CTCL and document trends in incidence that differed from those of previous reports. We noted a marked rise in incidence and substantial racial and geographic heterogeneity in rates of CTCL.

It is important to examine the incidence of all CTCLs as a group in the SEER program as opposed to the incidence for individual subgroups when analyzing trends over time because the classification changes resulting from the introduction of new ICD-O editions have caused sizeable shifts in the distribution of CTCLs among subcategories. These redistributions may have contributed to the apparent stabilization in the incidence of MF reported previously.

Our study included data from 4 additional registries of the SEER program for the period 1992 through 2002, allowing us to further explore the geographic differences in incidence and to look at other ethnic characteristics such as the incidence among Hispanics. Nearly 3 times as many cases were included in our analysis compared with the most recent report; hence, we were able to examine incidence patterns for various subgroups.

Some limitations of using the SEER program included the lack of independent verification of diagnoses and the lack of detail pertaining to each case. Each SEER registry is responsible for finding every case of cancer in
its defined registry area. Nevertheless, because validity of the diagnoses was not determined, cases could have been included that were not actually CTCL, and cases of CTCL in the study registries may have been excluded from the data. Underregistration of cutaneous malignancies in SEER registries has been documented. Missed cases from the data. Underregistration of cutaneous malignancies in SEER registries may have been included that were not actually CTCL, and cases that were interpreted as ambiguous histologic types were coded incorrectly. The Iowa Cancer Registry found that most grade codes were correct, but the histologic types were coded incorrectly. The Atlanta registry reported that the grade codes were correct, but the inconsistencies were caused by ambiguous histologic definitions.

The incidence of CTCL has risen dramatically and consistently since 1973. Changes in classification schemes may have contributed to the rise in incidence, as may improvements in detection or an increase in the underlying etiologic agent(s). Our demographic correlates show that incidence is strongly correlated with the density of physicians. Hence, the rise in incidence may be due, at least in part, to increased efficiency of detection resulting from improvements in medical care over the past few decades. Because of reporting delay, the actual rise in incidence may be greater than the rise found in our data. Reporting delay and reporting error occur when new cases are discovered or erroneous cases are detected in the existing SEER data. Clegg et al.11 found that initial incidence case counts accounted for only 88% to 97% of the estimated final counts in the SEER program and that it would take 4 to 17 years for 99% or more of cancer cases to be reported.

The geographic differences in incidence are substantial even after controlling for race. Incidence is correlated with high physician density and several indexes of socioeconomic status such as median family income, percentage of the population with a bachelor's degree or higher, and median home value. We did not confirm the previously reported correlation of incidence with population density.3 These geographic differences in incidence may be related, to some degree, by differences in access to medical care. Several studies have suggested that infectious agents or environmental exposures may play a role in CTCL. While the unusual geographic differences seen in our data could be explained by an environmental or viral exposure, our data neither directly support nor contradict such hypotheses. The relatively high rates and unique incidence trends observed in the San Francisco registry are similar to incidence trends for both non-Hodgkin lymphoma and Kaposi sarcoma.18 HIV-related cancers. However, unlike non-Hodgkin lymphoma and Kaposi sarcoma, a previous case-control study failed to find an increased risk for CTCL among never-married men.19-21 There are significant differences in incidence by race, ethnicity, and sex. While racial differences in incidence decrease with age and have not changed over time, sex differences in incidence increase with age and have decreased over time. Races with low incidence had higher male-female ratios.
Sézary syndrome, a rare type of CTCL, is characterized by erythroderma, generalized lymphadenopathy, and the presence of neoplastic T cells. Little data have been reported on the epidemiologic features of Sézary syndrome owing to the rarity of its occurrence. As with CTCL in general, we found this disease to be relatively more common among men than among women. However, contrary to CTCL, the incidence of this disorder is higher among whites than among blacks.

Our population-based study provides updated trends in the incidence of CTCL in the United States and describes patterns that have not been reported previously. These data may be useful in planning public health strategies, identifying risk factors, and understanding the etiology of this cancer so that it may some day be prevented.

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Correspondence: Vincent D. Criscione, AB, Dermato-epidemiology Unit-111D, VA Medical Center, 830 Chalkstone Ave, Providence, RI 02908-4799 (Vincent_Criscione@Brown.edu).

Author Contributions: Study concept and design: Criscione and Weinstock. Acquisition of data: Weinstock. Analysis and interpretation of data: Criscione and Weinstock. Drafting of the manuscript: Criscione and Weinstock. Critical revision of the manuscript for important intellectual content: Criscione and Weinstock. Statistical analysis: Criscione and Weinstock. Obtained funding: Weinstock. Administrative, technical, and material support: Weinstock. Study supervision: Weinstock.

Financial Disclosure: None reported.

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REFERENCES


Sun-Related Factors, Betapapillomavirus, and Actinic Keratoses

A Prospective Study

Penelope McBride, MBBS, MPhil; Rachel Neale, BVSc, PhD; Nirmala Pandeya, BSc, MMedSc; Adèle Green, MBBS, PhD

Objective: To examine prospectively the relationship among sun exposure, Betapapillomavirus, and development of actinic keratoses.

Design: Prospective, community-based cohort study.

Setting: Township of Nambour in Southeast Queensland, Australia.

Participants: A total of 291 randomly selected adults aged 36 to 86 years with the presence or absence of Betapapillomavirus DNA in eyebrow hair follicle cells known at baseline in August 1996 and with subsequently documented sun exposure histories.

Main Outcome Measures: Prevalence of actinic keratoses in March 2003 after 7 years of follow-up.

Results: Beyond the known determinants of multiple actinic keratoses, namely, advanced age, male sex, fair skin, and lifetime occupational sun exposure, Betapapillomavirus infection was associated with having more than 10 actinic keratoses (odds ratio, 1.8; 95% confidence interval, 0.7-4.4). However, Betapapillomavirus positivity led to a significant 13-fold increase in the risk of actinic keratoses among those 60 years or older, a nearly 6-fold increase in risk when combined with fair skin color, and a doubling in risk of actinic keratoses when combined with high sun exposure, recent or cumulative, compared with those who had neither Betapapillomavirus infection nor the respective risk factor of interest.

Conclusions: Although the presence of Betapapillomavirus DNA in eyebrow hair follicle cells had only a small independent association with actinic keratoses, Betapapillomavirus infection in combination with key risk factors increased the risk of actinic keratoses, which is consistent with a potentiation by Betapapillomavirus of the effect of established causal factors.

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Actinic keratoses (AKs) are sun-induced skin tumors that are strongly associated with squamous cell carcinomas (SCCs). Prevalence of AKs varies with latitude and skin type. For example, in England the prevalence of AKs is approximately 15% for men and 6% for women, whereas the prevalence in people of the same ancestry in subtropical Australia is approximately 40%. There is increasing evidence from epidemiological and molecular studies that Betapapillomavirus may play a role in the cause of AKs in addition to solar radiation.

Among more than 100 known human papillomavirus (HPV) types, a group of approximately 16 types were classified as epidermodysplasia verruciformis (EV)–HPV types because they were known to infect individuals with EV, who are predisposed to develop warts and skin tumors. Recently, these EV-HPV types and phylogenetically related HPV types were reclassified as the Betapapillomavirus genus. Betapapillomavirus types have been detected not only in SCCs, but also in basal cell carcinomas and AKs but also in hair follicle cells and healthy skin.

CME course available at www.archdermatol.com

The association between papillomaviruses and epithelial tumors was established originally in studies of rabbit SCCs in the 1950s. Early human studies of HPV and skin tumor development began in patients with EV, widened to immunosuppressed patients undergoing organ transplantation, who are at high risk of skin cancer, and more recently broadened...
to include healthy populations. All these studies have provided support for a positive association between Betapapillomavirus and skin tumorigenesis. Viral load was found to be highest in AKs rather than SCCs, indicating that studies of the association between Betapapillomavirus and AKs are a legitimate source of data in examining tumorigenesis.

Studies of this association have relied on various indicators of viral infection, including direct detection of Betapapillomavirus DNA with nested polymerase chain reaction primers in skin specimens, detection of Betapapillomavirus DNA in hair follicle cells, Betapapillomavirus DNA detection from skin swabs (could also indicate surface contamination), and determination of seroreactivity to Betapapillomavirus types. The exact role of Betapapillomavirus in skin tumor development cannot be determined from any of these laboratory methods in isolation; they need to be combined with epidemiologic studies for further etiological insight. All such studies to date have been cross-sectional, however, so the precise relationship among sun exposure as the chief cause of skin cancers, cutaneous HPV infection, and skin tumors in healthy individuals remains unclear. Indeed, the role of HPV infection remains much more controversial than that of sun exposure, with suggestions that the activity of HPV either decreases, increases, or has no influence on the effect of high UV radiation exposure.

The primary aim of this study was to investigate whether Betapapillomavirus influences the subsequent development of AKs independently or in combination with sun exposure. We therefore performed a prospective study to assess whether Betapapillomavirus infection of hair follicle cells was associated with subsequent development of AKs. If it was associated, we aimed to assess in more detail the relation of Betapapillomavirus to AKs, taking into account other known risk factors.

**METHODS**

The participants comprised a subset of the ongoing Nambour Skin Cancer Study, which has been described in detail previously (Figure). Briefly, participants aged 20 to 69 years were randomly selected from residents of Nambour, a subtropical Australian township (latitude 26°S), in 1986 and invited to complete a skin cancer prevalence survey in 1986. In 1992 they participated in a 5-year field trial of skin cancer prevention, which entailed full-body skin examinations by specialist dermatologists in February 1992, August 1994, and August 1996, including site-specific counts of all AKs. Participants gave written informed consent before taking part in skin examinations and collection of biological samples. Ethical approval for all aspects of the study was obtained through Bancroft Centre Ethics Committee, Queensland Institute of Medical Research.

**BASELINE DATA**

An unselected half of the 1250 trial participants who underwent skin examinations were invited to take part in a study of HPV and skin cancer in August 1996. Eyebrow hair samples were collected from 507 participants, and samples were analyzed for the presence of Betapapillomavirus types 5, 8, 9, 12, 14, 15, 17, 19 through 25, 36 through 38, and 47 using a nested polymerase chain reaction to detect Betapapillomavirus DNA. A participant was considered to be positive for HPV if DNA from any of these viruses was detected and negative otherwise. The Betapapillomavirus detection was performed according to methods described in detail by Boxman et al and Berkhout et al. The polymerase chain reaction primers used were designed to detect all EV-HPV types (now Betapapillomavirus types) known in 1995 at low viral DNA copy numbers. In the current study population, no negative controls were positive for EV-HPV DNA.

Information about skin color (fair, medium, or olive), skin response to short-term sun exposure (always burn, never tan; burn, then tan; or tan only), and lifetime sun exposure was obtained from questionnaires administered during the Nambour Skin Cancer Study. Sun exposure history included the proportion of time spent outdoors or in the sun each day during childhood and teenage years, lifetime occupational sun exposure, and daily sun exposure in a typical week (hardly ever [up to 1 hour], less than 50% of the time [more than 1 hour and up to 4 hours], or more than 50% of the time [more than 4 hours]) for each day of the week (separate average daily values were used for weekdays and weekend days). Baseline counts of AKs on the face, forearms, and hands by survey dermatologists in August 1996 were also used in the present analysis.

**FOLLOW-UP**

Of the 507 participants with known Betapapillomavirus infection status in August 1996, those who had consented to long-term follow-up were invited to take part in a follow-up study in March 2003. A single dermatologically trained clinician with several years of experience (P.M.) counted all AKs...
Participants were divided into 2 age categories (36-59 years and ≥60 years) based on the categories used previously and collapsed to allow for the cohort’s aging. The only significant difference between the characteristics of the 507 participants whose HPV status was measured in 1996 and those who were followed up in 2003 was that the 291 participants seen in 2003 were almost 4 years younger on average (P = .002) than the 216 who were not included (Table 1). Despite this preponderance of younger participants in 2003, the average age of those examined was 5 years older than the average age of the sample in 1996 (7 years earlier). The proportions of Betapapillomavirus DNA–positive participants were identical in those followed up and those not followed up (Table 1).

There were almost equal proportions of men and women (Table 1). Approximately half the participants reported fair skin color, and only 9.0% described their skin color as olive. More than two thirds reported that their skin burned, then tanned, after short-term sun exposure (Table 1). Almost half had an indoor occupation, and only 19.9% worked mostly outdoors (Table 1).

### RESULTS

Of the original 507 participants in the baseline Betapapillomavirus study in 1996, 359 participants were eligible for participation in the present follow-up study. The 148 participants not eligible for this study included 96 participants who had withdrawn completely from the Nambour Skin Cancer Study, 40 participants who consented only to tracking of their skin cancers through medical records, and 12 who had died. Approximately 60% of those who gave no consent for follow-up were men (mean age, 65 years). In most cases no reason was given, but of those with a reason, illness and geographical distance were the most common ones cited. Of the eligible participants, 10 refused to participate, 13 were unable to attend on the data collection dates, 4 had died since the last date of confirmation of their participation status, and 41 no longer lived in the region. Thus, 291 (81.1%) of the 359 eligible participants were successfully examined in 2003.

### AGE, SEX, AND SKIN PHENOTYPE

Participants were divided into 2 age categories (36-59 years and ≥60 years) based on the categories used previously and collapsed to allow for the cohort’s aging. The only significant difference between the characteristics of the 507 participants whose HPV status was measured in 1996 and those who were followed up in 2003 was that the 291 participants seen in 2003 were almost 4 years younger on average (P = .002) than the 216 who were not included (Table 1). Despite this preponderance of younger participants in 2003, the average age of those examined was 5 years older than the average age of the sample in 1996 (7 years earlier). The proportions of Betapapillomavirus DNA–positive participants were identical in those followed up and those not followed up (Table 1).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Followed Up (n=291)</th>
<th>Not Followed Up (n=216)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-59</td>
<td>168 (57.7)</td>
<td>98 (45.4)</td>
</tr>
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<td>≥60</td>
<td>123 (42.3)</td>
<td>118 (54.6)</td>
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<tr>
<td>Sex</td>
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<tr>
<td>Female</td>
<td>151 (51.9)</td>
<td>111 (51.3)</td>
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<tr>
<td>Male</td>
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<td>Skin color (self-reported)</td>
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<td>Olive</td>
<td>26 (9.0)</td>
<td>19 (8.8)</td>
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<td>Medium</td>
<td>113 (38.8)</td>
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<td>Fair</td>
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<tr>
<td>Tendency to sunburn</td>
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<td>Tan only</td>
<td>26 (8.9)</td>
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<td>Burn, then tan</td>
<td>212 (72.9)</td>
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<td>Always burn</td>
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<td>Average sun exposure in 2002</td>
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<tr>
<td>(n=287)</td>
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<td>&lt;50% time</td>
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</tr>
<tr>
<td>Yes</td>
<td>136 (46.7)</td>
<td>101 (46.8)</td>
</tr>
<tr>
<td>No</td>
<td>155 (53.3)</td>
<td>115 (53.2)</td>
</tr>
</tbody>
</table>
exposure from occupation or leisure increased the risk of prevalent AK, but the associations were not statistically significant after adjustment for age and sex (P = .15 for high occupational exposure and P = .15 for moderate leisure exposure). No effect of smoking on prevalent AK was found.

There was no independent association of AK prevalence in 2003 with Betapapillomavirus infection in 1996 (OR, 1.4; 95% CI, 0.7-2.7; for 1-10 AKs), although there was a nonsignificant association (P = .17) between Betapapillomavirus and the presence of more than 10 AKs (OR, 1.8; 95% CI, 0.7-4.4). A further logistic regression analysis was performed, including only those 149 participants who had no AKs at baseline in 1996. The odds of developing AKs in the Betapapillomavirus-positive group were similar to those observed overall, but the precision of estimated odds of effect was much lower. When change in individual AK counts was examined, an overall decrease in AK counts occurred in this population between 1996 and 2003, but the decrease was 11.0% greater in those without detectable Betapapillomavirus DNA in eyebrow hair follicles compared with those with detectable Betapapillomavirus DNA in 1996.

**JOINT EFFECT OF BETAPAPILLOMAVIRUS INFECTION AND OTHER RISK FACTORS FOR AKs**

To maximize the statistical power of the analysis of the joint effects of Betapapillomavirus infection and other risk factors, the presence or absence of AKs was used rather than several categories of AK counts. A stratified analysis according to Betapapillomavirus positivity or negativity and the main risk factors for AK, namely, age, sex, skin color, and propensity to sunburn, revealed substantially higher odds of AKs if another risk factor was combined with Betapapillomavirus positivity (Table 2). The subset of participants with advanced age and Betapapillomavirus positivity had double the odds of AKs compared with their Betapapillomavirus-negative counterparts. In men with Betapapillomavirus infection, the odds of having AKs were almost 3. In the fair-skinned subgroup with Betapapillomavirus infection, the odds of AKs compared with their

<table>
<thead>
<tr>
<th>Characteristic and Betapapillomavirus Status</th>
<th>AKs in 2003, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>None (n=178)</td>
</tr>
<tr>
<td>Age group, y</td>
<td></td>
</tr>
<tr>
<td>36-59</td>
<td>Negative (n=112)</td>
</tr>
<tr>
<td></td>
<td>Positive (n=56)</td>
</tr>
<tr>
<td>≥60</td>
<td>Negative (n=43)</td>
</tr>
<tr>
<td></td>
<td>Positive (n=60)</td>
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<tr>
<td>Sex</td>
<td>Female</td>
</tr>
<tr>
<td></td>
<td>Positive (n=72)</td>
</tr>
<tr>
<td></td>
<td>Male</td>
</tr>
<tr>
<td></td>
<td>Positive (n=64)</td>
</tr>
<tr>
<td>Skin color</td>
<td>Olive/medium</td>
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<tr>
<td></td>
<td>Positive (n=69)</td>
</tr>
<tr>
<td></td>
<td>Fair</td>
</tr>
<tr>
<td></td>
<td>Positive (n=67)</td>
</tr>
<tr>
<td>Tendency to sunburn</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>Tan or burn, then tan</td>
</tr>
<tr>
<td></td>
<td>Positive (n=24)</td>
</tr>
<tr>
<td></td>
<td>Always burn</td>
</tr>
<tr>
<td></td>
<td>Positive (n=112)</td>
</tr>
</tbody>
</table>

Abbreviations: AKs, actinic keratoses; CI, confidence interval; OR, odds ratio.

Table 3. Association of the Presence or Absence of AKs in 2003 With Betapapillomavirus Status and Occupational Sun Exposure and Sun Exposure in 2002

<table>
<thead>
<tr>
<th>Characteristic and Betapapillomavirus Status</th>
<th>AKs in 2003, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>None (n=178)</td>
</tr>
<tr>
<td>Cumulative sun exposure</td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>Negative (n=74)</td>
</tr>
<tr>
<td></td>
<td>Positive (n=52)</td>
</tr>
<tr>
<td>High</td>
<td>Negative (n=81)</td>
</tr>
<tr>
<td></td>
<td>Positive (n=84)</td>
</tr>
<tr>
<td>Weekday sun exposure in 2002</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td>Positive (n=59)</td>
</tr>
<tr>
<td></td>
<td>High</td>
</tr>
<tr>
<td></td>
<td>Positive (n=73)</td>
</tr>
</tbody>
</table>

Abbreviations: AKs, actinic keratoses; CI, confidence interval; OR, odds ratio.

a Adjusted for age and sex.
bers of AKs. Lifelong outdoor occupation increased the odds of having prevalent AKs but not significantly (P = .15). These results confirm known risk factors for AKs.\(^1,3,5,38,39\) We sought to investigate if Betapapillomavirus DNA detection in eyebrow hair follicle cells had any independent influence on the subsequent development of AKs, and if so, whether there might be a synergistic relationship with high sun exposure. When considered on its own, the presence of Betapapillomavirus DNA in eyebrow hair follicle cells appeared to increase the odds of developing AK, although this was not statistically significant (P = .24). Betapapillomavirus positivity increased the ORs for the presence of AKs for each confirmed risk factor.

Because AKs do not follow the course of typical skin tumors (ie, they frequently spontaneously regress),\(^3\) prevalence was considered the most appropriate measure to use in this study. We showed that against the background of an overall decrease in AK counts in this population (due to natural regression,\(^3\) lower rate of accumulation, treatment, or a combination of these factors), people with EV-HPV DNA detected in eyebrow hair follicles in 1996 had an 11.0% higher persistence rate of AKs compared with those without EV-HPV infection.

Evidence from several large studies\(^4,14,20,21\) that compared skin tumors with healthy skin in healthy people suggests a positive association between presence of Betapapillomavirus and development of SCCs and AKs. Studies of Betapapillomavirus DNA in plucked eyebrow hair follicle cells have also supported a role for Betapapillomavirus in the development of skin tumors, most convincingly in European studies\(^20,37\) with corroboration from research using serological methods.\(^23,36,40\) Studies of SCCs and AKs have been reviewed together because of the similar pathogenesis of both lesions.

The combination of high sun exposure and Betapapillomavirus infection was found to predispose to skin tumor development in previous studies,\(^3,21\) but findings have been contradictory, especially when different sample types are studied. Studies of tumor samples and healthy skin samples support the relationship. In a small study\(^8\) of Australian immunocompetent and immunosuppressed patients with skin cancer, a tendency was noted for HPV DNA to be present in more tumors from sun-exposed sites than nonexposed sites. Further evidence supporting a joint effect between UV radiation and HPV in tumorigenesis was found in a British study\(^23\) in which the association between Betapapillomavirus DNA and skin cancer on sun exposed sites was stronger than on nonexposed sites.

There was no such concurrence between 2 studies that relied on Betapapillomavirus detection in hair follicle cells. A recent study\(^22\) conducted in the Netherlands found that high lifetime sun exposure decreased the risk of Betapapillomavirus DNA positivity when plucked eyebrow hair follicle cells were examined. However, in a community-based study\(^5\) conducted in Nambour, high occupational sun exposure was significantly associated with higher risk of Betapapillomavirus DNA detection in hair follicles.

Serological investigations have yielded conflicting results. Feltkamp et al\(^32\) found no association between HPV seropositivity and sun exposure. Two more recent studies\(^41,42\) of SCCs have provided further evidence of a positive combined influence of sun exposure and HPV infection in tumor development. Karagas et al\(^41\) found that the highest risk of SCCs was found in those with antibodies to several HPV types and with a tendency to sunburn. Hall et al\(^42\) also found the risk of SCCs highest for the Betapapillomavirus-seropositive group, and a joint effect was observed for each separate classic risk factor (such as older age, male sex, fair skin, tendency to sunburn, and high sun exposure).

Laboratory evidence is conflicting regarding the possible role of Betapapillomavirus infection and UV radiation in the development of skin tumors. In support of a biological interaction, the promoter activity of HPV-77 (a cutaneous HPV type) has been directly stimulated by UV radiation,\(^43\) but other cutaneous HPV types (such as 1, 2, 3, 5, 20, 23, 27, 38, and 41) all reacted differently to UV radiation treatment in vitro.\(^44\)

In considering potential weaknesses of this study, it is likely that participants had developed different attitudes and behaviors with regard to sun exposure and possibly skin cancer treatment than the general Australian population because of their involvement in the Nambour Skin Cancer Study since 1986. The active participants who were followed up in 2003 are likely to represent an especially sun-aware, motivated subgroup with greater sun-avoidant behavior than other community members. Although this may contribute to the lower prevalence of AKs than in the general public, it is unlikely to have influenced the relationships in this study. Our measurement of the prevalence of AKs was dependent on clinical recognition and has been shown to have high validity in our previous studies,\(^32\) although no histopathological confirmation was available in this particular study.

The Betapapillomavirus DNA detection method used in 1996 was highly sensitive and was not likely to have biased results greatly,\(^27,45\) although with newer methods, other Betapapillomavirus types are being discovered, and thus there may have been a systematic underestimation of the prevalence of infection in this study. Although it is possible that Betapapillomavirus status changed during the observation period, it has been shown elsewhere that cutaneous HPV infection persists.\(^46\) None of the current common investigative methods alone are able to provide direct evidence to determine the role of Betapapillomavirus in skin tumor development, however. Currently, detection of the presence of Betapapillomavirus in tumors and comparison of the prevalence between individuals with and without tumors are the most frequent and probably the most accurate investigative approaches. Better evidence of an independent association between Betapapillomavirus infection and skin cancer is likely to come from further prospective studies using several markers of infection, such as tissue DNA detection and seroreactivity.

To establish a causal role for Betapapillomavirus in skin cancer, molecular techniques that examine possible
mechanisms of viral carcinogenesis may yield the vital clue. A recent study in the mechanisms by which Betapapillomavirus might induce tumors found that infected keratinocytes express viral genes.

In conclusion, the results of this prospective study show a weaker association between the presence of Betapapillomavirus in hair follicles and the increased prevalence of AKs than that established in previous cross-sectional analyses of viral infection of eyebrow hair follicle cells. However, the findings presented herein add to early evidence that suggests that Betapapillomavirus enhances the effects of increasing age, sun-sensitive phenotypes, and high-dose UV radiation to further increase the risk of developing AKs.

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Correspondence: Penelope McBride, MBBS, MPhil, Queensland Institute of Medical Research, PO Royal Brisbane Hospital, Brisbane, Queensland, Australia 4029 (penelope.mcbride@qimr.edu.au).

Author Contributions: Ms McBride had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: McBride, Neale, and Green. Acquisition of data: McBride and Green. Analysis and interpretation of data: McBride, Neale, Pandeya, and Green. Drafting of the manuscript: McBride and Green. Critical revision of the manuscript for important intellectual content: Neale, Pandeya, and Green. Statistical analysis: Neale and Pandeya. Obtained funding: Green. Study supervision: Neale and Green.

Financial Disclosure: None reported.

Funding/Support: This study was supported by the National Health and Medical Research Council of Australia.

Additional Contributions: Gail Williams, PhD, assisted with the early statistical analyses.

REFERENCES

Objectives: To assess the strength of 2.0 barbed polypropylene suture, and, specifically, to determine the load required to break this suture, and to compare this with the strength of nonbarbed polypropylene suture.

Design: Rater-blinded, controlled trial. The individual responsible for setting up the experimental conditions was not blinded.

Setting: Biomechanics laboratory in an academic medical center.

Materials: This study did not include human subjects. Materials used included six 2.0 barbed polypropylene sutures and 3 each of 2.0, 3.0, 4.0, and 5.0 nonbarbed polypropylene sutures. Each suture was randomly selected from a different batch or box of similar sutures.

Intervention: Each suture was strung between 2 (top and bottom) cylinders and tied with a surgeon’s knot. A tensile testing device was used to apply increasing force until the suture broke. Data were acquired through an analog-to-digital board on an IBM-compatible computer using commercially available software.

Main Outcome Measures: Ultimate strength, stiffness, and elongation before suture rupture.

Results: Strength of the barbed sutures (mean [SD] ultimate strength, 39.5 [9.0] N) was intermediate between that of 2.0 (55.0 N) and 3.0 (36.4 N) nonbarbed sutures and was not significantly different from that of 3.0 nonbarbed sutures (P = .5). Barbed 2.0 polypropylene sutures differed significantly (P < .001) from each of the other types of nonbarbed sutures on measures of stiffness and elongation. Elongation of barbed sutures was closest to that of 3.0 nonbarbed sutures (P = .002). Stiffness of the barbed sutures (mean [SD], 4.7 [0.7] N/mm) was markedly in excess of that of any of the other suture types (P < .001).

Conclusions: Barbed 2.0 polypropylene sutures seem to be at least as strong as 3.0 nonbarbed polypropylene sutures. As such, barbed sutures are significantly stronger than their rated strength, which has been stated as comparable to 4.0 nonbarbed sutures. This has implications for the long-term in vivo safety of barbed sutures.

Arch Dermatol. 2007;143(7):869-872
necessitate an invasive and potentially disfiguring procedure to remove the damaged suture. Third, because barbed suture is not designed to be removed or to biodegrade, it must remain safely imbedded for the long term. Potential suture weakness that results in breakage years after implantation may lead to suture extrusion or migration with resulting discomfort, scarring, or functional impediment.

In hands-on training courses on barbed suture placement for physicians that have been developed by one manufacturer (Surgical Specialties Corp), the issue of suture breakage is addressed. Specifically, users are instructed to apply firm but not spasmodic pressure to avert breakage. In addition, there are anecdotal reports of facial asymmetry caused by suture breakage in the early postplacement period, before the development of fibrosis around the implanted barbs; thread migration and partial expulsion has also been reported.3 Removal of imbedded sutures can require a surgical approach that is complicated by the risk of suture breakage. Experts in the use of barbed sutures note that short- to medium-term results are usually good, but long-term safety and efficacy have yet to be established.4,5

The purpose of this study was to objectively assess the strength of commonly used barbed sutures. Using accepted techniques for testing fiber strength, we compared barbed sutures with nonbarbed sutures of various calibers. The results of this study should help surgeons who use barbed sutures to deploy them in a manner consistent with their tensile properties.

METHODS

SUTURE MATERIALS

Experimental sutures were 6 barbed polypropylene sutures (Contour Threads; Surgical Specialties Corp). Control nonbarbed sutures were 3 sutures each from separate batches of 2.0, 3.0, 4.0, and 5.0 polypropylene (Prolene; Ethicon Inc).

TEST EQUIPMENT

The materials testing machine (model 1122; Instron Corp, Canton, Massachusetts) is shown in Figure 1. Data were acquired with an analog-to-digital board (DT 2821-G; Data Translation, Inc, Marlboro, Massachusetts) on an IBM-compatible computer using Global Laboratory software (Data Translation, Inc).

EXPERIMENTAL DESIGN

Each of 6 experimental and 12 control sutures was tested using the Instron device. Measurements were obtained for ultimate strength, stiffness, and elongation. Strength is the amount of force that can be applied to the ends of a suture before the suture breaks. Strength is measured in newtons. Before rupture, based on the intrinsic stiffness of the suture, the suture undergoes some degree of elongation, or lengthening. Stiffness is a measure of the tendency of a suture to stretch by application of increasing force before breakage. A suture that easily stretches (elongates) many millimeters is relatively less stiff than one that stretches only a few millimeters despite the application of a powerful force. Stiffness is measured in newtons per millimeter. Algebraically, stiffness is the slope of the linear portion of the load-displacement curve. Elongation is the cumulative distance a suture stretches (displacement) before breakage when force is applied. Stiffer sutures elongate relatively less, and less stiff sutures elongate more.

Before each test, the suture material was strung between 2 (top and bottom) cylinders with open jaws (Figure 2). Suture was threaded first around one cylinder, then around the other. The free ends were brought together halfway between the cylinders and attached via a surgeon’s knot tied by 1 of us (R.R.), who was not blinded as to the suture material. Machine-generated force was used by a technician (M.S.), who was blinded as to the suture material but was in the same room as the experimental apparatus, to pull on the sutures with increasing weight until the suture broke. The ability of the technician performing the experimentation to be an agent of systematic bias was further reduced in that he was unfamiliar with the caliber rating system for sutures (They were removed from the packaging and labeled with a code on an affixed sticker.) and was
not informed of the experimental hypothesis until after data collection. To minimize error from quality defects of particular sutures or suture batches, at least 3 separate sutures from different batches were used to represent each experimental and control suture type.

**STATISTICAL ANALYSIS**

Means and standard deviations were computed for strength, stiffness, and elongation for the barbed sutures as well as for the 4 types of control sutures. Means were compared using 1-way analysis of variance (F test). Pairwise comparisons were investigated using the Bonferroni adjustment for multiple comparisons. STATA software (version 9; StataCorp LP, College Station, Texas) was used.

**RESULTS**

All sutures (6 experimental barbed and 12 control nonbarbed sutures) were broken with the application of increasing force. Strength, stiffness, and elongation measurements were successfully completed for all sutures (Table 1).

As expected, breaking strength varied minimally for sutures of the same caliber but differed for sutures of different thickness (Figure 3). The thickest control sutures (2.0) were the strongest and the thinnest control sutures (5.0) were the least strong, with a gradual reduction in strength associated with diminishing thickness.

Comparison of means (Table 2) of strength for the 5 types of sutures, 1 experimental (barbed) and 4 control (nonbarbed), revealed that strength differed between these categories \( F = 25.45; P < .001 \). Similarly, stiffness \( F = 54.46; P < .001 \) and elongation \( F = 81.15; P < .001 \) differed across categories. Pairwise comparisons revealed that the barbed sutures differed significantly \( P < .001 \) from each of the other types of nonbarbed sutures on measures of stiffness and elongation. Strength of the barbed sutures was intermediate between that of 2.0 and 3.0 nonbarbed sutures and not significantly different from that of 3.0 nonbarbed sutures. Elongation of barbed sutures was closest to that of 3.0 nonbarbed sutures \( P = .002 \); stiffness of the barbed sutures was markedly in excess of any of the other suture types \( P < .001 \). Barbed sutures were stronger and stiffer than any nonbarbed sutures but also exhibited much greater intracategory variation in strength and stiffness, as measured by standard deviation, than any of the other suture types.

**COMMENT**

Breaking strength of barbed 2.0 polypropylene sutures seems to be intermediate between that of 2.0 and 3.0 nonbarbed sutures and closer to that of 3.0 nonbarbed sutures. In addition, barbed sutures seem to be significantly stiffer than nonbarbed sutures.

These findings suggest that manufacturers of barbed sutures are conservative in their estimate that the strength of 2.0 barbed polypropylene sutures is comparable to that of 4.0 nonbarbed polypropylene sutures. Based on our data, the breaking strength of the barbed sutures is in excess of even 3.0 nonbarbed sutures. While this does not suggest that surgeons do not need to be careful in placing barbed sutures, they may be reassured that such sutures are strong enough.
and unlikely to rupture during placement, the immediate postplacement period, or during the long term.

The high level of stiffness associated with barbed sutures may be a useful adaptation to their function. While sutures used for epidermal closure need to be stretchable to accommodate tissue edema, barbed sutures placed for facial lifting may benefit from increased stiffness, which prevents rapid loss of lifting activity. The purpose of lifting sutures is not to give but to maintain tension without sagging or slipping.

This study has limitations. First, the experimental sutures and the control sutures were produced by different manufacturers. However, this was deliberate, to ensure that the most common barbed sutures were compared with the most frequently used conventional sutures. Even most surgeons who use barbed sutures made by Surgical Specialties Corp are more familiar with the tensile strength and feel of conventional sutures made by Ethicon Inc than with conventional sutures made by the manufacturer of barbed sutures.

Second, the study had a cross-sectional, ex vivo design. Specifically, we neither imbedded the sutures in live tissue nor did we wait for several months or years to test the implanted suture. It is possible that tissue reactions or the passage of time may weaken barbed sutures beyond what we observed. In defense of our design, the comparison of barbed sutures with control sutures somewhat reduced this hazard; we do not assert an absolute, unchanging strength for barbed sutures but suggest that their strength is comparable to that of certain non-barbed sutures, which are made of the same material and likely to experience similar aging and tissue effects.

Third, there was potential for variability in knot tying by the individual tying the knots (R.R.), who was able to see and feel the difference in the materials and was not blinded. The operator of the strength-measuring machinery (M.S.), however, was not apprised as to the suture used. Positioned approximately 0.9 m (3 ft) from the knotted suture, the operator is unlikely to have been able to determine suture caliber or type.

While greater numbers of individual sutures can be tested to validate the findings of this study, we found that Food and Drug Administration–approved polypropylene barbed sutures are strong and stiff. Such sutures are likely to elongate minimally during and after placement. Further, such sutures are less vulnerable to breakage than conventional 3.0 sutures, and surgeons can be reassured that rupture is unlikely even with inadvertent application of excessive force.

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Correspondence: Murad Alam, MD, MSCI, Department of Dermatology, Northwestern University, 676 N St Clair St, Ste 1600, Chicago, IL 60611 (m-alam@northwestern.edu).

Author Contributions: Dr Alam had full access to all the data in the study and takes responsibility for the integrity and the accuracy of the data analysis. Study concept and design: Rashid, Villa, and Alam. Acquisition of data: Rashid and Sartori. Analysis and interpretation of data: White, Yoo, and Alam. Drafting of the manuscript: Rashid, Sartori, and Alam. Critical revision of the manuscript for important intellectual content: White, Villa, and Yoo. Statistical analysis: Alam. Administrative, technical, and material support: Sartori. Study supervision: Rashid.

Financial Disclosure: None reported.

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REFERENCES

Efalizumab in the Treatment of Discoid Lupus Erythematosus

Naila Usmani, MBChB, MRCP; Mark Goodfield, MBChB, MD

Background: Discoid lupus erythematosus is a chronic inflammatory condition in which the pathogenesis and the role of cell-mediated immunity remains unclear. Currently, the most effective treatments for severe disease are thalidomide, methotrexate, and cyclosporin, although the evidence for this is limited. Efalizumab is a monoclonal antibody directed against CD11a, the α-subunit of the leukocyte-functioning antigen 1, with a current license for use in psoriasis. Because discoid lupus erythematosus is known to be predominantly T-cell mediated, our aim was to use efalizumab as a T-cell modulator in patients with recalcitrant disease.

Observations: Thirteen patients received efalizumab, with treatment responses varying from good to excellent in 12 of 13 patients. There was a significant reduction in the cutaneous lupus activity and severity score (CLASS) score after therapy with efalizumab ($P = .002$).

Conclusions: We have presented efalizumab as a novel alternative treatment for patients with difficult discoid lupus erythematosus. The response to treatment in 12 patients was very encouraging, with the mean time to response being 5.5 weeks. However, patient numbers were small, and many remain in the early stages of therapy. A prospective randomized study with a long-term follow-up is required, especially in light of recent findings to evaluate both the effectiveness and safety profile of this monoclonal antibody.

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DISCOID LUPUS ERYTHEMATOSUS (DLE) is a chronic scarring condition with a predominantly lymphocytic histological picture. A mixed helper T cell lymphocyte profile, $T_h/T_i$, is seen with the role of autoantibodies remaining unclear. Most T cells express $1a$-like antigens and the $\gamma\delta$ T-cell receptor, with the ubiquitous presence of CD4+, CD8+, and HLA-DR+ in all types of cutaneous lupus erythematosus. Current treatments include antimalarial agents as well as a range of immunosuppressants, many of which have significant systemic adverse effects. Of these treatments, thalidomide, methotrexate, and cyclosporin appear to be the most effective, although the evidence for this is limited. In those situations in which clinical trial data exist, the overall response to therapy appears to be approximately 60%.

More recently, the potential role of biological therapies has been considered, with a number of cases reported in the literature showing good cutaneous response in patients with lupus. Fautrel et al described resolution of subacute cutaneous lupus erythematosus in a patient with rheumatoid arthritis who was treated with etanercept. A further study, which looked at tumor necrosis factor (TNF) blockade in systemic lupus erythematosus (SLE), demonstrated an overall decline in disease activity in all patients treated with infliximab. Efalizumab is a monoclonal antibody directed against CD11a, the α-subunit of the leukocyte-functioning antigen 1 (LFA-1), with a current license for use in psoriasis. Our aim was to use this T-cell modulator in patients with DLE to assess their response to treatment.

REPORT OF CASES

A retrospective review was conducted of 13 patients who had received efalizumab for severe recalcitrant DLE at the Department of Dermatology, Leeds General Infirmary, Leeds, England. All 13 patients had had severe DLE, which had failed to respond to a wide range of systemic therapies including steroids (intravenous and oral), antimalarial agents, dapsone, oral gold, azathioprine, methotrexate, and cyclosporin as well as repeated inpatient stays. Case notes were extensively reviewed to assess the course and outcome of treatment.
All patients were treated with efalizumab, 1 mg/kg subcutaneously once per week, with an initial dosage of 0.7 mg/kg. Before treatment was commenced, full blood cell count, routine biochemical analysis, and chest radiography were performed. During treatment, full blood cell count was performed monthly for the first 3 months and then once every 3 months. Routine biochemistry was performed once every 6 months.

As well as a general assessment of the patients’ clinical response to treatment, an objective assessment of therapeutic response using the cutaneous lupus activity and severity score (CLASS) was undertaken but without the scarring element. This is a validated scoring system used in the Leeds Connective Tissue Clinic to assess lupus severity. It is derived from the Psoriasis Area and Severity Index score, with measures of erythema, plaque elevation, and scaling assessed on a scale of 0 to 3, with a possible cumulative score of 0 to 9, and with disease extent scored from 1 to 5 in each affected area. The scores are then added together to produce a final result. Statistical analyses were performed with SPSS for Windows version 11.0 (SPSS Inc, Chicago, Illinois) using the Wilcoxon signed rank test for nonparametric paired values. P < .05 was considered significant.

Table 1 summarizes the salient features of the cohort of patients. The case series consisted of 9 women and 4 men, all with severe recalcitrant DLE. The age range was 32 to 66 years, and the main sites affected were the face and scalp. Of the 13 patients, 9 had a positive antinuclear antibody (ANA) test result, and 1 patient with a negative ANA test result had a positive result for extractable nuclear antigens. All 13 patients had a wide range of systemic immunosuppression as well as recurrent courses of intravenous steroids and repeated inpatient stays. Despite this, their disease had progressed relentlessly.

Patient 1 had a good response within 4 weeks of starting efalizumab therapy. Two months later, however, she noticed some lesions recurring, and acitretin was added to her treatment. For the past 12 months, her condition has been maintained with efalizumab and mepacrine with a small dose of prednisolone (7.5 mg/d). It should be emphasized that prednisolone and mepacrine were not able to control her condition before efalizumab was added to her treatment (Figure A and C). Patient 2 had an excellent response within 2 months of treatment, although her efalizumab dose was increased from 1 mg/kg to 1.25 mg/kg owing to a mild flare. Nine months after starting treatment, she developed superficial facial erosions, which responded well to fluocinolone acetonide ointment. At this time, her efalizumab treatment was discontinued for 1 month. Currently, her condition is maintained with efalizumab therapy, 75 mg/wk, and dapsone therapy, 50 mg/d. Again, it should be emphasized that this dose of dapsone had been used previously without success in this patient (Figure B and D).

Table 2 records the outcome to response to efalizumab in all 13 patients. The mean time to treatment response in patients was 5.5 weeks (Table 2). The mean treatment duration in all patients who received efalizumab was 14.1 months. The overall response to treatment in 11 of 13 patients was very good to excellent. The CLASS score was significantly reduced after therapy in 12 patients (P = .002). In 6 of 13 patients, the ANA titer improved after therapy. Although some adverse effects were experienced, this necessitated the cessation of treatment in only 1 patient (Table 3). Apart from patient 4, all patients currently receive efalizumab therapy, either alone or in conjunction with other therapies.

The pathologic nature of DLE remains poorly understood. In conjunction with the genetic and UV-mediated element, the general consensus is that it is a T-cell–mediated condition in which the role of autoantibodies remains unclear. Tissue damage occurs secondary to immune deposition in the skin with a resultant inflammatory response. The role of cytokines within this response is currently of much interest with recent reports suggesting that activated memory T cells, possibly clonally stimulated, may specifically target skin appendage cells.

Of these cytokines, TNF-α is well recognized in its role as an important proinflammatory mediator with pleiotropic properties. Meijer et al8 looked at cytokine profiles including TNF-α in 3 patients with SLE observed over 10 years. They demonstrated highly elevated levels of TNF-α in active as well as inactive periods of disease. In 2004, Aringer et al9 went on to report on an open-label study, which looked at the safety and efficacy of TNF-α blockade in SLE. The authors studied 6 patients with moderately active SLE who were given infliximab in addition

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Table 1. Clinical Features and Disease Duration of Patients Who Received Efalizumab

<table>
<thead>
<tr>
<th>Patient No./Sex/Age, y</th>
<th>Disease Duration, y</th>
<th>Sites Affected</th>
<th>Most Recent Autoantibody Titer Before Efalizumab Therapy (Date)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/F/49</td>
<td>9</td>
<td>Face, trunk, limbs</td>
<td>ANA neg, Ro/La pos (Oct 2005)</td>
</tr>
<tr>
<td>2/F/37</td>
<td>6</td>
<td>Face, scalp, trunk</td>
<td>ANA 1:40 (June 2004)</td>
</tr>
<tr>
<td>3/F/46</td>
<td>7</td>
<td>Face, scalp</td>
<td>ANA 1:160 (June 2002)</td>
</tr>
<tr>
<td>4/F/66</td>
<td>10</td>
<td>Face</td>
<td>ANA 1:40 (Oct 2005)</td>
</tr>
<tr>
<td>5/M/39</td>
<td>8</td>
<td>Face</td>
<td>ANA neg (June 2004)</td>
</tr>
<tr>
<td>6/F/51</td>
<td>5</td>
<td>Face</td>
<td>ANA 1:320 (Aug 2002)</td>
</tr>
<tr>
<td>7/F/58</td>
<td>10</td>
<td>Face</td>
<td>ANA 1:320 (Nov 2005)</td>
</tr>
<tr>
<td>8/M/52</td>
<td>20</td>
<td>Face, scalp</td>
<td>ANA 1:40 (Nov 2005)</td>
</tr>
<tr>
<td>9/F/62</td>
<td>30</td>
<td>Face, neck, hands</td>
<td>ANA 1:40 (Feb 2005)</td>
</tr>
<tr>
<td>10/M/37</td>
<td>5</td>
<td>Face</td>
<td>ANA 1:320 (Mar 2004)</td>
</tr>
<tr>
<td>11/F/47</td>
<td>11</td>
<td>Face</td>
<td>ANA neg (Jan 2006)</td>
</tr>
<tr>
<td>12/M/32</td>
<td>9</td>
<td>Trunk, arms</td>
<td>ANA neg (July 2003)</td>
</tr>
<tr>
<td>13/F/55</td>
<td>9</td>
<td>Trunk, face, scalp</td>
<td>ANA 1:40 (Feb 2006)</td>
</tr>
</tbody>
</table>

Abbreviations: ANA, antinuclear antibody; neg, negative; pos, positive.
to immunosuppression with either azathioprine or methotrexate. Although antibodies to double-stranded DNA and cardiolipin were increased in 4 patients, this was not associated with a decrease in complement, vascular events, or with flares of their condition. In all patients, disease activity declined during therapy.

However, TNF blockade has so far been treated with caution owing to reports of induction and, rarely, symptoms of lupus associated with use. In both rheumatoid arthritis and Crohn disease, TNF blockade has been reported to lead to the formation of antinuclear antibodies in 30% to 40% of patients and to the formation of autoantibodies to double-stranded DNA in approximately 15% of patients. Anticardiolipin antibodies have also been observed. Aside from this, there are also a number of reports in which patients have developed cutaneous and systemic features of lupus, with resolution occurring on cessation of therapy.
Given these potential difficulties of the use of anti-TNF agents and the presumed T-cell pathogenesis of cutaneous lupus, we decided to use efalizumab for our patients. Efalizumab is a monoclonal antibody to the CD11α-chain of LFA-1. In psoriasis it blocks the interaction of LFA-1 on the T cell with the intercellular adhesion mol-
ecule on the antigen-presenting cell. This interaction is important in the initial activation of T cells, in the adhesion of T cells to endothelial cells in the blood vessel wall, and, finally, in the migration of T cells to the site of inflammation.12 We suspect that efalizumab acts on similar T-cell-mediated targets in lupus. So far, its only licensed use is in the treatment of psoriasis with anecdotal reports in the treatment of granuloma annulare,13 dermatomyositis,14 and more recently, severe atopic dermatitis.15 Adverse effects of efalizumab include headache and/or flulike symptoms, arthralgia, thrombocytopenia, a transient pruritic eruption, and flares of psoriasis on discontinuation of treatment. In our case series of patients, there was an acute infective flare of lupus in 1 patient, superficial erosions in 2 patients, which was treated by temporary cessation of efalizumab therapy, and a symptomatic drug rash. Although arthralgia is a known adverse effect, 5 of the 12 patients in our case series have experienced such symptoms during their treatment with efalizumab. This quickly resolved with a short course of oral steroids in 2 patients, and in 2 others, the arthralgia had been an ongoing problem even before efalizumab therapy was started. In the remaining patient, the arthralgia has been severe and has warranted other systemic therapies. Since our case series of patients have been treated, there has also been a reported case of efalizumab-induced subacute cutaneous lupus erythematosus. This occurred in a woman aged 65 years, who was being treated with efalizumab for her oral and cutaneous lichen planus. Eight weeks after treatment, she developed a papulosquamous rash, which on biopsy was confirmed to be lupus. Her ANA test result was also positive, with an ANA titer of 1:160. Eleven weeks after the discontinuation of efalizumab therapy, her rash had cleared and her ANA titer had decreased to 1:80.16 Clearly, this is of concern and highlights the need for continued surveillance of patients who are receiving efalizumab therapy.

In conclusion, we have presented efalizumab as a novel alternative treatment for patients with difficult DLE. The response to treatment in 12 patients has been very encouraging, with the mean time to response being 5.5 weeks. Interestingly, in 6 of 13 patients, there was also a fall in the ANA titer. Although this may reflect an improvement in the disease activity, it may also suggest that efalizumab is also involved in some form of B-cell regulation in conjunction with its T-cell modulatory properties.

We do, however, acknowledge the limitations of our study. It is retrospective with a small number of patients, many of whom remain in the early stages of therapy. A prospective randomized study with long-term follow-up is required, especially in light of recent findings, to evaluate both the effectiveness and safety profile of this monoclonal antibody, which we hope to carry out in the future.

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Author Contributions: Dr Usmani had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

References

Dendritic Cells in Pigmented Basal Cell Carcinoma

A Relevant Finding by Reflectance-Mode Confocal Microscopy

Sonia Segura, MD; Susana Puig, MD; Cristina Carrera, MD; Josep Palou, MD; Josep Malvehy, MD

Background: Reflectance-mode confocal microscopy (RCM) is a new approach for the in vivo diagnosis of skin tumors. A few studies of RCM on basal cell carcinoma (BCC) have provided specific diagnostic criteria, but large studies on pigmented basal cell carcinoma are lacking. Proliferation of large dendritic-shaped cells within a melanocytic tumor has been associated with the diagnosis of melanoma by RCM. Benign melanocytes and Langerhans cells may populate BCC according to previous histological studies. We studied 3 consecutive pigmented BCC by means of RCM and performed a histological and immunohistochemical correlation focusing on the presence of dendritic structures.

Observations: Reflectance-mode confocal microscopy revealed highly refractive dendritic structures within tumor nests that correlated with the presence of melanocytes within the tumor by immunohistochemical analysis. In 1 case, dendritic structures on the overlying epidermis corresponding to Langerhans cells were also noted. Leaf-like areas observed on dermoscopy correlated with low-refractive cordlike structures and nodules by RCM and corresponded to nests of basaloid cells, whereas blue-gray globules presented as bright oval structures with ill-defined borders corresponding to melanophages.

Conclusions: Reflectance-mode confocal microscopy allows the study of pigmented BCC and the identification of specific criteria described previously. In these tumors, dendritic melanocytes can be easily identified with this technique.

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DIFFERENTIAL DIAGNOSIS BETWEEN pigmented basal cell carcinoma (BCC) and melanoma can be difficult. Reflectance-mode confocal microscopy (RCM) is useful in the recognition of BCC and melanocytic lesions. Three pigmented BCC were studied using RCM, dermoscopy, and histopathologic analysis. Emphasis was placed on the analyses of dendritic cells detected by RCM. Reflectance-mode confocal microscopy was performed with a commercially available, near-infrared reflectance confocal laser scanning microscope (Vivascope 1500; Lucid Inc, Henrietta, New York). Histological slides were stained with hematoxylin-eosin, and immunohistochemical studies were performed.

REPORT OF CASES

Patient 1 was a 78-year-old woman with a gray-brown papule on the back. Findings from dermoscopy showed leaflike structures and blue-gray globules suggestive of BCC (Figure 1A). Reflectance-mode confocal microscopy revealed locally elongated and polarized nuclei, multiple solid units of tumor cells forming cordlike structures and nodules surrounded by a dark area, and bright oval structures with ill-defined borders within tumor nests and surrounding them. Long, thin dendritic structures were observed all over the lesion and were located within tumor nests and on the overlying epidermis (Figure 1B). Dilated vessels with rolling phenomena were also noted. Histopathologic analysis confirmed the diagnosis of nodular BCC (Figure 1C). Immunohistochemical studies demonstrated S100 and CD1a+ dendritic cells on the epidermis and S100, MelanA, and HMB45+ within tumoral nests (Figure 1D), indicating the presence of melanocytes within tumoral nests and activated Langerhans cells on the epidermis.

Patients 2 and 3 exhibited similar dermoscopical, confocal, histological, and immunohistochemical findings (Figure 2).

COMMENT

Reflectance-mode confocal microscopy and dermoscopy are imaging techniques that allow the study of skin tumors in the

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horizontal plane. Reflectance-mode confocal microscopy allows a quasihistological resolution and an architectural view of the tumor that is better evaluated in combination with dermoscopy. As already been reported,\(^3\) in patient 1, low-refractive cordlike structures and nodules correlated with dermoscopic leaflike areas. In all 3 cases, blue-gray granules correlated with confocal bright oval structures and corresponded to melanophages. Typical arborizing vessels correlated with enlarged horizontal vessels.

González et al\(^1\) first described 5 criteria for the diagnosis of BCC by RCM,\(^1\) which was later validated in a larger study. Another study with 12 lesions found additional criteria for the diagnosis of BCC by RCM\(^4\) and described bright structures within tumor parenchyma that resembled dendritic cells. The same finding was recently reported by Agero et al\(^3\) and correlated with intratumoral melanocytes or Langerhans cells.

Melanocytes can be assessed in melanocytic lesions by RCM as bright roundish or dendritic cells within the epidermis, at dermoepidermal junction or in dermal papilla.\(^5\) Langerhans cells can be identified by RCM as dendritic cells within epidermal layers in inflamed nevi or scars of lesions recently removed.
In our study, dendritic cells in BCC nests correlated with melanocytes, whereas dendritic cells in the epidermis corresponded to Langerhans cells. Our findings are supported by previous studies that demonstrated the presence of melanocytes and Langerhans cells in BCC. The importance has to be stressed of being aware of the presence of dendritic cells in RCM of pigmented skin tumors to avoid the incorrect classification of a melanocytic tumor including melanoma. Larger studies are needed to elucidate the frequency, characteristics, and meaning of dendritic cells in pigmented skin tumors.

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Author Contributions: Study concept and design: Segura, Puig, and Malvehy. Acquisition of data: Segura, Palou, and Malvehy. Analysis and interpretation of data: Segura, Puig, Carrera, Palou, and Malvehy. Drafting of the manuscript: Segura and Carrera. Critical revision of the manuscript for important intellectual content: Puig, Palou, and Malvehy. Study supervision: Malvehy.
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REFERENCES


Correction

Errors in Author Contributions. In the Study titled “Store-and-Forward Teledermatology in Skin Cancer Triage: Experience and Evaluation of 2009 Teleconsultations” by Moreno-Ramirez et al. published in the April issue of the Archives (2007;143[4]:479-484), several errors occurred in the “Author Contributions” section. The corrected author contributions are reproduced here.

Author Contributions: Drs Moreno-Ramirez, Ferrandiz, and Nieto-Garcia had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Moreno-Ramirez, Ferrandiz, Nieto-Garcia, Carrasco, Moreno-Alvarez, Galdeano, and Camacho. Acquisition of data: Moreno-Ramirez, Ferrandiz, Bidegain, Moreno-Alvarez, Galdeano, and Rios-Martin. Analysis and interpretation of data: Moreno-Ramirez, Ferrandiz, Nieto-Garcia, Galdeano, and Camacho. Drafting of the manuscript: Moreno-Ramirez and Ferrandiz. Critical revision of the manuscript for important intellectual content: Moreno-Ramirez, Ferrandiz, Carrasco, Moreno-Alvarez, Galdeano, Rios-Martin, and Camacho. Statistical analysis: Moreno-Ramirez, Ferrandiz, and Nieto-Garcia. Obtained funding: Moreno-Ramirez, Carrasco, Bidegain, and Camacho. Administrative, technical, and material support: Moreno-Ramirez, Carrasco, Moreno-Alvarez, Galdeano, and Camacho. Study supervision: Moreno-Ramirez, Rios-Martin, and Camacho.
Treatment of Recurrent Squamous Cell Carcinoma of the Skin With Cetuximab

Julie E. Bauman, MD, MPH; Keith D. Eaton, MD, PhD; Renato G. Martins, MD, MPH

Background: Squamous cell carcinoma of the skin (SCCS) is rarely encountered by medical oncologists owing to success of local therapies. When advanced SCCS requires systemic palliation, treatment with conventional chemotherapy, such as cisplatin, is often precluded by a patient’s age or medical comorbidities. Cetuximab is a human and mouse chimeric antibody against epidermal growth factor receptor, a tyrosine kinase receptor richly expressed by SCCS cells, including lymph node metastases. This drug, approved for treatment of squamous cell carcinoma of the upper aerodigestive tract as well as colorectal cancer, is well tolerated. Toxic effects include acneiform rash and diarrhea. Preclinical data suggest that epidermal growth factor receptor is important in SCCS carcinogenesis.

Observations: Herein, we report 2 cases of elderly patients with extensive, in-transit recurrence of SCCS who have been treated with palliative cetuximab. The drug was well tolerated, with the exception of acneiform rash requiring dose reduction in 1 patient. Both patients had excellent responses to cetuximab: the first patient had complete response by week 16 of treatment and the second a near-complete response by week 12. In both cases, initial response to cetuximab was evident by week 4 of therapy.

Conclusions: To our knowledge, these are the first reported cases of cetuximab use in patients with SCCS. The encouraging responses justify the prospective study of cetuximab in SCCS.

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Nonmelanoma skin cancer is the most common malignant neoplasm diagnosed in white individuals in the United States. The American Cancer Society estimates that over 1 million new cases occur annually. Most patients receive successful local therapy. Death from the disease is very rare, with a case-fatality rate of 0.25% (approximately 2000 cases per year). Squamous cell carcinoma (SCC) of the skin (SCCS) represents approximately 15% of all nonmelanoma skin cancers.

Patients with advanced SCCS include those with extensive local recurrence of SCCS after surgical resection and radiotherapy or with metastatic disease. Such patients have few therapeutic options. Progressive disease leads to substantial morbidity and, ultimately, mortality. Clinical trials are difficult to conduct because of the small number of patients. Consequently, systemic treatment for advanced SCCS is based on small, single-arm trials or case series. Cisplatin-based, combination chemotherapy is the most commonly used treatment. Response rates can be high; however, the toxic effects of cisplatin are often prohibitive and include nausea, vomiting, nephrotoxic effects, and hearing loss. Given that SCCS is a disease of elderly individuals, the administration of cisplatin is frequently precluded by a patient’s age or medical comorbidities. Furthermore, most patients treated with chemotherapy for locally recurrent SCCS have received radiotherapy. Among analogous patients with SCC of the upper aerodigestive tract, prior treatment with radiotherapy predicts poor local response to conventional chemotherapy, such as cisplatin.

Cetuximab is a recombinant human and mouse chimeric antibody that competitively inhibits epidermal growth factor receptor (EGFR). This drug is active in the treatment of SCC of the upper aerodigestive tract, which richly expresses EGFR, even in cisplatin- or radiation-refractory disease. Cetuximab is well tolerated, particularly compared with conventional chemotherapy, and its common toxic effects include hypersensitivity reactions, acneiform rash, and diarrhea. We describe 2 elderly patients with extensive, in-transit recurrence of SCCS following surgery and radiation who have been treated with first-line cetuximab.

Report of Cases

Case 1

Patient 1, a white man, presented at age 73 years with a rapidly growing, erythem-
In October 2004, findings from a shave biopsy documented SCCS. The patient underwent complete excision by Mohs microsurgery in December 2004. In September 2005, he had recurrence of SCCS adjacent to the original resection scar. Mohs microsurgery was repeated, with histologic findings demonstrating SCCS within the dermis, without connection to the overlying epidermis. Although local recurrence was favored, in-transit metastasis could not be excluded. The patient was treated with adjuvant, intensity-modulated radiation therapy, completing 60 Gy to the temporal scalp in December 2005. In February 2006, he developed in-field recurrence. He underwent a third Mohs procedure in March 2006, and the histologic findings described poorly differentiated SCCS with satellitosis and perineural invasion. Two additional nodules within a 2-cm radius were biopsied, and the findings from both showed SCCS with positive margins. Computed tomography of the neck showed only postoperative changes, with no cervical adenopathy. A fourth Mohs procedure was performed 3 weeks later to encompass the 2 biopsied lesions, and clear margins were obtained. Within 2 weeks, the patient developed multiple subcutaneous nodules in a circumferential area around the wound, both within and outside the radiation field. Findings from 2 preauricular biopsy samples were positive for SCCS. At a multidisciplinary review, salvage surgery was not recommended owing to the patient’s medical comorbidities, which included severe chronic obstructive pulmonary disease, coronary artery disease, and congestive heart failure. She was referred to the medical oncology department for palliative therapy.

At medical oncology intake, the patient was noted to have multiple nodules across the left parietal scalp and preauricular area. His recent Mohs excisions were healing by secondary intent. He also had matted left submandibular lymphadenopathy measuring 2.5 × 1.5 cm (Figure 1A). Treatment with cetuximab was initiated on May 19, 2006. Within 1 week, the patient developed a characteristic acneiform rash on his face, posterior neck, upper back, and anterior chest. Despite treatment with topical emollients, a 3-day pulse of prednisone at 60 mg daily, and minocycline hydrochloride, a grade 3 rash evolved after 3 doses of cetuximab (Figure 2). A 2-week treatment break was required (Figure 2). Nonetheless, at week 4 the patient had marked flattening of skin nodules and decrease in size of palpable adenopathy (Figure 1B). Over the next 3 months, the patient had complete resolution of skin nodules and adenopathy (Figure 1C). Owing to flares of the grade 3 rash, 2 dose reductions have been required to date, and he has experienced no other toxic effects attributable to cetuximab. The patient’s response is currently maintained with weekly treatments of cetuximab, 150 mg/m².

**CASE 2**

Patient 2, a white woman, was diagnosed at age 71 years with moderately to poorly differentiated SCCS of the nasal tip and columnella. Owing to multiple medical comorbidities that precluded a major cosmetic reconstruction, the patient was treated with primary radiation. Treatment with 59.6 Gy of electron radiation was completed in November 2005. Two months later, the patient had a recurrence on her columnella, which was treated with Mohs microsurgery in February 2006. Six weeks later, the patient developed a nodule on her right upper lip that proved to be an in-transit metastasis. A concurrent papule on the left nasal sill was also in-transit SCCS. A second Mohs microsurgery was performed, and the lesion healed by secondary intent. A computed tomographic scan of the neck was negative for pathologic adenopathy. In May 2006, a new nodule appeared at the Mohs surgical site. Findings from a biopsy confirmed recurrent SCCS. At a multidisciplinary review, salvage surgery was not recommended owing to the patient’s medical comorbidities, which included severe chronic obstructive pulmonary disease, coronary artery disease, and congestive heart failure. She was referred to the medical oncology department for palliative therapy.
At medical oncology intake, the patient was noted to be wheelchair dependent, with an Eastern Cooperative Oncology Group performance status of 2. She had a complex nasal defect. Inferior to the nasal flap were 4 confluent subcutaneous nodules, with a punch biopsy site at the center. A 4-mm nodule was present within her right upper lip incision (Figure 3A). Treatment with cetuximab was begun on May 30, 2006. After 2 weeks, the patient developed grade 1 acneiform rash on her chin, which thereafter improved. During the first 12 weeks of therapy, the patient experienced near-complete resolution of her lesions. The nasal sill nodules resolved, exposing a portion of her prior Mohs surgical bed, and the nodule within her lip incision shrank from 4 to 2 mm (Figure 3B). Aside from a mild rash, the patient has experienced no notable toxic effects from cetuximab. The patient’s response is currently maintained with weekly treatment with cetuximab, 250 mg/m², 5 months after initiation.

COMMENT

The advent of molecularly targeted therapies has dramatically changed treatment approaches in oncology. This paradigm shift was pioneered by imatinib mesylate, which targets the bcr-abl oncogene in chronic myelogenous leukemia, and trastuzumab, which targets the erb2/HER2 receptor in breast cancer. Numerous other drugs have been designed to target growth and survival pathways important in carcinogenesis. One such pathway is initiated by EGFR, a tyrosine kinase receptor. Phosphorylation of EGFR results in a cascade of proliferative and antiapoptotic signaling, through mitogen-activated protein kinase, phosphotidylinositol-3 kinase, and signal transducer and activator of transcription. Epidermal growth factor receptor is overexpressed in a number of malignant neoplasms. Agents targeting this pathway have been approved in the treatment of nonsmall cell lung cancer (erlotinib hydrochloride, gefitinib), SCC of the upper aerodigestive tract (cetuximab), colon cancer (cetuximab, panitumumab), and pancreatic cancer (erlotinib). Anti-EGFR antibodies (cetuximab, panitumumab) block the extracellular domain of the receptor, inhibiting ligand binding. The small molecule inhibitors (erlotinib, gefitinib) block the intracellular tyrosine kinase inhibiting phosphorylation and activation of downstream signaling cascades.

Epidermal growth factor receptor is an attractive potential target in SCCS. When studied by immunohistochemical analysis, EGFR expression is noted in normal keratinocytes; it is expressed at increasingly higher levels in SCCS and in lymph node metastases from SCCS. In keratinocyte cultures, epidermal growth factor stimulates proliferation and suppresses markers of terminal differentiation. This is blocked by the EGFR tyrosine kinase inhibitor PD153035. With EGFR blockade, keratinocytes are more susceptible to induction of apoptosis by UV-B radiation or matrix detachment. In vitro and mouse models indicate that EGFR activation within malignant epithelial cells induces signal transducer and activator of transcription 3 activation, which drives carcinogenesis, and that EGFR blockade abrogates this response. Other preclinical research suggests that EGFR blockade may inhibit telomerase activity in SCCS and thus suppress tumor growth.

Owing to the relative rarity of advanced SCCS, there are no prospective clinical trials of novel targeted therapies in the published literature. Glisson et al recently reported in abstract form a phase II trial of the oral agent gefitinib in patients with metastatic or recurrent SCCS (http://clinicaltrials.gov/show/NCT00054691). A total of 20 patients were evaluable for response at the time of their report, of a planned enrollment of 40. Glisson et al observed a 15% partial response rate and a 45% stable disease rate.

Three other prospective trials of anti-EGFR therapy in advanced SCCS are ongoing. Gefitinib is being evaluated in the neoadjuvant treatment of patients whose disease is amenable to local therapy with surgery or radiation (http://clinicaltrials.gov/show/NCT00126555). A second trial examines erlotinib with postoperative radiotherapy in high-risk patients (http://clinicaltrials.gov/show/NCT00369512). The third study examines cetuximab in patients whose tumors express a high level of EGFR (http://clinicaltrials.gov/show/NCT00240682).
In conclusion, we have described 2 elderly patients with advanced SCCS who were treated with first-line cetuximab. The drug was well tolerated, with the exception of acneiform rash requiring dose reduction in 1 patient. Response to cetuximab was evident in both cases by week 4 of therapy. By week 16, 1 patient had a complete response, and the other a near-complete response. Although follow-up is limited, both responses were sustained after 5 months of maintenance therapy. To our knowledge, these are the first published cases of cetuximab use in SCCS, as well as the first documented responses. Clearly, these encouraging results justify further study of cetuximab in SCCS.

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Author Contributions: Drs Bauman, Eaton, and Martins had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Bauman, Eaton, and Martins. Acquisition of data: Bauman, Eaton, and Martins. Analysis and interpretation of data: Bauman, Eaton, and Martins. Critical revision of the manuscript for important intellectual content: Bauman, Eaton, and Martins. Administrative, technical, and material support: Bauman, Eaton, and Martins. Study supervision: Bauman, Eaton, and Martins.
Financial Disclosure: Dr Bauman receives research support from Novartis. Dr Eaton receives research support from Wyeth and Genentech Inc. Dr Martins receives research support from Novartis International AG, Genentech Inc, OSI Pharmaceuticals, Amgen Inc, Eli Lilly and Company, and ImClone Systems Inc. He has received honoraria from Eli Lilly and Company and Genentech Inc.
Additional Contributions: Jeffrey Slater, MFAW, provided manuscript assistance.

REFERENCES

**Endemic Pemphigus Vulgaris**

Rosicler Rocha-Alvarez, MD; Alex G. Ortega-Loayza, MD; Horacio Friedman, MD; Iphis Campbell, MD; Valeria Aoki, MD; Evandro A. Rivitti, MD; David Dasher, MD; Ning Li, PhD; Luis A. Diaz, MD; for the Cooperative Group on Fogo Selvagem Research

**Background:** Investigators from Brasilia, Brazil, observed several patients with a mucocutaneous disease that resembles pemphigus vulgaris clinically and histologically but with epidemiological features of fogo selvagem. Our objective was to characterize antidesmoglein 1 autoantibody profiles in these unique patients who reside in Goiânia and Brasilia, Brazil, known endemic regions of fogo selvagem.

**Observations:** We performed serological evaluation of 8 patients with a mucocutaneous disease clinically and histologically consistent with pemphigus vulgaris, as well as 27 healthy relatives of patients with fogo selvagem who reside in these endemic areas. Serum samples from all 8 patients bound desmoglein 3 by cold immunoprecipitation and from 6 patients by enzyme-linked immunosorbent assay, while serum samples from 4 patients bound desmoglein 1 by cold immunoprecipitation and by enzyme-linked immunosorbent assay. Antidesmoglein 3 autoantibodies were detected in 4 of 27 healthy donors by cold immunoprecipitation and by enzyme-linked immunosorbent assay, whereas antidesmoglein 1 autoantibodies were detected in 6 individuals by cold immunoprecipitation and in 3 individuals by enzyme-linked immunosorbent assay.

**Conclusion:** These findings provide serological evidence of a new endemic variant of pemphigus vulgaris.

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**Pemphigus Vulgaris (PV), Pemphigus Foliaceus (PF), and its endemic form fogo selvagem (FS) have distinct clinicopathological, epidemiological, and serological features.** Pemphigus vulgaris is a disease characterized clinically by flaccid blisters or erosions involving the skin and mucous membranes and histologically by suprabasilar acantholysis. Patients with PV possess pathogenic antidesmoglein 1 (anti-Dsg1) and antidesmoglein 3 (anti-Dsg3) autoantibodies in its mucocutaneous form and solely anti-Dsg3 antibodies in its mucosal form.1,2 Most PV cases in North America, Europe, and Asia are sporadic, without evidence of geographic clustering. However, a few rare familial cases of PV have been reported.4,8 In addition, a slightly higher frequency of PV has been observed among the Ashkenazi Jewish population.9

In PF and FS superficial cutaneous blisters and erosions are seen clinically along with histological subcorneal acantholysis. Patients lack mucosal involvement. Serologically, pathogenic anti-Dsg1 autoantibodies are detected in patient serum.10-12 While PF and FS are identical clinically, histologically, and serologically,13 the epidemiological features of FS are distinctive. Fogo selvagem is a disease of peasants dedicated to outdoor activities, and cases exhibit geographic and familial clustering.14,15 These observations led investigators to suspect that the autoimmune response in FS is triggered by as yet unknown environmental factors.16-18 Other forms of endemic PF have been reported in Colombia, Peru, and Tunisia.19-22

Curiously, recent reports describe the rare transition of phenotype from PV to PF23-27 and from PF to PV.26,28,29 In addition, anti-Dsg1 autoantibodies, typical of PF, have been detected in serum samples from patients with PV.2 Conversely, anti-Dsg3 autoantibodies have been detected in serum samples from patients with PF and FS.30,31

During the past 3 decades, Brazilian investigators from the University of Brasilia have evaluated and treated many patients with FS at university clinics.32,33 Another group of investigators from Goiânia have treated several hundred patients with FS at the Hospital do Penfigo de Goiânia.14,34,35 Some of us (R.R.-A., H.F., and I.C.) have observed several patients with a mucocutaneous disease that resembles PV clinically and histologically but with epidemiological features of FS. Specifically, we observed the disease in younger patients residing in known endemic areas of FS. The objective of this study was to charac-
characterize the anti-Dsg1 and anti-Dsg3 autoantibody responses in 8 of these patients initially seen and followed up at the University of Brasilia.

**METHODS**

**PATIENTS AND SERUM SAMPLES**

Between January 1, 1982, and September 30, 1989, serum samples were obtained from 8 patients with a mucocutaneous syndrome clinically and histologically resembling PV. Samples were kept frozen at −20°C at the research laboratories of the University of Brasilia until they were transported to the Dermatology Research Laboratories, University of North Carolina at Chapel Hill. Serum samples from healthy donors in Brasilia (n=5) and in neighboring Goiás (n=22) were also included in the study. Figure 1 shows the geographic areas of interest in this study. The depicted regions are known to be endemic foci of FS. The sites of origin of the 8 patients are given in the Table. These sites represent rural communities surrounding urban Brasilia. Patients often travel long distances seeking medical care at the University of Brasilia Hospital. Serological studies were performed under University of North Carolina at Chapel Hill and University of Brasilia guidelines and institutional review board regulations.

**PRODUCTION AND PURIFICATION OF RECOMBINANT Dsg1 AND Dsg3**

Recombinant forms of Dsg1 and Dsg3 containing the entire extracellular domain and a C-terminal histidine tag were gener-
ated in the baculovirus system and were purified by nickel affinity chromatography. Purified recombinant Dsg1 and recombinant Dsg3 proteins were used in cold immunoprecipitation (IP) and enzyme-linked immunosorbent assay (ELISA) procedures.

**Dsg1 AND Dsg3 ELISA ASSAYS**

Recombinant Dsg1 or recombinant Dsg3 was immobilized on microtiter plates (Costar, Cambridge, Massachusetts) by overnight incubation at 4°C. The strips were then washed with a Tris-buffered saline solution, pH 7.4, containing 3.7 mM calcium. Duplicate samples of a 1:100 dilution of serum were incubated for 60 minutes. The plates were washed and then incubated with a 1:3000 dilution of horseradish peroxidase–labeled mouse antihuman IgG (Zymed Laboratories, South San Francisco, California) for 60 minutes. The strips were washed again and were incubated with o-phenylenediamine substrate (Sigma-Aldrich Inc, St Louis, Missouri) dissolved in phosphate citrate buffer with sodium perborate (Sigma-Aldrich Inc) for 30 minutes. The reaction was stopped with 4 M sulfuric acid. ELISA values were expressed as an index value as previously reported by Amagai et al, using the following equation:

\[
\text{Index value} = \left( \frac{\text{test sample OD} - \text{negative control}}{\text{positive control OD} - \text{Negative Control}} \right) \times 100,
\]

where OD indicates optical density.

A cutoff value of 20 arbitrary units, previously determined by analyzing a set of 57 human serum samples from healthy donors in the United States, was used to separate positive from negative serum samples. Values below 20 were considered negative; those 20 and higher were considered positive. Well-characterized PV and FS serum samples were used as positive controls.

**INDIRECT IMMUNOFLUORESCENCE AND COLD IP**

Indirect immunofluorescence (indirect IF) was carried out as previously described. Cold immunoprecipitation was performed using recombinant Dsg1 and recombinant Dsg3 as previously described. Skin and mucosal biopsy specimens were obtained from patients and were tested by hematoxylin-eosin staining. All serum samples from patients and healthy control subjects were tested by indirect IF using monkey esophagus as substrate according to previously published procedures.

**RESULTS**

Figure 2 shows the clinical features of 2 patients with mucocutaneous lesions similar to the mucocutaneous form of PV. Skin and mucosal biopsy specimens showed suprabasilar acantholysis (not shown). The findings from the serum samples of 8 patients by indirect IF, cold IP, and ELISA for Dsg1 and Dsg3 are given in the Table and in Figure 3. Autoantibodies against the epidermal intercellular spaces were detected by indirect IF analysis in all
patients, with titers ranging from 1:40 to 1:1280. Three of 27 serum samples (11%) from healthy controls tested positive by indirect IF, with titers ranging from 1:80 to 1:320. Serum samples from all 8 patients and from 4 of 27 control subjects (15%) immunoprecipitated recombinant Dsg3. Antidesmoglein 1 antibodies were detected by cold IP in 4 of 8 patients and in 6 of 27 control subjects (22%) (Figure 3). Antidesmoglein 3 autoantibodies were detected by ELISA in 6 of 8 patients and in 4 of 27 control subjects (15%). Antidesmoglein 1 antibodies were detected by ELISA in 4 of 8 patients and in 3 of 27 control subjects (11%). Positive and negative results from both tests used to detect specific anti-Dsg1 and anti-Dsg3 autoantibodies were concordant in 6 patients.

This study evaluated 8 individuals initially seen with a mucocutaneous syndrome resembling the mucocutaneous form of PV who also had autoantibodies against Dsg3 and Dsg1. The clinical features of these patients were unique, as FS does not involve mucous membranes. All 8 patients resided in rural communities surrounding Brasilia and Goiânia, well-known endemic areas of FS (Figure 1). No patients were from metropolitan Brasilia. Patients with FS treated at the University of Brasilia Hospital commonly travel from the communities of origin of the study patients. These clinical observations and the description of autoantibodies against Dsg3 in healthy individuals living in endemic areas of FS raised the suspicion that the findings in these patients may represent a rare form of endemic PV observed in these rural communities of Brazil where FS is also seen. Four of 8 patients were females younger than 20 years, an unusual finding in patients with PV. This observation may reflect hormonal effects in the onset and progression of autoimmune disease in these patients. Further studies are needed to clarify these aspects of the disease.

It is possible that this disease phenotype was previously overlooked because of its rare occurrence. For example, between 1952 and 1970, the Hospital do Penfigo de Goiânia, located in the center of an endemic region of FS, admitted 2663 patients with FS compared with only 37 patients with possible PV (ratio, 72:1). In the western regions of the state of Parana, another known endemic area of FS, Empinotti et al. reported 213 FS cases and 11 PV cases (ratio, 19:1) between 1976 and 1988. Moreover, the Hospital Adventista do Penfigo in Campo Grande (state of Mato Grosso do Sul), Brazil, another hospital dedicated to the treatment of patients with FS, admitted 718 patients with FS and only 61 patients with PV (ratio, 12:1) between 1982 and 1988. In contrast, the University Hospital of Rio de Janeiro, Brazil, located in a nonendemic area, admitted 30 patients with FS and 14 patients with PV (ratio, 2:1) between 1959 and 1975. These admitted patients with FS had migrated from endemic regions of FS, whereas patients with PV resided within the city.

Antidesmoglein 1 antibodies have been detected in serum samples from most patients with FS and from one-third of healthy individuals living in the Limao Verde Reservation in Mato Grosso do Sul, Brazil, using ELISA. Autoantibodies against Dsg3 have also been detected in serum samples from 19 of 276 previously studied patients (7%) with FS and PF by ELISA. A recent study demonstrated anti-Dsg3 autoantibodies not only in 43% (9 of 21) of serum samples from patients with FS sera from the Limao Verde Reservation but also in 36% (53 of 146) of serum samples from healthy individuals living in and around this endemic area. A significant trend was observed in the proportion of positive test results for Dsg3 autoantibodies relative to distance from this endemic area. Despite this high observed prevalence of anti-Dsg3 autoantibodies among this population, no patients with FS or healthy individuals from this endemic area have displayed mucosal lesions suggestive of PV. In the present investigation, we detected anti-Dsg3 autoantibodies in the serum samples of 4 of 27 healthy individuals (15%) living in endemic areas of FS. Based on these findings, the emergence of pathogenic anti-Dsg3 autoantibodies and clinical variants of PV in the endemic regions of FS seems to be an uncommon occurrence. These results also reinforce the notion of potential environmental triggers relative to the emergence of these autoantibodies.

The lack of serological data before the development of disease in 8 patients presented herein limits our ability to more fully characterize the serological progression of this disease. However, given the observed sero-epidemiological findings of anti-Dsg3 antibodies in residents of the Limao Verde Reservation, Brasilia, and Goiânia, it is conceivable that populations at risk of developing FS may also be at risk of developing an endemic form of PV. These findings underscore the importance of continued close clinical, serological, and epidemiological observation of populations living in endemic areas of FS.

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Author Contributions: Drs Rocha-Alvarez, Ortega-Loayza, Dasher, Li, and Diaz had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Rocha-Alvarez and Diaz. Analysis and interpretation of data: Rocha-Alvarez, Ortega-Loayza, Friedman, Campell, Aoki, Rivitti, Dasher, Li, and Diaz. Drafting of the manuscript: Ortega-Loayza and Diaz. Critical revision of the manuscript for important intellectual content: Rocha-Alvarez, Ortega-Loayza, Aoki, Dasher, Li, and Diaz. Obtained funding: Li and Diaz. Administrative, technical, and material support: Ortega-Loayza and Dasher. Study supervision: Li and Diaz.

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Efalizumab-Associated Papular Psoriasis

Akmal S. Hassan, MD; Dagmar Simon, MD; Hans-Uwe Simon, PhD; Lasse R. Braathen, MD, PhD, MHA; Nikhil Yawalkar, MD

Background: Efalizumab is a human anti-CD11a monoclonal antibody used in the treatment of patients with moderate to severe plaque psoriasis. Some of the patients develop new papular lesions during treatment, which are predominantly located in the flexural regions.

Observation: Four patients with recalcitrant psoriasis undergoing treatment with efalizumab presented with erythematous, partly scaly papules and small plaques on previously unaffected areas after 4 to 10 weeks of efalizumab therapy. Tissue sections of biopsy specimens were stained with hematoxylin-eosin, and immunohistochemical staining was performed using monoclonal antibodies against CD3, CD4, CD8, T-cell–restricted intracellular antigen 1, granzyme B, neutrophil elastase, CD68, CD1a, CD11c, HLA-DR, CD25, CD20, and CD56. Histopathological and immunohistochemical examination of the lesions showed features consistent with psoriasis and activation of various leukocyte subtypes including T cells, dendritic cells, macrophages, and neutrophils.

Conclusions: Papular eruptions appearing during efalizumab therapy represent new psoriatic lesions and could be referred to as efalizumab-associated papular psoriasis (EAPP). They usually do not necessitate termination of efalizumab therapy and may optionally be treated with topical corticosteroids. Dermatologists should be aware of these lesions and inform their patients accordingly.

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tion is still unknown. In this study, we describe 4 patients with psoriasis who experienced cutaneous eruptions similar to those described previously as LMB. In addition, we analyzed the histopathological and immunohistochemical findings of skin biopsy specimens obtained from these lesions with the aim of providing a detailed description and an understanding of their nature.

REPORT OF CASES

Four patients (1 woman and 3 men, aged 42-59 years) with recalcitrant psoriasis were treated with weekly subcutaneous injections of efalizumab (1 mg/kg of body weight). The clinical data are summarized in Table 1. All patients had long-standing plaque psoriasis, and the female patient had concomitant severe palmoplantar pustular psoriasis. After 3 to 6 weeks of efalizumab therapy, signs of improvement of their original psoriatic plaques were observed. During the 4th to 10th weeks, all 4 patients developed nonitchy, well-demarcated, erythematous, partly scaly papules and some small plaques (1-2 cm in diameter) on previously unaffected areas (Figure 1). Pustular lesions were not observed. The new papular lesions were particularly noted in the flexural regions (axillae and groin) and on the trunk and extremities. No additional medications had been administered, and no signs of underlying infection were detected at the time of eruption of these papular lesions. In 3 patients, laboratory test results indicated absolute lymphocytopenia. Treatment with efalizumab was continued, and the papular lesions were treated with midpotent topical corticosteroids once daily. In 2 patients, the lesions resolved within 4 weeks. However, 1 patient who irregularly used the topical corticosteroid continued to experience a milder degree of such lesions for as long as 12 weeks. Three patients responded well to efalizumab therapy and achieved at least 75% reduction of the Psoriasis Area and Severity Index score after 12 weeks. However, 1 patient showed an initial amelioration of these papular lesions, but then progressively developed a GIF, which led to termination of efalizumab therapy at week 11.

METHODS

After obtaining informed consent from the patients, 5-mm punch biopsy specimens were taken from papular lesions located in the axillae. The biopsied lesions were about 5 days old in 2 patients and 14 days old in the remaining 2 patients. Tissue specimens were fixed in 10% buffered formalin, embedded in paraffin, and stained with hematoxylin-eosin according to standard procedures. Another biopsy specimen was processed for immunohistochemical analysis. Immunohistochemical studies were performed using the avidin-biotinperoxidase complex technique as described elsewhere. The primary monoclonal antibodies used for immunohistochemistry are shown in Table 2. In negative control specimens, the primary antibody was replaced with antibody dilution buffer. Furthermore, positive control specimens were stained in parallel with each series.

Immunofluorescence staining for the detection of tumor necrosis factor α (TNF-α) in formalin-fixed, paraffin-embedded sections was performed using anti-TNF-α antibody (R&D Systems, Minneapolis, Minnesota) followed by goat antirabbit antibody (Alexa Fluor 488; Molecular Probes Invitrogen AG, Basel, Switzerland) as described elsewhere. Substitution of the primary antibody with isotype-matched IgG served as negative control. Besides control antibodies, we preincubated anti-TNF-α antibody, 12.5 µg/mL (R&D Systems), with 200 ng of recombinant human TNF-α (R&D Systems) before the staining procedure to further demonstrate specificity.

HISTOPATHOLOGICAL FINDINGS

Histological examination of the 5-day-old skin lesions showed mild psoriasiform acanthosis with formation of mounds of parakeratosis, focal hypogranulosis, and mild spongiosis (Figure 1E). The dermis showed capillary dilatation with mild adjacent edema and a perivascular infiltrate consisting mainly of lymphocytes and macrophages in the upper dermis. Exocytosis of lymphocytes overlying the dilated vessels and also in association with

<table>
<thead>
<tr>
<th>Patient No./Sex/Age, y</th>
<th>Appearance of Lesions After Initiating Efalizumab Treatment, wk</th>
<th>Sites of Lesions</th>
<th>Lyphocyte Count at Beginning of Eruptions, Cells/µL</th>
<th>Course of Lesions/Response to Efalizumab Therapy at Week 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/F/59</td>
<td>4</td>
<td>Localized in the axillae and disseminated on the trunk (Figure 1)</td>
<td>3200</td>
<td>Resolution after 4 wk with regular use of topical corticosteroids/75% reduction of PASI score</td>
</tr>
<tr>
<td>2/M/56</td>
<td>6</td>
<td>Localized in the axillae</td>
<td>6140</td>
<td>Resolution after 4 wk with regular use of topical corticosteroids/75% reduction of PASI score</td>
</tr>
<tr>
<td>3/M/48</td>
<td>10</td>
<td>Localized in the axillae and groin (Figure 2)</td>
<td>5700</td>
<td>Lesion persisted for 12 wk with irregular use of topical corticosteroids/75% reduction of PASI score</td>
</tr>
<tr>
<td>4/M/42</td>
<td>7</td>
<td>Localized in the axillae and groin</td>
<td>5150</td>
<td>Initial amelioration, with development of GIF and termination of efalizumab therapy at week 11</td>
</tr>
</tbody>
</table>

Abbreviations: GIF, generalized inflammatory flare; PASI, Psoriasis Area and Severity Index.

aReference range, 1100 to 3500 cells/µL.
mild spongiosis was found. Furthermore, focal intracorneal collection of neutrophils (Munro microabscess) was noted. In addition, 1 biopsy specimen showed formation of a spongiform pustule of Kogoj in the subcorneal layer. The histopathological findings of these papular eruptions were consistent with acute psoriatic lesion resembling guttate psoriasis.

Histopathological findings of the 14-day-old lesions also demonstrated typical features of psoriasis and showed a more prominent psoriasiform hyperplasia with areas of agranulosis and overlying parakeratosis (Figure 1G). Focal accumulation of intracorneal neutrophils was typically present. Dermal changes consisted of capillary dilatation and elongation and a predominant perivascular infiltrate of lymphocytes and macrophages in the upper dermis.

**IMMUNOHISTOCHEMICAL FINDINGS**

A summary of the results and representative staining are shown in Figure 2 and Figure 3. Immunohistochemical analysis of the inflammatory infiltrate of the 5-day-old skin lesions showed a moderate to severe infiltration of CD3+ T cells with focal exocytosis and accumulation of CD3+ T cells in some areas of the epidermis (Figure 2). A slight predominance of CD4+ over CD8+ T cells was found. Immunostaining for neutrophil elastase confirmed the accumulation of intracorneal neutrophils and the marked presence of these cells in the spongiform pustule of Kogoj. Immunoreactivity for the cytotoxic markers T-cell–restricted intracellular antigen 1 and granzyme B was found on some cells in the epidermis and dermis. Immunoreactivity for CD25 was seen on indi-
individual cells infiltrating the epidermis and dermis, whereas immunoreactivity for CD56+ (natural killer cells) and CD20+ cells (B lymphocytes) was barely detectable (data not shown). Skin lesions demonstrated a moderate to strong expression of HLA-DR1 in the epidermal and dermal infiltrate. We used CD68, CD11c, and CD1a to analyze the presence of macrophage and DC subpopulations. Moderate immunoreactivity for CD68 was present in the dermis, and some CD68+ cells present at the basal layer were found protruding into the epidermis. A large number of CD11c+ cells were found in the dermis. Furthermore, some CD1a+ DCs were observed in the epidermis.

Immunohistochemical analysis of the inflammatory infiltrate of the 14-day-old lesions showed a milder infiltration of CD3+ T cells (CD4+ > CD8+ T cells) (Figure 2), as well as the presence of T-cell–restricted intracellular antigen 1+ and granzyme B+ cells compared with findings in the more acute lesions. Immunostaining for neutrophil elastase was also less prominent and revealed some scattered neutrophils in the dermis and focal collection of these cells within the stratum corneum. Strong immunoreactivity was seen for HLA-DR and moderate to strong immunoreactivity for CD11c and CD68. As in the more acute lesions, only a few CD1a+ cells were observed.

**IMMUNOFLORESCENCE FINDINGS**

Positively stained cells for TNF-α were detected throughout the dermis. There was staining associated with perivascular inflammatory cells and blood vessels in the papillary dermis (Figure 3).

In this study, we investigated 4 patients who developed new psoriatic lesions during therapy with efalizumab. The lesions presented clinically as papules and plaques resembling guttate psoriasis. They appeared during the 4th to 10th weeks of treatment, while the preexisting plaques were responding well to efalizumab therapy. The lesions were located in the flexural areas (ie, axillae and/or groin) in all patients and were additionally disseminated on the trunk of 1 patient. On histopathological examination, these lesions showed typical features of acute (resembling guttate psoriasis) or chronic psoriasis. Previous reports have shown that drug-induced psoriasis may demonstrate histopathological features similar to those observed in our cases.11,12 Notably, characteristic histopathological signs of psoriasis, such as Munro microabcesses, were found throughout the dermis. Moreover, focal formation of a spongiform pustule of Kogoj was observed in the biopsy specimen of 1 patient. That patient had concomitant palmoplantar pustular psoriasis, possibly indicating the presence of a distinct immunologic background with an increased susceptibility for the recruitment and activation of neutrophils compared with plaque-type psoriasis. Immunohistochemistry results demonstrated that the mononuclear cellular infiltrate consisted mainly of CD3+ T cells, with CD4+ T-cell predominance and CD11c+ and CD68+ cells. Furthermore, production of the proinflammatory cytokine TNF-α was demonstrated by immunofluorescence studies. Taken together, our histological and immunohistochemical data indicate that these papular eruptions represent psoriatic lesions with activation of various leukocytes, including T cells, DCs, macrophages, and neutrophils.

**COMMENT**

In this study, we investigated 4 patients who developed new psoriatic lesions during therapy with efalizumab. The lesions presented clinically as papules and plaques resembling guttate psoriasis. They appeared during the 4th to 10th weeks of treatment, while the preexisting plaques were responding well to efalizumab therapy. The lesions were located in the flexural areas (ie, axillae and/or groin) in all patients and were additionally disseminated on the trunk of 1 patient. On histopathological examination, these lesions showed typical features of acute (resembling guttate psoriasis) or chronic psoriasis. Previous reports have shown that drug-induced psoriasis may demonstrate histopathological features similar to those observed in our cases.11,12 Notably, characteristic histopathological signs of psoriasis, such as Munro microabcesses, were found throughout the dermis. Moreover, focal formation of a spongiform pustule of Kogoj was observed in the biopsy specimen of 1 patient. That patient had concomitant palmoplantar pustular psoriasis, possibly indicating the presence of a distinct immunologic background with an increased susceptibility for the recruitment and activation of neutrophils compared with plaque-type psoriasis. Immunohistochemistry results demonstrated that the mononuclear cellular infiltrate consisted mainly of CD3+ T cells, with CD4+ T-cell predominance and CD11c+ and CD68+ cells. Furthermore, production of the proinflammatory cytokine TNF-α was demonstrated by immunofluorescence studies. Taken together, our histological and immunohistochemical data indicate that these papular eruptions represent psoriatic lesions with activation of various leukocytes, including T cells, DCs, macrophages, and neutrophils.

Previous reports indicate that some patients may develop psoriatic adverse events (the onset of new psoriasis morphologies or worsening of psoriasis) during efalizumab therapy. Two main presentations have been described so far, namely LMB, which simulates the papular skin lesions investigated in this study, and a more infrequent and extensive condition known as GIF.7-9 Localized mild breakthrough was previously described as...
a transient, papular eruption that typically does not involve the existing psoriatic plaques and is commonly seen on the neck, torso, or flexural areas during the first 4 to 8 weeks of therapy. The exact incidence of LMB is unknown but has been estimated to occur in one-quarter to one-third of the patients receiving efalizumab therapy. It may appear in patients responding or not responding to efalizumab. Furthermore, LMB has minimal impact on the patients’ general response to efalizumab and can resolve throughout the treatment period, with or without the use of topical corticosteroids. Most of these features were also present in our patients. However, as demonstrated in 1 of our patients, the lesions may not be exclusively localized but can also be widespread. Moreover,
they may take months to resolve, indicating that the current terms—LMB and transient localized papular eruption—do not adequately describe these lesions. We believe that an appropriate description of such eruptions could be reached by simply defining their nature. Therefore, we propose the term efalizumab-associated papular psoriasis (EAPP). Carey et al. suggested that the occurrence of these lesions does not indicate or predict any further severe psoriasis flare-ups. Although 3 of our patients had a favorable course and achieved a 75% reduction in the Psoriasis Area and Severity Index score, 1 patient developed a GIF, which led to termination of efalizumab therapy. Thus, we recommend close monitoring and treatment of patients with new papular psoriatic lesions, although the risk of developing a GIF might be small.

The underlying pathomechanisms leading to these new psoriatic lesions, particularly in patients responding to efalizumab therapy, remain elusive. Previous reports indicate that a dysfunction of both innate and acquired immune responses are involved in the initiation and maintenance of psoriatic lesions. Nonlesional psoriatic skin is not completely normal but may harbor various cell types such as plasmacytoid DCs and pathogenic effector T cells. In nonlesional skin, these proinflammatory cells seem to be dormant or controlled by down-regulatory mechanisms. The in situ activation of these cells by danger signals such as local trauma or infection may alter the fine balance between proinflammatory and anti-inflammatory signals. The up-regulation of certain proinflammatory cytokines, eg, TNF-α and interferon γ, which are not targeted by efalizumab, together with the up-regulation of adhesion molecules (eg, intercellular adhesion molecule 1) and the subsequent recruitment of T cells may then trigger a breakthrough of an acute psoriatic lesion. The fact that flexural areas are highly colonized with microorganisms and more prone to frictional trauma may alter the appearance of the new psoriatic lesions in these areas. In addition, we speculate that these papular eruptions may occur more readily when lymphocytosis (known to occur in 40% of patients receiving efalizumab) is present. With more pathogenic T cells accumulating in the blood circulation, some may leak into certain areas more prone to danger signals as mentioned already. Indeed, all of our patients had lymphocytosis or high lymphocyte counts. These findings could also partly explain why these lesions are not seen at baseline but tend to occur during the 4 to 10 weeks after induction of efalizumab therapy. Finally, these lesions may represent a minor flare-up that remains limited in severity and resolves with time, because continuing efalizumab administration may prevent further influx of leukocytes (ie, effector T cells) and their local activation in the affected areas.

In conclusion, the papular eruptions appearing during efalizumab therapy in patients responding or not responding to treatment represent new psoriatic lesions and could be named efalizumab-associated papular psoriasis (EAPP). The appearance of these lesions usually does not necessitate termination of efalizumab therapy, and they may optionally be treated with topical corticosteroids with appropriate monitoring of the patient’s condition. Further investigation is warranted to elucidate why such eruptions occur with efalizumab. Dermatologists should be aware of this kind of lesion and inform their patients accordingly.

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Funding/Support: This study was partially supported by grant 31000-107526 from the Swiss National Science Foundation.

Additional Contributions: Andreas Kappeler, PhD, Department of Pathology, Inselspital, helped with the immunostaining; Helga Nievergelt, MD, Department of Dermatology, Inselspital, helped with digital photography; Serono Pharma Switzerland provided the efalizumab.

REFERENCES


Correction

Incorrect Dose. In the Study titled “Randomized Double-blind Trial of Treatment of Vitiligo: Efficacy of Psoralen–UV-A Therapy vs Narrowband–UV-B Therapy” by Yones et al, published in the May issue of the Archives (2007;143(5):578-584), the dose for 5-methoxypsoralen was incorrectly reported. On page 579, left-hand column, “Administration of Oral Psoralen or Placebo” subsection of the “Methods” section, the last sentence should have read as follows: “During the course of the study, patients intolerant of 8-MOP because of nausea instead were given identical-appearing 5-methoxypsoralen (5-MOP) tablets (20-mg Pentaderm tablets; Crawford Pharmaceuticals Ltd) at a dose of 50 mg/m² (range, 60-80 mg) 3 hours before phototherapy.” This article was corrected online prior to publication of the correction in print.
Observation

Childhood Flexural Comedones

A New Entity

Margarita Larralde, MD, PhD; Maria Eugenia Abad, MD; Andrea Santos Muñoz, MD; Paula Luna, MD

Background: Comedones are usually found in acne and involve the seborrheic areas of the skin. Disseminated comedones can be found in other skin disorders. Flexural comedones are characterized by double orifices connected by a thin layer of epidermis that reveals the comedo content below it. To the best of our knowledge, flexural comedones have not been previously described as an entity. Our objective was to characterize this disorder.

Observations: A cross-sectional descriptive study was performed from April 2004 to July 2006. We included 40 pediatric and adolescent patients with flexural comedones; 21 were female (52%), and 19 were male (48%) (mean age, 6.2 years). In 29 cases the lesions were single (72%) and in 32 cases (80%) unilateral. The lesions were located in the axilla in 88% of the patients. We performed biopsies of skin samples in 6 cases.

Conclusions: To our knowledge, flexural comedones have not been previously described as an entity, and we felt that they deserved attention owing to the relative frequency of cases in our clinical practice. Because of its clinical appearance, flexural localization, and age distribution, we named this disorder childhood flexural comedones. Further investigation and follow-up of a larger number of patients is needed.

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Comedones are an essential feature of acne and can present as open or closed. They have a typical distribution involving the most seborrheic areas of the skin (e.g., the face, chest, and back). They may also be the hallmark of other forms of acne, such as steroid acne and acne venenata. Disseminated comedones can be found in some skin disorders, such as familial dyskeratotic comedones, idiopathic disseminated comedones, and extensive nevus comedonicus. Comedones have also been reported secondary to chronic actinic damage (Favre-Racouchot disease), radiotherapy, trauma, hidradenitis suppurativa (HS), and on the site of previous herpes zoster infection. Flexural comedones of infancy are characterized by a double opening connected by a thin layer of epidermis that reveals the comedo content below.

To the best of our knowledge, flexural comedones have not been previously described as an entity. Our objective was to characterize this disorder.

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Departments of Dermatology, Aleman Hospital (Drs Larralde and Santos Muñoz), Ramos Mejia Hospital (Drs Larralde and Abad), and Churruca-Visca Hospital (Dr Luna), Buenos Aires, Argentina.
sions were most commonly located in the axilla in 35 (88%), the groin in 3 (8%), the antecubital fossa in 2 (5%), and the neck in 1 (2%). Flexural comedones represented the main complaint in 9 cases (22%), whereas in the other cases (26 [78%]), 13 patients or their parents had concerns regarding molluscum contagiosum; 5 had concerns regarding atopic dermatitis; 2, inflammatory acne; 1, comedonal acne and milium cysts; 1, eruptive milia; 1, morphea; 1, vitiligo; 1, scabies; and 1, keratosis pilaris. One patient had a personal history of ovarian cysts associated with an infundibular cyst on the axilla, and 1 had juvenile rheumatoid arthritis. Four cases were familial (10%).

Findings from skin biopsy samples from 6 patients showed follicular plugging and infundibular dilatation (Figure 4).

**COMMENT**

There was no sex preponderance in our series of cases. Although flexural comedones were the main concern in 9 patients (22%), in most of the cases they were an incidental finding during dermatologic examination for other conditions. In 25 cases the patient’s age at onset of the disease was unknown; it is remarkable that in 1 case the lesion was congenital. The lesions were single in 72% of cases and unilateral in 80% of them. Of the 11 patients presenting multiple lesions, 8 were bilateral and 3 unilateral. The most common site was the axilla (35 [88%]). The other affected sites were much less frequent. In 1 case we found both axillary and groin lesions. Four cases were familial.
Findings from skin biopsy samples from 6 cases showed the typical open comedo picture, with follicular plugging and infundibular dilatation. Remarkable associated features were inflammatory acne in 2 cases, comedonal acne in 1 case, and ovarian cysts with an axillary infundibular cyst in 1 patient.

To our knowledge, flexural comedones have not been previously described as an entity. We felt that they deserved attention owing to the relative frequency of cases in our clinical practice. Because of the typical clinical appearance, flexural localization, and age distribution, we refer to this disorder with the descriptive term childhood flexural comedones.

The chronic disease HS is characterized by painful suppurative or inflammatory lesions in the axilla or genitofemoral region. Because comedones are clinically and histopathologically precursor lesions of HS,7,8 we hypothesize that childhood flexural comedones are related to HS. In addition, 13 of our patients had associated molluscum contagiosum. The clinical and histopathologic coexistence of molluscum contagiosum and open comedones was reported by Brandrup and Asschenfeldt10 in 1989, but not in a flexural distribution. Another possibility is that local trauma caused by friction in the affected areas could induce comedone formation. Further investigation and follow-up of a larger number of patients are needed.

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Author Contributions: Drs Larralde, Abad, Santos Muñoz, and Luna had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Larralde, Abad, Santos Muñoz, and Luna. Acquisition of data: Abad and Santos Muñoz. Analysis and interpretation of data: Larralde and Luna. Drafting of the manuscript: Larralde, Abad, Santos Muñoz, and Luna. Critical revision of the manuscript for important intellectual content: Larralde and Luna. Administrative, technical, and material support: Abad and Santos Muñoz. Study supervision: Larralde and Luna.

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Poor Adherence to Treatments

A Fundamental Principle of Dermatology

The long-term longitudinal follow-up study of a cohort of psoralen UV-A (PUVA)-treated patients by Jones-Caballero et al. published in this issue of the Archives provides insight into the complexities of treating psoriasis and the impact of the disease on patients’ lives. Psoriasis is a chronic, frustrating condition, and much of the frustration comes from the need to continually use treatments over time. None of the treatments are entirely satisfactory, and as time goes by many patients grow progressively less tolerant of treatment. In the 1970s, PUVA treatment might have seemed to be a relief from the messy and time-consuming Goeckerman treatment. Jones-Caballero et al. found that most patients treated with PUVA eventually gravitated to other treatment options. Those leaving PUVA for biological treatments were younger, had more formal education, and were more likely to have a greater extent of psoriasis. For these patients, the decision to switch treatment was probably the natural result of a search to identify a more satisfying long-term treatment. These patients sought new approaches even in the face of high cost, possible carcinogenesis (PUVA), or increased risk of infection (biological treatments).

See also pages 846 and 950

This study also shows another unexpected finding: 42% of patients who switched from PUVA to treatment with biological agents had moderate or severe disease at the time of final assessment. Though the average duration of treatment with biological agents was not reported, biological therapy in this cohort would seem to be significantly less effective than might be predicted based on previous clinical trials, which report that as many as 70% to 80% of patients remain clear or nearly clear of psoriasis. Could compliance be an issue here? Patients regularly become frustrated with psoriasis treatments, particularly messy or ineffective ones. We suggest that poor adherence to medication regimens is a fundamental principle of dermatology that governs many important, interesting, and heretofore puzzling phenomena.

THE RESISTANCE OF SCALP PSORIASIS TO TOPICAL TREATMENT

Scalp psoriasis is one of the most frustrating forms of psoriasis, for both patients and their dermatologists. It should not be. Percutaneous absorption through normal scalp is similar to the axilla, a region in which even low-potency topical corticosteroids are effective psoriasis treatment. Topical treatments penetrate the altered barrier of diseased skin even better than they do normal skin.

The resistance of scalp psoriasis to topical treatment is explained by poor adherence to therapy. About 10% of psoriasis patients report that treatment is the most unpleasant aspect of the disease. Forty percent report non-adherence. Even the most elegant regimens for the scalp require time and patience to follow. We learn in medical school that patients often do not take their oral medications; adherence to topical treatment on non-scalp skin is worse. Treating hair-bearing scalp with topical treatment is even more difficult.

Instead of continually trying new treatments for scalp psoriasis, it is better to get patients to use the first treatment well. Choose a potent topical corticosteroid in a vehicle that patients are willing to use; ask them to use it twice a day for just 3 or 4 days (it is much easier to be compliant for 3 or 4 days than for 8 weeks); and have the patient return to the office to be rechecked. Patients will see considerable improvement in that time. After that, patients will know that they have a treatment that works and will use it as needed to keep their scalp psoriasis under control.

CORAL REEF PSORIASIS

Coral reef is a term used to describe psoriasis plaques covered with thick, almost rocklike scale. These plaques are generally resistant to topical treatment. However, diseased skin—even very thick, scaly skin—has inherently poor barrier function, evidenced by increased transepidermal water loss. The use of descaling agents is not necessary. Clinical trials of topical corticosteroids do not use descaling agents, yet such trials show good efficacy.

Dermatologists should recognize that coral reef plaques are likely markers of poor compliance. Patients who let plaques get this thick are not using topical treatment. Coral reef plaques should be red flags signaling dermatologists to pay particular attention to these patients’ adherence to their topical regimen.

USE NEW MEDICATIONS AS SOON AS THEY ARE INTRODUCED, BEFORE THEY STOP WORKING

Jones-Caballero et al. cite work suggesting that new medications often work better in clinical trials than in clinical practice. This phenomenon is well illustrated by topi-
cal calcipotriene trials in which monotherapy was found to be highly effective, with 70% of patients’ disease described as clear or almost clear in 8 weeks. And yet when used alone in clinical practice, it is not nearly so effective; in the clinic, calcipotriene had to be used with a topical corticosteroid to achieve optimal results.15,16

How is it possible that medications are so effective in studies and so ineffective in clinical practice? There is no difference between the drug in the trial and the agent used in clinical practice. Adherence is different, however. Compared with clinic patients, clinical trial subjects are more adherent to medication regimens. The payments research subjects receive and the monitoring of their medication use are 2 factors driving compliance. The frequent return visits for evaluation of efficacy and adverse effects are strong contributors to improved adherence. (Imagine how flossing would be affected if the dentist said, “I’m worried about your gums. I want you to floss every day. I’ll see you back here in the office in 1 week.”) Clinical trials of medications foster better adherence behavior resulting in far more impressive results than is often observed in usual clinical practice.

SEVERE ATOPIC DERMATITIS-clears rapidly in hospitalized patients

A short hospitalization can rapidly clear severe atopic dermatitis that is unresponsive to outpatient management. What accounts for the rapidity of improvement in the hospital setting? Is it a change in the environment—in the case of a pediatric patient, removing the child from dust mites or stress in the home? Not likely. The rapid improvement is easily explained by improved compliance when midpotency topical corticosteroids are administered by a hospital nurse. We should not be surprised by poor adherence to topical corticosteroid regimens in children with atopic dermatitis in the home environment. To begin with, mothers are often terrified of applying steroids to their children. And those of us who are parents will recognize how difficult it is to apply sunscreen or other topical agents to our own children. By not mentioning the term steroid (referring to the drugs instead as “cortisone-type” medications) and limiting the initial treatment interval to a week or less, better compliance and outcomes can be achieved.

PSYCHONEUROIMMUNOLOGY

Antidepressants can improve psoriasis and atopic dermatitis. A psychoneuroimmunologic mechanism, one in which the mind affects neurons affecting the immune system, could account for the action of the antidepressant. Psychoneuroimmunology can also explain the changes in disease severity that patients with psoriasis report in response to stress.

Another explanation for these phenomena is that treatment of depression results in improved adherence as patients’ energy and interest in life improves, while stress reduces patients’ compliance with their treatment regimen. Any study of interventions designed to affect skin disease by affecting the mind must consider the possibility that the effect is mediated by changes in behavior, particularly compliance changes.

PHARMACOGENOMICS

There is tremendous variation between patients in their response to treatment. Proponents of pharmacogenomics explain observed differences in terms of genetic variations that affect response to treatment. This explanation is plausible and probably does play a role in some situations (particularly those in which treatments are administered by a health care worker). Alternatively, variations in treatment outcomes may be due to variation in adherence levels. Focusing resources on identifying the genes that relate to efficacy of treatment may be beneficial, yet we may be able to wring far greater efficacy out of the medications we already have through better understanding and improvement of patients’ adherence behavior.

GREATER PATIENT SATISFACTION IMPROVES TREATMENT OUTCOMES

Researchers tested the effect of patient satisfaction on treatment outcomes by assessing satisfaction 3 days after an office visit and measuring outcomes 1 month later. Better satisfaction at 3 days predicted better outcomes at 1 month. Why would patients who are more satisfied after their office visit have a better outcome? Patients who are more satisfied with their visit are more trusting of their physician, worry less about adverse effects, and use their medication more regularly. Simply put, greater satisfaction leads to better adherence, and better adherence results in better outcomes.

ZINC PYRITHIONE SPRAY

In the mid-1990s, dermatologists were amazed by the effectiveness of a new product for psoriasis, zinc pyrithione spray, sold under the proprietary name “Skin-Cap” (Cheminova Internacional SA, Madrid, Spain). Writing in Cutis, Shelley and Shelley11(p182) reported that

No longer do the patients need steroids inducted, ingested or injected, and no more methotrexate or PUVA visits. It seems unbelievable that a product not even requiring a prescription can be so effective.... Last week one of our patients jumped when we came in the room to exclaim, “It’s a miracle,” as she showed us the spray can. Her psoriasis of the scalp... was now gone. It had taken just four days.

Then the presence of clobetasol propionate was detected in the cans. “It can’t be just the clobetasol,” dermatologists thought. “I’ve been prescribing that for years and it never worked as well as Skin-Cap.” Some thought the efficacy of Skin-Cap was due to a synergy with the zinc pyrithione, but zinc pyrithione added nothing to the efficacy of topical clobetasol in a psoriasis clinical trial.21

Three things were special about the Skin-Cap product: compliance, compliance, and compliance. First, it was a nonmessy spray, so patients were more likely to use it than a messy ointment. Those who taught us that one needs to prescribe ointments for psoriasis were mistaken. While moisturization may have some benefit of
its own, moisturization clearly is not necessary for clearing psoriasis. Systemic agents that reduce inflammation (such as cyclosporine and infliximab) are very effective psoriasis treatments. The effectiveness of topical clobetasol when it is actually applied has been verified by the excellent response rates to nonmessy clobetasol products in clinical trials. Prescribing an ointment may, for some patients, discourage good compliance.

Second, adherence was better with Skin-Cap because people thought they were using just zinc pyrithione. Topical clobetasol is often prescribed with the admonition, “This is the most powerful steroid known to man. If you use it for more than 2 weeks, seriously bad things may happen to you.” It’s not surprising that fear of adverse effects would reduce the use of prescription clobetasol when compared with Skin-Cap.

Finally, people were highly motivated to use Skin-Cap because they paid for the medication themselves; having bought into the medication, they were going to use it. Poor adherence to topical treatments explains why clobetasol propionate worked so well in the blue can but not in the prescription ointment.

IS POOR ADHERENCE EVER A GOOD THING?

Considering how frequently dermatologists prescribe topical corticosteroids, including super high-potency topical corticosteroids, steroid atrophy and hypothalamic-pituitary axis suppression are uncommonly seen in our patients. This is probably because of nonadherence to medication as disease improves. Steroid atrophy is rarely, if ever, observed on hair-bearing scalp, where patients find it difficult to apply topical agents. Atrophy is more commonly observed on the shins of women, where concern with appearance has the potential to contribute to overuse of the medication.

TACHYPHYLAXIS

Tachyphylaxis owing to topical corticosteroids, a decreased clinical effectiveness seen over time, is a clinically well-recognized phenomenon that has been elusive to identify in clinical trials. It commonly occurs with long-term topical corticosteroid treatment of chronic skin diseases such as psoriasis and atopic dermatitis. Tachyphylaxis is thought to be caused by changes in the sensitivity of corticosteroid receptors. This is probably because there is a well-characterized acute form of tachyphylaxis to the vasoconstrictive effect of topical corticosteroids. The acute form, occurring over a few days, is commonly well-recognized phenomenon that has been elusive to identify in clinical trials. It commonly occurs with long-term topical corticosteroid treatment of chronic skin diseases such as psoriasis and atopic dermatitis.

Clinical tachyphylaxis can be overcome by switching from one topical corticosteroid to a different brand of the same potency category. If the corticosteroid receptors were down-regulated, switching from one mid potency corticosteroid to another would not be of any benefit. The principle of poor adherence predicts that clinical tachyphylaxis is actually due to decreased use of medication over time. Patients simply get frustrated applying messy topical agents to their skin. Because patients adhere to their medication regimen more vigorously in clinical trials, the principle of poor adherence also explains why tachyphylaxis is commonly seen in clinical practice but is difficult to identify in clinical trials.

Tachyphylaxis cannot be described by the saying “the more you use the steroid the less it works”; a more appropriate maxim would be “the less you use the topical steroid, the less it works.” The 42% rate of moderate to severe psoriasis reported in the study by Jones-Caballero et al suggests that poor compliance with these injectable medications is a logical explanation that should be explored with the same vigor as considerations of the severity of psoriasis in this cohort of PUVA patients, neutralizing antibodies, and other pharmacodynamic factors.

SUMMARY

Advances in the understanding of our world require us to recognize underlying structure—structure that is often hidden from direct view. Recognizing this structure may depend on the development of better methods of observation. Galileo’s construction of the telescope and subsequent advances in electronic measuring devices contributed to the recognition of fundamental physical principles and advances in our understanding of the physical world. Similarly, measures of adherence have evolved that permit us to recognize human behavioral processes, which are often hidden from direct observation. Questionnaires, pill counting, and weighing medications reveal that patients may be noncompliant. These measures, however, clearly overestimate patients’ true adherence. New objective electronic measures demonstrate that noncompliance is even more pervasive than previously estimated and give us insight into underlying dynamic processes with broad implications for dermatology.

There is a growing awareness of the prevalence and importance of adherence in dermatology. We are on the verge of understanding that patient noncompliance is a nearly universal principle of dermatologic treatment. Recognizing that nonadherence is ubiquitous is essential for understanding many dermatologic phenomena and for addressing many of the recalcitrant skin disease dilemmas seen in dermatology. All long-term trials in dermatology should have measures of compliance built into their design. Equally important, physicians must develop practical measures to improve patients’ compliance behavior: establishing a strong, trusting physician-patient relationship; choosing vehicles that can fit patients’ lifestyles; using patient education materials designed to motivate without overly stressing risks; and scheduling a follow-up visit shortly after initiating a new treatment. Physician-administered treatments that assure adherence (such as intraleisional corticosteroid injections and, as described by Soares and Davis in this issue, Goeckerman treatment) have important advantages and will always find useful application. By addressing adherence, we can achieve better success for patients with psoriasis and other chronic skin diseases.
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Cutaneous T-Cell Lymphoma Epidemiology

Patients Providing the Power

**Cutaneous T-Cell Lymphoma (CTCL)** is a term currently used for the classification of a variety of subtypes of T-cell lymphoma that primarily affect the skin. The initial use of the term CTCL, however, was coined by Edelson to describe the most common variant of CTCL, mycosis fungoides (MF), and its leukemic variant, Sézary syndrome (SS). In this editorial, the term CTCL will specifically refer to MF and SS, which is the subject of the current epidemiologic study of Criscione and Weinstock presented in this issue of the Archives. Because this study was funded by a grant from the Cutaneous Lymphoma Foundation, it represents a unique paradigm in clinical research: a population-based study made possible by advocates for the patient population under investigation.

*See also page 854*

For 200 years, since Alibert’s initial description of patients in 1806, the etiology of CTCL has remained an enigma. Like all lymphomas, CTCL is an acquired disease. Recent studies of familial clustering suggest a predisposing immunogenotype based on certain HLA class II alleles (HLA-DRB1 and HLA-DQB1). The most commonly advanced hypothesis of the pathogenesis of CTCL is that it represents a model of chronic antigen stimulation (ie, from a background of polyclonal inflammation emerging a monoclonal neoplastic T-cell population). This model begs the critical question, what is the antigen driving the process? Many etiologic factors have been advanced and studied, but none have been conclusive. These have included occupational exposures, viruses (Epstein-Barr virus, human T-lymphotropic virus 1 [HTLV-1], and human herpesvirus 6) and bacteria (staphylococcal superantigens).

Despite the elusive identification of the etiologic agent in CTCL, molecular advances have provided us with greater insights into its immunobiologic characteristics and some intriguing correlations between pathogenesis and the role of chronic antigen stimulation. Two preliminary reports are particularly noteworthy. Jones et al reported that patients with CTCL harbor antibodies capable of cross-reacting with keratin-13 (K-13) protein, histone ribonucleoprotein-A1, and HTLV-1 tax protein. Parenterically, HTLV-1 tax protein cross-reactivity provides an explanation for some of the past inconclusive and contradictory reports attempting to link HTLV-1 and CTCL. The germane observation, however, is that patients with CTCL appear capable of generating an immune response to nonskin antigens that can cross-react with skin-based proteins (K-13). This supports a role of molecular mimicry in which T-cell antigen stimulation results in T-cell clones cross-reacting with skin-based antigens and contributing to the skin-homing nature of the disease. Furthermore, recent preliminary experimental data from Muthukuru et al demonstrate that T cells isolated from the skin of CTCL lesions undergo chronic T-cell receptor stimulation and exhibit impaired apoptosis.

These tantalizing molecular observations can only partially solve the puzzle regarding the etiology and pathogenesis of CTCL. Solving it will require correlation of molecular findings to populations affected by CTCL and those who are at risk. Thus, epidemiologic studies provide a critical piece of the CTCL puzzle. A relevant example of epidemiologic findings correlating and supporting molecular findings is the elucidation of the association of HTLV-1 retrovirus with adult T-cell leukemia/lymphoma (ATL). Detection of viral DNA in ATL tissues became compelling evidence of the etiologic role of HTLV-1 only when linked to epidemiologic data demonstrating the geographic distribution of HTLV-1 infection and the increased incidence and prevalence of ATL in endemic regions, such as southwestern Japan and the Caribbean Islands. Conversely, the low prevalence of HTLV-1 infection in the United States is the strongest evidence of the failure to link HTLV-1 as a causative agent in CTCL in the United States with the previously spurious reports of HTLV-1 detection in patients with CTCL.

In this issue of the Archives, Criscione and Weinstock describe incidence trends for CTCL in the United States from 1973 to 2002, using data obtained from 13 population-based cancer registries of the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute and representing 14% of the US population. The report represents an update of the last report by Weinstock and Gardstein of CTCL incidence trends in the SEER database from 1973 through 1992. They determined that the overall annual age-adjusted incidence of CTCL was 6.4 per million. This represents a more than doubling of the incidence, as last determined using SEER data. Incidence was higher among blacks and men. Racial differences in incidence decreased with age and have not changed over time. Sex differences in incidence increase with age and have decreased over time. Geographic variation in incidence was found and correlated with high physician density, high family income, high percentage of population with a bachelor’s degree, and high home values.
These are important observations with potential etiologic significance, though the exact cause for the observed increase in CTCL incidence is unknown. If the geographic variation in incidence (correlated with high physician density, family income, and higher education) is related to access to health care, then the finding of a higher incidence in blacks requires closer attention. Since racial disparities in health are traditionally attributed to lack of access to health care, the higher incidence in blacks may be providing us with important clues regarding either immunogenetics or the interaction of genetic susceptibility and the environment in CTCL. Framing questions to address the biological basis of this disparity may provide us with new insights to CTCL pathogenesis.

Does the new statistic represent shifts in population genetics or environment exposures and interactions? It is difficult to make such determinations; however, one factor may have influenced a rise in incidence. During the past 2 decades, the histologic diagnosis of CTCL has undergone great scrutiny and refinement. The International Society for Cutaneous Lymphomas (http://www-usz.unizh.ch/iscl/isclhome.htm), formed in 1992 to promote collaborative efforts to increase the knowledge of lymphoproliferative skin diseases, has recently developed an algorithm for the establishment of the diagnosis of early CTCL, incorporating clinical, histologic, immunohistochemical, and molecular (T-cell receptor gene rearrangement) attributes. Such efforts have generally moved the diagnostic threshold of CTCL, enabling the inclusion of more early cases and potentially impacting the new incidence calculation.

In keeping with refinements in diagnostic criteria, it is of interest to note that since the last SEER analysis by Weinstock and Gardstein who queried cases using diagnostic codes for MF and SS, the SEER database has adopted a global classification of cutaneous lymphomas and now requires morphologic subclassifications of specific cutaneous T-cell lymphomas. When Criscione and Weinstock defined CTCL as primary cutaneous lymphomas and included histologic subtypes of MF and SS, they uncovered discrepancies in several cases of cutaneous lymphoma classification in the SEER database, including 4% of “CTCL” cases as having B-cell lineage.

While the increased incidence of CTCL remains unexplained, it demonstrates the increasing importance of the role of the dermatologist to remain at the forefront of diagnosis and treatment of CTCL. The findings provide an important framework in which to design clinical and experimental studies. The study by Criscione and Weinstock demonstrates the clear and immediate need to codify cutaneous lymphoma classification in tumor registries, including SEER, to improve the accuracy of CTCL classification.

In addition to incidence, other important epidemiologic factors of CTCL require investigation. Death rate and mortality, prevalence, and factors influencing survival will provide a greater picture of the impact of CTCL. Retrospective, case-control studies of the 1990s have demonstrated that a complete response to skin-directed therapies in patients diagnosed as having stage IA CTCL (less than 10% body surface area involvement) correlates with a lack of disease progression and a normal life span. Recent combinations of biological response modifiers appear to have prolonged survival in advanced stages of CTCL. Future prospective trials will further delineate the impact of treatment on CTCL survival.

Finally, it is not surprising that the increase in incidence of CTCL in the United States parallels an increase in patient involvement with their advocacy. In 1996, Judy Jones established an online support group for patients with CTCL. From this support group emerged the Cutaneous Lymphoma Foundation, a patient advocacy group dedicated to advancing education, clinical care, and research. Ms Jones now serves as its executive director. The Cutaneous Lymphoma Foundation’s involvement with this study serves as an example of the empowerment of patients and their capacity to partner with physicians and scientists to advance the agenda of CTCL. Thus, the current population study by Criscione and Weinstock and patient population involvement provide new power and promise to solving the 200-year-old puzzle of the etiology of CTCL.

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Cutaneous T-Cell Lymphoid Dyscrasia

A Unifying Term for Idiopathic Chronic Dermatoses With Persistent T-Cell Clones

Joan Guitart, MD; Cynthia Magro, MD

It often takes several years before the diagnosis of mycosis fungoides is clearly established. During this period preceding the diagnosis of cutaneous T-cell lymphoma (CTCL), some patients experience a variety of distinct skin conditions of ambiguous origin. With refinement in the methods of T-cell clonal detection in skin biopsy specimens, we can now establish that many of these preceding entities are characterized by a T-cell clone. Therefore, we studied the association of these clonal conditions with CTCL. We identified 8 distinct clinicopathological conditions characterized by the frequent detection of T-cell clonality, a chronic course often recalcitrant to topical therapy, lack of a known triggering event, and lack of morphologic evidence of a T-cell lymphoma with potential for progression to CTCL. We propose the term cutaneous T-cell lymphoid dyscrasias to unify these entities. Defining the preceding stages of CTCL is important to properly categorize these conditions and to help us understand and redefine the evolution of idiopathic clonal dermatoses and their potential for lymphoma progression.

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Recent advancements in polymerase chain reaction–based assays have facilitated the detection of T-cell clones in cutaneous biopsy specimens. We have now witnessed numerous studies reporting T-cell clonality (TCC) in a myriad of cutaneous conditions traditionally classified as inflammatory dermatoses, such as parapsoriasis, pityriasis lichenoides, and pigmented purpura. This confusing trend has elicited some debate about the relevance of TCC in cutaneous infiltrates and the lack of specificity of TCC in the diagnosis of cutaneous T-cell lymphoma (CTCL). However, the detection of TCC in certain inflammatory dermatoses is probably a real event and confirms the lack of specificity of TCC in the diagnosis of cutaneous T-cell lymphoma (CTCL). We propose the term cutaneous T-cell lymphoid dyscrasias (CTLD) to unify a number of dermatoses characterized by a recalcitrant and, in most instances, insidious clinical course and a T-cell–dominant infiltrate manifesting a molecular and phenotypic profile related to CTCL. We propose CTLD as a theoretical model characterized by persistent cutaneous infiltrates of a clonal or oligoclonal population of T cells. While most of these cases have an innocuous clinical course, they share a potential to evolve into true CTCL. Although they may define infiltrates that are precursors to CTCL, we would not suggest using the designation premycotic per se because the evolution to overt CTCL is uncommon.

Dyscrasia is defined as an abnormal or physiologically unbalanced state of the body, which in our opinion accurately reflects the nature of these entities. Another term to be considered is lymphocytosis, defined as blood or skin conditions containing an unusually high number of lymphocytes. The lymphocytes cannot be considered normal, a point that will be discussed with supportive phenotypic and molecular studies. Furthermore, the density of lymphocytic infiltration in CTLD may be sparse. Conversely, there are many...
dense reactive T-cell infiltrates, such as lupus erythematosus, that are without any significant malignant potential. We propose the concept of CTLD defined by the following criteria:

1. Chronic conditions with tendency to relapse after topical treatment.

2. Unknown triggering event with no evidence of hypersensitivity or allergic reaction, or associated connective-tissue disorder or other lymphoproliferative conditions.

3. Lack of overtly malignant cytomorphic features. The dominant lymphocyte is small to intermediate, not fulfilling histologic criteria for the diagnosis of CTCL. We also excluded lymphomatoid papulosis and pagetoid reticulosis because these lymphoproliferative conditions are already included in the World Health Organization–European Organization for Research and Treatment of Cancer classification of cutaneous lymphomas and are morphologically characterized by overtly atypical lymphocytes.

4. Monoclonality or oligoclonality. The inability to detect a T-cell clone in all cases may be in part due to current technical limitations. Nevertheless, the concept of CTLD encompasses cases that may show a polyclonal pattern or a restricted T-cell repertoire that could potentially define the molecular fingerprint of a particular case, in which one or a few clones may become dominant over time.

5. Clinically and pathologically distinct from CTCL, having the potential for overt progression to CTCL. We define CTCL as a neoplasia of skin-homing T cells characterized by a gradual clonal expansion of atypical lymphocytes and clinically characterized by a natural propensity for progression of cutaneous and potentially extracutaneous lesions. Cutaneous T-cell lymphoid dyscrasias is an all-encompassing term that includes distinct skin disorders that fail to fulfill our definition of CTCL, including the following: hypopigmented interface variant, pigmented purpuric variant, atypical lobular panniculitis, syringolymphoid hyperplasia with alopecia, idiopathic follicular mucinosis (IFM), pityriasis lichenoides (PL) chronica, parapsoriasis, and clonal erythroderma.

HYPOPIGMENTED INTERFACE VARIANT

In 1982, Zackheim et al first reported a series of patients with hypopigmented macules with the histologic attributes of mycosis fungoides (MF). The term hypopigmented MF was introduced. The classic clinical presentation is one of hypopigmented patches characteristically affecting young patients with a dark complexion. The clinical differential diagnosis includes vitiligo, pityriasis alba, sarcoidosis, syphilis, and tinea versicolor. However, the lesions of hypopigmented interface CTLD variant are often asymmetric, with minimal scale, and with no associated atopic diathesis.

The biopsy specimens show an epidermotropic lymphocytic infiltrate often centered on the basal cell layer, while other cases may resemble pagetoid reticulosis. T-cell clonality is commonly detected, and the infiltrating lymphocytes often have a CD8 phenotype. However, cytotoxic proteins such as TIA-1 may be absent. Among the hypopigmented MF cases reported by Ardigó et al, a CD8+ CD4– phenotype was seen mostly in children. Other cases with similar clinical and pathological features have been reported as juvenile or junctional variants of MF. The lesions tend to persist for a long time, but they respond well to phototherapy or topical chemotherapy with resolution of the lesions and often repigmentation. However, persistent dyschromia can occur.

Many of the reported cases are atypical and poorly documented, raising the possibility that some cases may not be obvious MF. Volkenandt et al also reported cases with hypopigmented patches and a T-cell clone but without the morphological criteria for diagnosis of MF. They concluded that these cases might represent early evolving MF. Conversely, Petit et al and Cribier et al also described patients with a similar presentation resembling hypopigmented MF but without a detectable clone. Some of these patients were diagnosed as having a vitiligo-like condition, while others developed typical vitiligo. We have encountered cases that manifest the typical clinical features described for hypopigmented MF but have morphologic findings insufficient for a definitive diagnosis and overall did not fulfill the International Society for Cutaneous Lymphomas diagnostic criteria. Some of the cases reported as hypopigmented MF lack convincing histologic criteria and may be better classified as CTLD. Nevertheless, we recognize that there are clear cases of MF and even Sézary syndrome that present with hypopigmented lesions.

PIGMENTED PURPURIC DERMATOSES

Pigmented purpura is a term used to describe a heterogeneous group of disorders that share petechiae and bronze discoloration of the skin with predominant localization to the legs. The spectrum includes Schamberg disease, Majocchi purpura, Gougerot-Blum purpura, lichen aureus, and the eczematoid purpura of Doucas and Kapetanakis. There is now an emerging body of clinical, phenotypic, and molecular data that suggests that certain forms of idiopathic pigmented purpura may precede the development of MF. Coinciding with the more widespread distribution of lesions is the concomitant development of other lesions more characteristic of MF.

From a morphologic perspective, those cases of pigmented purpura that may represent a form of CTLD typically present with a handlike lymphocytic infiltrate with supervening dermatosclerosis along with hemosiderin deposition. The lymphocytes are small, without significant atypia. As with large plaque parapsoriasis, there is usually a diminution of both CD7 and CD62L expression, in some cases approaching the extent of diminution encountered in cases of MF. Clonality has been described in pigmented purpura.

ATYPICAL LYMPHOCYTIC LOBULAR PANNICULITIS

The clinical course of our series of cases of lymphocytic lobular pan-
niculitis is characterized by waxing and waning bruiselike plaques unassociated with constitutional symptoms, without clinical stigmata of collagen vascular disease. Light microscopic, phenotypic, and molecular studies suggest that this entity may represent a continuum with subcutaneous panniculitislike T-cell lymphoma (SPTCL).29,30 We designated this condition atypical lymphocytic lobular panniculitis (ALLP). Clinically, the distribution and appearance of the lesions are similar, manifesting a predilection to involve the proximal extremities; however, the lesions in ALLP have a tendency for spontaneous regression, in contrast to those of SPTCL, which remain as persistent and progressive plaques.

Morphologically, ALLP shares with SPTCL infiltration of the panniculus by small to intermediate-sized, slightly atypical lymphocytes (Figure 3). Other critical discriminating features that allow the distinction of ALLP from SPTCL are as follows: (1) the degree of angiodestructive changes with striking luminal thrombosis accompanied by extensive fat necrosis encountered in SPTCL is not seen in ALLP; (2) the density of infiltration is significantly less, albeit the pattern is similar, being one of permeation of the interstitial spaces of the fat lobule; and (3) prominent hemophagocytosis is not seen. Hyalinosis of the fat lobule, germinle centers, and prominent mucin deposition, while characteristic of lupus panniculitis, are uncommon in ALLP and SCTCL. However, some degree of mucin, typically in the middle and deeper reticular dermis, can be observed. Phenotypically, some cases are similar to SCTCL by virtue of a significant CD5, CD62L, and CD7 deletion.29,30 In addition, while the CD4:CD8 ratio may be reduced, the striking dominance of cytotoxic CD8 lymphocytes seen in SPTCL or the double CD4:CD8 negativity of γ-δ T-cell lymphomas is not observed. Expression of β-F1, as a marker of the αβ T-cell receptor heterodimer, is important to confirm the diagnosis. From a molecular standpoint, a persistent TCC is common to both SPTCL and ALLP.29,30

SYRINGOLYMPHOID HYPERPLASIA WITH ALOPECIA

Syringolymphoid hyperplasia with alopecia, first reported by Sarkany,31 is a rare chronic skin disorder presenting with sharply demarcated erythematous or hypopigmented hairless patches, often with anhidrosis.31,32 Other clinical signs of adnexotropism, such as prominent punctate erythema resembling keratosis pilaris or signs of follicular mucinosis, have been reported.33 We observed a patient for many years who presented with a single patch of alopecia on the abdomen. Eventually, he developed extensive pruritus with diffuse areas of follicular prominence and punctate erythema of the soles (Figure 4). The biopsy specimen demonstrated changes of MF with prominent eccrine and follicular tropism. This punctate erythema with frequent involvement of eccrine-rich areas such as the palms and soles is characteristic of syringotropic MF.34,35 There are some reports in the literature of patients with lesions present for many years that did not transform to a cutaneous lymphoma.36 The patches are asymptomatic to slightly pruritic and persist chronically, without significant improvement with the use of topical corticosteroids. It has been suggested that some of these cases with hypohidrosis associated with a chronic syringotropic lymphoid infiltrate may be associated with Sjögren syndrome.37

Skin biopsy specimens show a lymphoid infiltrate around the eccrine coil with variable hyperplasia of the eccrine epithelium. Nuclear atypia is not prominent, and the lymphocytes are, for the most part, small to intermediate. A folliculotropic lymphoid infiltrate with or without mucinosis is often observed.38 In regard to the molecular profile, TCC has been reported in 4 of 6 cases.32,39 The clinical differential diagnosis includes alopecia areata, keratosis pilaris, and dyshidrotic eczema when the palms or soles are involved. Uni-
lateral laterothoracic exanthema is a pruritic morbilliform eruption seen in children that can also present with a deep lymphoid infiltrate centered on the eccrine coil. Histologically, the combined features of lymphocytes infiltrating the eccrine coil with epithelial hyperplasia is a distinct feature. The main dilemma for the histopathologist is to decide whether there are sufficient histologic criteria for the diagnosis of adnexotropic lymphoma.

IDIOPATHIC FOLLICULAR MUCINOSIS

The term follicular mucinosis was proposed by Jablonska et al41 to describe the histologic finding of mucin deposits within the hair follicle commonly seen with alopecia mucinosa. Focal mucinous changes of the follicular unit, especially involving the infundibulum but sometimes even deeper epithelial mucinosis, can be seen in a variety of inflammatory conditions, such as Ofuji disease, rosacea, allergic contact dermatitis, drug reactions, and angiolymphoid hyperplasia with eosinophilia. All of these conditions should be considered and excluded before IFM is diagnosed.

Another point of controversy is the concept introduced by Braun-Falco44 of a distinction between primary (or inflammatory) and secondary (or neoplastic) alopecia mucinosa. Clearly, histologic features of follicular mucinosis with or without obvious changes of MF can be seen in patients with CTCL. Meanwhile, many cases with similar histologic features may have a solitary lesion and never evolve into CTCL. Cerroni et al45 demonstrated that follicular mucinosis, even when presenting as a single lesion in a young patient, is often characterized by a persistent T-cell clone, and accordingly they set forth the idea that IFM is a localized form of CTCL.

Unlike follicular MF, IFM tends to present with a single tumid erythematous plaque or confluent follicular-based papules with a predilection for the face and scalp of children and young adults (Figure 5A). Alopecia may be the presenting concern, but when the area affected is rich in vellus hair follicles, hair loss may not be noted. The condition is often difficult to treat and can last for years. Eventually, spontaneous resolution occurs in most patients. Follicular MF should be suspected when the lesions are extensive and signs of tumor progression are evident. Follicular MF tends to affect older patients and is characterized by tumid alopecia with intense pruritus. The lesions involve areas with high follicular density, such as the head, neck, and upper torso. Patients can also present with acneiform papules, deep cysts, pustules, and mucin secretion. Histomorphologic examination shows infiltration of the outer root sheath by lympho-

Figure 2. Pigmented purpuric dermatosis. A, Long-standing lesion of pigmented purpuric dermatosis involving the lower leg. B, Skin biopsy specimen showing a superficial interstitial and perivascular lymphocytic infiltrate with erythrocyte extravasation and hemosiderin deposits (hematoxylin-eosin, original magnification ×20). C, Golden brown poikilodermatous patches involving the abdomen that developed a few years later in the same patient. D, Biopsy specimen obtained at the time of C showing an atypical lymphoid infiltrate along the dermoepidermal junction with characteristic features of the poikilodermatous presentation of mycosis fungoides (hematoxylin-eosin, original magnification ×4).
cytes, with mucinous degeneration of the epithelium (Figure 5B and C). The infiltrate in true juvenile classic IFM is typically brisk and can be accompanied by a significant eosinophilic infiltrate, which in conventional MF is uncommon; nevertheless, it is common in the follicular variant of MF. Other features of IFM include follicular dilation with keratin retention and comedone formation. Kossard and Rubel introduced the term folliculotropic T-cell lymphocytosis to classify such cases presenting with a folliculocentric infiltrate of slightly atypical lymphocytes resulting in hyperkeratosis and keratin retention without mucin deposits and lacking the attributes of follicular MF. These cases also tend to be clonal and probably represent variants of CTLD or IFM.

There is a poor correlation between the histologic finding of follicular mucinosis and the clinical presentation. Biopsy specimens from patients with extensive patches and plaques of MF may show follicular mucinosis with an unimpressive infiltrate composed primarily of small lymphocytes without significant atypia. A similar histologic presentation, even with positive TCC, can...
be seen in IFM. When follicular mucinosis is seen under the microscope, biopsy specimens should be interpreted with caution and clinical correlation is essential. Clearly, strict morphologic, phenotypic, or molecular criteria cannot be applied to predict the course of follicular mucinosis.

**PITYRIASIS LICHENOIDES**

Pityriasis lichenoides exists as 2 subtypes: an acute variant, pityriasis lichenoides et varioliformis acuta (PLEVA), which is more common in the first 2 decades of life, and a chronic variant more common in adulthood. The lesions of PL chronica have a characteristic red-brown color with an adherent scale,
while those of PLEVA are mostly infiltrative and hemorrhagic. The natural course of PL is variable. While the chronic variant tends to persist with waxing and waning lesions for many years, PLEVA may resolve after a few eruptive episodes. Febrile ulceronecrotic PLEVA is a rare and severe variant characterized by the sudden onset of diffuse ulcerated, confluent patches associated with high fever and constitutional symptoms. This presentation is often fatal and has been associated with Epstein-Barr virus infection and cytotoxic lymphomas. T-cell clonality is a common finding reported in both variants of PL, and occasional cases of progression to MF have been reported. The progression of PL to MF is questionable, but there are insufficient clinical and pathological criteria to establish a definitive MF diagnosis; however, in many cases, there are insufficient clinical and pathological criteria to establish a definitive MF diagnosis. The epidermis can have variably thickened layers of the epidermis. Extensive red blood cell extravasation is seen amid a superficial interstitial and perivascular lymphocytic infiltrate (hematoxylin-eosin, original magnification ×20).

**PARAPSORIASIS**

The term parapsoriasis is used by dermatologists to classify a specific group of chronic dermatoses that bear some resemblance to psoriasis, with distinct scaly and erythematous patches of variable size. The notion of large-plaque parapsoriasis (LPP) as a distinct entity has been extensively debated. Some experts believe that cases of LPP are, for the most part, early patches of MF. This may be true for some of the cases carrying this diagnosis; however, in many cases, there are insufficient clinical and pathological criteria to establish a definitive MF diagnosis. The epidermis can have variable contour, but some keratin retention in the stratum corneum is often noted. There is a superficial perivascular and interstitial lymphocytic infiltrate composed of small lymphocytes without significant atypia. Although there is focal colonization of the basal layer, prominent epiteliotropism and Pautrier microabscesses are not present. Other inflammatory cells, such as plasma cells and eosinophils, are noticeably absent. Reticular fibroplasia of the papillary dermis is a sign of chronicity of the infiltrate, which is often present in biopsy speci-
ments of parapsoriasis. The infiltrate is predominated by CD4 lymphocytes, with some diminution in CD7 and CD62L expression, but variable numbers of CD8 cells are also noted. In a recent study we conducted, of 8 cases of LPP, 6 were monoclonal with a polyclonal background, while 2 additional cases showed a restricted T-cell repertoire. In 2 cases in which multiple biopsies were performed, the same molecular profile was observed at each of the different sites (unpublished observations, 2006). The model of parapsoriasis as a CTLD is in agreement with the concept of “clonal dermatitis” introduced by Siddiqui et al. They identified a TCC in 7 of 11 cases of LPP and concluded that these conditions were at risk for progression to CTCL. Interestingly, the detection of a TCC in the skin is not associated with a circulating clone, as is often seen in patients with MF.

The small-plaque variant of parapsoriasis preceding MF is exceedingly rare. With an oval contour, the patches have the approximate size and shape of fingerprints, and thus the alternate appellation for this condition is digitate dermatosis. The histopathological examination shows significant overlap with LPP and, to some extent, with PL chronic. There are also rare cases of MF manifesting digitate morphologic features, underscoring the importance of careful morphologic assessment in all such cases of so-called digitate dermatosis.

CLONAL ERYTHRODERMA

Many cases of generalized erythroderma are eventually labeled as idiopathic because a triggering event, such as a drug eruption or associated dermatoses, is never established. Sézary syndrome is generally defined as erythroderma with more than 1000 circulating Sézary cells per square millimeter. Other hematologic criteria set forth by the International Society for Cutaneous Lymphomas include the detection of a TCC on peripheral blood, aberrant phenotype on flow cytometry results, and a CD4:CD8 ratio of more than 10:1. The identification of the same TCC in peripheral blood and skin in combination with one of the above-mentioned criteria has been suggested as an absolute criterion for Sézary syndrome. Patients with chronic recalcitrant idiopathic erythroderma who lack the peripheral-blood criteria for the diagnosis of Sézary syndrome are often labeled as having “pre-Sézary syndrome.” These patients experience the common signs and symptoms of generalized erythroderma, including pruritus, palmoplantar keratoderma, dystrophic nails, ectropion, and alopecia. Yet only a small proportion of these patients (5%-10%) will develop frank CTCL. Cases with a similar constellation of clinical and laboratory findings (erythroderma, lymphocytosis, and hyper-IgE) have also been reported under the term Ofují papuloerythroderma, which, in our opinion, most likely encompasses the same patient population.

Recently, Gniadecki and Łukowsky reported on a series of elderly patients with monoclonal T-cell dyscrasia of undetermined significance associated with recalcitrant erythroderma. The patients had characteristics similar to those of the previously reported pre-Sézary cases, including low counts of Sézary cells, hyper-IgE, and mild eosinophilia. In 5 of 10 patients there was T-cell clonal lymphocytosis. In addition, phenotypic studies showed a modest expansion of T cells with immunophenotype features of Sézary cells (CD4+, CD7+, CD26+), yet morphologically the isolated cells were mostly small lymphocytes, with a minority of cells displaying the typical morphologic characteristics of Sézary cells. None of the patients developed Sézary syndrome during a follow-up period that ranged from 4 to 13 years. The authors drew a parallel between idiopathic erythroderma and monoclonal gammopathy of undetermined significance. The presence of T-cell monoclonality in this setting is not necessarily neoplastic. T-cell clones have been reported in healthy elderly individuals, as well as in patients with autoimmune conditions.

COMMENT

Cancer arises from a stepwise accumulation of genetic alterations freeing the neoplastic cells from the homeostasis mechanisms that control normal cell proliferation. Besides the initial clonal expansion that may define a neoplasia at the molecular level, we now know that additional mutations are required for the development of cancer as conventionally defined by the morphologic appearance and clinical behavior of the condition. There is substantial evidence that a precancerous stage presenting with chronic inflammatory features is common in CTCL. This evolution may explain the commonly encountered difficulties in the early diagnosis of CTCL, which can take years from the time of initial presentation to diagnosis.

For the most part, the conditions presented herein follow an entirely benign course. However, they may also represent various scenarios of the preliminary stages in the development of CTCL. Awareness of these precursor conditions, which are not observed in many CTCL cases, should help us understand the link between certain recalcitrant dermatoses and CTCL and may facilitate our dialogue and therapeutic approach to the patients. Most of these conditions have been historically classified as inflammatory dermatoses with potential for malignant transformation, while others, like the hypopigmented variant, may have been prematurely diagnosed in some instances as MF.

The inflammatory nature of CTLD is in agreement with the theory that links inflammation with neoplasia. This theory, championed by Burg et al., recognizes that the early stages of MF are characterized by a persistent inflammatory state conducive to lymphocyte proliferation and perpetuation with gradual acquisition of proliferative and antiapoptotic features. Cutaneous T-cell lymphoma is a malignancy of postthymic mature and primed T lymphocytes. There is probably an initial T-cell clonal event, perhaps at the stem-cell level, which will define the profile of the lymphoproliferative process throughout the course of the disease. This clonal T-cell population may be initially characterized by a slight morphologic and genetic deviation from the normal repertoire of T cells. Consequently, the cells require similar homoeostatic mechanisms for clonal ex-
pansion. During the early stages of CTCL, the clonal T cells proliferate as a response to stimuli provided by immature antigen-presenting cells. Berger et al recently suggested that CTCL is a malignancy of T-regulatory cells. Although this hypothesis has not been confirmed by others, the cytokine profile of T-regulatory cells (interleukin 10, transforming growth factor β) is intuitively consistent with the evolution of CTCL from an initial antigen-driven immune reaction. Interleukin 10 deters antigen-presenting cells from maturing and eliciting an antitumor cell-mediated response. This immunosuppressive quality of the clonal cells is important to counteract the cell-mediated immune response primarily composed of clonotypic cytotoxic CD8 cells. It may contribute to the ultimate progression of the clone to a malignant lymphoma with abrogation of the cell-mediated reaction. Transforming growth factor β may initially inhibit expansion of the clone but will stimulate the local recruitment of immature antigen-presenting cells (Langerhans cells), which are required for maintenance of the T-cell clone. In vivo CTCL cells are noted in close contact to Langerhans cells in the epidermis, with the formation of Pautrier microabscesses, and similar aggregates can be seen in the dermis with T cells in proximity to dermal dendrocytes. In vitro studies have shown that CTCL cells are unable to proliferate in tissue culture unless they are exposed to autologous dendritic cells. The nature of the stimuli driving the T-cell clone and the significance of this codependency of CTCL cells and antigen-presenting cells has not been fully elucidated. Retroviruses and members of the herpesvirus family have been suggested as possible antigenic stimuli driving these early MF cells, but substantial evidence is lacking.

It is also conceivable that an inflammatory condition characterized by a chronic lymphocytic infiltrate could precede the initial T-cell clonal event. The detection of an oligoclonal T-cell profile in some early MF lesions and premycotic conditions support this option, at least in some cases. The significance of these oligoclonal patterns and their relationship with polyclonality and monoclonality is not yet fully understood and will require further investigation. However, in our experience, oligoclonality with a few restricted T-cell clones is common in CTLD. The clonal population could emerge from inflammatory cells that failed to respond to self-regulatory immune mechanisms. Interestingly, pseudoclonal or oligoclonal MF cases characterized by the lack of a dominant or reproducible clone tend to have a more indolent course than cases with identical clones in more than 1 site. This theory of inflammation leading to lymphoma is also supported by a recent epidemiologic study indicating an increased risk of CTCL among patients with psoriasis. The association of other chronic inflammatory dermatoses such as atopic dermatitis or lichen planus has not been studied, but some reports suggest a possible increased risk of CTCL. An alternative argument that could explain the static nature of CTLD, the slow evolution, and the difficulties in the early diagnosis of MF is the predominance of a reactive and polyclonal T-cell infiltrate over the clonal T cells in the initial stages of the disease. Efforts to harvest MF cells have been hampered by the growth of T cells with clonotypic cytotoxicity against the clonal T-cell receptor protein. Expansion of the T-cell clone may eventually overcome this cell-mediated reaction that keeps the T-cell clone in check during the early disease stages.

Gniadecki et al have presented evidence suggesting that CTCL may be initiated by a mutant occult stem cell with low proliferative features. This theory provides a basis for understanding many features of CTCL, including the multicentricity of skin lesions, lack of sustained remissions after chemotherapy, and common coexistence of CTCL with other lymphoproliferative disorders. The concept of CTLD is in partial agreement with the hypothesis of neoplastic stem cells. The lesions in CTCL are often multicentric, with lack of sustained response after skin-directed therapies. The emergence of lymphomas in such patients could be secondary to malignant progression from the CTLD lesions at the skin level or from the emergence of new subpopulations from the progenitor cells. However, some conditions, such as alopecia mucinosa, may remain confined to one area, suggesting an essentially localized cutaneous process.

Inherent to the group of disorders that we designate CTLD is the presence of persistent T-cell clones and phenotypic abnormalities defined by the reduction in CD7 and CD62L expression. While TCC is a feature characteristic of CTCL, it is also a feature of a variety of immunogenetic-based inflammatory conditions. However, the circumstances under which clonal infiltrates develop in the latter scenario as opposed to CTCL and, likely, CTLD appear different. In particular, T-cell clones have been reported in other states of long-term immunostimulation, including multiple sclerosis, rheumatoid arthritis, inclusion body myositis, lupus erythematosus, and solid organ transplant. It has been shown in both experimental animal models and humans that these autoreactive T-cell clones escape peripheral tolerance, expand, and accumulate at varying sites. The immunophenotype of these T-cell clones in autoimmune conditions may differ from that of CTLD by the absence of CD28 expression, which may correlate with senescent T cells. The critical difference in all of these is the pathogenetic basis, namely one of response to restricted T-cell epitopes on autoantigens such as immunodominant myelin basic peptide in the setting of multiple sclerosis or alloantigens in the transplant setting. Although it is possible that the inciting trigger in the CTLD may have been a specific exogenous or endogenous neoantigen, what is established with reasonable certainty is the failure to demonstrate recognizable T-cell epitopes that could provide an ongoing stimulus for regulated T-cell clonal expansion.

Decreased expression of CD7 is not a unique feature of CTCL and CTLD, but is also noted in reactive settings. Subsets of postthymic memory T-helper lymphocytes (CD45RO+CD28−) with skin homing characteristics do not express CD7. Another marker with decreased expression in CTLD is the selectin
CD62L. While naive T cells in human peripheral blood uniformly express CD62L, there is variation in CD62L expression among the memory T-cell population. However, most memory T-cell lymphocytes homing to the skin express CD62L and CLA.105 Hence, the accumulation of memory T cells without CD62L or CD47 expression defines a phenotypic profile that is more akin to CTCL than one of the inflammatory conditions.

Lymphomagenesis is a dynamic process and, with time, the initial T-cell clonal population expands at different cutaneous sites, giving the appearance of subclones with slight variations in their genetic profile.106 Eventually, expansion and diversification of the initial indolent T-cell clone may result in tumor progression with the emergence of more aggressive subclones. Genomic instability is associated with proliferation of the clone, increasing the risk of additional cumulative mutations. At this stage, the neoplastic T cells acquire distinct morphologic features, often with large-cell transformation. Tumor cells are then capable of growth independent of the microenvironment provided by antigen-presenting cells. This triumph of the malignant clone over the immune system results in immunosuppression with infectious complications and tumor cells capable of rapid growth beyond the confines of the skin.

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The Off-Center Fold

IN THE DECEMBER 1984 ISSUE OF THE ARCHIVES, then-Editor-in-Chief Kenneth A. Arndt, MD, announced a new section of the journal that would debut the following month. Dr Arndt described his vision of a six-page foldout section in which clinicopathologic cases will be presented. Clinical descriptions will appear on the front page, with the diagnosis and discussion on the reverse side. If desired, the entire section may be removed from the journal and posted as a clinicopathologic case quiz.

Under the direction of Antoinette F. Hood, MD, as section editor, the section, originally called Clinicians’ Corner, but soon retitled Off-Center Fold, made its debut the following month, in January 1985, and appeared every other month during that year. The 3 vignettes outlined in the first appearance described cases of peripheral giant cell granuloma of the gingiva, multiple trichoepitheliomas, and Melkersson-Rosenthal syndrome. The Off-Center Fold quickly became a popular feature, with Dr Arndt reporting in an editorial on the feature’s first anniversary that there had been “enthusiastic reviews” by the readership and the contributors. Over the next few years, the section format eventually settled into the 4-cases-per-month format that we have today. There have been 3 section editors to date, with Lori Lowe, MD, taking the reins from Dr Hood prior to my term.

The intent of the Off-Center Fold remains the same as it did when it first began in 1985: to provide the visual presentation of case-related teaching materials for the educational benefit of dermatologists and dermatologists-to-be. In general, cases presented in the Off-Center Fold are either classic cases of the diagnosis in question or cases showing an important new feature of the disease. Each manuscript has a consistent structure, beginning with a “Report of a Case” section describing the important findings known to the dermatologist at the time the patient was seen, with both clinical and microscopic photographs presented on the front side. On the reverse side of the page, the diagnosis is given (along with a description of the microscopic findings, other laboratory and radiologic findings, and the clinical course if appropriate), as well as a short discussion and a reference list. Unique among the different sections of the journal, the Off-Center Fold has very strict space limitations, since there is no leeway for the 4 monthly cases to expand beyond the foldout pages. As a result, the articles should be limited to 150 words for the “Report of a Case” section,
350 words for the “Discussion” section, and 500 words in total for the text of the reverse side, with no more than 9 references. The core purpose of the Off-Center Fold is to provide illustrations of the diseases described, and figure quality is paramount, with high-resolution photographs of extreme importance.

I am fortunate to have a wonderful group of assistant section editors to share in editorial duties. These 5 individuals, who are all trained as both clinical dermatologists and dermatopathologists, are Carrie Ann R. Cusack, MD (Philadelphia, Pennsylvania), Senait W. Dyson, MD (Irvine, California), Jacqueline M. Junkins-Hopkins, MD (Philadelphia), Vincent Liu, MD (Iowa City, Iowa), and Karla S. Rosenman, MD (New York, New York). I would also like to thank Dee Egger, the manuscript editor for this section, whose input has been invaluable; Chris Meyer and Fred Furtner of the graphics unit, who create the crisp images each month; the composition group, who incorporate these images and all the text into a tight layout in every issue; and the rest of the journal’s production team in Chicago. Finally, I would like to express my thanks to Natalie Rossi for editorial assistance, to Drs Hood and Lowe for their helpful advice when I began this position, and to the 2 editors of the journal with whom I have worked, Drs Kenneth Arndt and June Robinson. When Dr Arndt reported on the first anniversary of the Off-Center Fold, he said that he believed that the new section “will add to the diversity and interest of the Archives.” It is my hope that the Off-Center Fold serves those goals and provides the readership with stimulation, education, and enjoyment.

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REFERENCES

Editor’s Note

• Before preparing a manuscript authors should review the Instructions for Authors available at http://www.archdermatol.com.
• Manuscripts are submitted to all sections of the Archives by Web access at http://manuscripts.archdermatol.com.
• Authors may check the status of their manuscript as it proceeds through the review and decision process by logging into http://manuscripts.archdermatol.com.
• It is important for authors to update their contact information, especially their e-mail addresses, by logging into http://manuscripts.archdermatol.com. Publication of accepted manuscripts may be delayed by our inability to locate authors, who need to approve copyedited manuscript proofs.
Acute Blue Patch on the Forearm

Vera M. R. Heydendael, MD, PhD; Rick Hoekzema, MD, PhD; Koningim Gasthuis, Haarlem (Dr Heydendael), and Onze Lieve Vrouwe Gasthuis, Amsterdam (Dr Hoekzema), the Netherlands

REPORT OF A CASE

A 29-year-old woman presented with a 4-month history of a large, approximately 20 cm blue patch on her left forearm that had appeared overnight (Figure 1). She told us that she had noticed the blue patch after she had driven “nonstop” from Amsterdam, the Netherlands, to Spain in a state of rage after a fight with her partner.

She had a several-year-history of diabetes mellitus, for which she injected insulin. She used no other medications. A dissociative disorder had previously been diagnosed by a psychiatrist. Examination of the left forearm showed striking clear-blue dyschromia of the skin, without induration or any sign of trauma. A skin biopsy was performed (Figure 2).

What is your diagnosis?

Painful Nodule on the Knee

Michael P. Heffernan, MD; Danette D. Bentley, MD; Beatriz Tapia, MD; Paul Klekotka, MD, PhD; Wright State University School of Medicine, Dayton, Ohio (Dr Heffernan), and Washington University, St Louis, Missouri (Drs Bentley, Tapia, and Klekotka)

REPORT OF A CASE

A previously healthy 42-year-old white woman presented with a 1-year history of a painful nodule on her left knee. A biopsy specimen of the lesion had been obtained 9 months earlier, revealing a necrobiotic granuloma consistent with granuloma annulare. The patient was unavailable for follow-up until the lesion recurred and she returned to our clinic because of the discomfort.

Physical examination revealed a 2.0 cm brownish pink nodule with a variegated surface on the lateral aspect of the left knee (Figure 1). The patient was otherwise asymptomatic, and no other abnormalities were noted on physical examination. Punch biopsy specimens were obtained (Figure 3).

What is your diagnosis?

Diffuse Cutaneous Nodules

Mark Abdelmalek, MD; Jennifer Han, BS; Herbert Allen, MD; Drexel University College of Medicine, Philadelphia, Pennsylvania

REPORT OF A CASE

A 71-year-old man with a history of prostate carcinoma developed multiple nontender subcutaneous nodules over a 3- to 6-month period. Initial treatment of his prostate cancer included radiation therapy and leuprolide acetate injections. Because his response to treatment was minimal, he was labeled hormone refractory. He was subsequently unavailable for follow-up, but 4 years later, he was admitted to the inpatient medicine unit with a bleeding rectal mass.

Physical examination revealed a cachectic elderly man with multiple firm, mobile, nontender, subcutaneous nodules ranging from 1 to 3 cm on the face, chest, anterior aspect of the right shoulder (Figure 1, white arrows), back, epigastric region, perirectal area, and thighs. An ulcerated right axillary nodule was also present (Figure 1, black arrow). A punch biopsy specimen (Figure 2 and Figure 3) was obtained from the right axillary nodule.

A Blue-Gray Subungual Discoloration

Stephane Dalle, MD, PhD; Sandra Ronger-Savle, MD, PhD; Lorenza Cicale, MD; Brigitte Balme, MD; Luc Thomas, MD, PhD; Hopital de l’Hotel-Dieu, Lyon, France

REPORT OF A CASE

A 34-year-old white woman presented with a 10-year history of pigmentation of the second right fingernail. A blue-gray, well-limited, semicircular spot was seen in the middle of the lunula (Figure 1). Superficial linear erosion of the nail plate extended from the distal part of the tumor process to the distal nail plate. Hutchinson sign was absent. Dermoscopic examination revealed a homogeneous blue discoloration on the distal matrix, with a few linear hemorrhages on the nail plate (Figure 2). There was no clear history of local trauma. Only 1 finger was affected. An x-ray film of the phalanx showed no abnormalities.

Surgical exploration of the fingernail, with the patient under local anesthesia, showed a well-delineated area of blue pigmentation located in the lunula. The entire subungual tumor was excised and submitted for histopathologic evaluation (Figure 3).
The skin biopsy specimen showed many dark-colored parakeratotic lamellae. The clinical presentation may vary considerably as a result of the spectrum of possible presentations. The diagnosis also includes subungual hemorrhage; however, the commercially available ink-containing syringes used to site prism carriers. However, she denied this pos- ability.

The final diagnosis was subungual common blue nevus. The histopathological findings were typical of this entity. 5

Acute Blue Patch on the Forearm


diagnosis: Blue nevus is either a congenital or an acquired benign skin tumor characterized by dermal proliferation of melanocytes. It may occur anywhere on the skin but is most common on the lower legs. It is usually a solitary lesion, but multiple cases have been reported.

Diagnosis: Acute Blue Patch on the Forearm

DISCUSSION

Acute Blue Patch on the Forearm

Diagnosis: Paget disease of the breast.

Microscopic Findings and Clinical Course

Diagnosis: Diffuse Cutaneous Lymphoma

REFERENCES

Increasing evidence supports the diagnostic accuracy of epiluminescence microscopy (ELM) in the noninvasive diagnosis of mucosal pigmented lesions. In everyday clinical practice, routine ELM examination of mucosal lesions necessarily requires sterile instruments to prevent the potential transmission of infections between patients. Since sterilization of instrumental probes is usually difficult to perform, an adequate level of safety in routine dermoscopy procedures could be achieved by covering the instrument with disposable material. Suitable material should be inexpensive, easily available, prevent contamination, and permit an unmodified view of the pigmented lesions.

The results of a previous study show that polyvinyl chloride (PVC) food wrap (mean±SD thickness, 9±1 µm) (Domopak; Comital Cofresco SpA, Volpiano [Torino], Italy) covering the dermoscopy probe with the interposition of mineral oil both between the glass plate and the film and between the film and the skin does not significantly change the perception of skin colors and color differences compared with the usual ELM procedure. Furthermore, the submicron observation of PVC film samples performed by scanning electron microscope revealed the absence of pores on the film surface even at an original magnification of ×50,000. However, the absence of pores on the PVC surface does not exclude a potential permeability to viruses.

Methods. In the present article, we addressed this problem using the polymerase chain reaction (PCR) assay to evaluate the safety of PVC film in preventing virologic contamination of the probe and thus potential cross-contamination between patients. Herpes simplex virus 2 (HSV-2) and human immunodeficiency virus 1 (HIV-1) were chosen as challenge viruses being potential sources of probe contamination during dermoscopic scanning of mucosal surfaces.

Samples of PVC were tested as unaltered naive samples and as samples exposed to simulated controlled clinical use in which the PVC film was placed on a dermoscopic probe with mineral oil placed on both surfaces and rubbed for 2 minutes on the skin while exerting light pressure. To verify whether the PVC film was effective in preventing diffusion of virus particles during an incubation time comparable to that needed for the dermoscopic examination, increasing concentrations of HSV-2 and HIV-1 suspended in sterile solution were placed on 1 side of the membrane and incubated in sterile conditions for up to 30 minutes at room temperature. Virus diffusion through the membrane was evaluated by PCR and reverse transcriptase–PCR. The PCR reactions had a sensitivity of about 50 copies of HIV-1 and HSV-2 in first-round amplifications, and up to 1 copy of HIV-1 and HSV-2 in nested reactions.

Results. The results shown in the Figure and summarized in the Table demonstrate that PVC film efficiently prevented the diffusion of HSV-2 and HIV-1 for

![Figure](https://example.com/figure.png)

**Figure.** Permeability of polyvinyl chloride (PVC) film to herpes simplex virus 2 (HSV-2) and human immunodeficiency virus 1 (HIV-1). The transfer of virus particles across PVC sheets was investigated by incubating for 30 minutes 50 µL of virus suspension on 1 side of the membrane and placing it on 1 drop of phosphate-buffered saline solution. The drop was then collected and analyzed for the presence of HSV-2 and HIV-1 by polymerase chain reaction (PCR) and reverse transcriptase–PCR, respectively. Human β-actin gene was used as a control. Lane numbers indicate virus concentration, expressed as copies per milliliter. C+ Indicates positive control; gag, group-specific antigen; and UL-48, unique long 48.

<table>
<thead>
<tr>
<th>Virus</th>
<th>First-round PCR</th>
<th>Nested PCR</th>
</tr>
</thead>
<tbody>
<tr>
<td>HSV-2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>UL-48</td>
<td>C+ 10^7, 10^6, 10^4, 10^2, 10^-1</td>
<td>C+ 10^7, 10^6, 10^4, 10^2, 10^-1</td>
</tr>
<tr>
<td>β-Actin</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| HIV-1       |                 |            |
| gag         | C+ 10^7, 10^6, 10^4, 10^2, 10^-1 | C+ 10^7, 10^6, 10^4, 10^2, 10^-1 |
| β-Actin     |                 |            |
respectively, virus concentrations up to $10^7$ and $10^6$ copies/mL (corresponding to about $10^8$ plaque-forming units for HSV-2 and $10^5$ median tissue culture infectious dose for HIV-1). No differences were observed between control and treated membranes.

**Comment.** Literature data show that in asymptomatic infected patients, virus shedding can be observed for both HSV and HIV in the genital mucosa, and disease must be considered potentially transmissible during clinical examinations. Human immunodeficiency virus is found in concentrations of up to $10^7$ copies/mL in cervical swabs. Likewise, HSV-2 shedding can reach $10^5$ copies/mL during asymptomatic infections.

Our results show that PVC film completely blocks the passage of viruses even when virus concentrations are 100-fold higher than those reported in asymptomatic patients. These results were obtained in harsher conditions than would normally apply during clinical examination (i.e., incubation time of 30 minutes and high viral concentrations).

Therefore, the use of PVC film during dermoscopic examination of mucosal surfaces acts as a safe barrier for virologic contamination and prevents infection in sequential patients. This could improve the role of dermoscopy in clinical assessment of mucosal melanoma from other melanocytic and nonmelanocytic mucosal pigmented lesions.

**Granuloma Annulare: Long-term Follow-up**

Granuloma annulare is a peculiar skin disorder of unknown cause. Asymptomatic, annular, skin-colored to violaceous papules and plaques mysteriously erupt on nonfacial skin, usually without any obvious cause. A loose collection of histiocytes surrounds or infiltrates a more amorphous and rather acellular zone of degenerated connective tissue and mucin. Often the disorder resolves with or without treatment.

Perhaps inflammation is aberrant, and the nature of inflammation differs from person to person, based on some genetic perturbation. Perhaps an “ordinary” event such as a tuberculin skin test, trauma, infection, insect bite, or solar exposure starts an inflammation that deviates from its usual path and morphs into a persisting necrobiotic granuloma instead of resolving. Based on this hypothesis, one might predict that patients with granuloma annulare would develop other bizarre inflammatory disorders or odd sequelae, even many years later. Perhaps they might even die from an odd disease or disorder.

**Methods.** To test this prediction, we identified the Mayo Clinic records of patients with granuloma annulare. The institutional review board approved a retrospective medical chart review of these records in a study designed to survey the development of subsequent disease among affected patients. The study was a qualitative pilot study. No attempt was made to age- or sex-match subjects.

The study group consisted of 32 patients with granuloma annulare seen at Mayo Clinic between 1950 and 1970. All subjects had follow-up visits at Mayo Clinic for at least 20 years. The charts were screened for unusual diseases and for diseases related to connective tissue, odd inflammations, or unusual diseases. There were 21 female and 11 male subjects. The average age at diagnosis was 48 years (age range, 4-58 years). Only 3 were children younger than 12 years. The mean follow-up was 35 years (follow-up range, 20-53 years).
Results. The patients seemed remarkably healthy, even in old age. No patient had granuloma annulare at last examination. Interesting comorbidities are listed in the Table. Most patients with conditions or diseases had only ordinary ones such as hypertension, hyperlipidemias, degenerative joint disease, and atherosclerosis.

In summary, patients who develop granuloma annulare usually heal, remain remarkably healthy, and do not ordinarily develop other odd diseases.

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Table. A Sample of Other Diseases Found in Patients Who Had Granuloma Annulare

<table>
<thead>
<tr>
<th>Comorbidity</th>
<th>Patients, No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thyroid disorders</td>
<td>5</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>3</td>
</tr>
<tr>
<td>Lichen planus</td>
<td>2</td>
</tr>
<tr>
<td>Insulin-dependent diabetes mellitus</td>
<td>3</td>
</tr>
<tr>
<td>Aortic ectasias</td>
<td>2</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>1</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>1</td>
</tr>
<tr>
<td>Mitral valve prolapse</td>
<td>1</td>
</tr>
<tr>
<td>Guillain-Barré syndrome</td>
<td>1</td>
</tr>
</tbody>
</table>

Overexpression of Matrix Metalloproteinases, Chemokines, and Chemokine Receptors Relevant for Metastasis in Experimental Models Not an Indication of Lymph Node Metastases in Human Melanoma

Morphologic characteristics such as tumor thickness and ulceration are the major accepted indicators of risk for metastatic spread. Since matrix metalloproteinases and chemokines and their receptors are involved in the complex process of metastasis, we tested whether their expression predicts the risk of melanoma progression. To this end, the relative messenger RNA (mRNA) expression of chemokine receptors CCR7 and CXCR4, the chemokine CXCL8, and the matrix metalloproteinases MMP2 and MT1-MMP in primary cutaneous melanomas from 28 patients was correlated with the presence of micrometastases in the respective sentinel lymph nodes.

Methods. We gained approval from our local ethics committee, and analyses were performed with the patients’ informed consent. Primary tumors were trimmed to remove most of the surrounding unaffected skin, and total RNA was isolated from frozen tissue sections. After complementary DNA was generated from this RNA, relative expression of CCR7, CXCR4, CXCL8, MMP2, and MT1-MMP was determined by real-time polymerase chain reaction and the comparative delta-delta threshold cycle ($\Delta \Delta C_T$) method where glyceraldehyde-3-phosphate dehydrogenase served as endogenous control. The results were statistically tested after log-normal transformation using the 2-tailed nonpaired t-test.

Results. For CXCR4 ($P = .01$) and MMP2 ($P = .04$), an inverse relationship between mRNA expression and presence of lymph node metastases was detected (Figure). Primary tumors associated with concurrent lymph node metastasis, while not reaching statistical significance, also showed lower expression of CCR7 ($P = .06$) and MT1-MMP ($P = .09$). For CXCL8 ($P = .96$), no correlation was observed.

Comment. The statistically significant inverse correlation of the expression of genes known to promote metastasis (CXCR4 and MMP2) and the presence of lymph node micrometastases was unexpected. For example, Muller et al$^1$ detected an increased expression of CXCR4 and CCR7 in human melanoma cells compared with primary melanocytes. In a murine melanoma model, however, CXCR4 expression did not enhance occurrence of lymph node metastasis.$^2$

Notably, cell signaling is influenced not only by the amount of expressed chemokine receptors or their ligands but also through regulatory mechanisms. Indeed, despite high expression of CXCR4 on germinal center T cells, their migration to CXCL12 was diminished owing to follicular dendritic cell–mediated expression of regulators of G protein signaling 13 and 16.$^3$ In addition, tumor cells are highly flexible, ie, they can change from proteolytic migration to proteolysis-independent movement in an ameboid manner.$^4$ Furthermore, heterogeneity of tissues has to be taken into account; in contrast to tumor cell lines, tumors consist of different proportions of tumor, fibrocytic, vascular, and inflammatory cells. Therefore, the variances in mRNA expression could partly be due to variances in cell composition. Thus, polymerase chain reaction analyses of microdissection samples should reflect the cytokine expression in single cells more accurately.

Nevertheless, since tumor cells and surrounding host cells form a complex environment, the investigation of the whole tumor is in accordance with physiologic conditions. Such an analysis, however, forecloses identification of individual cells characterized by overexpression of a given mRNA, which may be essential for the metastatic potential. In addition, similar RNA levels may result in different protein expression by differences in the protein turnover, ie, translation and degradation. Therefore, our results do not exclude the relevance of the in
vestigated factors for promoting metastasis but demonstrate the unsuitability of global analysis of these transcripts for determining patient prognosis.

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Methods. Anonymous surveys were sent to 122 dermatology department chairpersons and/or chiefs. Chairpersons were identified through medical school Web sites and publications of the American Medical Association. Survey questions focused on demographics, tenure, and future plans of current department chairpersons. In addition, questions were asked about prevailing attitudes in the department toward academic medicine, faculty retention, and the adequacy of the pool of candidates for future leadership positions. Analysis was performed using t tests on continuous variables (Excel 2003; Microsoft Inc, Redmond, Washington). P < .05 was considered significant.

Results. Sixty percent of the surveys were returned (n = 73). The reported average age of current chairpersons was 56 years, and the average age at which they became chairperson was 45 years. Chairpersons identified several leading factors that motivated faculty members to leave academia, including the pressure to publish (cited by 68% of chairpersons [n = 50]), financial concerns (60%; n = 44), and family concerns (31%; n = 23) (Table). Moreover, 66% of chairpersons (n = 48) did not feel academic salaries in their area were competitive with salaries in private practice. By contrast, teaching was the primary reason chairpersons cited for faculty members remaining in academia (Table).

The anticipated average retirement age of the chairpersons was 62 years. Five chairmanship positions (7%) were reported as open at the time of the survey; 14% of chairpersons (n = 10) were planning to resign within the year; and 32% (n = 23) anticipated resigning within 3 years. Therefore, a 10% turnover rate in chairmanships per year is likely to persist. Current chairpersons felt that an average of 1.4 faculty members within their department would be appropriate chairperson candidates within 1 to 5 years.
Of the chairpersons who responded to this survey, 12% were women (n = 9). A few sex differences were noted. Chairwomen were an average of 6 years younger than their male counterparts (mean age, 51 vs 57 years) (P = .06) and had correspondingly shorter tenures (5.5 vs 12.0 years) (P = .06). Both men and women became chairpersons at approximately the same age (women, age 45.9 years; men, age 44.6 years). However, chairwomen anticipated leaving their chair positions at age 59 years, an average of 3 years younger than chairmen (age 62 years).

Comment. The results of our survey indicate that a leadership gap is not an imminent concern among current chairpersons. Recent practice profile surveys have shown that women occupy nearly 40% of academic dermatology positions. They also tend to be younger, which reflects the overall demographic changes in dermatology. Given the number of women in academic positions, it is reasonable to expect that the number of chairwomen should increase in the future. However, it is notable that while dermatology has one of the highest proportions of women in any area of medicine, the proportion of chairwomen remains very similar to the average across fields.

Limitations of this study include the inability to verify or validate the chairpersons’ assessments of their faculty. There also may have been more chairs vacant than those that responded; if no chairperson was available to fill out the survey, it may not have been returned. Strengths include the high response rate for a mailed survey.

At present, a premature departure of junior faculty members does not appear to threaten the perceived ability of dermatology departments to fill future leadership positions. Nevertheless, the annual rate of turnover among chairpersons and the current age distribution of academic dermatologists suggest that departments need to continue to devote close attention to the task of retaining and promoting younger faculty members. While some factors that cause people to leave academia may not be easy to reverse, difficulty with publication demands appears to be a common concern and may be a manageable problem that departments can readily address with appropriate mentoring and training.

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Paraneoplastic Relapsing Polychondritis

I read with interest the report by Yanagi et al in which the authors not only describe a 60-year-old Japanese woman with newly diagnosed relapsing polychondritis 3 years following the detection and subsequent successful treatment of stage IIA splenic non-Hodgkin lymphoma but also speculate that some cases of relapsing polychondritis may be paraneoplastic. Mucocutaneous paraneoplastic syndromes may be associated with hematologic malignant neoplasms, solid tumors, or both. Also, albeit less commonly, individuals with cancer may concurrently or sequentially demonstrate more than 1 mucocutaneous paraneoplastic syndrome.

The potential association of relapsing polychondritis in patients who have or subsequently develop myelodysplastic syndrome is well established. In addition to lymphoma, paraneoplastic relapsing polychondritis has also occurred in patients with other hematologic malignant neoplasms and dyscrasias, including aplastic anemia, dys-
gamma-globulinemia, various leukemias, myeloma, and myeloproliferative disorders. Individual reports have also been published of paraneoplastic relapsing polychondritis in oncology patients with solid tumors such as adenocarcinoma of unknown primary, chondrosarcoma, malignant fibrohistiocytoma, and others affecting the bladder, breast, bronchus, colon, lung, pancreas, rectum, and vocal cords.

The simultaneous or subsequent occurrence of more than 1 mucocutaneous paraneoplastic syndrome in a person who has a systemic malignant neoplasm has also been observed. For example, the concurrent or sequential development of paraneoplastic neutrophilic dermatoses (such as leukocytoclastic vasculitis, pyoderma gangrenosum, and/or Sweet syndrome) in patients with cancer has recently been summarized. Interestingly, the appearance of relapsing polychondritis and Sweet syndrome in patients with either myelodysplastic syndrome or a visceral tumor (urothelial carcinoma) has also been described.

Hence, similar to other dermatologic conditions and systemic disorders that are less commonly considered to occasionally present in a paraneoplastic setting (such as granuloma annulare, sarcoidosis, and systemic lupus erythematosus), relapsing polychondritis may occur as a mucocutaneous paraneoplastic syndrome associated either more frequently with hematologic malignant neoplasms or less often with solid tumors.

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VIGNETTES

Success of Goeckerman Treatment in 2 Patients With Psoriasis Not Responding to Biological Drugs

Goeckerman treatment was effective for 2 patients referred to Mayo Clinic with psoriasis not responding to treatment with biological agents. In patient 1, psoriasis flaring during etanercept therapy cleared completely with Goeckerman treatment; in patient 2, psoriasis not responding to etanercept and alefacept therapy cleared with Goeckerman treatment and with the initiation of highly active antiretroviral therapy (HAART) for newly diagnosed human immunodeficiency virus (HIV).

Report of Cases. Case 1. Patient 1 was a 22-year-old man who had a 5-year history of psoriasis that was recalcitrant to treatment with topical corticosteroids, methotrexate, and psoralen-UV-A (PUVA). He received etanercept therapy for 18 months before presentation and reported mixed results, but his lesions never completely cleared. While taking etanercept, he had an acute flare of symptoms, with multiple guttate psoriatic plaques covering about 70% of his skin. A throat swab tested positive for Streptococcus pyogenes; a course of cephalaxin was initiated (Keflex, 500 mg, 4 times daily; Advancis Pharmaceutical Corp, Germantown, Maryland). Etanercept therapy was stopped, and the patient began a 21-day course of the Goeckerman treatment with tars and phototherapy. By the end of the therapy, the psoriatic plaques had completely cleared, with only residual postinflammatory hyperpigmentation.

Case 2. Patient 2 was a 38-year-old man who presented with a 9-month history of psoriasis involving 90% of his skin. Over the 7-month period before presentation, treatment with the following medications had been tried sequentially to control his psoriasis, but there was no response: cyclosporine, methotrexate, etanercept, and alefacept. Evaluation revealed that he was HIV positive. Therapy with the biological medications was stopped, and HAART and Goeckerman treatment were initiated. On completion of the Goeckerman treatment (3 weeks following presentation), his psoriasis had completely resolved, leaving postinflammatory hyperpigmentation.

See also pages 846 and 912

Comment. Psoriasis treatment with the use of artificial UV-B and crude coal tar in a petroleum base was first reported by Goeckerman in 1925. He observed that the regimen not only cleared psoriasis but also resulted in long remissions. In 1983, Menter and Cram reported a multicenter study of 300 patients with severe psoriasis who received the Goeckerman treatment. There was a mean of 90% improvement in the psoriasis in 18 days. In 90% of the patients, the skin remained clear for at least 8 months; in 73%, clearance lasted for at least 1 year. Menter and Cram also found that the cost-effectiveness was comparable with that of PUVA therapy. Similar efficacy was reported by Jordan et al in 1981 for patients who used home-based tar and UV-B treatments in a modified Goeckerman treatment.

These cases demonstrate that psoriasis does not always respond to biological drugs. In those cases, underlying causes of recalcitrant psoriasis, such as HIV infection, should be sought. Goeckerman treatment remains effective for extensive psoriasis and should not be abandoned.

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Dissemination of a Localized Cutaneous Infection With Mycobacterium chelonae Under Immunosuppressive Treatment

We report a case of an initially localized cutaneous infection with Mycobacterium chelonae on the left breast. Owing to the failure to recognize the causative agent, high-dose immunosuppressive treatment was administered for 2 years. As a result, infection disseminated with the development of multiple ulcerating and fistulating nodules on the right leg.

Report of a Case. A 60-year-old woman presented to a local district hospital in December 2001 with a 1-year history of an ulcerating abscess on her left breast, which had appeared after a blunt trauma. Between 2001 and 2003, repeated aspirates from the abscess were found to be sterile. Histopathologic examinations revealed poorly formed granuloma with chronic inflammation and suppuration in the dermis and subcutis. Ziehl-Neelsen staining was not performed. Short-term antibiotic treatments (with clindamycin, vancomycin, ciprofloxacin, and cotrimoxazole) and repeated extensive surgical debridements performed between 2001 and 2003 proved ineffective.

Finally, in 2003, the diagnosis of ulcerative pyoderma gangrenosum was made, and immunosuppressive treatment with high-dose corticosteroids and cyclosporine A was started. Two months later, abscesses appeared on the right leg, which were again diagnosed as necrotizing form of pyoderma gangrenosum. Subsequently, additional treatment with mycophenolate mofetil was started and maintained over the next 2 years.

In October 2005, the patient was transferred to our hospital. Physical examination revealed multiple subcutaneous nodules (23 nodular lesions) on the right leg with surrounding erythematous induration and ulcers with serosanguineous and purulent discharge (Figure, A and B). The whole left breast was covered by scars. At the time of presentation, she was taking 16 mg/d of methylprednisolone, 300 mg/d of cyclosporine A, and 2 g/d of mycophenolate mofetil.

Results of routine bacteriologic and mycologic cultures of several swabs and aspirates of purulent material taken from the ulcers were negative. Deep skin biopsy specimens were obtained from 2 nodules of the right leg under sterile conditions. A fluorescent staining of a smear test during a biopsy procedure revealed many auramine-positive rods. Histopathologic analysis showed suppurative granulomatous inflammation in the subcutis with BCG-positive (bacille Calmette-Guérin) immunolabeling of histiocytes. Nontuberculous mycobacteria were identified by polymerase chain reaction (PCR) technique in paraffin sections (amplification of the hsp65 gene and subsequent automatic sequencing of the PCR products). Finally, a culture yielded M chelonae, a rapidly growing nontuberculous mycobacterium. Results of retrospective PCR-based analysis of skin biopsy specimens taken in 2003 from the left breast (the origin of the disease) were also positive for M chelonae. Magnetic resonance imaging of the right leg revealed extensive inflammation and subcutaneous abscesses without fascial or bony involvement. Furthermore, sonography of the inguinal and axillary lymph nodes and computed tomography of the thorax and abdomen showed no systemic infection.

Immunosuppressive therapy was stopped, and treatment with 500 mg/d of clarithromycin and 600 mg of linezolid twice daily was initiated. Interestingly, in the following 2 weeks, the skin lesions increased in size and began to display a pyoderma gangrenosum–like aspect (Figure, B, inset), which was most probably due to a reconstitution of the patient’s immune system. After 3 months, linezolid treatment was stopped owing to anemia and thrombocytopenia. Monotherapy with clarithromycin was continued. Nine months after initiation of antibiotic treatment, nearly all nodules had resolved (21 of 23 nodules) (Figure, C and D). Additional microbiologic examinations for M chelonae by Ziehl-Neelsen stainings and subsequent mycobacterial cultures yielded negative results. Continuation of antibiotic treatment for another 3 months was planned.
Comment. *Mycobacterium chelonae* is a rapidly growing, nontuberculous mycobacterium that is present ubiquitously in the environment (soil, water, and dust particles). Infection occurs most commonly after skin trauma from surgery, injections, and minor injuries and clinically presents as localized cellulitis or a nodule. In immuno-competent patients, such infections usually stay localized and in most cases spontaneously resolve after several months. However, in immunosuppressed individuals, infections persist or even disseminate. In our case, we proved by PCR-based analysis that the disease had started years before at the left breast and finally spread to the right leg as a result of immunosuppressive therapy with methylprednisolone, cyclosporine A, and mycophenolate mofetil.

Optimal treatment of cutaneous mycobacterial infections is poorly established. Besides surgical procedures, long-term antimicrobial treatment is recommended. Monotherapy with clarithromycin has been reported to be effective in cutaneous infections with *M. chelonae*, but the use of combination therapy (eg, clarithromycin and linezolid) seems prudent initially because of the possibility of acquired resistance. Indeed, recent reports have described the development of resistance to clarithromycin monotherapy in patients infected with *M. chelonae*.

Cutaneous infections with *M. chelonae* are frequently misdiagnosed because of its nonspecific clinical appearance. The clinical manifestation depends on the stage of the disease and can present as a cellulitis, vasculitis, abscesses, ulcerating nodules, or even display a pyoderma gangrenosum–like aspect, as described in the present report. This case highlights the importance of recognizing cutaneous nontuberculous mycobacterial infections and demonstrates the serious consequences of immunosuppressive treatment.

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Financial Disclosure: None reported.


Verruca Plana–Like Papules as a New Manifestation of Erdheim-Chester Disease

Report of a Case. In March 2005, a 41-year-old Japanese woman was referred to our department with asymptomatic skin lesions on her face (Figure 1A-C). Since she had right lower leg pain for 6 months, evaluations included radiography, technetium Tc 99m bone scintigraphy, magnetic resonance imaging, and a bone biopsy of the tibia. By radiography and bone scintigraphy, multiple lesions on both femur and tibia bones were detected (Figure 2A and B). A bone biopsy specimen from the right tibia showed a mixed infiltrate of histiocytic foamy cells, lymphocytes, and multinucleate giant cells. Most of the infiltrating histiocytic foamy cells were CD68 positive but negative for S100 stain and CD1a (Figure 2C). From these examination results, her bone lesions were diagnosed as indicating Erdheim-Chester disease 1 month before her visit to the dermatology clinic.

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She had first noticed these skin lesions 10 years previously, and over the intervening 10 years, they had gradually worsened and increased in number. The skin lesions had been diagnosed at another dermatologic clinic as verruca plana 2 years before and treated with topical urea ointment. However, the eruptions failed to improve.

Physical examination revealed diffuse, asymptomatic erythematous papules that were scattered over her entire face. Increased numbers of lesions were observed around her nasolabial groove and forehead, which resembled verruca plana (Figure 1A-C). We suspected that skin lesions on her face might be associated with Erdheim-Chester disease and took a skin biopsy specimen from a papule on the right side of her temple. The specimen showed infiltrations of dermal histiocytic foamy cells, lymphocytes, and a few multinuclear giant cells (Figure 1D). Immunohistochemical analysis showed that most of the infiltrating foamy cells were CD68 positive, but negative for S100 and CD1a, which clearly demonstrated that the histiocytic foamy cells in the dermis showed similar immunohistologic characteristics to the abnormal cells found in her leg bone (Figure 1D, inset). From this observation, we inferred that the eruptions were a specific skin manifestation of Erdheim-Chester disease. Organ manifestations of this disease other than bone and skin were not found. Since the patient had no expectations for skin disease treatment, we observed her carefully, and the skin lesions have shown no remarkable changes.

Comment. Erdheim-Chester disease is a rare, non-Langerhans form of histiocytosis characterized by infiltrates of foamy, lipid-laden histiocytes with bilateral symmetric foci of sclerotic areas identified from bone radiographs in appendicular long bones.1 It is classified as a non-Langerhans cell histiocytosis, and cells test positive for CD68 and factor XIIIa but negative for CD1a and S100.2,3 Extraskeletal manifestations can occur in almost any organ, including the lungs, pericardium, the orbit of the eye, retroperitoneum, and skin.1 Several reports have shown that xanthelasma-like and xanthomalous eruptions were the main skin manifestations.4,5 Other cutaneous manifestations described include subcutaneous nodules, pretibial dermatopathy, pigmented lesions on the lips and buccal mucosa, and/or rashes.2,3 The skin lesions in our patient did not fit the typical clinical findings of skin manifestations in either xanthelasma or xanthoma. A definite diagnosis of skin lesions was confirmed from the skin biopsy specimen after the diagnosis of bone lesions. Common dermatologic textbooks have failed to adequately describe Erdheim-Chester disease; however, we should be aware that this disease may present with a variety of skin manifestations, including xanthelasma, xanthoma, and diffuse verruca plana–like papules.

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**Blaschko Linear Nodular Morphea With Dermal Mucinosis**

Report of a Case. An 18-year-old man presented with a 15-month history of a unilateral, progressive, linear area of thickening of the skin and hair loss involving the right leg. Over the previous 3 to 4 months, he had developed multiple, firm, asymptomatic nodules within the area of induration. He denied a history of trauma, injections, drug intake, or prolonged immobilization. He had no clinical features suggestive of progressive systemic sclerosis and no personal or family history of keloid formation.

Examination revealed a hyperpigmented linear area of sclerosis with indistinct margins over the posterior aspect of the right lower extremity extending from the gluteal region to the lateral aspect of the foot (Figure 1A). Multiple, flesh-colored to brown nontender nodules and plaques 5 to 15 mm in diameter were present within the sclerotic lesion (Figure 1B). The nodules were prominent over the middle of the leg and palpable elsewhere. The lesion was anhidrotic with decreased hair density and normal sensations. There was no deformity or atrophy of the limb and no evidence of truncal or acral sclerosis.

Laboratory analysis showed leukocytosis (13 500 white blood cells/µL) with eosinophilia (760 cells/µL) and raised erythrocyte sedimentation rate (35 mm/h in the first hour); renal and liver function test results were normal. Findings for antinuclear, anti-DNA, and antihistone antibodies were negative. Radiographic results were unremarkable. A biopsy specimen from indurated skin showed classic histologic features of morphea. Another biopsy specimen from a nodule showed hyalinized thick collagen bundles in the papillary dermis with abundant mucin throughout the reticular dermis (Figure 2), consistent with morphea with dermal mucinosis. The diagnosis of nodular morphea in a linear pattern was made. The patient was treated with oral steroids but without any benefit.

Comment. Nodular scleroderma is a rare variant that may occur in association with systemic sclerosis or morphea.1 Most reported cases of nodular scleroderma have been associated with systemic sclerosis.2 It affects primarily young and middle-aged women and is clinically characterized by firm, long-lasting nodules on the upper trunk, chest, neck, and proximal parts of the limbs.3
As suggested by Micalizzi et al, the designation nodular morphea seems more appropriate in our patient because no features of systemic involvement were present. The cutaneous nodules have been described by some authors as keloidal. Modest interstitial and focal deposits of mucin in the reticular dermis are a frequent finding in both localized and systemic scleroderma. In our patient, a biopsy specimen from a nodule revealed unusually abundant mucin in the dermis along with superficial sclerosis, while the rest of the indurated area showed characteristic features of morphea. To our knowledge, this histologic finding in nodular morphea is novel.

Our patient showed Blaschko linear involvement of the lower limb. We are aware of 2 earlier cases of nodular morphea manifesting in a linear pattern, but these were not along the Blaschko lines. Linear scleroderma along the Blaschko lines is a controversial entity. Jackson was the first to describe it but later observed that it was probably dermatomal. Bolognia et al could not find a single case of linear scleroderma following the Blaschko lines. Subsequently, to our knowledge, only 4 cases of this rare presentation have been reported.

In our patient, nodules appeared within linear scleroderma along the Blaschko lines on the lower extremity. In a recent review, Redlick and Shaw suggested that genetic mosaicism can clinically present in a dermatomal or Blaschko pattern, depending on the nature of mutated cell. This concept might explain the Blaschko distribution in our case with formation of skin cell clones including possibly fibroblasts. The uniqueness of this case lies in the Blaschko linear presentation of nodular morphea and dense deposition of mucin confined to the nodules within areas of sclerosis.

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An Unusual Presentation of Cutaneous Larva Migrans

Cutaneous larva migrans (CLM) is a tropically acquired dermatosis that resolves spontaneously within 2 to 8 weeks. Rare case reports have been published in which the eruption persisted for up to a year. Herein, we report such a case.

Report of a Case. A 36-year-old healthy white woman presented with a 4-month history of intense pruritus on the right planter surface of the second toe, which began 2 weeks after returning from Jamaica where she walked barefoot on the beach. Within weeks, the pruritus spread to involve the third and fourth toes and eventually the planter surface of the instep. She denied the presence of vesicles, papules, or a serpiginous rash. She claimed that her symptoms waxed and waned and that she experienced several week–long periods with no symptoms or visible rash.

Initial examination revealed a 3-mm deep-seated vesicle with a surrounding 2-cm ring of ecchymosis on the right planter surface of the instep. She was symptomatically treated for eczematous dermatitis with 0.05% clobetasol ointment and oral antihistamines. Cutaneous larva migrans was considered; however, the intermittent course, the longevity of the eruption, and the morphologic characteristics of the lesion made this diagnosis less likely.

At follow-up 2 weeks later, an erythematous, spongiotic, serpiginous plaque (5 cm in length) was noted on the right lateral surface of the foot (Figure). Analysis of a punch biopsy specimen from the leading edge revealed spongiosis, mild hemorrhage, and dense superficial and deep dermal infiltrate with numerous eosinophils. Based on classic clinical appearance, the diagnosis of CLM was made. Given the degree and longevity of the symptoms, she was treated with 1500 mg of oral thiabendazole twice daily for 5 days. The dermatitis resolved within 1 week of completing treatment. To date, she has been symptom free.

Comment. Cutaneous larva migrans is caused by penetration and migration within the epidermis of nematode parasites; it is characterized by erythematous, pruritic, serpiginous plaques usually occurring on the feet or other exposed sites. It is self-limited because the larvae lack the lytic collagenase enzymes needed to cross the epidermal basement membrane. Disease of extended duration, as occurred in our patient, is uncommon because the larvae are unable to complete their life cycles in the human body and usually die within 2 to 8 weeks. Ancylostoma braziliense and Ancylostoma caninum are species most frequently involved.

The most common therapy for CLM is thiabendazole cream, 15%, applied topically 2 to 3 times daily for 5 to 10 days. If symptoms are severe or persistent, oral thiabendazole (25-50 mg/kg) may be given in divided doses for up to 5 days. Albendazole and ivermectin are also effective. Topical or oral therapy usually leads to symptom resolution within 1 week.

We present this case to raise awareness that the eruption of CLM can persist for months, as occurred in our patient.

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Dermoscopy of Port-Wine Stains

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The illustrated port-wine stain (PWS) lesions are from the leg of a 14-year-old girl (Figure 1), the face of a 25-year-old woman (Figure 2) (scaled in millimeters), the neck of an 11-year-old boy (Figure 3), and the face of a 15-year-old girl (Figure 4). The dermoscope serves herein to determine the depth of ectasia of the PWS and to help predict the outcome of its treatment. Two different dermoscopic vascular patterns are illustrated. Figure 1 and Figure 2 disclose red linear vessels and represent the deep, subpapillary form of PWS, showing horizontally oriented capillaries. Figure 3 and Figure 4 show red, rounded, globular vessels and represent the superficial or papillary form of PWS, disclosing vertically oriented capillaries. This differentiation has prognostic significance because superficial, papillary PWS responds best to laser therapy. These cases illustrate the 2 different patterns of PWS lesions under dermoscopy.