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Archives of Dermatology Masthead

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Mission Statement: The Archives of Dermatology publishes information concerning the skin, its diseases, and their treatment. Its mission is to explicate the structure and function of the skin and its diseases and the art of using this information to deliver optimal medical and surgical care to the patient. We attempt to enhance the understanding of cutaneous pathophysiology and improve the clinician's ability to diagnose and treat skin disorders. This journal has a particular interest in publishing clinical and laboratory studies that reveal new information pertinent to the interests and needs of the medical dermatologist, dermatologic surgeon, and all those concerned with state-of-the-art care of cutaneous disease. We believe that knowledge derived from well-designed clinical trials and studies of cost-effectiveness are especially important for improving the practice of dermatology. Studies that increase the understanding of the outcome of treatment or the means by which the burden of dermatologic disease can be measured and reduced to promote the health of patients with skin disease will receive special priority. The Archives regularly publishes reports on clinical investigations, editorials, and reviews. It also features reports and discussions on clinical-pathologic correlations; clinical disorders of unique didactic value; pharmacologic, medical and surgical therapies; and ethical, moral, socioeconomic, and political issues.

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Treatment of Severe Pemphigus With Rituximab

Pemphigus is a mucocutaneous blistering disease mediated by circulating autoantibodies directed against desmogleins. Systemic steroids remain the mainstay of therapy, but adverse effects of corticosteroids and complications from long-term immunosuppressive therapy contribute substantially to the morbidity and mortality from this disease. Additional therapies include pulsed steroid administration, cyclophosphamide, plasmapheresis, intravenous immunoglobulins, and mycophenolate mofetil. In this case series, Cianchini et al demonstrate the safety, efficacy, and tolerability of the chimeric murine-human anti-CD20 monoclonal antibody rituximab in treating patients with pemphigus resistant to conventional therapy.

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Nephrogenic Systemic Fibrosis

Nephrogenic systemic fibrosis (NSF) is an acquired, progressive, systemic fibrosing disorder that develops in the setting of renal disease. Plaquelike waxy induration of the skin may involve deeper tissues as well as systemic sites such as skeletal muscle, pericardium, lung, and dura mater. The fact that NSF appeared only within the past 10 years suggests a causal link to a new medication or chemical or infectious agent. In this case series, Richmond et al describe a cohort of 8 patients with NSF and an etiologic link with gadolinium contrast dye exposure, specifically gadodiamide. Extracorporeal photopheresis therapy proved useful by some objective measures of response.

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Narrowband UV-B Phototherapy, Alefacept, and Clearance of Psoriasis

The classic erythematous plaques of psoriasis are clinical signs of chronic skin inflammation accompanied by hyperproliferation of keratinocytes and dermal infiltration by certain lymphocyte subtypes. A new generation of antipsoriatic drugs specifically target the T-cell–mediated pathways involved in the pathogenesis of this disease. Alefacept is an immunomodulatory, fully human, fusion protein that targets the memory-effector T-cells implicated in sustaining psoriatic lesions. In this randomized half-side comparison study, Legat et al demonstrate the synergistic effect of alefacept with narrowband UV-B therapy in the treatment of psoriasis.

See page 1016

Distance to Diagnosing Provider as a Measure of Access for Patients With Melanoma

Survival for patients with melanoma is dependent on stage at diagnosis, and early diagnosis may substantially improve patient outcomes. Because melanoma can only be diagnosed definitively based on biopsy findings, diagnosis requires detection of suspicious lesions and subsequent biopsy. Although some primary care providers perform diagnostic biopsies, many prefer to refer patients to dermatologists or surgeons. Thus early diagnosis is dependent on access to specialists comfortable with diagnosing melanoma. In this analysis of all incident cases of melanoma in 2000 from 42 North Carolina counties, Stitzenberg et al demonstrate that Breslow thickness at diagnosis was directly related to distance to diagnosing provider, increasing 0.6% for every 1-mile increase in distance away from diagnosing provider. Once barriers to melanoma care are identified, interventions can be developed to minimize the effect of travel distance on access to melanoma care.

See page 983

Skin Cancer Awareness and Sun Protection Behaviors in White Hispanic and White Non-Hispanic High School Students in Miami, Florida

Increasing incidence and delayed diagnosis of skin cancer in the rapidly growing Hispanic population in the United States represent an emerging health issue. While there are substantial data describing sun protection practices in white populations, data on awareness and risk perception in Hispanic populations are lacking. In this pilot survey study, Ma et al demonstrate that white Hispanic (WH) high school students were more likely to tan deeply than white non-Hispanic (WNH) students, and they were less likely to have heard of or been told how to perform skin self-examination. In additions, WH students were less likely to wear sun-protective clothing or sunscreens and were 2.5 times more likely than WNH students to have used a tanning bed. These disparities in knowledge, perceived risk, and sun-protective behaviors between WH and WNH students signal the need for primary and secondary prevention strategies directed toward Hispanic patients.

See page 1025
DISCUSSION ON RADIOTHERAPY BY THE CHICAGO
DERMATOLOGICAL SOCIETY.
INTRODUCTORY REMARKS.
By JOSEPH ZEISLER, M. D., Chicago.

The wave of enthusiasm which a few years ago had carried the X-rays to a point where they seemed to supersede all former and well-established modes of treatment in dermatological practice, seems now to have calmed down; and we may well ask the question which is the theme of our present discussion: have the X-rays and their co-geners kept their early promises, and, also, has radiotherapy been a real and lasting benefit to scientific dermatology?

***

Before concluding these brief remarks, I cannot suppress one thought which has often occurred to me. I have found that a great many physicians, without any dermatological training, and with a stupendous ignorance in the differential diagnosis of skin diseases, have had the boldness to undertake the treatment of all sorts of such cases, simply because they happened to possess an X-ray apparatus and knew in a general hear-say way that X-rays were often beneficial for skin diseases. This is in many ways a deplorable fact, and it has helped to create a class of would-be dermatologists who have no right to such a title. That therein lies also a danger to the material interests of legitimate dermatologists cannot be denied.

J Cutan Dis.
August 1907;25(8):346-349

Dear June:

I’m stymied. I’m afraid that all my comments on this month’s selection will offend someone. If I quote articles showing that general practitioners can’t touch dermatologists in diagnosing melanomas, I’ll upset the GPs. If I point out that nondermatologists overprescribe shotgun therapies, I’ll tick off all the nondermatologists and the makers of shotgun therapies! If I discuss how family practitioners and plastic surgeons don’t begin to approach dermatologists’ diagnostic accuracy of common diseases as determined by skin biopsies, I’ll probably upset the FP’s, plastics guys, and—for all I know—even the pathologists! I considered diffusing these criticisms by showing that our situation was not unique within medicine. For example, ophthalmologists were more cost-effective at monitoring patients with glaucoma than optometrists, and patients with heart failure did statistically better when treated by cardiologists than internists or family practitioners. This will probably only widen the potential pool of critics without placating anyone. I thought about a different tack and the historical punishments for poaching (50 different types were capital offenses under the English Black Act of 1723!), but our professional colleagues might take offense at being labeled poachers. I entertained discussing the International Code of Medical Ethics prohibition against enticing patients from a medical colleague, but realized that this was so quaintly antiquated that even I couldn’t get excited!

It would be cute to point out my local Yellow Pages carries 24 ads for laser hair removal, of which 11 are from nondermatologists, but I dare not piss off the phone company! I contemplated bringing up the $400 000 paid Dr Christiaan Barnard to shill for skin-care products, but that depressingly reminded me of all the stories I’ve lately heard about cardiothoracic surgeons giving up their practices to open medical spas: As I get older I worry more about who is going to keep me alive, not who’s going to make me prettier!

June, I think it might be best if we reprint verbatim the 1907 article as my editorial comment, merely changing each use of the term “X-ray” to “laser.”

If you have no objections,
I remain,
Yours,
Mark
Successful Treatment of Notalgia Paresthetica With Botulinum Toxin Type A

Pamela Kirschner Weinfield, MD; Division of Dermatology, Newton-Wellesley Hospital, Newton, Massachusetts

Notalgia paresthetica is a chronic condition that, while not life threatening, produces symptoms that are incessant and onerous to many patients. To date, there has been no effective, long-lasting, noninvasive treatment for this condition, which decreases the patient’s quality of life.

**REPORT OF CASES**

**CASE 1**

A 52-year-old white woman presented with a 2- to 4-year history of pruritus of her upper back, which she described as a 7 on a severity scale of 1 to 10. She reported scratching her back twice a day. She had tried moisturizers and topical corticosteroids with no improvement. She recalled that her father had had a similar itch on his back for years that induced him to repeatedly scratch his back on a doorpost. Her medical history was remarkable only for gastroesophageal reflux disease, which was responsive to ranitidine, and for rosacea, for which she used topical metronidazole. She had no drug allergies. On physical examination, there was a 4-cm hyperpigmented patch on her right mid to upper back. Her presentation was consistent with notalgia paresthetica.

**For editorial comment see page 1062**

**CASE 2**

A 39-year-old white woman presented with a 20-year history of pruritus of her upper back. She described the itch as a 5 on a severity scale of 1 to 10 and reported scratching her back on a doorpost 3 to 4 times a day. She also described an altered sensation in the area when it was touched. Previous treatments, including topical class I steroids, pramoxine hydrochloride cream, 1%, and doxepin hydrochloride cream, 1%, had provided only minimal temporary relief. On physical examination, there was a 4 × 4-cm hyperpigmented patch on her right mid to upper back. Her presentation was consistent with notalgia paresthetica.

**THERAPEUTIC CHALLENGE**

Common treatments for notalgia paresthetica that have provided variable relief to patients include local anesthetics, topical corticosteroids, and topical capsaicin; however, results with these treatments have been inconsistent at best.1 With capsaicin, many patients reported burning, tingling, and pain with treatment, and most patients experienced a relapse of symptoms within a month.2 Oxcarbazepine was reported to reduce the severity of symptoms in a few cases; however, these patients reported only an improvement in their symptoms but not resolution of them.3 One patient with a severe case of notalgia paresthetica was treated successfully with paravertebral nerve blocks, with bupivacaine and methylprednisolone acetate injected into the T3-T4 and T5-T6 intervertebral spaces.4 She remained symptom-free 1 year after treatment. To date, there is no effective, long-lasting, noninvasive treatment for patients with notalgia paresthetica.

**SOLUTION**

The patients described in this article were treated with intradermal injections of botulinum toxin type A using a method similar to that used for postherpetic neuralgia.5 Specifically, the area to be treated was demarcated based on questioning and physical examination. Injection points were marked 2 cm apart, and 4 U of botulinum toxin type A was injected superficially into each point, using a 3-mL dilution with preserved (0.9%) saline. The first patient was treated with a total of 16 U. She remains completely symptom free to date (more than 18 months following treatment), and the hyperpigmentation on her back is barely perceptible. The second patient was treated with 24 U and had a considerable improvement in symptoms after her first
treatment. Although prior to treatment she had been scratching her back on a doorpost 3 to 4 times every day, after 3 months she reported scratching her back only twice a day. After 18 months she reported that she was not even scratching her back every day; however, she still felt some intermittent pruritus. At that time, a second treatment of 48 U was given. Within a week she was symptom free and has remained so. The hyperpigmentation on her back decreased in size and color (Figure) but was still evident 1 month after the second treatment.

**COMMENT**

Notalgia paresthetica is a sensory neuropathy that can include symptoms of pruritus, tenderness, burning pain, and hyperalgesia. It is unilateral and usually occurs on the mid to upper back. There is often a hyperpigmented patch over the affected area. Other names for this condition have included puzzling posterior pigmented purpuric patches, hereditary localized pruritus, and puncta pruritica (itchy points). Patients often describe symptoms ranging from mild itching to severe, relentless itching that drives them to rub their backs on doorposts and walls when they cannot reach the area of skin to scratch. The cause of notalgia paresthetica is unknown. One study demonstrated an increase in the density of intradermal nerves in a biopsy sample of involved skin. Another study suggested that nerve root impingement may be causative because several patients had degenerative changes of the vertebrae corresponding with the affected dermatome. A genetic basis has been suggested. Treatment options to date have been unsatisfactory.

Botulinum toxin type A is a purified protein that inhibits acetylcholine release at the neuromuscular junction by cleaving SNAP-25 (synaptosomal-associated proteins of 25 kDa). This leads to paresis of muscle by chemical denervation or blocked glandular secretion of the exocrine glands. In the laboratory, botulinum toxin type A has also been found to affect several neurotransmitters involved in nociception. It has been found to inhibit release of substance P from cultured embryonic dorsal root ganglion neurons and to reduce stimulated release of calcitonin gene-related peptide from cultured trigeminal ganglia neurons. Substance P is released by primary nociceptive afferent C fibers, and calcitonin gene-related peptide colocalizes with substance P in most sensory ganglia neurons. Botulinum toxin type A was also found to suppress the release of glutamate and noradrenaline.

Although the mechanism of the effect of botulinum toxin type A on pain and itch signals in human beings has not been completely elucidated, botulinum toxin type A has been shown clinically to be effective for several pain syndromes, including postherpetic neuralgia and trigeminal neuralgia. It has also been reported to be effective for the pruritus of lichen simplex chronicus. For postherpetic neuralgia, injections of 2 to 5 U every 1 to 2 cm have been found to relieve patients' pain. Up to 4 sessions, 1 to 4 weeks apart, may be necessary to achieve complete pain relief. A similar technique has been used for the treatment of painful scars, such as sternotomy scars, and for treatment of reflex sympathetic dystrophy. For lichen simplex chronicus, 20 U was injected into each lesion.

Interestingly, although the muscle paresis and blocked glandular secretion induced by botulinum toxin type A wear off after 3 to 6 months, the effect of botulinum toxin type A injection on these pain syndromes seems to be long term. It has been hypothesized that botulinum toxin type A alters feedback loops leading to changes in pain signaling. This may also be true for the pruritus of lichen simplex chronicus, but follow-up beyond 4 months was not reported in the literature.

Patients who develop notalgia paresthetica often describe vexing and relentless symptoms that interfere with their daily lives. Given the lack of effectiveness of topical treatments and the invasiveness of paravertebral nerve block, injection of botulinum toxin type A has provided these patients with a comparatively safe and effective, as well as durable, treatment for their notalgia paresthetica. Given the duration of their symptom improvement—more than 18 months—further research should be conducted to confirm the effectiveness of this treatment.

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Financial Disclosure: None reported.

Figure. Case 2. A, Before second treatment with botulinum toxin type A. Note hyperpigmentation as well as erythema and recent scratch marks on her right mid upper back. B, One month after second treatment with botulinum toxin type A. Although there is some residual hyperpigmentation on the right mid upper back, the area of involvement is much smaller and somewhat faded. Erythema and scratch marks are absent.
Additional Contributions: Allergan Inc, Irvine, California, provided the botulinum toxin type A used in this study.

REFERENCES


Clinicians, residents, and fellows are invited to submit cases of challenges in management and therapeutics to this section. Cases should follow the established pattern. Manuscripts should be prepared double spaced with right margins nonjustified. Pages should be numbered consecutively with the title page separated from the text (see Instructions for Authors [http://archderm.ama-assn.org/misc/fora_dtl] for information about preparation of the title page). Clinical photographs, photomicrographs, and illustrations must be sharply focused and submitted as separate JPEG files with each file numbered with the figure number. Material must be accompanied by the required copyright transfer statement (see authorship form [http://archderm.ama-assn.org/misc/auinst_crit.pdf]). Preliminary inquiries regarding submissions for this feature may be submitted to George J. Hruza, MD (ghruza@aol.com). Manuscripts should be submitted via our online manuscript submission and review system (http://manuscripts.archdermatol.com).
Skin Cancer Awareness and Sun Protection Behaviors in White Hispanic and White Non-Hispanic High School Students in Miami, Florida

Fangchao Ma, MD, PhD; Fernando Collado-Mesa, MD; Shasa Hu, MD; Robert S. Kirsner, MD, PhD

Objective: To examine skin cancer awareness and behavior in white Hispanic (WH) and white non-Hispanic (WNH) high school students because increasing incidence and delayed diagnosis of skin cancer in the growing Hispanic population in the United States represent an emerging health issue.

Design: Pilot survey study.

Setting: A high school in Miami, Florida.

Participants: A total of 369 high school students (221 WHs and 148 WNHs) were surveyed in the study.

Main Outcome Measures: Survey data were collected regarding skin cancer knowledge, perceived risk, and sun protection behaviors. Differences between the 2 groups were compared with χ² tests.

Results: White Hispanic students were more likely to tan deeply (P = .04) but less likely to have heard of (P < .01) or been told how to perform (P < .01) skin self-examination. White Hispanics were less likely to wear sun-protective clothing or to use sunscreen with a sun protection factor of 15 or higher and reported a greater use of tanning beds. White Hispanic students also thought their chance of developing skin cancer was less than that of WNH students (P < .01), which remained significant after adjustment for age, sex, family history, and skin sensitivity to sun. After adjustment, WHs were 2.5 times more likely than WNHs to have used a tanning bed in the past year. White Hispanics were also 60% less likely to have heard of skin self-examination (P < .01) and 70% less likely than WNHs to have ever been told to perform the examination (P = .03). White Hispanics are about 1.8 and 2 times more likely to never or rarely wear protective clothing (P < .01) and to use sunscreen (P < .01), respectively.

Conclusion: There are disparities in knowledge, perceived risk of skin cancer, and sun-protective behaviors among WH and WNH high school students.

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Skin Cancer is the most common cancer in the United States, with the incidence of both melanoma and nonmelanoma skin cancers increasing at an alarming rate.¹ Excessive exposure to UV radiation in the form of sunlight is a major risk factor for melanoma and nonmelanoma skin cancers.² Children and adolescents receive the majority of their lifetime UV exposure before the age of 18 years.³ Childhood sun exposure is particularly important in melanoma development. For example, more than 1 severe sunburn in childhood is associated with a 2-fold increase in melanoma risk.⁴⁻⁶

For editorial comment see page 1058

Most studies that have evaluated the association of skin cancer with sun exposure patterns have focused on light-skinned whites, as their lighter constitutive pigmentation confers higher risk for skin cancer than other racial or ethnic groups. While Hispanics do have lower age-adjusted incidence rates for melanoma (4.3 compared with 20.8 per 100 000 among whites),⁷ the importance of Hispanics in the epidemiology of skin cancer remains, as they are the fastest growing minority group in the United States.⁸ The US Census Bureau reported 41 million Hispanics living in the United States in 2004, surpassing blacks as the second largest population. Both primary and secondary prevention efforts of melanoma may be needed in Hispanic populations. For example, the incidence of melanoma in Hispanics increased annually by 2.9% in the last 15 years.⁹ White Hispanics (WHs) with melanoma are more likely than white non-Hispanics (WNHs) to present with regional or distant-stage disease.⁹⁻¹² The latter data suggest that there are differences in knowledge and behavior related to the
prevention of skin cancer in WH and WNH populations; therefore, we hypothesize that these differences may exist in students and may be related to early acquisition of knowledge.

While there are substantial data for sun protection practice in white populations, data on awareness and perception of risk of skin cancer in WHs are sparse. One study in suburban employees in Illinois reported less awareness of melanoma and nonmelanoma skin cancer and perception of risk among Hispanics than among non-Hispanics. Only 1 study examined sunscreen use in white populations, data on awareness and perception of risk of skin cancer in WH and WNH students based on survey responses. If an expected number in any cell was less than 5, we used the Fisher exact test instead. We then performed multivariate logistic regression analysis to compare awareness, perception, and protective behaviors between the 2 ethnic student groups; age, sex, family history of skin cancer, and skin type were included in the multivariate logistic regression model. We used questions related to sensitivity to sun to classify students into 2 skin-type groups: sun sensitive and sun insensitive. The significance level was set at \( P \leq .05 \). All statistical analyses were performed with SAS software version 8 (SAS Institute Inc, Cary, North Carolina).

Based on the only other published study (to our knowledge) comparing awareness and perception of skin cancer risk and self skin-examination in WHs and WNHs, a total sample size of 216 (108 in each group) was needed to detect a 2-sided, \( P \leq .05 \) level of significance, with a study power of 80%.

### RESULTS

A total of 369 students participated in the survey. Of the 369 students, 221, or 60%, were WH and 148, or 40%, were WNH. These numbers represent 15% and 13% of the school’s WH and WNH students, respectively. The basic demographics and skin sensitivity to sunlight of these 2 groups are presented in Table 1. The WH students were slightly older than the WNH students (17.2 vs 16.5 years; \( P < .01 \)). Approximately 49% of WHs were male compared with 45% of WNHs (\( P = .42 \)). As expected, WHs were more likely than WNHs to have been born outside the United States (43% vs 10%; \( P < .01 \)). When exposed to strong sun in summer without protection, WNHs reported proportions of “some redness” and “deep red painful burn” that were similar to those of WHs (these responders were categorized as sun-sensitive skin type, while the other responders were categorized as sun-insensitive skin type). However, WHs were significantly more likely than WNHs (31%) to tan deeply (44%) (\( P = .04 \)).

Table 2 summarizes the awareness and perceived risk of skin cancer in WH and WNH students. Overall, time spent in the sun on weekdays or weekends was similar among WHs and WNHs. There was a trend toward sta-
tistical significance regarding the number of tanning booth/bed uses during the last year. The WH students reported a greater number of uses than the WNH students; they also tried to tan more frequently than WNHs. After adjustment for age, sex, skin type (sun sensitive or sun insensitive), and family history, WHs were 2.5 times more likely than WNHs to have used a tanning bed the past year (95% confidence interval, 1.1-5.6).

The proportion of students who considered exposure to sun to be the most important factor causing skin cancer was comparable among WHs and WNHs, with about three-quarters of both groups agreeing with this statement. More WNHs than WHs had heard of (37% vs 19%; P < .01) and been told how to perform skin self-examinations (11% vs 3%; P < .01). This difference remained significant after age, sex, sun sensitivity, and family history of skin cancer were controlled for, with WH students less likely both to have had heard of (P < .01) and to have been told how to perform (P = .03) skin self-examinations. The WNH students also reported a significantly higher proportion of having a close relative with a history of skin cancer than WH students (26% vs 11%; P < .01). When asked about the chances of developing skin cancer in the future, 19% and 4% of WHs considered their chances to be about average or higher than average, respectively, compared with 26% and 14% of WNHs (P < .01). After age, sex, sun sensitivity, and family history of skin cancer were adjusted for, WHs still believed their chances of developing skin cancer to be low compared with WNHs (P = .02).

The use of protective measures for skin cancer was also compared between WH and WNH students (Table 3). The 2 groups sought shade equally. However, WNHs were more likely than WHs to wear sun-protective clothing as well as sunscreen with a sun protection factor of 15 or higher: 18% of WNHs wore sun-protective clothing most of the time and 6% always wore sun-protective clothing compared with 9% and 3% of WHs, respectively.

---

Table 2. Awareness and Perceived Risk of Skin Cancer in White Hispanic and White Non-Hispanic High School Students in Miami, Floridaa

<table>
<thead>
<tr>
<th>Awareness</th>
<th>White Hispanics (n = 221)</th>
<th>White Non-Hispanics (n = 148)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Time usually spent in the sun (typical weekday)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 1 h</td>
<td>61 (41.8)</td>
<td>83 (38.1)</td>
<td>.48</td>
</tr>
<tr>
<td>≥ 1 h</td>
<td>85 (58.2)</td>
<td>135 (61.9)</td>
<td></td>
</tr>
<tr>
<td><strong>Time usually spent in the sun (typical weekend day)</strong></td>
<td></td>
<td></td>
<td>.99</td>
</tr>
<tr>
<td>&lt; 1 h</td>
<td>43 (19.6)</td>
<td>29 (19.6)</td>
<td></td>
</tr>
<tr>
<td>≥ 1 h</td>
<td>177 (80.4)</td>
<td>119 (80.4)</td>
<td></td>
</tr>
<tr>
<td><strong>Times used a tanning booth/bed during last year</strong></td>
<td></td>
<td></td>
<td>.06</td>
</tr>
<tr>
<td>Never</td>
<td>185 (84.9)</td>
<td>139 (93.9)</td>
<td></td>
</tr>
<tr>
<td>1-2 times</td>
<td>18 (8.2)</td>
<td>5 (3.4)</td>
<td></td>
</tr>
<tr>
<td>3-4 times</td>
<td>6 (2.8)</td>
<td>1 (0.7)</td>
<td></td>
</tr>
<tr>
<td>≥ 5 times</td>
<td>9 (4.1)</td>
<td>3 (2.0)</td>
<td></td>
</tr>
<tr>
<td><strong>Tries to get a tan</strong></td>
<td></td>
<td></td>
<td>.52</td>
</tr>
<tr>
<td>Never</td>
<td>59 (26.8)</td>
<td>46 (31.1)</td>
<td></td>
</tr>
<tr>
<td>Rarely or sometimes</td>
<td>130 (59.1)</td>
<td>86 (58.1)</td>
<td></td>
</tr>
<tr>
<td>Most of the time or always</td>
<td>31 (14.1)</td>
<td>16 (10.8)</td>
<td></td>
</tr>
<tr>
<td><strong>Considers exposure to sun rays to be the most important factor</strong></td>
<td></td>
<td></td>
<td>.88</td>
</tr>
<tr>
<td>that can cause skin cancer</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>163 (74.1)</td>
<td>108 (73.0)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>No</td>
<td>24 (10.9)</td>
<td>15 (10.1)</td>
<td></td>
</tr>
<tr>
<td>Do not know</td>
<td>33 (15.0)</td>
<td>25 (16.9)</td>
<td></td>
</tr>
<tr>
<td><strong>Ever heard of skin self-examination</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>41 (18.6)</td>
<td>55 (37.2)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>No</td>
<td>180 (81.4)</td>
<td>93 (62.8)</td>
<td></td>
</tr>
<tr>
<td><strong>Ever told how to perform skin self-examination</strong></td>
<td></td>
<td></td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Yes</td>
<td>7 (3.2)</td>
<td>16 (10.8)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>214 (96.8)</td>
<td>132 (89.1)</td>
<td></td>
</tr>
<tr>
<td><strong>Close relative had skin cancer</strong></td>
<td></td>
<td></td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Yes</td>
<td>24 (10.9)</td>
<td>38 (26.0)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>141 (63.8)</td>
<td>67 (45.9)</td>
<td></td>
</tr>
<tr>
<td>Do not know</td>
<td>56 (25.3)</td>
<td>41 (28.1)</td>
<td></td>
</tr>
<tr>
<td><strong>Perceived risk</strong></td>
<td></td>
<td></td>
<td>&lt;.01</td>
</tr>
<tr>
<td><strong>Chances of developing skin cancer in the future</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Higher than average</td>
<td>9 (4.1)</td>
<td>20 (13.5)</td>
<td></td>
</tr>
<tr>
<td>Average</td>
<td>42 (19.0)</td>
<td>39 (26.4)</td>
<td></td>
</tr>
<tr>
<td>Lower than average</td>
<td>114 (51.6)</td>
<td>62 (41.9)</td>
<td></td>
</tr>
<tr>
<td>Do not know</td>
<td>56 (25.3)</td>
<td>27 (18.2)</td>
<td></td>
</tr>
</tbody>
</table>

a Some columns may not add up to the total because of missing data.
In 2002, the Centers for Disease Control and Prevention set forth policy guidelines for skin cancer prevention in schools.17 The fast-growing Hispanic population includes school-aged children; therefore, closer examination of the epidemiology of skin cancer in this population is warranted. We investigated skin cancer awareness among WH and WNH students in a Miami-Dade County high school and found disparities in the perceived risk of skin cancer and sun-protective behaviors. The WH students were less aware of skin self-examination, and they perceived themselves to be at lower risk for skin cancer. They were also less likely to wear sun-protective clothing and sunscreen. These differences between WH and WNH students remained significant after age, sex, sun sensitivity, and family history of skin cancer were controlled for (Table 4).

A few limitations of the study should be noted. This survey was completed at a Miami-Dade County high school because of the school’s racial and ethnic diversity. The school is located in a middle-class neighborhood. The use of a single school in this pilot study and the limited sample size suggest that these findings should be generalized with caution. We used the term Hispanic, which is considered an ethnicity by the US Census Bureau, to identify persons who indicate that their origin is from a Spanish-speaking country. Hispanic refers to persons whose origin is Mexican, Puerto Rican, Cuban, South or Central American, or other Hispanic/Latino, regardless of race. As Hispanic persons can be further described by race, it is critical to stratify risk based on skin type and analyze the results after controlling for skin type, as in the present study.18 Similar to US Census data gathering on race/ethnicity information, our survey lacked a standardized definition of WHs; however, to our knowledge, self-report of Hispanic ethnicity in school-aged children has not been previously studied. The self-reported information on sun exposure and sun protection is likely reliable, as a previous study that examined the solar protection reported by adolescents and by parents or guardians suggested that adolescents’ self-reporting of solar protection was relatively valid.19 Finally, while most of the questions asked were from a validated questionnaire, we attempted to minimize bias in the rest of the survey by asking questions with objective and clear answer choices.

In our study, we controlled for differences in skin sensitivity to sun in 2 groups with variably constitutive pigmentation and response to sun exposure and found that WH and WNH students reported little differences in sun burning when exposed to the strong sun in summer but

### Table 3. Use of Protective Measures Against Skin Cancer Among White Hispanic and White Non-Hispanic High School Students in Miami, Florida

<table>
<thead>
<tr>
<th>Action</th>
<th>White Hispanics (n=221)</th>
<th>White Non-Hispanics (n=148)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seeks shade</td>
<td></td>
<td></td>
<td>.32</td>
</tr>
<tr>
<td>Never</td>
<td>15 (6.9)</td>
<td>11 (7.4)</td>
<td></td>
</tr>
<tr>
<td>Rarely</td>
<td>51 (23.3)</td>
<td>33 (22.3)</td>
<td></td>
</tr>
<tr>
<td>Sometimes</td>
<td>101 (46.1)</td>
<td>64 (43.2)</td>
<td></td>
</tr>
<tr>
<td>Most of the times</td>
<td>40 (18.3)</td>
<td>37 (25.0)</td>
<td></td>
</tr>
<tr>
<td>Always</td>
<td>12 (5.5)</td>
<td>3 (2.0)</td>
<td></td>
</tr>
<tr>
<td>Wears sun-protective clothing</td>
<td></td>
<td></td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Never</td>
<td>55 (24.9)</td>
<td>19 (12.9)</td>
<td></td>
</tr>
<tr>
<td>Rarely</td>
<td>71 (32.1)</td>
<td>42 (28.6)</td>
<td></td>
</tr>
<tr>
<td>Sometimes</td>
<td>69 (31.2)</td>
<td>50 (34.0)</td>
<td></td>
</tr>
<tr>
<td>Most of the times</td>
<td>20 (9.1)</td>
<td>27 (18.4)</td>
<td></td>
</tr>
<tr>
<td>Always</td>
<td>6 (2.7)</td>
<td>9 (6.1)</td>
<td></td>
</tr>
<tr>
<td>Wears sunscreen with SPF ≥ 15</td>
<td></td>
<td></td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Never</td>
<td>72 (32.6)</td>
<td>21 (14.2)</td>
<td></td>
</tr>
<tr>
<td>Rarely</td>
<td>88 (39.8)</td>
<td>58 (39.2)</td>
<td></td>
</tr>
<tr>
<td>Sometimes</td>
<td>40 (18.1)</td>
<td>42 (28.4)</td>
<td></td>
</tr>
<tr>
<td>Most of the times</td>
<td>17 (7.7)</td>
<td>15 (10.1)</td>
<td></td>
</tr>
<tr>
<td>Always</td>
<td>4 (1.8)</td>
<td>12 (8.1)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: SPF, sun protection factor.

### Table 4. Awareness and Perceived Risk of Skin Cancer in White Hispanic and White Non-Hispanic High School Students in Miami, Florida: Results of Multivariate Logistic Regression

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>White Hispanics vs White Non-Hispanics, OR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Awareness</td>
<td>Time usually spent in the sun in a typical weekday (1 h or more)</td>
<td>0.9 (0.6-1.5)</td>
</tr>
<tr>
<td></td>
<td>Time usually spent in the sun in a typical weekend day (1 h or more)</td>
<td>0.9 (0.5-1.7)</td>
</tr>
<tr>
<td></td>
<td>Used a tanning booth/bed during last year (at least once)</td>
<td>2.5 (1.1-5.6)</td>
</tr>
<tr>
<td></td>
<td>Tried to get a tan (yes)</td>
<td>1.4 (0.9-2.4)</td>
</tr>
<tr>
<td></td>
<td>Considers exposure to sun rays to be the most important factor that can cause skin cancer (yes)</td>
<td>0.9 (0.5-1.6)</td>
</tr>
<tr>
<td></td>
<td>Ever heard of skin self-examination (yes)</td>
<td>0.4 (0.2-0.7)</td>
</tr>
<tr>
<td></td>
<td>Ever told of how to perform skin self-examination (yes)</td>
<td>0.3 (0.1-0.9)</td>
</tr>
<tr>
<td>Perceived risk</td>
<td>Chances of developing skin cancer in the future (average or above)</td>
<td>0.6 (0.3-0.9)</td>
</tr>
<tr>
<td></td>
<td>Seeks shade (never or rarely)</td>
<td>0.9 (0.6-1.5)</td>
</tr>
<tr>
<td></td>
<td>Wears sun-protective clothing (never or rarely)</td>
<td>1.8 (1.2-2.9)</td>
</tr>
<tr>
<td></td>
<td>Wears sunscreen with SPF ≥ 15 (never or rarely)</td>
<td>2.0 (1.3-3.2)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; OR, odds ratio; SPF, sun protection factor.

*Adjusted for age, sex, skin type, and family history of skin cancer.*
did report differences in tanning. While there was no difference in time spent in the sun between the 2 groups, we did control for sun sensitivity in logistic regression analysis, and among the significant findings, we found that WH students were 2.5 times more likely than WNH students to have used a tanning bed.

Consistent with findings from a previous survey in Hispanic adults,13 we found that WHs perceived themselves to be at lower risk for skin cancer, knew less, and were less likely to have been taught about skin self-examination than their WNH peers. This difference remained significant after differences in age, sex, skin sensitivity, and family history of skin cancers were controlled for, which suggests that even among WH and WNH students of similar skin type and family history (and presumably similar risk profile for skin cancer), WH students were less knowledgeable about skin cancer. Although there is no formal recommendation or guidelines on performing self-skin-examination in adolescents, knowledge about skin self-examination was included in the survey as an additional parameter to measure adolescents’ awareness about skin cancer prevention. Skin self-examination in adolescents may be valuable as an additional step in secondary prevention in high-risk young individuals. Data show that the rate of increase in melanoma incidence in children and young adults (age, <20 years) was 2.8% per year from 1981 to 2001, which is comparable to the rate of increase in adults.20 According to Robinson et al,21 people gain most of their skin cancer information through multimedia sources in the United States, with messages defining high-risk populations as those with fair skin, those who burn easily, and those who participate in outdoor or recreational sun exposure. One possible explanation for the difference in skin cancer knowledge is that WNH students may have received more skin cancer–related information, including skin self-examination, through family members, as they reported having a significantly higher number of close relatives with a history of skin cancer (26% of WHN students vs 11% of WH students). Studies have shown that teenagers who practice skin cancer prevention tend to be those with a family or friend with skin cancer; however, even those teenagers tend to use sunscreen infrequently, inconsistently, and incorrectly.22,23 However, in our study, the difference in skin cancer knowledge between WHs and WNHs remained significant after adjustment for family history of skin cancer. Therefore, it is possible that an overall lack of public education on skin cancer risk in minority populations may be contributing to the differences observed between WHs and WNHs.

We found that 10% of WH and 18% of WNH high school students frequently (most of the time or always) used sunscreen with a sun protection factor of 15 or higher. Although these rates are similar to those previously reported among Hispanic (11%) and white (17%) high school students in the United States,24 they are relatively low compared with those reported for young persons (age, >12 years) in Canada (68%)25 and Australia (73% of females and 54% of males).23 Considering the warm weather and year-round sun exposure in southern Florida, we would have expected a higher rate of sunscreen use. Experts recommend the use of sunscreen, as well as other sun-protective measures (eg, wearing protective clothing, wearing wide-brimmed hats, and avoiding the sun), to protect persons from sun exposure.14 Sunscreen use has been shown to be effective in preventing sunburn. Recent epidemiological studies also suggest that sunscreen use can prevent squamous cell carcinoma26 and reduce the number of acquired nevi that are associated with sun exposure as a risk marker for melanoma.27

Our survey indicated that a significantly lower proportion of WHs than WNHs wore sun-protective clothing or used sunscreen with a sun protection factor of 15 or higher, regardless of skin sensitivity to sun. Such gaps indicate that there is a need to include WH students in skin cancer prevention programs targeting young persons. While WHs generally have a lower incidence of melanoma than WNHs,7 we recently reported that increased UV radiation exposure is associated with increasing melanoma incidence in persons with darker constitutive pigmentation (including Hispanics).28 This finding, combined with the increasing number of Hispanics in the United States, supports the rationale for recommending primary melanoma prevention (ie, sun protection) in darker-skinned populations. Further studies are needed to determine whether WH and WNH students improve to a similar degree after formal education regarding skin cancer, and such studies are currently under way. Finally, our findings of significant differences in skin self-examination are important given recent reports of later-stage melanoma diagnosis in WHs compared with WNHs.9 This suggests a need for further research and possible intervention.

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Correspondence: Robert S. Kirsner, MD, PhD, Department of Dermatology, University of Miami, 1201 NW 16th St, Miami, FL 33125 (Rkirsner@med.miami.edu).

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

Financial Disclosure: None reported.

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REFERENCES

Distance to Diagnosing Provider as a Measure of Access for Patients With Melanoma

Karyn B. Stitzenberg, MD, MPH; Nancy E. Thomas, MD, PhD; Kathleen Dalton, PhD; Sarah E. Brier, BS; David W. Ollila, MD; Marianne Berwick, PhD; Dianne Mattingly, RN; Robert C. Millikan, DVM, PhD

Objective: To examine the effect of travel distance and other sociodemographic factors on access to a diagnosing provider for patients with melanoma.

Design: Analysis was performed of all incident cases of melanoma in 2000 from 42 North Carolina counties.

Setting: Academic research.

Participants: Patients and providers from 42 North Carolina counties were geocoded to street address.

Main Outcome Measures: Associations between Breslow thickness and clinical and sociodemographic factors (age, sex, poverty rate, rurality, provider supply, and distance to diagnosing provider) were examined.

Results: Of 643 eligible cases, 4.4% were excluded because of missing data. The median Breslow thickness was 0.6 mm (range, 0.1-20.0 mm). The median distance to diagnosing provider was 8 miles (range, 0-386 miles). For each 1-mile increase in distance, Breslow thickness increased by 0.6% (P = .003). For each 1% increase in poverty rate, Breslow thickness increased by 1% (P = .04). Breslow thickness was 19% greater for patients aged 51 to 80 years than for those aged 0 to 50 years (P = .02) and was 109% greater for patients older than 80 years than for those aged 0 to 50 years (P < .001). Sex, rurality, and supply of dermatologists were not associated with Breslow thickness.

Conclusions: For patients with melanoma, distance to the diagnosing provider is a meaningful measure of access that captures different information than community-level measures of rurality, provider supply, and socioeconomic status. Future work should be targeted at identifying factors that may affect distance to diagnosing provider and serve as barriers to melanoma care.

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have had mixed results. We hypothesize that for patients with melanoma greater distance to a diagnosing provider is associated with increased Breslow thickness or stage at diagnosis.

### METHODS

Genes, Environment, and Melanoma is an international study that used a multisite population-based ascertainment to examine causative factors associated with melanoma. The North Carolina (NC) ascertainment included all incident cases of invasive cutaneous melanoma in 2000 from a 42-county area. Eligible cases were identified for the Genes, Environment, and Melanoma study through collaboration with the NC Central Cancer Registry. This registry collects data on all incident cases of invasive melanoma among NC residents through mandatory reporting. State law allows use of deidentified data for approved research. Hospitals are the primary sources of data, but these data are supplemented with data from private physicians, pathology laboratories, and death certificates. The registry obtains additional clinical information through direct review of original medical records. For the Genes, Environment, and Melanoma study, all dermatologists in the 42 counties were notified of the study, were encouraged to report cases of melanoma to the registry, and were asked where their histopathology specimens were processed. With separate institutional review board approval, the NC study population was used for our study.

### RESULTS

There were 643 patients with at least 1 incident invasive cutaneous melanoma in the 42-county NC ascertainment area in 2000. Twenty-eight cases (4.4%) were excluded because of missing Breslow thickness or street address information; this included patients diagnosed as having metastatic melanoma for whom no primary tumor was identified. Clinical and sociodemographic characteristics of the remaining 615 patients are given in Table 1.

Two hundred seventy-seven distinct diagnosing providers were identified. Only 15 providers diagnosed the melanomas in at least 1% (range, 0.2%-2.9%) of pa-

---

**Table 1. Clinical and Sociodemographic Characteristics of the Study Population**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No.</th>
<th>Median (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breslow thickness, mm</td>
<td>615</td>
<td>0.6 (0.1-20.0)</td>
</tr>
<tr>
<td>Distance to diagnosing provider, miles</td>
<td>615</td>
<td>8 (0-386)</td>
</tr>
<tr>
<td>Age, y</td>
<td>614</td>
<td>65 (10-97)</td>
</tr>
<tr>
<td>Census tract poverty rate</td>
<td>615</td>
<td>8.1 (0.7-42.9)</td>
</tr>
<tr>
<td>Dermatologists in county, No.</td>
<td>615</td>
<td>6 (0-30)</td>
</tr>
<tr>
<td>Density of dermatologists in county, No. per 100,000 population</td>
<td>615</td>
<td>4.3 (0-19.5)</td>
</tr>
<tr>
<td>T classification</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>426</td>
<td>69.3</td>
</tr>
<tr>
<td>2</td>
<td>116</td>
<td>18.9</td>
</tr>
<tr>
<td>3</td>
<td>45</td>
<td>7.3</td>
</tr>
<tr>
<td>4</td>
<td>28</td>
<td>4.5</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>333</td>
<td>54.1</td>
</tr>
<tr>
<td>Female</td>
<td>282</td>
<td>45.9</td>
</tr>
<tr>
<td>Rurality</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metropolitan</td>
<td>478</td>
<td>77.7</td>
</tr>
<tr>
<td>Rural</td>
<td>137</td>
<td>22.3</td>
</tr>
<tr>
<td>Dermatologists in county</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>530</td>
<td>86.2</td>
</tr>
<tr>
<td>Absent</td>
<td>85</td>
<td>13.8</td>
</tr>
<tr>
<td>Primary tumor site</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Head or neck</td>
<td>121</td>
<td>20.3</td>
</tr>
<tr>
<td>Trunk</td>
<td>263</td>
<td>44.0</td>
</tr>
<tr>
<td>Upper extremity</td>
<td>116</td>
<td>19.4</td>
</tr>
<tr>
<td>Lower extremity</td>
<td>97</td>
<td>16.3</td>
</tr>
<tr>
<td>Specialty of diagnosing provider</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dermatologist</td>
<td>373</td>
<td>63.2</td>
</tr>
<tr>
<td>Surgeon</td>
<td>171</td>
<td>29.0</td>
</tr>
<tr>
<td>Other</td>
<td>46</td>
<td>7.8</td>
</tr>
</tbody>
</table>

Note: Data are given as percentages unless otherwise indicated. The total number of participants varies because of missing data.
All cases were diagnosed by providers in NC. Ninety-nine percent of patients traveled less than 120 miles to reach their diagnosing providers; the remaining 1% traveled between 233 and 386 miles. Patients were mapped to street address, and distance to diagnosing provider was visually examined (Figure 1). Although most patients who traveled long distances were from the same region, their melanomas were diagnosed by different providers at different institutions, and no pattern could be identified. Within a given region, there was substantial variability in distance, with some patients traveling short distances to reach their diagnosing providers and other patients traveling much longer distances.

In the bivariate analysis, Breslow thickness was statistically significantly associated with distance to diagnosing provider (Table 2). For distances not exceeding 120 miles, each 1-mile increase in distance increased Breslow thickness by 0.6% (P=.003). In other words, each 10-mile increase in distance corresponded with a 6% increase in Breslow thickness. After dichotomizing distance at 15 miles (75th percentile), patients who traveled more than 15 miles had 20% thicker tumors on average than patients who traveled 0 to 15 miles (P=.02).

Consistent with historical evidence,28-32 Breslow thickness was associated with age at diagnosis (Table 2). The relationship between age at diagnosis and Breslow thickness was nonlinear, so age was categorized as 0 to 50 years (245 cases), 51 to 80 years (329 cases), or older than 80 years (93 cases). In the bivariate analysis, patients aged 51 to 80 years averaged 19% thicker tumors than patients aged 0 to 50 years (P=.02), and patients older than 80 years averaged 109% thicker tumors than patients aged 0 to 50 years (P=.001). Sex and primary tumor site were unassociated with Breslow thickness (P>.05).

Poverty rate was statistically significantly associated with Breslow thickness in the bivariate analysis; for every 1% increase in census tract poverty rate, Breslow thickness also increased by 1% (P=.04). No association between Breslow thickness and rurality could be identified using the Office of Management and Budget or US Department of Agriculture classifications (P>.05). However, when patients were stratified as rural vs metropolitan, the effect of distance to diagnosing provider on Breslow thickness seemed greater for cases from rural areas compared with cases from metropolitan areas. Every 10-mile increase in distance corresponded with a 10% increase in Breslow thickness (P=.06) for cases from rural counties compared with a 5% increase in Breslow thickness (P=.03) for cases from metropolitan counties.

The median Breslow thickness for cases diagnosed by dermatologists (0.5 mm) was statistically significantly less than the median Breslow thickness for cases diagnosed by surgeons (1.04 mm) or by other providers (0.62 mm) (P<.001). When the supply of dermatologists was examined using the density of dermatologists per 100,000 residents in the county, there was no association between Breslow thickness and dermatologist supply (P>.05). Similarly, there was no association between the dichotomous dermatologist present or absent variable and Breslow thickness (P>.05). However, using the absolute number of dermatologists, Breslow thickness decreased by 0.9% for every additional dermatologist in the county (P=.004).

There was no statistically significant correlation between any of the sociodemographic factors (distance, poverty, rurality, and dermatologist supply), so all were included in the multivariate analysis. Because provider specialty cannot directly affect Breslow thickness, provider specialty was not included in the multivariate model. After adjusting for other factors, only age and distance to diagnosing provider were statistically significantly associated with Breslow thickness (Table 2). Because estimates of some variables can be unstable when the number of variables in the model is high relative to the number of observations, the final model did not include gender, rurality, and primary tumor site. Despite removal of these statistically nonsignificant variables, poverty rate and ab-
The number of dermatologists were not statistically significantly associated with Breslow thickness. Age remained statistically significantly associated with Breslow thickness in the multivariate analysis: patients aged 51 to 80 years had 16% thicker tumors than patients aged 0 to 50 years (P = .04), and patients older than 80 years had 108% thicker tumors than patients aged 0 to 50 years (P < .001). Similarly, distance to diagnosing provider was statistically significant with each 10-mile increase in distance associated with a 6% increase in Breslow thickness (P = .009). Even when the analysis was limited to tumors less than 2.0-mm thick, Breslow thickness increased by 5% for every 10-mile increase in distance (P = .002).

Further exploration was performed to identify predictors of distance to diagnosing provider. Age, sex, and primary tumor site were unassociated with distance to diagnosing provider (P > .05) (Table 3). Although there was a statistically significant difference in distance traveled according to the specialty of the provider, the difference was too small to be clinically relevant: compared with patients whose melanomas were diagnosed by dermatologists, patients whose melanomas were diagnosed by surgeons traveled on average 1.3 miles farther (P = .03). The difference in distance to diagnosing provider between patients whose melanomas were diagnosed by dermatologists and those whose melanomas were diagnosed by nonsurgeon and nondermatologist providers was not statistically significant. The difference in distance to diagnosing provider based on poverty rate was also too small to be clinically relevant: for every 1% increase in poverty rate, distance decreased by 0.1 miles (P = .01).

Patients from rural counties traveled a modest 2.4 miles farther on average than patients from metropolitan counties (P = .001). Using the US Department of Agriculture classifications, distance to diagnosing provider was in-

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**Table 2. Predictors of Breslow Thickness at Diagnosis**

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Bivariate</th>
<th>Multivariate, All Variables (n = 596)</th>
<th>Multivariate, Final Model (n = 614)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distance traveled, 0-12 miles, continuous</td>
<td>0.6 (0.2 to 1.1)²</td>
<td>0.5 (0.1 to 1.0)²</td>
<td>0.6 (0.1 to 1.0)²</td>
</tr>
<tr>
<td>Distance traveled, 120-386 miles, continuous</td>
<td>-1.20 (-2.20 to -0.04)²</td>
<td>-1.10 (-2.10 to -0.03c)²</td>
<td>-1.10 (-2.10 to -0.06)²</td>
</tr>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-50</td>
<td>1 [Reference]</td>
<td>1 [Reference]</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>51-80</td>
<td>19.2 (3.4 to 37.3)c²</td>
<td>14.0 (-1.9 to 32.4)²</td>
<td>16.3 (0.9 to 34.1)c²</td>
</tr>
<tr>
<td>&gt;80</td>
<td>108.9 (57.4 to 177.2)d²</td>
<td>101.7 (49.9 to 171.3)d²</td>
<td>102.7 (53.0 to 168.5)d²</td>
</tr>
<tr>
<td>Census tract poverty rate, continuous</td>
<td>1.00 (0.06 to 2.00)c²</td>
<td>0.3 (-0.7 to 1.3)²</td>
<td>0.6 (-0.4 to 1.6)²</td>
</tr>
<tr>
<td>Dermatologists in county, continuous</td>
<td>-0.9 (-1.5 to -0.3)b²</td>
<td>-0.70 (-1.40 to 0.02)²</td>
<td>-0.5 (-1.1 to 0.1)²</td>
</tr>
<tr>
<td>Head or neck</td>
<td>17.7 (-2.4 to 42.0)²</td>
<td>4.8 (-13.5 to 27.0)²</td>
<td></td>
</tr>
<tr>
<td>Trunk</td>
<td>1 [Reference]</td>
<td>1 [Reference]</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>Upper extremity</td>
<td>6.1 (-12.3 to 28.3)²</td>
<td>3.1 (-14.9 to 24.9)²</td>
<td></td>
</tr>
<tr>
<td>Lower extremity</td>
<td>10.8 (-9.5 to 35.7)²</td>
<td>10.1 (-10.5 to 35.3)²</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>1 [Reference]</td>
<td>1 [Reference]</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>Male</td>
<td>6.5 (-7.3 to 22.3)²</td>
<td>7.6 (-7.0 to 24.4)²</td>
<td></td>
</tr>
<tr>
<td>Rurality</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metropolitan</td>
<td>1 [Reference]</td>
<td>1 [Reference]</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>Rural</td>
<td>5.1 (-11.0 to 24.1)²</td>
<td>-8.7 (-24.3 to 10.2)²</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: Ellipses, not applicable.

²Results are given as the percentage change in Breslow thickness associated with a 1-U change in the independent variable. For patient characteristics that are captured as dichotomous variables (categorical variables), the percentage change in tumor thickness compared with the reference category was calculated by subtracting 1 from the exponent of the β coefficient (e^β−1).

³P ≤ .01.

²P < .05.

¼P ≤ .001.

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Figure 2. Bivariate relationship between Breslow thickness and distance traveled to diagnosing provider. The natural log of Breslow thickness is plotted against the distance traveled for a given case. The line represents the lowess, a locally weighted regression of the natural log of Breslow thickness on distance traveled. The bandwidth for the regression is 0.8. The 1% of outlier patients who traveled more than 120 miles were excluded.
versely related to the size of the town-dwelling population of the county (Table 3). Compared with patients from metropolitan areas, patients from rural areas were also older (mean age, 58.2 vs 53.7 years, \( P = .007 \)) and were more likely to live in poverty (12.3% vs 9.1%, \( P < .001 \)). There were no statistically significant differences in patient sex or provider specialty between cases from rural areas and those from metropolitan areas.

Patients from counties with at least 1 dermatologist traveled on average 8.3 miles less than patients from counties with no dermatologist (\( P < .001 \)). This association was independent of the specialty of the actual diagnosing physician. In other words, the presence of a dermatologist resulted in a shorter mean distance, even for patients whose melanomas were not actually diagnosed by a dermatologist, suggesting that the presence of a dermatologist does not directly affect distance to diagnosing provider but rather is a marker of an increased supply of local health care resources. To further explore this idea, the dermatologist variable was replaced with other measures of physician supply (number of primary care physicians, number of non–primary care physicians, and total number of physicians). Because they were correlated, only 1 provider supply variable was included in the model at a time. The relationships between each variable and distance to diagnosing provider were similar and substantial, and the magnitudes of the effects of the other coefficients in the model were stable regardless of which measure of provider supply was used.

### COMMENT

Findings from previous studies\(^1,18-22\) suggest that socioeconomic status, and physician supply may affect stage at diagnosis and prognosis for patients with melanoma. MacKie and Hole\(^18\) examined the medical records of 3142 patients diagnosed as having melanoma in Scotland between 1979 and 1993. They found that patients from the most affluent areas were consistently more likely than those from the least affluent areas to be diagnosed as having a melanoma less than 1.5 mm thick. In addition, patients from the least affluent areas had a higher mortality to incidence ratio for patients from lower socioeconomic status areas compared with those from more affluent areas (0.33 vs 0.27, \( P < .05 \)), and patients from lower socioeconomic status areas were more likely to have distant or regional metastases at diagnosis (rate ratio, 1.64, 95% confidence interval, 1.20-2.25). Investigations of incident melanoma cases in Florida in 1994 examined physician supply and rurality, as well as socioeconomic status and education.\(^20-22\) Using area-based measures of each factor, investigators found that advanced-stage disease, defined by distant or regional metastases, was associated with education and physician supply but not with socioeconomic status or rurality.

To our knowledge, this study is the first to examine distance to diagnosing provider and area-based sociodemographic measures. Breslow thickness at diagnosis was directly related to distance to diagnosing provider, but there were no statistically significant associations between poverty rate, rurality, or provider supply and Breslow thickness. It is possible that associations existed but were too small to detect in a study of this size. However, the differences between our findings and those of previous investigators\(^18,19\) might also be attributed to the inclusion of potential confounders such as patient age and travel distance.

### Table 3. Predictors of Distance to Diagnosing Provider

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Bivariate Change (95% Confidence Interval)</th>
<th>Multivariate Change (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, continuous</td>
<td>-0.007 (-0.040 to 0.003)</td>
<td>-0.020 (-0.050 to 0.008)</td>
</tr>
<tr>
<td>Census tract poverty rate, continuous</td>
<td>-0.005 (-0.010 to 0.000)</td>
<td>-0.005 (-0.015 to 0.005)</td>
</tr>
<tr>
<td>Dermatologists in county, present or absent</td>
<td>-10.44 (-11.92 to -8.96)</td>
<td>-8.27 (-9.95 to -6.59)</td>
</tr>
<tr>
<td>Primary tumor site</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Head or neck</td>
<td>0.10 (0.56 to 1.76)</td>
<td>0.64 (-0.83 to 2.11)</td>
</tr>
<tr>
<td>Trunk</td>
<td>1 [Reference]</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>Upper extremity</td>
<td>-0.28 (-1.97 to 1.40)</td>
<td>-0.37 (-1.84 to 1.11)</td>
</tr>
<tr>
<td>Lower extremity</td>
<td>-0.07 (-1.87 to 1.73)</td>
<td>-0.16 (-1.74 to 1.42)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>1 [Reference]</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>Male</td>
<td>0.48 (0.73 to 1.69)</td>
<td>0.13 (-1.26 to 0.99)</td>
</tr>
<tr>
<td>Rurality(^d)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;2500 Nonmetropolitan</td>
<td>15.87</td>
<td>8.94</td>
</tr>
<tr>
<td>2500-20 000 Nonmetropolitan</td>
<td>18.64</td>
<td>14.38</td>
</tr>
<tr>
<td>&gt;20 000 Nonmetropolitan</td>
<td>5.68</td>
<td>3.25</td>
</tr>
<tr>
<td>&lt;2500 000 Metropolitan</td>
<td>2.07</td>
<td>1.87</td>
</tr>
<tr>
<td>250 000-1 000 000 Metropolitan</td>
<td>3.16</td>
<td>2.49</td>
</tr>
<tr>
<td>&gt;1 000 000 Metropolitan</td>
<td>-0.08 to 6.40</td>
<td>-0.92 to 5.51</td>
</tr>
<tr>
<td>Specialty of diagnosing provider</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dermatologist</td>
<td>1 [Reference]</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>Surgeon</td>
<td>1.45</td>
<td>1.29</td>
</tr>
<tr>
<td>Other</td>
<td>-2.88 (-13.24 to 7.49)</td>
<td>-2.43 (-11.46 to 6.60)</td>
</tr>
</tbody>
</table>

\( a \)Results are given as the absolute change in distance in miles associated with a 1-U change in the independent variable. For dichotomous variables, this is the absolute change in distance in miles compared with the reference category. The specialty of the diagnosing provider was unavailable for one case that has been included in the analysis.

\( b \)\( P < .05 \).

\( c \)\( P < .001 \).

\( d \)Rurality based on US Department of Agriculture Rural Urban Classification Codes. Numbers represent the size of the town-dwelling population of the county. Nonmetropolitan counties do not contain or are not part of a metropolitan area. Metropolitan counties contain or are part of a metropolitan area.

\( e \)\( P < .01 \).
Little is known about the relationship between distance to diagnosing provider and stage at diagnosis for patients with cancer. Rushton et al.\textsuperscript{33} examined distance to diagnosing provider and stage at diagnosis for patients with cancer. They found that patients who traveled longer distances were more likely to be diagnosed as having late-stage disease. In our study, Breslow thickness increased 0.6% for every 1-mile increase in distance to diagnosing provider. Consequently, a 10- to 15-mile increase in distance could explain a clinically relevant difference in Breslow thickness. The relationship between distance to diagnosing provider and Breslow thickness was linear for all travel distances except the most extreme: Breslow thickness began to decline for the 1% of patients who traveled more than 120 miles. These cases may represent statistical outliers, or they may be systematically different from the remainder of the population. Studies\textsuperscript{35,24}\textsuperscript{35} have shown a protective benefit for patients who travel long distances; it is theorized that these cases represent the most empowered patients, who are not hindered by barriers such as travel distance.

Investigations addressing travel distance often examine distance to the nearest provider, which is by definition a proxy for geographic isolation.\textsuperscript{17} We found that many patients bypassed local providers on their way to the actual diagnosing provider (Figure 1). Consequently, we know that distance to diagnosing provider captures more than just distance to the nearest provider. Of the factors examined, the greatest predictor of distance to diagnosing provider was the supply of providers in the county. Still, only a few clinical and sociodemographic factors could be explored using our data set. It is likely that many other factors influence distance to diagnosing provider. Most important, the role of the referring provider and the effect of health insurance could not be explored. The conceptual model shown in Figure 3 includes some of the factors that may ultimately affect the “choice” of diagnosing provider. Further work is needed to delineate which factors most directly affect distance, and consequently access, to the diagnosing physician.

**STUDY LIMITATIONS**

Euclidian distance was used for this study. Although not as precise as road distance, Euclidian distance has been shown to be a meaningful measure of travel distance for geographic areas without major topographical barriers.\textsuperscript{28} Our study was limited by the chosen ascertainment area of the Genes, Environment, and Melanoma study. Although many rural counties were included, some mountain and coastal areas of the state were not included. These excluded areas contain substantial topographical barriers, including mountains and waterways. While this limits generalizability of our results, it is reasonable to infer that any disparity identified based on rurality or distance to diagnosing provider would only be magnified if more geographically isolated areas were included.

Referral bias can confound attempts to examine the effect of distance to diagnosing provider. For tumors in which the size is apparent before a diagnosis is confirmed, large tumors may be preferentially referred to high-volume centers. Because Breslow thickness cannot be accurately determined without a biopsy specimen,\textsuperscript{34} this referral bias could contribute to the differences in the mean thickness between melanomas diagnosed by dermatologists and those diagnosed by surgeons. However, patients whose melanomas were diagnosed by surgeons traveled on average only 1.3 miles farther than patients whose melanomas were diagnosed by dermatologists. Consequently, preferential referral of worrisome lesions to surgeons alone cannot explain the relationship between Breslow thickness and travel distance. Further support for the
limited role of referral bias is provided by the fact that fewer than 5% of patients had tumors greater than 4.0 mm thick, and the relationship between distance and Breslow thickness was constant even when cases with tumors greater than 2.0 mm thick were excluded from analysis.

Information on the interval between initial patient encounter and diagnostic biopsy was unavailable for this study. The relationship between distance traveled and delay in diagnosis should be addressed in future studies. It is likely that time to diagnosis and travel distance are intermediate outcome measures that capture similar information about access to care.

CONCLUSIONS

For this population, distance to diagnosing provider seems to be a more complete measure of access to a melanoma diagnosis than proxy measures of rurality, socioeconomic status, and provider supply. Distance to diagnosing provider is not simply a measure of geographic isolation, as many patients bypass closer providers on their way to the diagnosing provider. The farther that patients travel to reach their diagnosing providers, the more advanced their stage at diagnosis is likely to be. Although we do not yet have survival data, it is reasonable to surmise that differences in Breslow thickness at diagnosis could translate into differences in overall survival.1,3 However, on a population-level these differences likely will be too small to be meaningful or to even detect because most patients are diagnosed as having thin melanoma and already have greater than 90% survival.

Further work is needed to characterize the determinants of distance to diagnosing provider, as well as the pathways and barriers to melanoma care. Once potential barriers are identified, interventions can be developed to minimize the effect of travel distance and other sociodemographic factors on access to melanoma care. Such interventions could potentially translate to other settings in which access to specialists is critical to patient outcomes.

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Author Contributions: Dr Sitzenberg 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: Sitzenberg, Ollila, and Berwick. Acquisition of data: Sitzenberg, Thomas, Brier, Mattingly, and Millikan. Analysis and interpretation of data: Sitzenberg, Thomas, Brier, Mattingly, and Millikan. Drafting of the manuscript: Sitzenberg, Thomas, Dalton, Brier, and Millikan. Critical revision of the manuscript for important intellectual content: Sitzenberg, Dalton, Ollila, Berwick, Mattingly, and Millikan. Statistical analysis: Sitzenberg, Thomas, Dalton, and Millikan. Obtained funding: Sitzenberg, Ollila, and Millikan. Administrative, technical, and material support: Sitzenberg, Thomas, Berwick, and Millikan. Study supervision: Sitzenberg, Thomas, Brier, Berwick, and Millikan.

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Role of the Sponsors: The Agency for Healthcare Research and Quality did not have a direct role in the design or conduct of the study; in the collection, management, analysis, or interpretation of the data; or in the preparation, review, or approval of the manuscript.

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Call for Papers

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Immunohistochemical Expression of Platelet Growth Factor and Vascular Endothelial Growth Factor in Patients With Melanoma With and Without Redness (Brenner Sign)

Jacob Mashiah, MD; Yonit Wohl, MD; Yoav Barnea, MD; Shlomo Schneebaum, MD; Andrea Gat, MD; Faina Misonzhnik-Bedny, BSc; Sarah Brenner, MD

Objective: To assess whether an erythematous eruption in the vicinity of or distant from a melanoma lesion might be related to the vascular endothelial growth factor, the platelet-derived endothelial cell growth factor, or both.

Methods: Biopsy specimens from 13 patients with primary melanoma, 6 of whom had erythematous eruptions and 7 who did not, were studied by immunohistochemistry for the expression of vascular endothelial growth factor and platelet-derived endothelial cell growth factor.

Results: Vascular endothelial growth factor was positive in 3 of 6 patients (50%) with melanoma and redness (Brenner sign) and in 4 of 7 patients (57%) with melanoma without redness. Platelet-derived endothelial cell growth factor was positive in all 6 patients (100%) with melanoma and redness and in 4 of 7 patients (57%) with melanoma without redness.

Conclusion: Platelet-derived endothelial cell growth factor may have a part in the pathogenesis of the redness observed in patients with melanoma, called Brenner sign, by affecting vasculature function.

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The rise in incidence of malignant melanoma is among the greatest for all kinds of cancer, with an annual rise of 3% to 8% in newly diagnosed melanomas worldwide.1 The increase is especially great in regions of the world where intense sun, especially in the Middle East, and a trend toward more revealing clothing expose people to untoward amounts of UV radiation. Despite efforts to achieve early detection and recognition of the unfavorable prognostic factors and the development of novel treatment modes, progressive disease has a dismal prognosis. Tumor progression and development cannot be attributed to a single process. The escape of the tumor from the regulatory mechanisms includes excessive production of cytokines and autocrine growth factors, substituting for cytokines and exogenous growth factors,2 self-tolerance to melanoma antigens, and down-regulation of class II major histocompatibility complex molecules.3 Neoplasms including melanoma are known to induce angiogenesis, which is believed to have a role in the development and spread of the melanoma.4,5

Previous publications6-8 described an observation of patients with malignant melanoma who had a particular reddish appearance that could not be attributed to any medical cause including photosensitivity. In one study 8 of 14 patients (57%) with melanoma exhibited an erythematous rash adjacent to and in the general vicinity of the melanoma that was confluent with the surrounding tissue and had no distinguishable borders.3 These authors labeled the rash Brenner sign (Figure 1).

In an effort to identify visible signs that can alert the clinician to the possible presence of melanoma, we investigated the expression of 2 cytokines secreted by melanoma cells—vascular endothelial growth factor (VEGF) and platelet-derived endothelial cell growth factor (PDGF)—and their role in the pathogenesis of the rash.

METHODS

PATIENTS

All biopsy specimens were obtained from the tissue files of 13 patients in the Pathology Department, Tel Aviv-Sourasky Medical Center, Tel Aviv, Israel. The study was approved by the...
hospital ethics committee. The formalin-fixed, paraffin-embedded melanocytic lesions represented 13 primary melanomas. One group of patients with melanoma who had the erythematous rash called Brenner sign included 6 patients (4 men and 2 women), with an age range of 31 to 86 years, and a Breslow level range of 0.1 to 10 mm. The group of patients with melanoma without the Brenner sign consisted of 7 patients (3 men and 4 women), with an age range of 43 to 74 years, and a Breslow level range of 0.9 to 23 mm. There was no difference between the 2 groups in the distribution of subtypes of melanoma or in the outcome.

Immunoreactivity to VEGF and PDGF was evaluated by light microscopy following immunohistochemical staining. Ten high-power fields were viewed for each sample and graded as follows: negative, no cells stained; low, 1% to 10% cells stained; moderate, 15% to 30% cells stained; and high, 40% or more cells stained.

Formalin-fixed, paraffin-embedded tissues were stained by an automated immunostainer (Nexes-Immunohistochemistry; Ventana Medical Systems, Tuscon, Arizona), after which they were deparaffinized and subjected to a 3-step indirect process based on the labeled (strept) avidin-biotin (LABORATORY-SA) peroxidase complex method, using the I-VIEW detection kit (Ventana Medical Systems). Sections were pretreated with buffer (pH 6.0, Target Retrieval; Zymed, San Francisco, California) for 12 minutes at 97°C by temperature-controlled microwave treatment using a processor (model H28900; Energy Beam Sciences, Inc, Ayawa, Maine). The Ventana Medical System dispensed the primary antibodies; consecutive sections were incubated for 32 minutes with polyclonal antibodies: 1:90 dilution of VEGF (CT) clone (Z-CVF3 Zymed), and 1:50 dilution of PDGF-α CLONE: C-20 (Santa Cruz, California). 3,3′-Diaminobenzidine tetrahydrochloride, which produces a dark brown precipitate chromogen, was used to localize the immunoreactions. Slides were counterstained with hematoxylin, dehydrated, and coverslipped with a permanent mounting medium for microscopic examination.

Immunoreactivity for VEGF was positive (moderate and high staining grades) (Figure 2) in tissue specimens of 3 of 6 patients (50%) with melanoma and redness and in 4 of 7 patients (57%) with melanoma without redness. No VEGF was detected in any of the melanomas with a Breslow depth of 1 mm or less.

In contrast, immunoreactivity for PDGF was positive (moderate and high staining grades) (Figure 3) in tissue specimens of 6 of 6 patients (100%) with melanoma and redness and in 4 of 7 patients (57%) with melanoma without redness. There was no difference between the 2 groups in Breslow depth.

An erythematous rash accompanying malignant melanoma lesions, confined mainly to the face, was first described by Brenner and Wolff6 and Tamir and Brenner.7 Another study8 confirmed this observation, reporting the
rash in 57% of patients with melanoma classified as stages I through III, and in none of the keratinocyte-derived tumor group or healthy individuals. Subject to further investigation and confirmation of the significance of this phenomenon, the rash could serve as an additional tool for the diagnosis of melanoma (asymmetry, border, color variegated, and diameter >6 mm) as well as a measure of progression or regression of the disease. Explanation of this phenomenon probably lies in the pathogenesis of malignant melanoma. Melanoma cells can express cytokines and growth factors, having autocrine, paracrine, or both effects that permit autonomous growth of cells, including tumor cells as well as fibroblasts, monocytes, lymphocytes and granulocytes, keratinocytes, and endothelial cells.2

Angiogenesis is a crucial component of growth, invasive progression, and metastatic spread of solid tumors, including melanoma. The interaction and reciprocal signaling between melanoma cells and endothelial cells are thought to guide the progression and growth of tumor cells. Melanoma cells produce a plethora of angiogenic cytokines, including VEGF, PDGF, and others. These cytokines are in constantly changing equilibrium with antiangiogenic agents.3

Platelet-derived growth factors are a family of dimeric disulfide-bonded growth factors that activate tyrosine kinase receptors that are expressed on mesenchymal origin cells such as pericytes, fibroblasts, glial cells, and smooth muscle cells.10 Platelet-derived growth factors participate in the process of solid tumor development in several ways, including recruitment of tumor stroma fibroblasts, stimulation of tumor angiogenesis, autocrine stimulation of tumor cell growth,11 and paracrine stimulation of vascularized stroma growth.12

Pericytes are formed in the connective tissue and remain there. These smooth muscle–like cells, smaller than fibroblasts, are located mainly along the blood capillaries and stabilize the capillary wall. Platelet-derived growth factors regulate embryonic pericyte recruitment.13 Neovessels in melanoma show perivascular PDGF-receptor staining of pericytes and possibly perivascular fibroblasts. Melanoma-derived PDGF is associated with enhanced tumor growth rate and increased coverage of tumor vessels with pericytes (not at late tumor growth phase), but with no increase in vessel density. This may reflect a pericyte-mediated protection from regression of immature vessels, because pericyte deficiency in mice causes endothelial hyperplasia, vessel dilation, vessel leakage, and rupture. The effect of PDGF on tumor vasculature is functional; it increases functionality of tumor vessels, decreases the fraction of nonperfused vessels, and promotes endothelial cell maturation through pericyte-derived signals.11 Our findings of positive PDGF immunoreactivity in tissue specimens of all 6 patients (100%) with melanoma and redness and in 4 of 7 patients (57%) without redness are in accord with the known activity of PDGF in melanoma. The erythema observed in cases of melanoma may reflect the higher percentage of mature endothelial cells and functional and perfused vessels.

Vascular endothelial growth factor is a glycosylated dimeric polypeptide that comprises a multifunctional cytokine expressed by most tumors. It acts on endothelial cells through tyrosine kinase receptors by being a selective endothelial cell mitogen and by causing an increase in microvessel permeability.14 Melanocytic tumors but not benign melanocytic proliferations display strong VEGF expression. Vascular endothelial growth factor is expressed in thicker melanoma, appears later in melanoma development, and correlates with the presence of metastases. It is also associated with an increase in vascular density.3 In our study the immunoreactivity for VEGF did not differ statistically between patients with melanoma with (50%) and without (57%) redness, indicating that the Brenner sign cannot be attributed to VEGF. Because VEGF is expressed in thick melanoma, no melanoma with a Breslow depth 1 mm or less was found to express VEGF.

Platelet-derived growth factors may have a role in the pathogenesis of the redness by affecting the function of the vasculature rather than its abundance. The number of patients is too small to draw definitive conclusions about these differences, but there seems to be a pattern that warrants further study. We continue to investigate other cytokines, angiogenic growth factors, and their promoters such as mitogen-activated protein kinase,15,16 and vascular leak promoters such as angiopoietin 2. We are also examining the red area for increased vascular density. While our search for the pathogenesis of Brenner sign continues, there is evidence that it could possibly serve as a red flag to primary care physicians, as another prognostic factor, or as a marker of the efficacy of treatment.

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Author Contributions: Study concept and design: Mashiah and Brenner. Acquisition of data: Mashiah, Wohl, Gat, and Brenner. Analysis and interpretation of data: Mashiah, Wohl, Gat, Misonznhik-Bedny, and Brenner. Drafting of the manuscript: Mashiah. Critical revision of the manuscript for important intellectual content: Mashiah, Wohl, Barnea, Schneebaum, Gat, Misonznhik-Bedny, and Brenner. Administrative, technical, and material support: Brenner. Study supervision: Brenner. Performed the surgery: Barnea and Schneebaum. Pathological interpretation: Gat. Immunohistochemistry sample analysis: Misonznhik-Bedny.

Financial Disclosure: None reported.

Additional Contributions: The manuscript was read and corrected by an English-speaking editor.

REFERENCES


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**Manuscript Submission**

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Age- and Site-Specific Variation in the Dermoscopic Patterns of Congenital Melanocytic Nevi

An Aid to Accurate Classification and Assessment of Melanocytic Nevi

Lily Changchien, JD; Stephen W. Dusza, MPH; Anna Liza Chan Agero, MD; Adam J. Korzenko, MD; Ralph P. Braun, MD; Dana Sachs, MD; M. Haris U. Usman, MD; Allan C. Halpern, MD; Ashfaq A. Marghoob, MD

Objectives: To describe the dermoscopic features of congenital melanocytic nevi (CMN) and assess whether predominant dermoscopic patterns present in CMN are related to an individual’s age (<12 years vs ≥12 years), sex, or lesional site (head, neck, and trunk vs extremities).

Design: Nonrandomized observational study.

Patients: A total of 77 consecutive patients, each with 1 CMN (n=77 lesions), from an outpatient dermatology clinic. A diagnosis of CMN was established by (1) documentation of a melanocytic nevus during the first year of life or (2) by clinical examination and either clinical history or biopsy findings.

Main Outcome Measures: Images of CMN were evaluated for specific dermoscopic structures and patterns. The distribution of patterns was assessed by age, sex, and lesional site.

Results: Most of the 77 lesions exhibited 1 of the following predominant dermoscopic patterns: reticular (18 lesions [23%]), globular (14 [18%]), or reticuloglobal (12 [16%]). Globular CMN were present in 5 of the 19 individuals who were younger than 12 years (26%) but in only 9 of the 58 individuals 12 years or older (16%). Reticular CMN were seen exclusively in the individuals who were 12 years or older. Congenital melanocytic nevi exhibiting no predominant pattern were more commonly present in the individuals younger than 12 years. Globular CMN were present in 11 head, neck, and trunk lesions (30%) compared with 3 extremity lesions (8%). Conversely, reticular CMN were present in 16 extremity lesions (40%) compared with 2 head, neck, and trunk lesions (5%). The predominant dermoscopic pattern did not vary based on sex. The most commonly observed dermoscopic structures were globules (in 64 lesions [83%]), hypertrichosis (in 61 [79%]), and reticular networks (in 55 [71%]).

Conclusions: Our results suggest that the predominant dermoscopic patterns of CMN vary according to age and lesional site. These differences may inform future studies on the pathogenesis of CMN.

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CONGENITAL MELANOCYTIC nevi (CMN) are melanocytic nevi that are present at birth. In some cases, CMN may not be evident at birth owing to an initial lack of visible pigment and may become apparent only after the development of pigment months to years after birth.1 Melanocytic nevi with clinical features consistent with CMN, but without a clinical history to conclusively establish their presence since early life, are termed congenital nevus–like nevi (CNLN). It is estimated that 1% to 6% of infants are born with 1 or more CMN,2,3 whereas 2% to 6% of the general population have 1 or more CNLN.4,4

The identification of distinct dermoscopic features of CMN may provide an important diagnostic tool for distinguishing between CMN and other pigmented lesions. Previous studies7,9 indicate that CMN exhibit distinct dermoscopic features that may be helpful in distinguishing CMN from acquired melanocytic nevi and Becker nevi. There is also evidence that suggests that dermoscopy may be effective in detecting early malignant changes.10

The recognition of age-, sex-, and lesional site–related differences in the dermoscopic appearance of CMN may facilitate the accurate diagnosis and assessment of subsequent changes observed in follow-up dermoscopy. To date, little is known about the relationship of the dermoscopic appearance of CMN with factors such as age, sex, and lesional site. However, there is recent evidence sug-
gesting that the predominant dermoscopic pattern present in CMN may vary according to an individual’s age and lesional site. Accordingly, the purpose of this study was to provide a comprehensive description of the common dermoscopic features of CMN and to assess whether the predominant dermoscopic patterns present in CMN relate to an individual’s age, sex, or lesional site.

**Methods**

Seventy-seven consecutive patients, each diagnosed with 1 CMN or CNLN (n=77 lesions), who were seen in the outpatient clinic of one of the authors (A.A.M.) during the period of May 1996 to April 2001 were recruited for our study. With the exception of patients with large CMN, almost all other patients presented to the clinic for a primary purpose unrelated to their CMN. A total-body skin examination of each patient was performed, and the presence of any lesions with clinical features suggestive of CMN was noted. A diagnosis of CMN was established by documentation of the presence of a melanocytic nodule in the first year of life by birth record, baby photographs, or the examining physician. In cases in which such documentation was unavailable, a diagnosis of CMN or CNLN was established by the presence of (1) clinical features consistent with CMN, such as homogeneity, mamillated topography, well-defined borders, and hypertrichosis, and (2) either histologic findings consistent with CMN or a clinical history of the lesion having been present since early life. Lesions located on the palms, soles, mucosal, or subungual sites were excluded from our study. Hereinafter, unless otherwise noted, “CMN” will refer to both CMN and CNLN.

After oral consent was obtained from each patient, lesions were photographed with a conventional 35-mm camera to document their clinical appearance. Representative dermoscopic images of each lesion were then obtained using a Dermaphot lens (Heine Optotechnik, Herrsching, Germany) mounted on a conventional 35-mm camera, at 10-fold magnification. If a lesion was larger than the field of view, images were obtained of (1) the border, (2) representative architecture of the center of the lesion, and (3) any other areas of special interest. All images were subsequently converted into digital format, and each digital image was evaluated by 2 examiners (L.C. and A.L.C.A.). Clinical images of the lesions were assessed for color, topography, shape, symmetry, borders, hypertrichosis, and homogeneity. Dermoscopic images were evaluated for color, symmetry, homogeneity, and the presence and quality of the structures listed in Table 1. Many of these structures have been previously described as common features of CMN.

<table>
<thead>
<tr>
<th>Table 1. Definitions of Dermoscopic Features</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Feature</strong></td>
</tr>
<tr>
<td>Reticular network</td>
</tr>
<tr>
<td>Broken network (branched streaks) or hyphal structures</td>
</tr>
<tr>
<td>Target network</td>
</tr>
<tr>
<td>Cobblestone globule</td>
</tr>
<tr>
<td>Target globule</td>
</tr>
<tr>
<td>Haloed globule</td>
</tr>
<tr>
<td>Diffuse background pigment</td>
</tr>
<tr>
<td>Blotches</td>
</tr>
<tr>
<td>Dot</td>
</tr>
<tr>
<td>Milialike cyst</td>
</tr>
<tr>
<td>Hypertrichosis</td>
</tr>
<tr>
<td>Perifollicular hyperpigmentation or hypopigmentation</td>
</tr>
<tr>
<td>Skin furrow hypopigmentation</td>
</tr>
<tr>
<td>Structureless area</td>
</tr>
<tr>
<td>Vascular structure</td>
</tr>
<tr>
<td>Bluish-white veil</td>
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</tbody>
</table>

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scoposcopic feature, and predominant dermoscopic pattern were calculated for the entire study population. The absolute number and frequency of each predominant dermoscopic pattern were then determined for each of the following subgroups of the study population: age (dichotomized at age 12 years), sex, and lesional site (head, neck, and trunk vs extremities). Age was dichotomized at 12 years to coincide with the onset of adolescence. In addition, owing to the small number of head and neck lesions in our study population and the similarity in the timing of melanoblast migration in the head, neck, and dorsal trunk during embryogenesis, head, neck, and trunk lesions were combined into a single category. Differences in frequency between subgroups were evaluated using the χ² test of independence (the Fisher exact test was applied if any expected cell value in the contingency table was <5). In addition, the absolute number and frequency of each predominant dermoscopic pattern were determined for small lesions vs medium and large lesions. A formal multivariate analysis of the predominant dermoscopic pattern was not attempted owing to limitations imposed by the size of our data set. Given that the predominant dermoscopic pattern is a categorical response variable, a multivariate analysis of a cohort of 77 lesions would be likely to result in unreliable parameter estimates.

This retrospective review was approved by the Memorial Sloan-Kettering Cancer Center (New York, New York) institutional review board.

**RESULTS**

We examined 77 CMN in a study population of 77 individuals, consisting of 36 females (47%) and 41 males (53%) aged 1 month to 70 years (median age, 26 years). Of these 77 individuals, 19 were younger than 12 years (mean age, 3.4 years) and 58 individuals were 12 years or older (mean age, 35.2 years). Of the 77 lesions included in our study, 48 lesions were small (<1.5 cm in diameter) (62%), 25 lesions were medium (1.5-19.9 cm) (33%), and 4 lesions were large (≥20.0 cm) (5%). The diameter of lesions ranged from 0.4 to 51.0 cm (median diameter, 1.3 cm). Lesions were located on the head and neck in 6 cases (8%), the trunk in 31 cases (40%), and the extremities in 40 cases (52%).

As summarized in Table 2, most of the lesions in our study appeared clinically brown (73 lesions [95%]) or black (19 [25%]) in color, with macular (51 [66%]) or mamillated (28 [36%]) topography. Most lesions were symmetric (53 [69%]), round or oval in shape (61 [79%]), homogeneous (50 [65%]), with regular borders (57 [74%]), and with hypertrichosis (41 [53%]).

Table 3 presents the frequencies of various dermoscopic features in our study. Nearly all lesions contained dark brown or light brown pigment (75 [97%] and 74 [96%], respectively), whereas blue or white pigment was rarely observed. Globules, present in 64 lesions (83%), were the most common dermoscopic structure observed in our study. Most frequently, a mixed or uniformly small population of diffusely distributed globules was observed. Another common dermoscopic structure was the reticular network, which was present in 55 cases (71%) and most often was of fine quality (in 22 cases [29%]) and distributed throughout the lesion (in 40 cases [52%]). The predominant dermoscopic patterns of the lesions are presented in Table 4.

<table>
<thead>
<tr>
<th>Table 2. Clinical Features of 77 CMN</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical Feature</strong></td>
</tr>
<tr>
<td>----------------------</td>
</tr>
<tr>
<td><strong>Color</strong></td>
</tr>
<tr>
<td>Brown</td>
</tr>
<tr>
<td>Black</td>
</tr>
<tr>
<td>Red</td>
</tr>
<tr>
<td>Blue</td>
</tr>
<tr>
<td>White</td>
</tr>
<tr>
<td><strong>Topography</strong></td>
</tr>
<tr>
<td>Macular</td>
</tr>
<tr>
<td>Papular</td>
</tr>
<tr>
<td>Mamillated</td>
</tr>
<tr>
<td><strong>Shape</strong></td>
</tr>
<tr>
<td>Round or oval</td>
</tr>
<tr>
<td>Irregular</td>
</tr>
<tr>
<td>Other</td>
</tr>
<tr>
<td><strong>Symmetry</strong></td>
</tr>
<tr>
<td>Symmetric</td>
</tr>
<tr>
<td>Asymmetric in 1 axis</td>
</tr>
<tr>
<td>Asymmetric in 2 axes</td>
</tr>
<tr>
<td><strong>Border</strong></td>
</tr>
<tr>
<td>Regular</td>
</tr>
<tr>
<td>Irregular</td>
</tr>
<tr>
<td>Homogeneous</td>
</tr>
<tr>
<td>Hypertrichosis</td>
</tr>
</tbody>
</table>

Abbreviation: CMN, congenital melanocytic nevi and congenital nevus–like nevi.

Overall, most of the lesions exhibited 1 of the following predominant dermoscopic patterns (Table 4): reticular (18 lesions [23%]), globular (14 [18%]), reticuloglobal (12 [16%]), diffuse background pigmentation (3 [4%]), and other (5 [7%]). No single predominant dermoscopic pattern was present in 25 lesions (33%). Of such lesions, 6 contained a reticulotic component (24%), 7 contained a globular component (28%), and 3 contained a diffuse background pigment component (12%). The dominant dermoscopic patterns according to age are graphically shown in Figure 1. A single predominant dermoscopic pattern was present in 12 individuals younger than 12 years (63%), and 40 individuals 12 years or older (69%). Predominant dermoscopic pattern varied by the age of the individual (Figure 1) (P = .02): a reticular pattern was present in 5 individuals younger than 12 years (26%) but was present in only 9 individuals 12 years or older (16%). A reticular pattern was seen exclusively in individuals 12 years or older. In addition, individuals 12 years or older were equally likely to demonstrate either a reticular pattern (18 [31%]) or no predominant pattern (18 [31%]), whereas those younger than 12 years were more likely to demonstrate no predominant pattern (7 [37%]) rather than a globular pattern (5 [26%]). The predominant dermoscopic pattern also varied by lesional site (Figure 2) (P = .006): a globular pattern was present in 11 head, neck, and axial lesions (30%) compared with only 3 extremity lesions (8%). Conversely, a reticular pattern was present in 16 extremity lesions (40%), compared with only 2 head, neck, and axial lesions (5%). The predominant dermoscopic pattern was not found to vary significantly based on sex (P = .50) or on size (P = .20). Small CMN were more likely
to demonstrate a reticular pattern (40 lesions [83%]) compared with larger lesions (5 [17%]). However, small CMN were also more likely to demonstrate a globular pattern (31 [64%]) compared with larger lesions (10 [36%]).

Table 3. Dermoscopic Features of 77 CMN

<table>
<thead>
<tr>
<th>Dermoscopic Feature</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Color</td>
<td></td>
</tr>
<tr>
<td>Light brown</td>
<td>74 (96)</td>
</tr>
<tr>
<td>Dark brown</td>
<td>75 (97)</td>
</tr>
<tr>
<td>Black</td>
<td>19 (25)</td>
</tr>
<tr>
<td>Red</td>
<td>25 (33)</td>
</tr>
<tr>
<td>Blue</td>
<td>0</td>
</tr>
<tr>
<td>White</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Bluish-gray</td>
<td>39 (51)</td>
</tr>
<tr>
<td>Homogeneous</td>
<td>46 (60)</td>
</tr>
<tr>
<td>Symmetric</td>
<td>25 (33)</td>
</tr>
<tr>
<td>Reticular network</td>
<td>55 (71)</td>
</tr>
<tr>
<td>Quality</td>
<td></td>
</tr>
<tr>
<td>Fine</td>
<td>22 (29)</td>
</tr>
<tr>
<td>Thick</td>
<td>15 (20)</td>
</tr>
<tr>
<td>Focal thickening</td>
<td>18 (23)</td>
</tr>
<tr>
<td>Distribution</td>
<td></td>
</tr>
<tr>
<td>Patchy</td>
<td>17 (22)</td>
</tr>
<tr>
<td>Central</td>
<td>0</td>
</tr>
<tr>
<td>Peripherally</td>
<td>14 (18)</td>
</tr>
<tr>
<td>Diffuse</td>
<td>23 (30)</td>
</tr>
<tr>
<td>Specific type</td>
<td></td>
</tr>
<tr>
<td>Broken network and/or hyphal structures</td>
<td>15 (20)</td>
</tr>
<tr>
<td>Target network with globules and/or dots</td>
<td>21 (27)</td>
</tr>
<tr>
<td>Target network with blood vessels</td>
<td>25 (33)</td>
</tr>
<tr>
<td>Globules</td>
<td>64 (85)</td>
</tr>
<tr>
<td>Quality</td>
<td></td>
</tr>
<tr>
<td>Small</td>
<td>27 (35)</td>
</tr>
<tr>
<td>Large</td>
<td>4 (5)</td>
</tr>
<tr>
<td>Mixed</td>
<td>27 (35)</td>
</tr>
<tr>
<td>Distribution</td>
<td></td>
</tr>
<tr>
<td>Diffuse sparse</td>
<td>29 (38)</td>
</tr>
<tr>
<td>Diffuse dense</td>
<td>19 (25)</td>
</tr>
<tr>
<td>Central</td>
<td>13 (17)</td>
</tr>
<tr>
<td>Peripheral</td>
<td>3 (4)</td>
</tr>
<tr>
<td>Quantity</td>
<td></td>
</tr>
<tr>
<td>Few</td>
<td>22 (29)</td>
</tr>
<tr>
<td>Many</td>
<td>42 (55)</td>
</tr>
<tr>
<td>Specific type</td>
<td></td>
</tr>
<tr>
<td>Cobblestone</td>
<td>6 (8)</td>
</tr>
<tr>
<td>Target</td>
<td>18 (23)</td>
</tr>
<tr>
<td>Haloed</td>
<td>13 (17)</td>
</tr>
<tr>
<td>Diffuse brown background pigment</td>
<td>23 (30)</td>
</tr>
<tr>
<td>Remnant structures present</td>
<td>23 (30)</td>
</tr>
<tr>
<td>Reticular network</td>
<td>4 (5)</td>
</tr>
<tr>
<td>Globules</td>
<td>11 (14)</td>
</tr>
<tr>
<td>Reticular network and globules</td>
<td>8 (10)</td>
</tr>
<tr>
<td>Remnant structures absent</td>
<td>0</td>
</tr>
<tr>
<td>Blotches</td>
<td>4 (5)</td>
</tr>
<tr>
<td>Dots</td>
<td>30 (39)</td>
</tr>
<tr>
<td>Millilike cysts</td>
<td>40 (52)</td>
</tr>
<tr>
<td>Hypertrichosis</td>
<td>61 (79)</td>
</tr>
<tr>
<td>Perifollicular hyperpigmentation</td>
<td>3 (4)</td>
</tr>
<tr>
<td>Perifollicular hypopigmentation</td>
<td>32 (42)</td>
</tr>
<tr>
<td>Skin furrow hypopigmentation</td>
<td>36 (47)</td>
</tr>
<tr>
<td>Structureless areas</td>
<td>14 (18)</td>
</tr>
<tr>
<td>Bluish-white veil</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Vascular structures</td>
<td>52 (68)</td>
</tr>
</tbody>
</table>

Table 4. Predominant Dermoscopic Patterns of 77 CMN

<table>
<thead>
<tr>
<th>Dermoscopic Pattern</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reticular</td>
<td>18 (23)</td>
</tr>
<tr>
<td>Globular</td>
<td>14 (18)</td>
</tr>
<tr>
<td>Reticuloglobular</td>
<td>12 (16)</td>
</tr>
<tr>
<td>Diffuse brown background pigment</td>
<td>3 (4)</td>
</tr>
<tr>
<td>Remnant structures present</td>
<td>3 (4)</td>
</tr>
<tr>
<td>Remnant structures absent</td>
<td>0</td>
</tr>
<tr>
<td>Other</td>
<td>5 (7)</td>
</tr>
</tbody>
</table>

Although the differential diagnosis of CMN is relatively limited, the lack of sensitive, well-defined clinical and histologic criteria may impede accurate diagnosis. This is particularly the case for adults, who may have multiple acquired melanocytic nevi and, remote from early childhood, are less likely to accurately report when a given pigmented lesion developed. Furthermore, although a reliable clinical history or birth record indicating that a particular lesion was present at birth may be sufficient to establish the presence of CMN, it does not effectively distinguish an acquired nevus from a tardive nevus, which is not apparent at birth owing to the initial absence of visible pigment. Distinct clinical and histologic features may assist in differentiating CMN from acquired nevi; however, these features are not reliably present in all cases. In fact, some of the histologic and clinical features typically attributed to CMN may on occasion be seen in acquired nevi, particularly in dysplastic nevi.17-19 This histologic and clinical overlap, most commonly seen in small nevi,20 may therefore preclude accurate classification of melanocytic nevi. The identification of dermoscopic features common to CMN provides an additional diagnos-
tic tool that may help to differentiate CMN, particularly small CMN, from other pigmented lesions. Precise classification of melanocytic lesions is important not only for determining appropriate clinical treatment of such lesions but also for ensuring the integrity of epidemiological studies of CMN and acquired nevi. Although it is possible that some acquired nevi may have been classified as CMN in the study described herein, this is highly unlikely given our stringent inclusion criteria.

Previous studies describing the dermoscopic features of CMN have identified globules, reticular networks, dots, focal network thickening, perifollicular hypopigmentation, target networks with globules or dots, and target globules as common features of CMN. Overall, the results of our assessment of dermoscopic features are consistent with those reported by Seidenari et al.9 In addition, we observed an association between pre-existing network pattern and age. A globular pattern was observed in 13 individuals 12 years or older. A predominantly reticular pattern was observed in those with extremity lesions and those with extremity lesions. All frequencies were rounded to the nearest whole percentage.

Our results demonstrate dermoscopic structures that, to our knowledge, have not been identified as common features of CMN in previous studies. First, we note the frequent occurrence of milialike cysts, a characteristic dermoscopic finding of seborrheic keratoses.24 Second, we define the haloed globule, a dermoscopic structure that has not been previously described (Figure 3). We believe that the haloed globule, which was observed in 13 lesions (17%), is structurally distinct from the target globule. The target globule, which has been described as a globule containing a central dot,9,15 essentially appears as a dot encircled by a halo that is hyperpigmented relative to surrounding background pigment (Figure 4). In contrast, the haloed globule appears as a globule surrounded by a hypopigmented halo.

The most common predominant dermoscopic patterns in our study population were reticular (18 [23%]), globular (14 [18%]), and reticuloglobal (12 [16%]). In addition, we observed an association between predominant dermoscopic pattern and age. A globular pattern was seen commonly in individuals younger than 12 years but far less frequently in individuals 12 years or older. A predominantly reticular pattern was observed exclusively in individuals 12 years or older. Our results are consistent with those reported by Seidenari et al.9 In an examination of 384 small and medium CMN, Seidenari et al9 similarly found that a globular pattern prevailed in children younger than 11 years, whereas reticular and homogeneous patterns were more common in individuals 11 years or older. Analogous findings have also recently been reported in acquired melanocytic nevi.22 Some researchers may speculate that the age-related differences in dermoscopic patterns observed in our study may reflect dynamic changes in lesions over time; that is, CMN may initially show a globular pattern, which may with age eventually evolve into a reticular or homogeneous pattern. Such a change would correlate histologically with the presence of intradermal nevus cells initially, followed by the presence of intraepidermal and junctional nevus cells later in life.22 This is consistent with the concept of Hochsteigerung, the upward migration of melanocytes from the dermis to the epidermis.23 It may be plausible to speculate that factors such as intermittent exposure to UV light resulting in the release of growth factors and chemokines from epidermal cells may lead to Hochsteigerung. However, such dynamic changes have not yet been observed, and longitudinal studies of nevus patterns over time would be required to adequately address this hypothesis. In addition, it should be noted that any true dynamic changes in CMN should be independent of lesion size and anatomic distribution.

To our knowledge, to date, no longitudinal studies examining the evolution of the dermoscopic appearance of CMN have been undertaken, and few studies have specifically examined age-related histologic changes in CMN. One study of a series of 38 CMN found no noteworthy correlation between histologic pattern and age.23 But because most of the study participants were in the first decade of life and included only 2 individuals older than 20 years, these findings do not necessarily preclude the possibility that major histologic changes in CMN may become apparent after the first decade of life. In the study by Nickoloff et al,26 biopsy samples of 10 small CMN from individuals younger than 1 year were obtained and compared with findings from repeated biopsies obtained after a mean follow-up period of 10.23 years. The histologic appearance of the findings from the repeated biopsies revealed no noteworthy change compared with the ap-
pearance of the original biopsy findings. This suggests that major events in the evolution of CMN do not occur in the first and second decades of life but does not exclude the possibility that those events may occur later in life.

In addition, our results suggest that the dermoscopic pattern varies according to the lesional site. A reticular pattern was seen more frequently in lesions located on the extremities, whereas a globular pattern was more commonly seen in head, neck, and trunk lesions. Seidenari et al. similarly observed that lesions of the trunk were more likely to be of the globular type, whereas those of the extremities were more likely to be of the reticular type. Differences in the timing of the migration of melanocytic precursor cells during embryogenesis may be one possible explanation. It has been theorized that during embryogenesis, melanoblasts migrate from the neural crest to the dermis via the paraspinal ganglia and the sheaths of their peripheral nerves. Guided by chemotactic factors expressed within the developing epidermis, melanoblasts are thought to be present in the dermis only transiently and soon migrate to the basal layer of the epidermis. In general, the sequence of melanoblast migration follows a cephalo-caudal and proximal-to-distal sequence: melanoblasts have been identified by light microscopy in the dermis of the scalp, the nape of neck, and the sacrum by the 10th week of gestational life, whereas dermal melanoblasts are not apparent in the extremities and the ventral skin until the 12th week of development.

Although the pathogenesis of CMN is not well understood, it has been suggested that the perturbation in melanoblast migration and differentiation may result in the formation of CMN. There is evidence that epidermal expression of growth factors, such as stem cell factor, may be important in directing the migration of melanoblasts from the dermis to the epidermis. For

Table 5. Relative Frequency of Dermoscopic Features of CMN in This Study Compared With Those of Previous Studies

<table>
<thead>
<tr>
<th>Dermoscopic Feature</th>
<th>This Study</th>
<th>Seidenari et al. 2006</th>
<th>Seidenari et al. 2003</th>
<th>Ingordo et al. 2006</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reticular network</td>
<td>71</td>
<td>57</td>
<td>53</td>
<td>90</td>
</tr>
<tr>
<td>Target network with globules or dots</td>
<td>27</td>
<td>23</td>
<td>20</td>
<td>28</td>
</tr>
<tr>
<td>Focal thickening of network lines compared with network</td>
<td>33</td>
<td>33</td>
<td>21</td>
<td>46</td>
</tr>
<tr>
<td>Globules</td>
<td>83</td>
<td>NA</td>
<td>NA</td>
<td>43</td>
</tr>
<tr>
<td>Small globules</td>
<td>35</td>
<td>55</td>
<td>51</td>
<td>NA</td>
</tr>
<tr>
<td>Large globules</td>
<td>5</td>
<td>37</td>
<td>38</td>
<td>NA</td>
</tr>
<tr>
<td>Target globules</td>
<td>28c</td>
<td>23c</td>
<td>8d</td>
<td>39c</td>
</tr>
<tr>
<td>Peripheral globules</td>
<td>4</td>
<td>10</td>
<td>15</td>
<td>NA</td>
</tr>
<tr>
<td>Dots</td>
<td>39</td>
<td>51</td>
<td>68</td>
<td>NA</td>
</tr>
<tr>
<td>Diffuse background pigment</td>
<td>30</td>
<td>35</td>
<td>72</td>
<td>17</td>
</tr>
<tr>
<td>Blotches</td>
<td>5</td>
<td>23</td>
<td>23</td>
<td>20</td>
</tr>
<tr>
<td>Skin furrow hypopigmentation</td>
<td>47</td>
<td>16</td>
<td>18</td>
<td>49</td>
</tr>
<tr>
<td>Perifollicular hypopigmentation compared with follicles</td>
<td>53</td>
<td>75</td>
<td>71</td>
<td>77</td>
</tr>
<tr>
<td>Vascular structures</td>
<td>68</td>
<td>10</td>
<td>6</td>
<td>66</td>
</tr>
<tr>
<td>Target network with blood vessels</td>
<td>33</td>
<td>4</td>
<td>4</td>
<td>9</td>
</tr>
</tbody>
</table>

Abbreviations: CMN, congenital melanocytic nevi and congenital nevus-like nevi; NA, not available.

a Data are presented as percentages.

b The number of observations of focal network thickening was compared with the number of lesions with a reticular network.

c The number of target globules was compared with the number of lesions with globules.

d The number of target globules was compared with the total number of lesions.

e The number of observations of perifollicular hypopigmentation was compared with the number of observed follicles.

Figure 3. Dermoscopic image of a congenital melanocytic nevus with haloed globules (arrows).

Figure 4. Dermoscopic images of congenital melanocytic nevi. A, Target network with a target globule (arrow). B, Target globule (arrow).
example, in one recent study,28 mice were injected with melanocytes genetically altered to express an endog- nous constitutively active mutant Kit receptor. The altered melanocytes were observed to migrate through the dermis, ultimately settling near the dermal-epidermal junction and epidermis, whereas wild-type melanocytes remained within the lower dermis.29 A delay in epidermal development or disruption of cellular pathways resulting in global delay of epidermal expression of growth factors required for dermal migration may have a differential effect on the ultimate location of nevomelanoblasts at different lesional sites. A transient delay in the expression of epidermal migratory factors is more likely to affect nevomelanoblasts destined for the head, neck, and dorsal trunk, which are programmed to reach the dermis at an earlier time. Such a delay may result in the arrest of nevomelanoblasts in the dermis, leading to the formation of nevi of the globular type. In contrast, nevomelanoblasts destined for the extremities, which are programmed to arrive at the dermis at a later time, may be relatively unaffected by a slight delay in the expression of epidermal migratory factors. In such cases, nevomelanoblast proliferation may occur more superficially, leading to formation of junctional nevi.

In our study, we use the term target network to refer generally to a reticular network that contains dots, globules, or blood vessels within its spaces. We note that this network has been previously described as a reticular network centered by a dot.7,9 However, a variety of different structures, such as dots, globules, and vessels, may occupy the spaces of a reticular network (Figure 5). Because the spaces of the network have a targetlike appearance in each case, strictly speaking, a network may be accurately described as a target network regardless of the exact type of structure present. As a result, we propose redefining the term target network more generally to avoid confusion and to better conform with the definition of target globule (in which “target” similarly refers to the structure with a targetlike appearance).

A limitation of our study is the small size of our sample, which was in part a function of the application of relatively stringent inclusion criteria. The accurate diagnosis of CMN is considerably less certain in the absence of a reliable clinical history. For this reason, we required documentation of CMN by photograph, birth record, or medical record. If such documentation was unavailable, inclusion of a lesion required not only demonstration of clinical morphologic characteristics consistent with CMN but also a clinical history or biopsy finding suggestive of CMN.

In conclusion, our study describes the normal dermoscopic features of CMN, including the haloed globule, a new structure that to our knowledge has not yet been described. Our findings suggest that the predominant dermoscopic patterns of CMN vary according to age and lesional site but not sex. Globular CMN were more commonly observed in individuals younger than 12 years and on the head, neck, and trunk. In contrast, a reticular pattern was seen more frequently on the extremities and in individuals 12 years or older. Familiarity with the dermoscopic patterns commonly present in CMN may facilitate accurate classification of nevi and early detection of malignant change and therefore assist in the determination of whether prophylactic surgical excision of a given pigmented lesion is truly warranted. In addition, the identification of age- and site-related differences in dermoscopic patterns may inform future longitudinal studies examining the pathogenesis and subsequent evolution of CMN.

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Financial Disclosure: None reported.

REFERENCES

Objective: To determine whether the addition of 311-nm narrowband UV-B (NB UV-B) phototherapy accelerates and improves the therapeutic efficacy of alefacept, a biological antipsoriatic drug approved for the treatment of moderate to severe psoriasis.

Design: Randomized half-body comparison study.

Setting: Ambulatory section of a university hospital photodermatology unit.

Patients: Fourteen patients with moderate to severe psoriasis.

Interventions: All patients were treated with 7.5 mg of intravenous alefacept once weekly for 12 weeks. Three times each week, a randomly selected body half (left or right) was treated with NB UV-B light until complete remission, defined as a reduction in the Psoriasis Area Severity Index (PASI) to 3 or lower, was achieved on the irradiated body half.

Main Outcome Measures: Modified PASI, self-assessed visual analogue scale rating of skin lesions, and self-assessed therapeutic efficacy.

Results: After 12 weeks of treatment, the mean PASIs on UV-irradiated and nonirradiated body halves were significantly reduced by 81% and 62%, respectively ($P < .001$). From week 3 to week 12, the mean PASI was significantly lower on UV-irradiated body halves than on nonirradiated body halves ($P < .001$). At week 12, PASI reductions of greater than 75% had been achieved significantly more often on UV-irradiated body halves (86%, 12 of 14) than on nonirradiated body halves (43%, 6 of 14), and complete remission had been achieved significantly more often on UV-irradiated body halves (43%, 6 of 14) than on nonirradiated body halves (0 of 14) (McNemar test $P = .03$).

Conclusions: In this randomized half-side comparison of alefacept with and without phototherapy for psoriasis, alefacept with NB UV-B phototherapy accelerated and improved the clearance of psoriasis. This suggests a promising future for this combination as antipsoriatic therapy.

Trial Registration: clinicaltrials.gov Identifier: NCT00407342

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Psoriasis is an inflammatory skin disease that affects an estimated 2% to 3% of the world's population. The lesions typical of this disease—erythematous psoriatic plaques covered with silvery white scales—are clinical signs of chronic skin inflammation accompanied by hyperproliferation of keratinocytes and dermal infiltration by lymphocytes consisting mainly of memory type 1 helper T cells (CD4$^+$) and type 1 cytotoxic T cells (CD8$^+$). These memory T cells are abundant in psoriatic skin lesions and the blood of patients with psoriasis and are considered to be of major importance for the expression of psoriatic skin lesions. A wide range of local and systemic clinical treatments and agents are available for clearing, or at least reducing the expression of, psoriatic skin lesions. Among these is a new generation of antipsoriatic drugs that specifically target T-cell–mediated inflammatory pathways and that are approved for the treatment of moderate to severe psoriasis in the United States. One of these new drugs is alefacept, an immunomodulatory recombinant, fully human fusion protein and biological agent that combines the lymphocyte function–associated antigen 3 (LFA-3) with the Fc portion of IgG1. Alefacept targets memory-effector T cells by binding the CD2 receptors on their surface, thereby blocking interaction between LFA-3 and...
CD2. In addition, through its IgG1 moiety, alefacept binds the Fc receptors located on the surface of natural killer cells and macrophages, thereby inducing them to cause the apoptosis of T lymphocytes and in particular the memory-effector T cells implicated in sustaining psoriatic skin lesions.8 Alefacept appears to be therapeutically efficacious: several studies have demonstrated a correlation between reductions in the number of memory-effector T cells in the peripheral circulation9-11 and in skin lesions of patients with psoriasis and reduced Psoriasis Area Severity Index (PASI).12

Alefacept appears to have several advantages over other systemic antipsoriatic agents such as methotrexate and cyclosporine and also over other agents in its own class such as infliximab, etanercept, and efalizumab. Alefacept is very well tolerated by patients, producing relatively weak adverse effects that in most cases are comparable to those seen in placebo controls. Concerns about an increased risk of infections and malignancies as well as systemic immunosuppression due to reductions in lymphocyte count (particularly CD4+ T lymphocytes) have been allayed by the clinical experience in patients with psoriasis.13 Unlike the case for tumor necrosis factor α blockers infliximab and etanercept, there have been no reports of alefacept-induced reactivation of tuberculosis.14,15 Unlike efalizumab, alefacept does not appear to cause sudden flare-ups of psoriasis during or after abrupt termination of therapy.16 Conversely, as one recent study has shown,17 alefacept clears moderate to severe psoriatic skin lesions in patients with psoriasis at approximately the same rate as do etanercept and efalizumab. In that study, weekly administration of alefacept for 12 weeks reduced the PASI by greater than 75% in 30% of patients.17

The maximum antipsoriatic effect, however, apparently occurs after the 12-week course has ended.18 Recently, Sugiyama et al19 have suggested that alefacept’s antipsoriatic effect may be augmented when it is administered in combination with UV-B phototherapy. In their in vitro study, Sugiyama et al observed that apoptosis increased and interferon gamma production decreased in activated T cells after they had been irradiated with UV-B light in the presence of alefacept. This observation is supported by several case reports of increased clinical anti-psoriatic efficacy of alefacept when combined with UV-B phototherapy.20,21 Together, these findings prompted us to conduct a prospective, randomized, half-body comparison study in which we investigated whether the clinical response of psoriatic lesions to alefacept could be improved by combining alefacept with standard narrowband (311-nm) UV-B (NB UV-B) phototherapy.

METHODS

STUDY DESIGN AND PARTICIPANTS

This was a single-center, prospective, randomized, half-body (left vs right) comparison study. It was approved by the local ethics committee of the Medical University of Graz and was conducted according to principles of the Declaration of Helsinki and the good clinical practice guidelines of the European Community. All patients gave their informed consent before enrollment in the study. The study end points were modified PASI, self-assessed visual analog scale (VAS) rating of skin lesions, and self-assessed therapeutic efficacy. The outcome after the first 12 weeks of antipsoriatic treatment was considered to be the overall result. The active phase of the study was performed between February and June 2004 in patients at our institution.

Inclusion criteria for enrollment into the study were as follows: moderate to severe plaque-type psoriasis for more than 6 months and PASI above 10. Exclusion criteria were as follows: age younger than 18 years; pregnancy or lactation; presence of a dysplastic nevus syndrome, photosensitive skin disease, autoimmune disease, or severe renal or hepatic disease; presence or history of malignant skin tumors; presence of antinuclear antibodies; a history of previous treatments with arsenic, methotrexate, or x-rays; recent history (within the last 4 weeks before enrollment into the study) of UV-B or psoralen-UV-A (PUVA) treatment, immunosuppressive and/or immunomodulating drugs including corticosteroids, cyclosporine, and biological agents such as infliximab, etanercept, or efalizumab. During the study, besides alefacept and UV-B, no concomitant antipsoriatic treatment (including retinoids) was allowed. However, patients were allowed to use topical emollients ad libitum; on treatment days, emollient use was not allowed until after the NB UV-B treatment had been delivered.

ALEFACEPT THERAPY

All patients received weekly intravenous bolus injections of alefacept (7.5 mg) for a total of 12 weeks. Every week during alefacept treatment, CD4+ T-cell counts were determined. Weekly injections were not given when CD4+ T-cell counts fell below 250 cells/µL, and were resumed when CD4+ T-cell counts rose above this threshold. If CD4+ T-cell counts remained below 250 cells/µL for more than 4 consecutive weeks, alefacept treatment was discontinued.

NB UV-B THERAPY

All patients were treated with NB UV-B phototherapy on a randomly selected body half (left or right side) 3 times per week until complete remission of psoriasis on the irradiated body half was observed. For this study, complete remission was defined as a reduction in PASI to 3 or lower on the irradiated body half. Narrowband UV-B light was delivered by a Waldmann UV 7001 cabin equipped with TL-01/100 W fluorescent lamps and an integrated UV radiometer (Waldmann Medizinische Technik, Gevelsberg, Germany). For each patient, NB UV-B was delivered at a starting dose of 50% of the patient’s individual minimal erythema dose, determined as previously described by Hofer et al,22 and increased depending on erythema reaction to previous treatments.

DISEASE SCORING

Before and during the weekly alefacept treatment regimen, psoriatic skin lesions of all patients were scored in a nonblinded fashion by 1 of 2 physicians (E.J.L. or A.H.). Each patient’s PASI was determined separately for both the irradiated and non-irradiated body halves; psoriatic lesions on the head were not included in these evaluations. Thus, the PASI values recorded in this study ranged from 0 to 64.8, instead of the possible maximum of 72 originally described by Fredriksson and Pettersson.23 After the 12-week alefacept treatment regimen was completed, the PASI was evaluated every 4 weeks for 12 weeks. In addition, at each scoring session, patients were asked to assess (1) the severity of their skin lesions and (2) the overall therapeutic effect of combined treatment for each body half by using a continuous VAS ranging from 0 (no skin lesions and no therapeutic effect, respectively) to 10 (most severe skin lesions ever and best therapeutic effect imaginable, respectively).
Fourteen individuals (4 women and 10 men) with moderate to severe psoriasis (PASI > 10) were enrolled in this study. The mean patient age was 48 years (range, 25-59 years). The mean disease duration was 22 years (range, 4-50 years). The median total NB UV-B dose was 28.8 J/cm² (range, 13.7-58.9 J/cm²). The median number of NB UV-B treatments delivered was 21 (range, 16-34).

**STATISTICAL ANALYSES**

**Power Analysis**

Sample size was estimated using 1-sample t test with a power of 0.9 and a 2-sided type I error of 0.05. An increase in PASI reduction by 10 percentage points through the addition of UV-B treatment (eg, increase in PASI reduction from 50% to 60%) within 12 weeks was considered to be a clinically significant treatment effect. Using data from a half-body comparison study of PUVA treatment, and assuming a dropout rate of 20%, we estimated the sample size needed to be 14 patients.

**Data Analysis**

For patients who did not receive all 12 alefacept treatments, the scores at termination of alefacept treatment were carried forward to the 12-week time point. For patients who missed follow-up assessments at 4, 8, or 12 weeks after termination of alefacept treatment, the last observation was carried forward. The paired t test (or Wilcoxon signed-rank test if normality tests failed) was used to compare PASI and VAS scores for skin lesions on contralateral body sides and for self-assessed VAS scores of therapeutic effects of antipsoriatic treatment applied to contralateral body sides. The McNemar test was used to compare the number of patients reaching complete remission at 12 weeks.

**RESULTS**

Figure 1. Mean ± SEM changes over time in the Psoriasis Area Severity Index (PASI) during antipsoriatic half-side treatment with alefacept alone and in combination with narrowband UV-B (NB UV-B) phototherapy. The dashed line indicates the level at which complete remission (PASI = 3) was achieved.

*P < .001 for the difference between the PASIs for contralateral body sides at the end of a particular treatment week or after the end of alefacept treatment (ie, 1 week after the final alefacept treatment).

Within the first 12 weeks of antipsoriatic half-body treatment, the mean PASIs on irradiated and nonirradiated body halves were reduced by 81% and 62%, respectively (Figure 1). From week 3 to week 12, the mean PASIs for irradiated body halves were significantly lower than those for nonirradiated body halves (Figure 1). The lowest PASIs reached during the first 12 weeks of treatment were significantly lower on the UV-irradiated body halves than on the nonirradiated body halves at the same time points (Figure 2A). By week 12, PASI reductions of greater than 75% had been achieved significantly more often on UV-irradiated body halves (86%, 12 of 14) than on nonirradiated body halves (43%, 6 of 14) (Figure 2B) (McNemar test *P = .03). More remarkably, complete remission (PASI = 3) was achieved significantly more frequently on UV-irradiated body halves than on nonirradiated body halves (43%, 6 of 14 vs 0) (McNemar test *P = .03). A good clinical response to treatment (PASI reduction of ≥ 50%) was achieved at a similar rate on irradiated and nonirradiated body halves (Figure 2B).

Overall, most patients achieved a good antipsoriatic response to alefacept (PASI reduction of ≥ 50%) within the first 12 weeks of treatment with or without NB UV-B treatment (Figure 2B). The response to treatment in a representative patient is shown in Figure 3A-C. Only 1 patient responded moderately (PASI reduction of < 50%), and only 1 patient responded poorly (PASI reduction of < 25%) to alefacept without NB UV-B. While the poor responder had a moderate response to combination therapy on the other body half, the moderate responder had a very good response (PASI reduction of > 75%) to combination therapy (Figure 3D-F).

**CLINICAL RESPONSE**

**PATIENT SELF-ASSESSMENT**

The patients’ self-assessed VAS scores for skin lesion severity (data not shown) and therapeutic efficacy paralleled the physician-based PASI evaluations. According to the self-assessments, combination treatment with alefacept and NB UV-B was therapeutically more effective than treatment with alefacept alone from the second week of treatment on (Figure 4).
FOLLOW-UP

One week after the last administration of alefacept, a good clinical response to antipsoriatic treatment (PASI reduction of ≥50%) was achieved on the irradiated body half in 14 patients (100%) and on the nonirradiated body half in 12 of 14 patients (86%). During the 12-week follow-up period, the 2 patients who had PASI reductions of <50% on the nonirradiated body half required further NB UV-B irradiation to control their psoriasis. Another 2 patients whose psoriatic lesions on the nonirradiated body half did not completely clear during alefacept treatment also requested further NB UV-B phototherapy. Each of these 4 patients received whole-body NB UV-B phototherapy for at least 4 weeks during follow-up, which further reduced PASIs on the previously nonirradiated body half (Figure 5). The remaining 10 patients (71%) required no further phototherapy during follow-up and remained clear, or almost clear, of psoriatic lesions on both body halves (Figure 5).

ADVERSE EVENTS

Alefacept-related adverse events occurred. During the 12-week alefacept treatment phase, 9 of 14 patients reported at least 1 adverse event. The most frequent adverse event was fatigue (7 of 9 patients). Other, much less frequent adverse events were painful muscles, joints, or head (2 of 9 patients each) and numbness, dizziness, nausea, fever, and diarrhea (1 of 9 patients each). Most adverse events occurred only during the first weeks of alefacept treatment and lasted very briefly (usually less than 1 day) after intravenous alefacept administration. Two of 14 patients had to interrupt their weekly alefacept treatments (3 and 7 times, respectively) because their CD4+ T-cell counts fell below 250 cells/µL. These 2 patients also had upper respiratory tract infections (ie, common colds) for 1 week during 1 of these pauses. In 1 patient’s case, the CD4+ T-cell count fell below 250 cells/µL after the third weekly alefacept administration and remained below that level for more than 4 consecutive weeks. As a result, alefacept treatment was discontinued in this patient, per protocol.

No erythematous reactions or other adverse events related to NB UV-B half-body treatments were observed in this study.

COMMENT

In this study, the addition of NB UV-B phototherapy to alefacept treatment accelerated and improved the overall antipsoriatic treatment effect in our patients. In previous studies, the therapeutic effects of weekly intramuscular or intravenous alefacept administration in patients with psoriasis was first detected 4 to 8 weeks after the start of therapy. In our study, they were first noted within 2 to 3 weeks. Alefacept had a significantly better therapeutic effect when given in combination with NB UV-B phototherapy than when given alone, and this superior therapeutic effect was maintained throughout the active phase of alefacept treatment. Within the 12-week window of antipsoriatic treatment with alefacept, PASI reductions of more than 75% were achieved significantly more often on irradiated body halves than on contralateral nonirradiated body halves (McNemar test P = .03). Moreover, the rate of complete remission (PASI ≤ 3) during the 12 weeks of alefacept treatment was significantly higher on irradiated body halves (86%, 12 of 14 patients) than on nonirradiated body halves (0) (McNemar test P < .001). Although stopping NB UV-B treatment of an irradiated body half after clearance led to a slight increase in PASI until the end of the 12-week alefacept treatment regimen, 6 of 14 patients (43%) still remained completely clear of psoriasis on the irradiated body halves (P = .03).

According to a recent survey by the Psoriasis Foundation, patient satisfaction with an antipsoriatic treatment regimen depends on whether the treatment regimen can significantly reduce or cause complete remission.
of psoriatic skin lesions. Patient satisfaction, however, also depends on the number of adverse events the treatment will cause and how fast the treatment will restore the patient to an acceptable and/or satisfying skin condition and quality of life. There is an urgent need for new innovative treatment regimens that can rapidly clear psoriatic lesions and produce long disease-free intervals while producing relatively few adverse effects. The combination of alefacept and NB UV-B therapy partly meets this need and thus may have a promising future as antipsoriatic therapy.

Alefacept produces a durable therapeutic effect that reaches its maximum efficacy several weeks after the active phase of treatment has ended. Narrowband UV-B phototherapy is well tolerated by patients, is easy to use, and becomes effective more quickly than alefacept does, improving psoriasis lesions within only a few weeks of treatment. Theoretically, combining a new antipsoriatic biological treatment (alefacept) with an established antipsoriatic phototherapy (NB UV-B) would make perfect sense. The results of our present study, to our knowledge the first randomized trial of such a combination, support this theory. The addition of NB UV-B phototherapy not only significantly sped up the clearance of psoriatic skin lesions, but PASIs in most patients also remained stable or tended to de-

Figure 3. Clinical images of a patient with a good response (Psoriasis Area Severity Index [PASI] reduction ≥50%) on both UV-irradiated and nonirradiated body sides (A-C) and of a patient with no response on the nonirradiated body side but complete response (PASI reduction to =3) on the UV-irradiated side (D-F). The photographs in panels A and D were taken before treatment started; those in panels B and E and in panels C and F were taken after 6 and 12 weeks of therapy, respectively. Both patients received weekly intravenous alefacept treatments and narrowband UV-B (NB UV-B) phototherapy 3 times per week. The patient shown in panels A, B, and C interrupted the regimen with both alefacept and NB UV-B for 1 week because of personal reasons (holidays).
crease even further in the 12 weeks following the last alefacept administration. The combination was well tolerated by our patients, confirming previous reports.29 Adverse events related to intravenous alefacept treatment were generally mild, brief, and similar to those reported elsewhere in the literature.8,11,13,17,18 Meanwhile, no adverse events related to NB UV-B phototherapy and no increased susceptibility to NB UV-B on irradiated body halves were detected during alefacept treatment. However, little is known about possible long-term effects of using biological treatments such as alefacept in combination with other systemic antipsoriatic treatments including UV-B. While an increased photocarcinogenic effect due to the combined treatment of alefacept with NB UV-B cannot be totally excluded, the likelihood appears to be rather small since alefacept apparently lacks general immune suppression13 and does not increase short-term photosensitivity, consistent with the observations of our study.

The findings of this half-body comparison study lead us to conclude that NB UV-B accelerates and improves the clearance of psoriatic skin lesions in alefacept-treated patients. Combining alefacept with phototherapy thus appears to be a viable approach to the treatment of psoriasis that warrants further study, particularly comparing the combination of the 2 treatments against phototherapy alone. Possible future trials would also combine NB UV-B phototherapy or PUVA phototherapy with other biological agents such as the tumor necrosis factor α inhibitors (eg, etanercept or infliximab) or other biological agents that interfere with T-cell activation.

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Author Contributions: Dr Wolf 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.

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Nephrogenic Systemic Fibrosis

Relationship to Gadolinium and Response to Photopheresis

Heather Richmond, BA; Jeffrey Zwerner, MD, PhD; Youn Kim, MD; David Fiorentino, MD, PhD

Background: Nephrogenic systemic fibrosis (NSF), previously known as nephrogenic fibrosing dermopathy, is an idiopathic condition seen in patients with renal disease that is characterized by cutaneous sclerosis that can often result in contractures, pain, and functional disability as well as systemic complications. Recent reports have suggested a possible link with exposure to gadolinium, a commonly used radiocontrast agent. No current therapy has clearly demonstrated efficacy for NSF, although case reports suggest that extracorporeal photopheresis (ECP) may be of benefit. The purpose of this study was to explore the plausibility of a gadolinium linkage with NSF as well as to assess the efficacy of ECP in the treatment of a cohort of patients with NSF.

Observations: We report our experience with 8 consecutive patients with NSF seen at the Stanford Medical Center, Palo Alto, California, from 2004 to 2006. Of the 8 patients, 6 had a history of arterial or venous thrombotic disease and 7 had a documented exposure to gadolinium within 1 week to several months prior to the onset of NSF. Specifically, all patients were exposed to gadodiamide. We treated 5 of the patients with ECP. After a mean number of 34 treatment sessions over a mean of 8.5 months, 3 patients experienced a mild improvement in skin tightening, range of motion, and/or functional capacity.

Conclusions: Our data support the hypothesis that exposure to gadolinium, perhaps specifically gadodiamide, plays a role in the pathogenesis of NSF. Larger epidemiologic studies will be needed to confirm this association. In addition, our experience suggests that, if used for extended periods, ECP might have some mild benefit for patients with NSF. Larger, randomized, placebo-controlled trials of ECP should be performed to more specifically assess the benefit of ECP in the treatment of NSF.
model for the development of NSF involves a bloodborne cell of bone marrow origin, the circulating fibrocyte, which is involved in the normal wound healing process and is thought to be recruited to the sites of involvement and to subsequently cause the fibrotic changes that are associated with this disease. Cowper and colleagues suggest that recruitment of circulating fibrocytes to the tissues is a normal occurrence in patients with NSF, representing a physiologic response to stimuli that trigger a normal wound healing response (ie, clotting and endothelial injury) or possible passively in some cases (ie, secondary to edema). The authors contend that preexisting deposition of allergens, medications, or radiographic contrast agents might then serve to activate and initiate of the fibrotic process. Consistent with this notion, gadolinium, the contrast agent used for magnetic resonance imaging (MRI), has been implicated as an associated agent in 2 case series.

Treatment of patients with this disease is challenging, and even among the few patients who regain normal kidney function, many do not experience resolution of their symptoms. Many treatments under investigation include plasmapheresis, extracorporeal photopheresis (ECP), systemic and topical steroids, topical calcipotriene, selective histamine blockade, thalidomide, psoralen-UV-A (PUVA) light, cyclophosphamide, cyclosporine, methotrexate, interferon alfa, intravenous immunoglobulin, oral retinoids, and aggressive physical therapy. Unfortunately, none of these has been shown to be broadly efficacious, and many patients do not improve with these therapies. Extracorporeal photopheresis has been reported to be effective in reversing some of the symptoms of NSF in affected patients even in the face of persistent renal insufficiency.

The purpose of our study was to document our data pertaining to gadolinium exposure as well as the effects of ECP in our patients with NSF.

**RESULTS**

All patients had renal insufficiency or renal failure of varying causes at the time of disease onset, and all patients received some form of dialysis (Table 1). Of the 8 patients, 6 had a history of arterial or venous thrombotic disease. Of the 4 patients undergoing evaluation for a hypercoagulable state, 3 were found to have elevated homocysteine levels, and 1 patient was also positive for anticardiolipin antibodies (Table 2). Two patients had possible extracutaneous disease: 1 patient (patient 4) had pleural nodularity on chest radiography (without diagnostic biopsy) and a second patient (patient 1) had yellow scleral plaques, a finding previously documented in NSF.

In light of recent data implicating gadolinium exposure with NSF, we attempted to obtain complete documentation regarding gadolinium exposure in our cohort. Of 8 patients, 7 had documented radiographic imaging using gadolinium contrast prior to the onset of symptoms, and all received gadodiamide (Table 1). Patients 1, 2, 3, 7, and 8 received the contrast agent during MRI. Patient 6 was exposed to gadodiamide during a concurrent head MRI/magnetic resonance angiography. Patient 4 developed symptoms consistent with NSF shortly after a radiology-directed liver biopsy in which gadodiamide was used. For the 5 patients with available records, the mean time to onset of symptoms was 3 to 4 weeks (range, 1-8 weeks) following gadodiamide exposure. Records regarding the exact date of onset of symptoms were not obtainable for 2 patients with documented gadolinium exposure, but the onset of symptoms occurred within months of the specified procedure. One patient (patient 4) had transient acute renal failure that lasted only 10 days, during which time she was given gadodiamide contrast. Although her renal failure subsequently resolved, she developed NSF within 8 weeks of gadodiamide exposure but continues to slowly improve without therapy. Another patient (patient 3) underwent a successful renal...
transplantation in 2004 and, despite normal renal function, continued to experience stable cutaneous disease (for over a year) before therapy.

We treated 5 of our patients with ECP (Table 3). At the time of treatment, all of these patients had progressive disease (based on patient history and physician global assessment of skin sclerosis) that had been present for a mean of 2.75 years. After a mean number of 34 treatment sessions (17 courses) over a mean of 8.5 months, 3 patients experienced mild improvement in both skin tightening and/or objective range of motion despite persistent renal insufficiency (Table 3; data not shown). The mean number of treatments before improvement was observed was 20 (range, 6-30). These patients were able to perform activities limited to them before ECP treatment, such as walking without mechanical assistance (patients 2 and 7) or climbing a flight of stairs unassisted (patient 3), leading to a significant improvement in their quality of life.

### Table 1. Clinical Features of Patients With Nephrogenic Systemic Fibrosis (NSF)

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Sex/Age, y</th>
<th>Renal Disease</th>
<th>Dialysis (Dates)</th>
<th>NSF Onset</th>
<th>Other Findings</th>
<th>Documented Gadolinium Exposure?</th>
<th>Type of Gadolinium Agent</th>
<th>Onset After Exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/M/71</td>
<td>M/71</td>
<td>Pyelonephritis/gentamycin</td>
<td>HD (Aug 2002–present)</td>
<td>2003</td>
<td>Scleral yellow plaques</td>
<td>Yes</td>
<td>Gadodiamide</td>
<td>Months</td>
</tr>
<tr>
<td>7/M/59</td>
<td>M/59</td>
<td>ESRD due to HTN/diabetes</td>
<td>History of HD, currently receiving PD</td>
<td>July 2005</td>
<td>None</td>
<td>Yes</td>
<td>Gadodiamide</td>
<td>1 wk</td>
</tr>
<tr>
<td>8/M/66</td>
<td>M/66</td>
<td>CRI due to PSGN</td>
<td>HD (Nov 2003–Apr 2004)</td>
<td>May 2005</td>
<td>None</td>
<td>Yes</td>
<td>Gadodiamide</td>
<td>3-4 wk</td>
</tr>
</tbody>
</table>

Abbreviations: ARF, acute renal failure; CRI, chronic renal insufficiency; ESRD, end stage renal disease; HD, hemodialysis; HTN, hypertension; NA, not available; PBC, primary biliary cirrhosis; PD, peritoneal dialysis; PSGN, post–streptococcal glomerulonephritis; RCC, renal cell carcinoma; →, followed by.

### Table 2. Thrombosis History in Patients With Nephrogenic Systemic Fibrosis

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Thrombosis History</th>
<th>Hypercoagulable Workup</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DVT in 2003 and 2005</td>
<td>Serum homocysteine level normal; factor V Leiden, prothrombin gene, antithrombin III gene, protein C, and protein S all within normal limits; LAC/anti-CL negative</td>
</tr>
<tr>
<td>2</td>
<td>DVT in 2000</td>
<td>None performed</td>
</tr>
<tr>
<td>3</td>
<td>DVT in 1945 and 1990, PE in 1990</td>
<td>None performed</td>
</tr>
<tr>
<td>4</td>
<td>None</td>
<td>None performed</td>
</tr>
<tr>
<td>5</td>
<td>Acute graft rejection secondary to renal artery thrombosis in 2003</td>
<td>Elevated serum homocysteine level; factor V Leiden, prothrombin gene, antithrombin III gene, protein C, and protein S all within normal limits; LAC/anti-CL negative</td>
</tr>
<tr>
<td>6</td>
<td>Internal jugular vein thrombosis in 2005</td>
<td>None performed</td>
</tr>
<tr>
<td>7</td>
<td>None</td>
<td>Elevated serum homocysteine level</td>
</tr>
<tr>
<td>8</td>
<td>DVT</td>
<td>Elevated serum homocysteine level; LAC negative; anti-CL IgG positive/IgM negative</td>
</tr>
</tbody>
</table>

Abbreviations: Anti-CL, anticardiolipin antibodies; DVT, deep venous thrombosis; LAC, lupus anticoagulant; PE, pulmonary embolism.

We report our experience with NSF in a cohort of 8 patients at the Stanford Medical Center. Consistent with other reports, all of our patients had renal insufficiency or failure (1 transient and 7 chronic), and as in the majority of documented cases, all were receiving some form of dialysis. Consistent with previously published data on this disease process, improvement in renal function does not necessarily result in remission of NSF; of our patients who had transient renal failure (patient 4), significant improvement in renal function (patient 8), or a successful renal transplantation (patient 3), all continue to manifest symp-
toms of NSF. Only 1 of these patients (patient 4) demonstrated improvement without therapy.

Interestingly, 6 of 8 patients had a history of arterial or venous thrombosis. This has been described in patients with NSF,\textsuperscript{10} and circulating anticardiolipin antibodies were a consistent finding in at least 1 cohort,\textsuperscript{20} although this is not a consistent finding.\textsuperscript{21,22} Of the 4 patients in this series evaluated for anticardiolipin antibodies, only 1 was found to have a detectable level. Serum homocysteine level, another risk factor for thrombosis, was elevated in 3 of the 4 patients tested. This result is not surprising, since multiple reports have linked even mild renal disease with elevated homocysteine levels, and the prevalence of hyperhomocysteinemia in hemodialysis patients is between 80\% and 100\%.\textsuperscript{23,24} It is unclear if a hypercoagulable state is associated with NSF or simply represents the known association with renal failure.\textsuperscript{25,26}

It is tempting to speculate that some form of endothelial damage might play a role in the pathogenesis of NSF, perhaps leading to the physiologic recruitment of circulating fibrocytes to the skin.\textsuperscript{1,12}

Our data are consistent with a potential causative link between gadolinium contrast and NSF. All patients for whom we have a definitive set of complete records demonstrated improvement without therapy.

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Treatment Period (State of Disease Before ECP)\textsuperscript{a}</th>
<th>Prior Failed Treatments</th>
<th>Frequency</th>
<th>Total No. of Treatments</th>
<th>Adjuvant Medications</th>
<th>Response to ECP/Time to Response\textsuperscript{b}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Feb 2006–Aug 2006 (3 y/progressive)</td>
<td>Calcipotriene, thalidomide, intravenous immunoglobulin</td>
<td>Every 2 wk</td>
<td>30</td>
<td>Acitretin, 25 mg 3 times per wk (Apr 2006–Oct 2006); prednisone 7 mg/d (Feb 2006–present)</td>
<td>Stable disease</td>
</tr>
<tr>
<td>2</td>
<td>Feb 2006–Nov 2006 (9 mo/progressive)</td>
<td>Plasmapheresis,\textsuperscript{c} acitretin</td>
<td>Every 3 wk</td>
<td>36</td>
<td>Acitretin, 25 mg 3 times per week (June 2006–present)</td>
<td>Mildly improved skin tightness (proximal UE MRS decreased from 1 to 0; distal UE MRS decreased from 2 to 1; LE MRS, 3 [stable] and objective ROM (knee flexion right increased from 120\° to 150\°; left decreased from 120\° to 100\°); marked improvement in self-ambulation (45 wk)</td>
</tr>
<tr>
<td>3</td>
<td>Apr 2005–continued (7 y/progressive)</td>
<td>None</td>
<td>Every 2 wk</td>
<td>44</td>
<td>None</td>
<td>Mildly improved skin tightness (abdomen MRS decreased 3 to 1; distal UE MRS decreased from 2 to 1; LE MRS, 3 [stable]); marked improvement in self-ambulation, patient able to climb stairs unassisted (6 wk)</td>
</tr>
<tr>
<td>7</td>
<td>Aug 2006–continued (13 mo/progressive)</td>
<td>Calcipotriene</td>
<td>Every 1 wk</td>
<td>22</td>
<td>Acitretin, 25 mg 3 times per week (Aug 2006–present); physical therapy</td>
<td>Mild improved skin tightness (hand MRS decreased from 3 to 1; distal UE MRS decreased from 3 to 1; LE MRS, 3 [stable]); marked improvement in ambulation, increased perceived flexibility (20 wk)</td>
</tr>
<tr>
<td>8</td>
<td>June 2006–continued (2 y/progressive)</td>
<td>Thalidomide/dexamethasone,\textsuperscript{d} acitretin</td>
<td>Every 2 wk</td>
<td>22</td>
<td>Acitretin, 25 mg/d (May 2005–present); prednisone, 3 mg/d (June 2006–present); physical therapy</td>
<td>Stable disease</td>
</tr>
</tbody>
</table>

Abbreviations: ECP, extracorporeal photopheresis; LE, lower extremity; MRS, modified Rodnan score; ROM, range of motion; UE, upper extremity.

\textsuperscript{a} Progressive disease was defined as worsening symptoms in the 6 months prior to starting ECP.

\textsuperscript{b} Included MRSs are those measured before ECP and then at the end of the quoted number of treatments.

\textsuperscript{c} Patient had to discontinue this therapy after 1 session because of hypotension.

\textsuperscript{d} Patient had to discontinue this therapy after 1 month secondary to the development of deep venous thrombosis.
nance angiography may have been administered. A discussion with the patient's family members, primary care physician, and nephrologist, however, failed to uncover records of any such procedure.

There are 5 different gadolinium-based contrast agents that are approved by the Food and Drug Administration (FDA) for medical use in the United States including gadopentetate dimeglumine (Magnevist; Bayer HealthCare Pharmaceuticals Inc, Wayne, New Jersey), gadoteridol (ProHance; Bracco Diagnostic Inc, Princeton, New Jersey), gadodiamide (Omniscan; Nycomed Inc, Princeton), gadoversetamide (OptiMARK; Mallinckrodt, Hazelwood, Missouri), and gadobenate dimeglumine (MultiHance; Bracco Diagnostics Inc). These were approved by the FDA in 1988, 1992, 1993, 1999, and 2004, respectively, for use in MRI.

Interestingly, all of our patients were exposed specifically to gadodiamide. This is consistent with previous studies.11,14,27 Gadodiamide is a nonionic chelate of gadolinium and diethylenetriaminepentaacetic acid bis(methylamide),26 and is characterized by having excess chelate and being less stable. This is due to the high propensity for this particular substance to undergo transmetallation with endogenous ions.29 It is possible that either free gadopentetate dimeglumine or the chelate itself could bind to endogenous ions in the tissues.30 This ion is poorly soluble and it can form salt precipitates with phosphates and other anions that are frequently elevated in patients with renal failure, which may lead to increased tissue deposition and inflammation.13 Indeed, gadolinium has been detected in the skin of patients with NSF, most likely in intracellular deposits.15,30 This is consistent with the hypothesis that this might be a trigger for resident CD34+ cells to synthesize extracellular matrix components, including collagen. According to the FDA Web site, NSF has been associated with 3 of the 5 FDA-approved gadolinium-containing agents, and they warn that all of the available agents might have the potential for this association.27

Case reports suggest that ECP might be an effective treatment for some patients with NSF. In one report of 3 patients, all demonstrated significant improvement in terms of joint mobility and both objective and subjective skin softening following at least 4 cycles of ECP. One patient developed complete resolution of symptoms after 16 cycles of treatment.16,17 Auron et al17 report 1 case of a pediatric patient who experienced symptomatic improvement following 1 year of 2-day sessions occurring every other week. Finally, although the report by Gilliet et al15 suggests that significant improvement can be seen as early as 8 weeks, other patients have required much longer treatment periods to show benefit. Although none of our patients had as dramatic a response as those in the previous reports, results were encouraging. Of the 5 patients treated with ECP, 3 had some form of objective response. In all of the responding patients, the decreased sclerosis was primarily seen in the upper extremities. Such “minor” objective improvement can offer significant hope and benefit in the quality of life of patients, since all patients had a notable improvement in function. The 2 patients without objective improvement demonstrated stabilized disease while receiving ECP, because the disease was progressive before therapy, this might also indicate a therapeutic benefit. It is unclear whether technical differences in the ECP treatment are responsible for the varied outcomes between our cohort and those previously reported. In addition, the time lapse between disease onset and the start of ECP treatment was not mentioned in the previous reports. Our patients had a mean disease duration of 2.75 years before they received ECP. It is possible that patients treated early in their disease course, before extensive sclerosis has developed, would benefit most from this therapy. It should also be noted that acitretin therapy was used as adjuvant therapy in many of our patients, based on positive personal experience from the authors (Y.K. and D.F.) in other sclerosing disorders of the skin, such as scleromyxedema and chronic graft-vs-host disease (and limited data in NSF). For 2 of our patients responding to ECP (patients 2 and 7), the contribution of the retinoid cannot be discounted.

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Author Contributions: Dr Fiorentino 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. Ms Richmond and Dr Zwerner contributed equally to this work. Study concept and design: Richmond, Kim, and Fiorentino. Acquisition of data: Richmond, Zwerner, Kim, and Fiorentino. Analysis and interpretation of data: Richmond, Zwerner, Kim, and Fiorentino. Drafting of the manuscript: Richmond. Critical revision of the manuscript for important intellectual content: Zwerner, Kim, and Fiorentino. Administrative, technical, and material support: Richmond, Zwerner, and Fiorentino. Study supervision: Kim and Fiorentino.

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REFERENCES

Treatment of Severe Pemphigus With Rituximab

Report of 12 Cases and a Review of the Literature

Giuseppe Cianchini, MD; Rosamaria Corona, DSc, MD; Alessandra Frezzolini, BSc; Marina Ruffelli, BSc; Biagio Didona, MD; Pietro Puddu, MD

Background: Treatment of pemphigus vulgaris can be challenging. Systemic steroids associated with other immunosuppressant agents are the mainstay of therapy and have dramatically reduced morbidity and mortality from pemphigus vulgaris. In some patients, however, these agents are not able to control the disease or have severe adverse effects. Rituximab (MabThera; Roche, Basel, Switzerland), a chimeric monoclonal anti-CD20 antibody, induces depletion of B cells in vivo and has shown efficacy in patients with refractory antibody-mediated autoimmune disorders. We report 10 cases of pemphigus vulgaris and 2 cases of pemphigus foliaceous treated with rituximab—to our knowledge the largest series of patients so far—and review the existing literature on the topic.

Observation: The 12 patients were selected for treatment with the anti-CD20 antibody. Rituximab was administered intravenously at a dosage of 375 mg/m² once weekly for 4 weeks. The treatment was well tolerated, and all 12 patients showed a good clinical response during an 18-month follow-up period, along with a consensus decline of the serum anti-desmoglein titers. No infectious complications were observed.

Conclusions: Rituximab is able to induce a prolonged clinical remission in patients with both pemphigus vulgaris and pemphigus foliaceous after a single course of 4 treatments. The preliminary experiences worldwide make rituximab a promising therapeutic option for patients with autoimmune diseases. The high costs and the limited knowledge of long-term adverse effects, however, limit its use to selected patients with treatment-resistant or life-threatening disease.

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Pemphigus vulgaris (PV) and pemphigus foliaceous (PF) are autoimmune blistering diseases that affect the skin and mucous membranes, mediated by circulating autoantibodies directed against desmogleins, which are desmosomal proteins responsible for keratinocyte adhesion. Pemphigus foliaceous is caused by autoantibodies directed against desmoglein 1 (Dsg1), whereas in PV the autoantibodies heat desmoglein 3 (Dsg3) with or without concomitant damage to Dsg1. The binding of autoantibodies results in loss of cell-cell adhesion and blister formation. Systemic steroids, in combination with immunosuppressive agents, are the mainstay of therapy in PV and have dramatically improved the prognosis, but adverse effects and complications from long-term immunosuppressive therapy still contribute substantially to morbidity and mortality from this disease. Furthermore, a number of patients are resistant to conventional therapy. For these patients, alternative treatments (eg, pulse administration of high-dose steroids or cyclophosphamide, plasmapheresis, photopheresis, intravenous immunoglobulins, mycophenolate mofetil, immunoabsorption) have been used.

More recently, rituximab (MabThera; Roche, Basel, Switzerland), a chimeric murine-human anti-CD20 monoclonal antibody directed against pre-B lymphocytes and mature B lymphocytes, has been used in a small number of patients affected with severe PV and PF after the failure of conventional and alternative therapies. Rituximab induces depletion of B cells in vivo and has been shown to be effective and well tolerated in several autoimmune antibody-mediated conditions.

We report 10 cases of recalcitrant or rapidly progressive PV and 2 cases of widespread PF treated with rituximab, discuss the indications for and adverse effects of this therapy, and provide a review of the existing literature on the topic.

Methods

Patients with an unequivocal diagnosis of mucocutaneous PV or PF according to clinical, histopathologic, and immunofluorescence criteria and level of anti-desmoglein antibodies were considered for treatment with rituximab if they had recalcitrant or rapidly progressive disease that was not controlled by conventional therapy and had severe adverse effects from long-term steroid therapy.
The severity of the disease was assessed according to the revised severity index for pemphigus described by Ikeda et al. Each item in the severity index was scored from a minimum of 0 to a maximum of 3 and included: (1) the ratio of the affected area of skin to the total skin area as a percentage (0, none; 1, <5%; 2, 5%-15%; and 3, >15%); (2) the presence or absence of the Nikolsky phenomenon (0, none; 1, focal; 2, positive; and 3, distinct); (3) the number of newly developed blisters per day (0, none; 1, occasional blisters; 2, 1-5 blisters; and 3, >5 blisters), and (4) the presence or absence of oral lesions as a percentage (0, none; 1, occasional blisters; 2, 1-5 blisters; and 3, >5 blisters). Consequently, the severity of a case was rated by the total of the scores and considered to be mild if the score was less than 5, moderate if 5 to 7, and severe if higher than 7.

Circulating levels of anti-Dsg3 and anti-Dsg1 IgG antibodies were measured in serum samples by a commercially available enzyme-linked immunosorbent assay (Medical & Biological Laboratories, Nagoya, Japan) based on recombinant human desmogleins produced in a baculovirus expression system. All sera, stored at -20°C until use, were assayed in duplicate, using a cutoff in quantity of 14 and 7 U/mL for anti-Dsg1 and anti-Dsg3 antibodies, respectively.

Rituximab was administered in 4 weekly infusions at a dosage of 375 mg/m², with a premedication of oral paracetamol, 500 mg, and chlorphenamine maleate, 10 mg. Follow-up examinations were performed weekly for the first month and monthly thereafter, and included assessment of the skin and mucous membranes, photographic documentation, routine blood tests, peripheral B-cell count, and antidesmoglein antibodies level measurement.

The primary efficacy criteria were the resolution of the mucocutaneous lesions and the subsequent control of the disease with low-dose immunosuppressive agents. Complete response was defined as the absence of lesions for at least 1 month and no treatment with glucocorticoid or adjuvants or treatment with 5 mg or less of prednisone per day; partial response was defined as the presence of 1 to 5 new oral or cutaneous blisters per week with treatment with 10 mg or less of prednisone and no adjuvants. Disease control was defined as the suppression of new blisters, together with the beginning of healing of the existing lesions and the Nikolsky phenomenon potentially present. Long-lasting complete response was defined as no treatment with glucocorticoids or adjuvant therapies for 6 months and being free of lesions.

REPORT OF CASES

Twelve patients (5 men and 7 women, aged 27-63 years) underwent rituximab treatment. Of these, 10 patients had PV with severe mucocutaneous involvement and 2 had PF. Patient 11 had PF induced by hydroxychloroquine prescribed for concomitant rheumatoid arthritis. All of the patients had refractory disease and had experienced severe adverse effects from long-term steroid therapy (Table).

In all the cases, the prednisone dosage before the beginning of the rituximab infusions was at least 40 mg/d. Steroid-sparing immunosuppressive therapy had already been administered in at least 2 different ways, in all but 2 cases (patients 8 and 11, whose clinical conditions were characterized by psychosis).

The prednisone dosage was reduced to 25 mg/d soon after the first rituximab infusion and was maintained until the end of the fourth infusion; then a dosage of 12.5 mg/d was continued with a subsequent gradual decrease according to the clinical conditions. Concomitant immunosuppressive therapies were stopped at the beginning of the first infusion in 9 patients; only patients 1 and 5 continued treatment with azathioprine and patient 2 with cyclophosphamide, respectively (see “Comment” section).

RESULTS

All patients had a positive response after treatment (Figure 1 and Figure 2). All the patients experienced disease control for 1 month after the end of the rituximab infusions. Patients 3 and 7 showed an early complete response 1 month after the completion of the treatment. Two months after therapy, 4 patients had complete response (patients 3, 4, 7, and 8) and 8 patients had a partial response. Six months after the end of the infusions only 3 patients had a partial response (patients 5, 10, and 12), whereas the other 9 had a complete response. Four patients experienced a long-lasting complete response for up to a year (patients 1, 2, 3, and 4). No relapses were recorded during follow-up. In 1 case (patient 5), 1 additional infusion of rituximab was given after 6 months. No serious adverse effects occurred after the infusion of rituximab; the only adverse effect was mild tachycardia during the infusions in patient 8.

Patients were given maintenance therapy with prednisone, beginning with 12.5 mg/d and thereafter in tapering doses. Two patients were also administered azathioprine, 100 mg/d, for 2 months in patient 1 and for 6 months in patient 5, and 1 patient was given cyclophosphamide, 50 mg/d, for 2 months.

Changes in anti-Dsg1 and anti-Dsg3 levels, consistent with the clinical response, are shown in Figure 3 and Figure 4, respectively. The antibody titer showed a slow but progressive decline over a 6-month period. In patient 3, a rapid decrease of anti-Dsp3 was observed 1 month after starting the treatment, with a consensual rapid clinical improvement; the patient remained stable 6 months after starting the treatment.

All patients underwent close surveillance for occurrence of infections, but none of them had such a complication. A slight decrease in the serum immunoglobulin level, not exceeding 20% of the basal value, was observed in all patients. As expected, the B-cell count in the peripheral blood dropped to 0 after the first infusion and remained undetectable for at least 6 months in all the treated patients.

After reviewing the literature, we found 17 case reports describing a total of 22 patients with PV and 3 with PF who had been treated with rituximab. Clinical characteristics, treatments, and outcomes for these patients are available in an eTable [http://archdermatol.com]).

COMMENT

The treatment of PV can be a challenge. Steroids are the first-line therapy, but long-term administration may lead to serious adverse effects. To control the disease, adjuvant therapy with other immunosuppressive agents, such as azathioprine, cyclophosphamide, or mycophenolate mofetil, are added as steroid-sparing agents, even though, to date, evidence on the best therapeutic regimen is scanty. In some patients, combined immunosuppressive regimens fail, and to date, treatment options have been limited.

Rituximab is a chimeric murine-human anti-CD20 monoclonal antibody that binds to the CD20 antigen on
pre-B, immature, and mature B cells. Because CD20 is not expressed on stem cells and plasma cells, depletion of the B-cell subpopulation is transient and does not affect immunoglobulin synthesis. Rituximab has become part of the standard therapy for patients with CD20-expressing B-cell lymphoma and is currently under investigation for other indications, including autoimmune diseases, in particular, lupus erythematosus and rheumatoid arthritis.3

In the literature, we found 17 case reports describing 22 patients with PV and 3 with PF who were treated with rituximab and followed up for 3 to 36 months.5-21 Three patients underwent an additional infusion,9,11 and 2 patients had multiple infusions of rituximab16,17 without serious adverse effects. In 20 cases there was a complete response, followed by a relapse in 1 patient in whom a second course of rituximab cleared the lesions, obtaining a new complete response.9 Only 1 patient with severe PF did not show a clinical response.18

A recent article by Ahmed et al22 reported the outcome of a combined treatment with CD20 and intravenous immunoglobulin treatment for 11 patients with PV. The patients were treated with 1 infusion of rituximab, 375 mg/m² weekly for 3 weeks, followed in the fourth week by a intravenous immunoglobulin infusion, 2 g/kg. This cycle was then repeated. At the start of each of the following 4 months the patients received a single infusion of rituximab plus a single infusion of intravenous immunoglobulin. That report22 represents the largest single series of patients with PV treated with rituximab published to date, but because of the concomitant use of intravenous immunoglobulin infusions and the repeated administrations of rituximab, these cases are not comparable with our series and those in the existing literature. However, the authors22 reported a good clinical response with no adverse effects or infections during a mean follow-up period of 31.1 months.

In previously reported cases, we noticed that a variety of immunosuppressive drugs were used as adjuvant therapy after rituximab administration (available in the eTable [http://archdermatol.com]). It is very difficult to compare drugs and dosages to clarify their single role in inducing the clinical response, but in 10 patients no drugs or only steroids were used after rituximab administration; follow-up in these cases was uncomplicated, and clinical remissions lasting up to 36 months were reported (available in the eTable [http://archdermatol.com]). One may assume from this examination that the use of an immunosuppressive drug other than a steroid does not result in much difference in the rate of response, period of remission, or incidence of relapses.

### Table. Description of Cases

<table>
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<tr>
<th>Patient/ Sex/Age, y</th>
<th>Pemphigus Type</th>
<th>Duration, y</th>
<th>Previous Treatments</th>
<th>Adverse Effects of Long-term Oral Steroid Therapy</th>
<th>Duration of Follow-up, mo</th>
<th>Maintenance Therapya</th>
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<td>PV</td>
<td>2.5</td>
<td>Oral steroids, HD IV steroids, azathioprine, methotrexate</td>
<td>Osteoporosis with multiple fractures, cataract, glaucoma</td>
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<td>Oral steroids, azathioprine</td>
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<td>2/M/63</td>
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<td>Oral steroids, HD IV steroids, azathioprine, oral cyclophosphamide, IV Ig</td>
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<td>12</td>
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</tr>
<tr>
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<td>Osteoporosis, dyslipidemia, arterial hypertension</td>
<td>10</td>
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</table>

Abbreviations: EP, extracorporeal photopheresis; HD, high-dosage; Ig, immunoglobulins; IV, intravenous; PF, pemphigus foliaceous; PLA, plasmapheresis; PV, pemphigus vulgaris.

*After rituximab administration.*
We treated 12 patients with recalcitrant PV or PF with rituximab, one of the largest series of patients reported to date. All tolerated the treatment well. Nine exhibited a complete response 6 months after 1 course of 4 infusions of rituximab, and only 1 patient was given an additional single dose 6 months after the first course.

All but 3 received maintenance therapy with low-dose steroids without other immunosuppressive agents. This is quite a different feature compared with those of
Similar cases showing an early clinical improvement have been described. We can hypothesize that this favorable response to rituximab therapy may be due to a late response to previous immunosuppressive therapy or to other immunological mechanisms, including a high percentage of CD20+ cells in the total amount of autoantibodies producing B cells. In fact, a late response may be observed: in the literature we have found several other cases that are similar to our case.

In most of our patients, a clinical response was observed 6 to 10 weeks after the completion of treatment. This outcome can be explained by assuming that rituximab depletes from peripheral blood and peripheral lymphoid organs the CD20+ B cells that are precursors of long-lived autoantibody-forming plasma cells and that these cells are not immediately replaced. This depletion lasts for 6 months or more in most patients, well beyond the persistence of rituximab itself. The extent of depletion of B cells from peripheral lymphoid organs is not known. Because long-lived plasma cells that are CD20+ survive and continue to produce antibodies, the levels of serum immunoglobulins do not fall substantially during the treatment. In 2 reported cases of patients treated with rituximab, the Dsg1 and Dsg3 levels correlated with clinical response to the therapy, whereas antibody levels against herpes simplex virus 1 and 2 and varicella-zoster virus were not significantly affected. To explain the fall in levels of specific autoantibodies, 1 hypothesis is that rituximab acts on distinct B-cell subsets and that different sensitivity to rituximab depends on factors derived from the cellular microenvironment.

In only 2 of our patients did we observe that a more rapid response manifested during the rituximab course. Similar cases showing an early clinical improvement have been described. We can hypothesize that this favorable response to rituximab therapy may be due to a late response to previous immunosuppressive therapy or to other immunological mechanisms, including a high percentage of CD20+ cells in the total amount of autoantibodies producing B cells. In fact, a late response may be observed: in the literature we have found several other cases that are similar to our case.

In most of the cases reported, the clinical response paralleled the serum decrease of autoantibodies measured by indirect immunofluorescence. In 13 patients, the levels of anti-Dsg1 and anti-Dsg3 were measured, and those levels were not always correlated with the clinical response. In fact, in some patients the clinical improvement was not accompanied by a simultaneous decrease of antidesmoglein titers. A possible explanation for these phenomena may be the existence of less pathogenic antidesmoglein autoantibodies or the suggestion that B-cell depletion and autoantibody reduction are not the only mechanisms involved in the therapeutic effect of rituximab. Several reports clearly underline the role of T lymphocytes in the control of the immune response in PV and PF, and, recently, the role of autoreactive Tp,1, Tp,2 cells, which may be involved in the regulation of the production of pathogenic autoantibodies by B cells, has been identified. Rituximab could influence T-cell activity through modulation of the cytokine network at different levels. This hypothesis could even explain the different rates of decline in the autoantibody titer in our patients. Further investigation is needed on the immunological effects of rituximab.

We did not observe any infectious episode in our patients. Over 500,000 patients with lymphoma worldwide have been treated with rituximab to date, and serious adverse reactions, including infections, have been reported in only a small minority of patients. Similar data have been obtained from clinical trials of rituximab in patients with rheumatoid arthritis. Little is known about the conditions that may act as predisposing factors in developing infections after rituximab therapy.
rituximab administration, but the age of the patient at the time of infusion does not seem to be an important feature.

In 4 of the cases of pemphigus reported in the literature, serious infections occurred following rituximab treatment. In the case reported by Salopek et al., sepseis from *Pseudomonas aeruginosa* and *Staphylococcus aureus* developed shortly after the first infusion of rituximab in an immunocompromised patient who had previously experienced similar episodes, so it is unlikely that rituximab had caused this complication. Dupuy et al. described the occurrence of hip arthritis caused by *P aeruginosa* in a patient with diabetes mellitus 12 weeks after the first infusion of rituximab, but this complication was a relapse of an already existing condition. In 6 only in 1 case was there a fatal case of pneumonia from *Pseudocystis carinii*, which occurred 4 months after the end of rituximab administration. It should be noted that, in all 4 cases, after rituximab administration the therapy was associated with steroids and immunosuppressive drugs (cyclophosphamide in 2 cases, azathioprine in 1 case, and cyclosporine A plus mofetil mycophenolate in 1 case), and in the fatal case there was concomitant administration of cyclophosphamide. These data seem to show that therapy with rituximab does not cause an increase in the rate of opportunistic infections in patients with serious and refractory PV or PF, keeping in mind that all these patients had experienced years of immunosuppressive therapy with high dosages of multiple drugs. We believe that only the addition of immunosuppressive drugs other than steroids could increase the risk of infectious adverse effects, but this choice does not seem to influence the clinical response of the disease or the incidence of relapses. However, the possibility of multiple courses of rituximab can be considered in refractory cases: the tolerability profile does not change, as Kong et al. have shown.

Finally, rituximab is a chimeric murine-human molecule, so there are some concerns about the long-term adverse effects of infusion of foreign protein, and a prior sensitivity to murine proteins has to be ruled out before administering this monoclonal antibody.

In conclusion, rituximab can be considered an important treatment option in patients with widespread recalcitrant or life-threatening PV. This drug has a good safety and tolerability profile and has shown a positive and long-lasting response in patients with PV after a single course. These characteristics make it a therapy that is potentially able to modify the natural history of PV. Unfortunately, rituximab is very expensive, and its long-term effects are still unknown. Although its use is currently limited to selected cases of PV, controlled clinical trials with a greater number of patients are urgently needed.

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Financial Disclosure: None.

Additional Information: The eTable is available at http://www.archdermatol.com.

REFERENCES

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<th>Previous Treatments</th>
<th>Response</th>
<th>Follow-up, mo</th>
<th>Remission</th>
<th>Relapse</th>
<th>Maintenance Therapy</th>
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<td>Steroids, IV HD steroids, azathioprine, oral cyclophosphamide, cyclosporin A, mofetil mycophenolate, IV Ig</td>
<td>Slow</td>
<td>12</td>
<td>C</td>
<td>No</td>
<td>Steroids, IV HD steroids, mofetil mycophenolate</td>
<td>None</td>
</tr>
<tr>
<td>Esposito et al21</td>
<td>M/45</td>
<td>10</td>
<td>1</td>
<td>Steroids, azathioprine, cyclosporin A, mofetil mycophenolate, IV Ig methotrexate</td>
<td>Fast</td>
<td>7</td>
<td>C</td>
<td>No</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>M/49</td>
<td>2</td>
<td>1</td>
<td>Steroids, azathioprine, cyclosporin A, IV Ig</td>
<td>Fast</td>
<td>6</td>
<td>C</td>
<td>No</td>
<td>None</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Niedermeier et al20</td>
<td>M/26</td>
<td>1.5</td>
<td>1</td>
<td>Steroids, azathioprine, oral cyclophosphamide, PLA</td>
<td>Slow</td>
<td>12</td>
<td>C</td>
<td>No</td>
<td>Steroids, mofetil mycophenolate</td>
<td>None</td>
</tr>
</tbody>
</table>

Abbreviations: C, complete; EP, extracorporeal photopheresis; HD, high-dose; IAd, immunoadsorption; Ig, immunoglobulins; IV, intravenous; MI, multiple infusions; NR, not reported; P, partial; PLA, plasmapheresis.

a After rituximab administration.

b The patient had pemphigus foliaceous.

c Follow-up of the case reported by Herrmann et al.6

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Active Angiogenesis in an Extensive Arteriovenous Vascular Malformation

A Possible Therapeutic Target?

Pedro Redondo, MD, PhD; Antonio Martínez-Cuesta, MD; Emilio G. Quetglas, MD; Michel Idoate, MD, PhD

Vascular malformations result from the aberrant development of vascular elements during embryogenesis and fetal maturation. Despite apparent endothelial quiescence, some vascular malformations can expand rapidly during adolescence or pregnancy, after a surgical procedure, or in response to trauma. The pathogenesis of vascular malformations is not well clarified, but their formation and progression are closely related to angiogenesis, a complicated network that is closely regulated by many angiogenic factors.1

REPORT OF A CASE

A 51-year-old man presented with an arteriovenous malformation in the left side of the trunk and arm (Figure, A). At the age of 20 years he underwent an amputation of his left arm because of incoercible repeated hemorrhagic episodes. Since then, the lesion has progressively grown, and soft, large, circumscribed blue-black tumors that repeatedly bleed have appeared.

Findings from a physical examination revealed a large vascular malformation in his trunk, thrill, and exophytic pediculated mushroomlike outgrowths. The exophytic lesions were extirpated, and findings from a biopsy specimen showed a benign vascular malformation (Figure, B and C). Serum levels of angiogenic factors are summarized in the Table. Vascular endothelial growth factor (VEGF) and matrix metalloproteinase 9 (MMP-9) serum levels (increased ×2), angiopoietin 2 (Ang-2) levels (increased ×10), and Tie-2 (receptor tyrosine kinase-2) levels (increased ×3) were increased in comparison to the control group. Platelet-derived growth factor (PDGF) AB (PDGF-AB) and PDGF-BB levels were decreased (in one-third of the control group).

The patient died of renal and multigorgan failure 3 months later while waiting for approval for bevacizumab treatment.

COMMENT

To our knowledge, there are no studies about serum angiogenic profiling in adult patients with vascular malformations. Marler et al2 showed that MMP and basic fibroblast growth factor levels are elevated in the urine of children with hemangiomas and vascular malformations when compared with controls.

Vascular endothelial growth factor, Ang-1, and Ang-2 have been reported as the most potent regulators for neovascularization. In the presence of VEGF, Ang-2 promotes a rapid increase in capillary diameter, remodeling of the basal lamina, and proliferation and migration of endothelial cells and stimulates sprouting of new blood vessels.3

In our patient, we found increased Ang-2 levels, which also occur in some brain arteriovenous malformations.4 We also detected increased levels of Tie-2 soluble receptor. Angiopoietin 2 is predominantly

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expressed in areas undergoing vascular remodeling. This could suggest that there is an abnormal disassembly level between endothelial cells and mesenchymal cells due to an abnormal balance in the Ang-2–Tie-2 system, leading to dilated vessels with insufficient mural cell components. All capillaries are partially covered by pericytes. The pericyte-deficient mutant microvessels of PDGF-deficient embryos show endothelial cell hyperplasia, hypertervariable diameter, abundant microaneurysms, and abnormal endothelial ultrastructure. Pericytes express PDGF receptor β and require PDGF-BB for their recruitment to new vessels in the course of angiogenesis. In our patient, the skin biopsy specimen demonstrated deficiency of mural cells in the newly formed exophytic lesions, in association with strikingly low serum levels of PDGF-AB and PDGF-BB.

Novel medical therapies are needed for active vascular malformations. The presence of an imbalance of angiogenic factors in this patient is in favor of their role in the pathogenesis of at least some vascular malformations. Dedicated studies with a many patients should confirm these findings, to define a therapeutic target in patients with active malformations who may be candidates for an antiangiogenic-specific medical treatment.1

Table. Expression of Angiogenic Factors in Arteriovenous Vascular Malformation

<table>
<thead>
<tr>
<th>Angiogenic Factora</th>
<th>Control Subjects (n = 10)b</th>
<th>Patient (n = 1)b</th>
</tr>
</thead>
<tbody>
<tr>
<td>VEGF level, pg/mL</td>
<td>250 (124-486)</td>
<td>541</td>
</tr>
<tr>
<td>VEGF-C level, pg/mL</td>
<td>6950 (4526-7812)</td>
<td>4712</td>
</tr>
<tr>
<td>VEGF-D level, pg/mL</td>
<td>725 (505-1087)</td>
<td>553</td>
</tr>
<tr>
<td>VEGF-R2 level, pg/mL</td>
<td>11 125 (8230-14 830)</td>
<td>9250</td>
</tr>
<tr>
<td>Ang-1 level, pg/mL</td>
<td>66 500 (51 212-82 124)</td>
<td>50 625</td>
</tr>
<tr>
<td>Ang-2 level, pg/mL</td>
<td>1350 (635-2418)</td>
<td>14 250</td>
</tr>
<tr>
<td>Tie-2 level, ng/mL</td>
<td>11.8 (6.4-20.8)</td>
<td>36.6</td>
</tr>
<tr>
<td>MMP-2 level, ng/mL</td>
<td>286 (160-390)</td>
<td>290</td>
</tr>
<tr>
<td>MMP-9 level, ng/mL</td>
<td>740 (304-1120)</td>
<td>1630</td>
</tr>
<tr>
<td>PDGF-AB level, pg/mL</td>
<td>28 094 (14 100-43 202)</td>
<td>9050</td>
</tr>
<tr>
<td>PDGF-BB level, pg/mL</td>
<td>2384 (1196-3985)</td>
<td>906</td>
</tr>
</tbody>
</table>

Abbreviations: Ang, angiopoietin; MMP, matrix metalloproteinase; PDGF, platelet-derived growth factor; Tie, receptor tyrosine kinase; VEGF, vascular endothelial growth factor.

a Levels of angiogenic factors were measured with quantitative enzyme-linked immunosorbent assay kits (Quantikine; R&D Systems, Inc, Minneapolis, Minnesota). Age- and sex-matched control findings were compared with our patient’s findings.

b Data are given as mean (minimum to maximum).

Figure. Extensive arteriovenous vascular malformation in the trunk. The edges and the surface of the lesion are outlined by a network of blue erythematous telangiectasias. A, Throughout the lesion there are exophytic pediculated mushroomlike blue-black outgrowths, some with central ulceration. B, Vascular malformation is characterized by anomalous and dilated channels. Vessels show a well-differentiated endothelium. Frequently the vessels contained a discontinuous smooth muscle layer (hematoxylin-eosin, original magnification ×200). C, An irregular and discontinuous anomalous smooth muscle coat is observed around malformed channels with immunostaining-specific myosin of smooth muscle (mouse anti-human smooth muscle myosin, heavy chain monoclonal antibody, unconjugated, clone SMMS1 [Dako, Glostrup, Denmark], original magnification ×200).
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Correspondence: Pedro Redondo, MD, PhD, Department of Dermatology, University Clinic of Navarra, PO Box 4209, 31008 Pamplona, Spain (predondo@unav.es).
Author Contributions: Dr Redondo 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: Redondo. Acquisition of data: Redondo, Quetglas, and Idoate. Analysis and interpretation of data: Redondo. Drafting of the manuscript: Redondo and Martínez-Cuesta. Critical revision of the manuscript for important intellectual content: Redondo, Quetglas, and Idoate. Statistical analysis: Redondo. Obtained funding: Redondo. Administrative, technical, or material support: Redondo, Martínez-Cuesta, Quetglas, and Idoate. Study supervision: Redondo.
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REFERENCES


Archives Web Quiz Winner

Congratulations to the winner of our May quiz, Ahmed Zahr Allayali, FRCP, FABD, Departments of Dermatology, Umm Al-Qura University, Makkah, and International Medical Center, Jeddah, Saudi Arabia. The correct answer to our May challenge was microcystic adnexal carcinoma. For a complete discussion of this case, see the Off-Center Fold section in the June Archives (Redd MA, Bray DW, Royer M. Asymptomatic cutaneous lip plaque. Arch Dermatol. 2007;143[6]:791-796).

Be sure to visit the Archives of Dermatology Web site (http://www.archdermatol.com) to try your hand at the interactive quiz. We invite visitors to make a diagnosis based on selected information from a case report or other feature scheduled to be published in the following month’s print edition of the Archives. The first visitor to e-mail our Web editors with the correct answer will be recognized in the print journal and on our Web site and will also receive a free copy of The Art of JAMA II.
Chronic Urticaria and Monoclonal IgM Gammopathy (Schnitzler Syndrome)

Report of 11 Cases Treated With Pefloxacin

Bouchra Asli, MD; Boris Bienvenu, MD; Florence Cordoliani, MD; Jean-Claude Brouet, MD, PhD; Yurdagul Uzunhan, MD; Bertrand Arnulf, MD; Marion Malphettes, MD; Michel Rybojad, MD; Jean-Paul Fermand, MD

Background: Schnitzler syndrome is characterized by chronic urticarial rash and monoclonal IgM gammopathy and is sometimes associated with periodic fever, arthralgias, and bone pain. Current treatment is unsatisfactory.

Observations: Eleven patients with Schnitzler syndrome were treated with oral pefloxacin mesylate (800 mg/d). In 10 patients, we observed a dramatic and sustained improvement of urticarial and systemic manifestations. Corticosteroid therapy could be stopped or reduced in 6 patients. In 9 patients, pefloxacin was administered for more than 6 months (≥ 10 years), with a good safety profile.

Conclusions: Pefloxacin therapy can be considered for patients with Schnitzler syndrome because it usually improves chronic urticaria and the systemic symptoms of the disease.

Arch Dermatol. 2007;143(8):1046-1050

THE FEATURES OF SCHNITZLER SYNDROME INCLUDE CHRONIC NONPRURIGINOUS URTICARIA AND MONOCLONAL IgM GAMMOPATHY. INTERMITTENT FEVER, ASTHENIA, ARTHRALGIA, AND BONE PAIN WITH IMAGING EVIDENCE OF OSTEOSCLEROSIS ALSO OCCUR FREQUENTLY. BIOLOGICAL FINDINGS USUALLY INCLUDE AN INCREASE IN WHITE BLOOD CELL COUNT AND ERYTHROCYTE SEDIMENTATION RATE, WHICH REFLECT AN INFLAMMATORY SYNDROME AND THE PRESENCE OF THE MONOCLONAL IgM.

Skin biopsy findings often include mononuclear or neutrophilic perivascular infiltrates. The link between urticaria, systemic symptoms, hyperostosis, and the monoclonal B-cell proliferation is unknown. Current treatment is unsatisfactory. The use of systemic corticosteroids may be effective but is hampered by corticoid dependence, with well-known attendant adverse effects. Chemotherapy may induce myelodysplasia. Many other therapies have been proposed in the context of isolated case reports.

We observed a dramatic and sustained improvement of manifestations of Schnitzler syndrome in a patient who was treated with pefloxacin mesylate for a urinary tract infection. This prompted our study of the efficacy of the antibiotic in 10 other consecutive patients.

METHODS

After the first patient, the drug was proposed to all patients who were referred to us and fulfilled the following criteria: (1) recurrent urticarial rash persisting more than 2 months; (2) presence of a serum monoclonal IgM; (3) a serum complement level within the reference range and no detectable cryoglobulinemia; (4) no associated systemic disease; and (5) no contraindication to treatment with quinolone agents. All patients gave informed consent.

Between January 1, 1995, and December 31, 2005, 11 patients (including the index case) were enrolled in the study. Before initiation of treatment and while receiving pefloxacin, patients were asked to note daily any symptom, particularly skin changes, and their temperature. They also had to note changes in dosages of any drug being used. Pefloxacin mesylate was administered orally at an initial dosage of 800 mg/d.

RESULTS

The main characteristics of the 11 patients are summarized in Table 1. Age at diagnosis of Schnitzler syndrome ranged from 44 to 80 years (mean age, 57.5 years). All patients presented with chronic urticaria, with a disease duration of 4 months to 16 years (mean duration, 4.6 years). Re-
current urticarial wheals usually consisted of sharply demarcated, raised maculopapular erythematous lesions that predominated on the lower limbs and abdomen and were asymptomatic. The wheals lasted from several hours to 1 week and were separated by periods of remission of various durations. Skin biopsy specimens showed few perivascular mononuclear or polymorphonuclear cells with or without mild edema (in 8 patients) and a clear perivascular infiltrate with leukocytoclastic vasculitis but without necrosis (in 2 patients). Skin biopsy results were normal in 1 patient.

In 9 patients, some urticarial wheals were accompanied by spiking fever (≥40°C). In these cases, arthralgias, myalgias (n = 11), fatigue (n = 7), and weight loss (n = 5) were typical. Such symptoms, particularly an unusual fatigue, were also reported by 1 of the nonfebrile patients. Nine patients reported bone pain, usually in the lower back, pelvis, and lower limbs, with radiographic evidence of bone densification and hyperfixation apparent on technetium Tc 99m scan findings in 2 of 7 and 8 of 9 patients, respectively. Increase in the erythrocyte sedimentation rate, hyperfibrinemia, decreased albuminemia, polymorphonuclear hyperleukocytosis, hypochromic anemia, and thrombocytosis were frequent (Table 1).

Results of searches for an infectious process or a connective tissue disorder were consistently negative. In all cases, test results for cryoglobulin and antinuclear antibodies were negative, and the serum level of the C3 complement component was within the reference range. Serum C4 level was within the reference range in all but 1 patient, in whom a heterozygous deficiency was documented. In all studied cases, results of searches for antibodies against hepatitis B or C viruses were negative.

A monoclonal serum IgM was detected in all patients. At diagnosis, the IgM level was low (≤0.5 g/dL), intermediate (≥0.5 to < 2 g/dL), and high (≥2 g/dL) in 4, 6, and 1 patient, respectively. During follow-up, the serum IgM level was higher than 2 g/dL in the 3 patients who developed an overt Waldenström macroglobulinemia (WM). The monoclonal IgM bore κ light chains in 10 patients and λ light chains in 1. Results of bone marrow aspirate and/or biopsy, available in 10 of the 11 patients, were normal in 7 and disclosed a lymphoplasmacytic infiltrate typical of WM in 3. At the first examination, small superficial lymph nodes were noted in the 3 patients with WM, 2 of whom also had splenomegaly. Chest radiogram, ultrasound examination results, or computed tomography did not disclose enlarged mediastinal or abdominal lymph nodes in any patient.

**TREATMENT**

As reported in Table 2, before enrollment in the study, patients had received a wide class of medications, including nonsteroidal anti-inflammatory drugs, antihistamines, colchicine, dapsone, and hydroxychloroquine or chloroquine hydrochloride. Although questionable and transient improvement was sometimes observed, these drugs were globally ineffective, particularly for controlling the rash. The only patient who received thalidomide experienced a clear improvement, but the therapy was stopped because of peripheral neuropathy. Corticosteroids were active against urticaria and systemic symptoms in all 7 treated patients when a precise threshold dosage was used; this threshold dosage varied from one patient to the next. The required mean daily dose of prednisone equivalent was 11.5 mg/d (range, 5-30 mg/d). Despite this treatment, persisting flares usually occurred, requiring a transient increase of the corticosteroid dose. Chlorambucil or cyclophosphamide was given to 4 patients without a corticosteroid-sparing effect or any improvement, including in the 3 patients with overt MW. Two of these patients achieved a partial remission, as assessed by decreases of 60% and 75% in the serum IgM level, whereas the last patient had a resistant disease. In one patient, repeated plasma exchanges were ineffective. In another, psoralen–UV-A therapy was ineffective as well.

In all cases, oral pefloxacin mesylate therapy, 400 mg twice a day, was begun during an urticarial flare and was added to the patient’s previous treatment. The antibiotic significantly reduced urticarial wheals, with a concomitant sensation of improved condition, in all but patient 7. The improvement occurred within 24 hours of taking the first tablet for 6 patients and within 48 to 72 hours for the others. Fever, when present, disappeared or decreased before the subsequent progressive clearing of the urticarial lesions.

In all but patient 7, pefloxacin mesylate was used as a maintenance treatment, initially at a dose of 800 mg/d. In all cases, it significantly reduced the frequency and intensity of the disease manifestations. This was exempli-

**Table 1. Main Characteristics of the 11 Patients With Urticarial Rash**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>9</td>
</tr>
<tr>
<td>Weight loss</td>
<td>5</td>
</tr>
<tr>
<td>Fatigue</td>
<td>8</td>
</tr>
<tr>
<td>Arthralgia or arthritis</td>
<td>11</td>
</tr>
<tr>
<td>Bone pain</td>
<td>9</td>
</tr>
<tr>
<td>Abnormal findings on bone morphology</td>
<td>8^a</td>
</tr>
<tr>
<td>Serum monoclonal IgM component^b</td>
<td>11</td>
</tr>
<tr>
<td>ESR &gt; 30 mm/h</td>
<td>5</td>
</tr>
<tr>
<td>CRP level &gt; 15 mg/L</td>
<td>6</td>
</tr>
<tr>
<td>Fibrin level &gt; 4 g/L</td>
<td>6</td>
</tr>
<tr>
<td>Leukocytosis &gt; 10,000 cells/µL</td>
<td>10</td>
</tr>
<tr>
<td>Hemoglobin level &lt; 11.0 g/dL</td>
<td>3</td>
</tr>
<tr>
<td>Platelet count &gt; 400 x 10^3/µL</td>
<td>7</td>
</tr>
<tr>
<td>Serum albumin level &lt; 3.5 g/dL</td>
<td>4</td>
</tr>
</tbody>
</table>

Abbreviations: CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.

SI conversion factor: To convert CRP to nanomoles per liter, multiply by 9.524.

^a Among the 9 patients who underwent bone survey.
^b Includes IgM κ light chains in 10 and λ light chains in 1.
^c Median ESR, 83 mm/h; range, 30 to 134 mm/h.
^d Median CRP level, 92 mg/L; range, 25 to 215 mg/L.
^e Median fibrin level, 7.1 g/L; range, 4.3 to 8.0 g/L.
^f Median leukocyte count, 11,900 cells/µL; range, 10,300 to 28,100 cells/µL.
^g Median hemoglobin level, 10.1 g/dL.
^h Median platelet count, 488 x 10^3/µL; range, 439 x 10^3/µL to 608 x 10^3/µL.
^i Median albumin level, 3.2 g/dL; range, 2.5 to 3.5 g/dL.
fied by 2 patients who attempted to quantify their symptoms using a personal semiquantitative scale. In these patients, the incidence of maximally quoted urticarial flares was reduced by a median of 80% when they compared periods of pefloxacin therapy with periods of no pefloxacin therapy. Increasing the pefloxacin mesylate dosage usually improved the control of flares that occurred with the 800-mg treatment. This dose effect was much less clear in terms of prevention of relapse, and persistent sustained remissions were rare, if they occurred at all, including in the 3 patients who took 1200 mg/d for longer than 1 month.

When pefloxacin therapy was stopped because the patient forgot to take the medicine (n = 8) or because of adverse effects (n = 2), flares recurred. When reintroduced, the drug therapy again allowed a rapid control of the disease manifestations. Pefloxacin treatment produced a corticosteroid-sparing effect, as assessed by the interruption or the dose reduction (by about two-thirds) of previous corticosteroid therapy in 4 and 2 patients, respectively. Therapy consisting of antihistamines, nonsteroidal anti-inflammatory drugs, or other analgesic drugs could be stopped or used at a reduced dosage in 4 and 6 patients, respectively.

Pefloxacin treatment did not result in a significant decrease in the serum level of the monoclonal IgM in any patient. The increased white blood cell counts, erythrocyte sedimentation rates, and serum levels of C-reactive protein and fibrin that were features of the urticarial flares usually decreased during spontaneous or drug-induced remission. For most patients, the periods when C-reactive protein values were within the reference range were longer during pefloxacin therapy than during periods without this treatment, suggesting the efficacy of the drug on the flare frequency.

A 88-year-old woman attributed insomnia to the drug and interrupted the treatment after a few days, although her skin lesions had improved. In the 10 other patients, the pefloxacin dose was maintained during a median time of 32 months (range 2-128 months). Within this follow-up, the treatment had to be stopped in 2 patients after 2 and 6 months because of sexual impotence (that reversed after treatment interruption) and tendon pain. An additional patient who had persistent moderate urticarial lesions and intermittent bone pain during an 8-month period of pefloxacin and nonsteroidal anti-inflammatory drug therapy decided to use the drug only in case of frank flare. In the remaining patients, the benefit on tolerance ratio of the treatment was persistently considered as positive. Achilles tendon pain occurred in 2 patients, and photosensitization with some face hyperpigmentation occurred in 3, without being troublesome enough to interrupt treatment. With the exception of 1 patient who experienced a nonfebrile urinary tract in-

Table 2. Patient Treatment

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Previous Therapy</th>
<th>Clinical Response to Pefloxacin&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Response Delay, h</th>
<th>Relapse Prevention&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Response Duration</th>
<th>Decrease in Corticosteroid Dose</th>
<th>Pefloxacin Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Prednisone, 20 mg; antihistamine; colchicine</td>
<td>+</td>
<td>72</td>
<td>+</td>
<td>32 mo (Follow-up)</td>
<td>Interrupted</td>
<td>Face hyperpigmentation</td>
</tr>
<tr>
<td>2</td>
<td>Thalidomide; betamethasone acetate, 1 mg; cyclophosphamide; antihistamine; dapsone; colchicine; plasmapheresis</td>
<td>+ (Less for bone pain)</td>
<td>24</td>
<td>+</td>
<td>10 y (Death)</td>
<td>Interrupted</td>
<td>Partial rupture of Achilles tendon</td>
</tr>
<tr>
<td>3</td>
<td>Antihistamine; NSAID; bisphosphonates</td>
<td>+</td>
<td>NA</td>
<td>+</td>
<td>6 mo (Poor tolerance)</td>
<td>Not administered</td>
<td>Achilles tendon pain</td>
</tr>
<tr>
<td>4</td>
<td>Prednisone, 15 mg; antihistamine; psoralen-UV-A</td>
<td>+</td>
<td>&lt;6</td>
<td>+</td>
<td>2 mo (Poor tolerance)</td>
<td>50% Decrease</td>
<td>Sexual impotence</td>
</tr>
<tr>
<td>5</td>
<td>NSAID</td>
<td>+ (Less for bone pain)</td>
<td>&gt;48</td>
<td>+</td>
<td>15 mo (Episodic)</td>
<td>Not administered</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>NSAID; antihistamine</td>
<td>+ (Less for urticaria)</td>
<td>24</td>
<td>+/-</td>
<td>42 mo (Stop owing to inefficacy)</td>
<td>Not administered</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Prednisone, 10 mg; antihistamine</td>
<td>+</td>
<td>24</td>
<td>+</td>
<td>&lt;5 d (Poor tolerance)</td>
<td>0</td>
<td>Insomnia, vertigo, diarrhea</td>
</tr>
<tr>
<td>8</td>
<td>Prednisone, 30 mg; chlorambucil&lt;sup&gt;c&lt;/sup&gt;</td>
<td>+</td>
<td>&lt;24</td>
<td>+</td>
<td>88 mo (Follow-up)</td>
<td>Interrupted</td>
<td>Face hyperpigmentation</td>
</tr>
<tr>
<td>9</td>
<td>Chlorambucil; colchicine; dapsone and ferrous oxalate (Disulone&lt;sup&gt;d&lt;/sup&gt;); prednisone, 20 mg</td>
<td>+</td>
<td>24</td>
<td>++ (2 y), then +/-</td>
<td>51 mo (Death)</td>
<td>Interrupted</td>
<td>Face hyperpigmentation</td>
</tr>
<tr>
<td>10</td>
<td>Prednisone, 25 mg; colchicine; dapsone, 50 mg; cyclophosphamide</td>
<td>+ (Less for urticaria)</td>
<td>72</td>
<td>++ (4 y), then +/-</td>
<td>10 y (Death)</td>
<td>80% Decrease</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>Antihistamine</td>
<td>+</td>
<td>NA</td>
<td>+</td>
<td>24 mo (Follow-up)</td>
<td>Not administered</td>
<td>Achilles tendon pain</td>
</tr>
</tbody>
</table>

Abbreviations: NA, not available; NSAID, nonsteroidal anti-inflammatory drugs.

<sup>a</sup> Indicates efficacy for cutaneous eruption, bone pain, and fever (when present).

<sup>b</sup> Relapse prevention was assessed by evaluating flare frequency as follow: + (+ +) if reduced by at least 50% (75%) during at least 3 months; +/- if reduced without achieving previous criteria. All patients experienced relapse when therapy was stopped.

<sup>c</sup> Added during follow-up, shortly after initiation of pefloxacin therapy, because of evidence of overt Waldenström macroglobulinemia.

<sup>d</sup> Manufactured by Sanofi-Aventis, Paris, France.
Schnitzler syndrome is a rare clinical entity first described in 1972.1 So far, about 50 cases have been reported in the literature. The mean delay to diagnosis is more than 5 years, suggesting that the syndrome may be underdiagnosed.1 The diagnosis should be evoked in the case of any chronic urticaria, particularly when that urticaria is atypical because of persistent and nonpruritic lesions or because of associated arthralgia, bone pain, or systemic symptoms, including recurrent fever. Laboratory findings of an elevated erythrocyte sedimentation rate and leukocytosis or thrombocytosis, sometimes associated with inflammatory anemia, should also suggest this diagnosis. Histopathologic findings usually show a mild perivascular monocellular or neutrophilic infiltrate.2 In all cases, the diagnosis must be corroborated by the presence of a serum monoclonal IgM, which is, in addition to the urticarial lesions, the key feature of the syndrome,1 although cases of a variant-type Schnitzler syndrome characterized by a monoclonal IgG have been reported.3 Serum protein electrophoresis should be recommended for all patients presenting with chronic urticaria. We herein report a series of 11 patients who presented with most of the characteristic features of Schnitzler syndrome (Table 1). In particular, all had chronic urticarial lesions and a serum monoclonal IgM. Most of the patients received various therapies (Table 2) that had no clear efficacy. Whereas nonsteroidal anti-inflammatory drugs usually alleviated articular and bone pain,1 corticosteroids represented the only treatment that continued to influence the course of the urticarial, systemic, and osteoarticular symptoms.4 Corticosteroid therapy improved urticarial manifestations only when used at a precise threshold dosage, which varied from one patient to another but was most often about 10 mg/d (range, 5-30 mg). Even when an appropriate dose was taken, some patients still presented with flares requiring transient increases of the corticosteroid dose, and dose-related adverse effects consecutive to long-term treatment were frequent. In our series, as in the literature, therapeutic attempts to reduce the serum IgM level by means of plasma exchanges (patient 1)1 or chemotherapy were most often ineffective. This remained true in the 3 patients with WM who achieved a significant but partial remission while receiving chlorambucil (patients 8 and 9) or no remission while receiving cyclophosphamide (patient 10). One of the patients who received alkylating agents died of myelodysplasia, emphasizing that chemotherapeutic drugs should be used only in patients with symptomatic WM.6 Thalidomide, which was used in patient 2 and in 3 patients in the literature,3,7 also carries long-term toxic risks, in particular because of its neurotoxic effects. Other innovative therapeutic approaches, such as interferon alfa, interleukin 1 (IL-1) receptor antagonist (anakinra), and cyclosporine, were recently reported to be effective on the basis of isolated case reports3,8,9 and warrant further evaluation.

As illustrated by our data, pefloxacin rapidly improves urticarial and systemic symptoms of the Schnitzler syndrome. It reduces the frequency and intensity of disease flares, resulting in a significant corticosteroid-sparing effect. When used as a preventive treatment, pefloxacin remains active and has a relatively good safety profile, despite associated tendinopathy, the incidence of which is low.10 However, its efficacy is only symptomatic and often incomplete. In addition, pefloxacin usually reduces the cutaneous and systemic symptoms of the syndrome while being less active on its osteoarticular component. Pefloxacin appears to reduce the duration of the biological inflammatory syndrome that features disease flares. We did not observe AA amyloidosis in any patient in the present series and found no reports of it in the literature.

The role of IgM gammopathy in the pathogenesis of urticaria and the other manifestations of the Schnitzler syndrome is poorly understood. It likely does not depend on whether the underlying lymphoid disorder is an overt WM or a monoclonal gammopathy of undetermined significance.1 In our patients, as in the literature, immunofluorescence studies did not document a pathogenic role for monoclonal IgM because the studies showed cutaneous IgM deposits in only some cases with, in addition, different localizations from one case to another.1 Similarly, antiskin autoantibody activity of the IgM could be documented by Western blotting in only few patients.11 Conflicting data were also reported on potential anti–IL-1α autoantibody activity of the monoclonal immunoglobulin.12,13 An alternative hypothesis would not implicate the monoclonal IgM by itself but rather the production of 1 or several cytokines or chemokines by clonal B-cell proliferation or by its cellular environment.13 This hypothesis might be more in accordance with the effect of pefloxacin we noted, which occurred without modifying the level of the monoclonal IgM in any case. As with all fluorinated 4-quinolones, pefloxacin, a nalidixic acid analogue, exerts its bactericidal effect by inhibiting DNA gyrase (a type II topoisomerase), most probably by binding to DNA.14 In addition to their antibacterial properties, fluoroquinolones have been shown to modify immune and inflammatory responses implicating T cells and macrophages, by mechanisms that may involve regulation of messenger RNA for cytokines such as IL-1, IL-2 and its receptors, interferon-γ, granulocyte-macrophage colony-stimulating factor, and IL-3.15 Modulation of the production of other cytokines, including IL-8 and IL-6, were also observed in experimental models.15 Although other antibiotic classes such as macrolides may have immunomodulatory effects,16 only quinolone appears to be effective in the treatment of Schnitzler syndrome. Within the quinolone class, pefloxacin appears to be the most efficient (B.A. and J.-P.F., unpublished data, March 2006). It is ineffective in classical chronic urticaria (data not

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shown), whereas we did not have the opportunity to assess its efficacy in urticarial vasculitis without monoclonal IgM gammopathy.

In conclusion, pefloxacin must be added to the small list of drugs that are active in the treatment of Schnitzler syndrome. Because of its efficacy and good safety profile, we propose that this drug be the first-line treatment for Schnitzler syndrome. If too-frequent flare-ups persist despite treatment and if the patient feels uncomfortable, we recommend adding low-dose corticosteroid therapy, eventually continuing pefloxacin therapy for the benefit of its corticosteroid-sparing effect.

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Author Contributions: Dr Fermand 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: Fermand. Acquisition of data: Asli, Bienvenu, Cordoliani, Brouet, Uzunhan, Arnulf, Malphettes, Rybojad, and Fermand. Analysis and interpretation of data: Asli, Bienvenu, and Fermand. Drafting of the manuscript: Asli, Bienvenu, and Fermand. Critical revision of the manuscript for important intellectual content: Asli, Bienvenu, Cordoliani, Brouet, Arnulf, Malphettes, and Rybojad.

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REFERENCES

Combination Immunosuppressive Therapies

The Promise and the Peril

Maria R. Robinson, MD; Benjamin D. Korman, BS; Neil J. Korman, MD, PhD

Background: Targeted immunotherapeutic agents (TIs), also known as biological agents, are efficacious treatments for many immunologically mediated disorders, including psoriasis. In several of these diseases, including rheumatoid arthritis, Crohn’s disease, and multiple sclerosis, certain TIs have been studied in combination with nonspecific immunosuppressive agents and with other TIs.

Observations: Recently, the rheumatology, neurology, and gastroenterology literature has reported several examples of possible associated toxic effects when certain TIs are used in combination with other immunosuppressive agents. These toxic effects have included an increased risk of infection and malignancy.

Conclusions: Combination therapies are often used by dermatologists. Several TIs have been approved for psoriasis; however, clinical trials using these drugs in combination with other immunosuppressive agents have not yet been performed. The implications for dermatologists of the toxic effects associated with TI combination therapy are unclear. However, combination therapy with certain TIs should be used with caution until more data are available.

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IN RECENT YEARS, ENORMOUS progress has been made in our understanding of the immune system’s role in the pathogenesis of immunologically mediated disorders, including psoriasis and psoriatic arthritis, rheumatoid arthritis (RA), multiple sclerosis, Crohn’s disease, and ankylosing spondylitis. Many broad-based, nonspecific immunosuppressive agents such as glucocorticoids, methotrexate, mycophenolate mofetil, 6-mercaptopurine, azathioprine, cyclosporine, and cyclophosphamide have been used to treat these disorders, but their use may be limited by toxic effects.

SUCCESSFUL USE OF TIs IN COMBINATION THERAPY FOR NONDERMATOLOGIC DISEASES

Targeted immunotherapeutic agents have been used successfully as combination therapy to treat several diseases. For the treatment of RA, the combination of tumor necrosis factor (TNF) inhibitors (etanercept, infliximab, and adalimumab) with nonspecific immunosuppressive agents, including methotrexate and other disease-modifying antirheumatic drugs (DMARDs), is superior to monotherapy with nonspecific immunosuppressive agents.1-3 Patients with RA have been treated with infliximab in combination with cyclosporine in a small trial (n = 18)4 and in combination with azathioprine or leflunomide in a retrospective analysis (n = 225)5 with good efficacy and minimal toxic effects. The addition of azathioprine or 6-mercaptopurine to the infliximab regimen is more effective than azathioprine or 6-mercaptopurine alone for the treatment of corticosteroid-dependent Crohn’s disease.6 Furthermore, when infliximab was used to treat Crohn’s disease, the addition of the immunosuppressive agent methotrexate, azathioprine, or 6-mercaptopurine reduced
the formation of infliximab antibodies, which play an etiologic role in infliximab infusion reactions.\(^7\)

Much of the data from the rheumatology and gastroenterology literature suggest that TIs can often be used safely and effectively in combination therapy. In fact, the US Food and Drug Administration has approved infliximab and etanercept in combination with methotrexate for the treatment of RA. The excellent clinical results that have been obtained using TIs have led many physicians to use them as the first-line approach in many patients, and for patients with the most severe disease, the combination of TIs with nonspecific immunosuppressive agents is becoming more common.

**TOXIC EFFECTS ASSOCIATED WITH TIs USED IN COMBINATION THERAPY FOR NONDERMATOLOGIC DISEASES**

The success of TIs as monotherapy and combined with nonspecific immunosuppressive agents has prompted further exploration of synergistic efficacy when TIs are used in combination. A great deal of excitement has been generated by the success of combination therapy and the hope it may hold for major disease control or perhaps even a cure. However, certain TIs used in combination with each other or with certain nonspecific immunosuppressive agents cause serious adverse effects, including severe infections and malignancies. Herein, we examine several examples that illustrate the potential perils of using TIs in combination therapy (Table 1).

### INFECTIONS

The first example of combination therapy leading to increased infections occurred when etanercept and anakinra, an interleukin 1 receptor antagonist, were evaluated for potential synergistic efficacy in patients with RA.\(^8\) In this study, the quality of evidence was high (1) (Table 2). A total of 244 patients with RA were randomly assigned to 1 of 3 treatment groups: (1) 25 mg of etanercept twice weekly (full dose) plus placebo; (2) 25 mg of etanercept once weekly (half dose) plus 100 mg of anakinra daily; or (3) 25 mg of etanercept twice weekly (full dose) plus 100 mg of anakinra daily. Patients continued taking stable doses of methotrexate and corticosteroids. While no patients in the etanercept-only group developed serious infections, those who received combination etanercept and anakinra had a marked increase in serious infections: 3.7% of the patients in the combination group with half-dose etanercept and 7.4% in the combination group with full-dose etanercept developed serious infections. These serious infections included pneumonia and cellulitis (3 patients each), herpes zoster (1 patient), pneumonitis (1 patient), and pyelonephritis (1 patient).\(^8\)

Abatacept, a fusion protein that binds to the CD80 and CD86 ligands present on antigen-presenting cells, was recently studied in combination with other therapies for the treatment of RA (quality of evidence, I).\(^9\) In a randomized controlled trial of 1441 participants, patients were randomized to 4 treatment groups: (1) abatacept (10 mg/kg) and DMARDs; (2) abatacept (10 mg/kg) and TIs; (3) placebo and DMARDs; and (4) placebo and TIs. The TIs included etanercept, infliximab, adalimumab, or anakinra. Some patients were treated with concurrent DMARDs, including methotrexate, hydroxychloroquine, sulfasalazine, leflunomide, gold, and azathioprine. Overall, the abatacept and placebo groups had similar incidences of adverse events, but patients receiving abatacept in combination with other TIs had more than twice the rate of serious infections (defined as fatal or life-threatening, resulting in hospitalization or persistent or significant disability or incapacity, or deemed a significant medical event by the investigator) when compared with other treatment groups.

### Table 1. Summary of Toxic Effects Associated With Targeted Immunotherapeutic Agent (TI) Combination Therapy

<table>
<thead>
<tr>
<th>Toxic Effect</th>
<th>Drug Combination</th>
<th>Quality of Evidence</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections</td>
<td>Anakinra/etanercept</td>
<td>I</td>
<td>Genovese et al(^8)</td>
</tr>
<tr>
<td></td>
<td>Abatacept/several TIs(^b)</td>
<td>I</td>
<td>Weinblatt et al(^10)</td>
</tr>
<tr>
<td></td>
<td>Natalizumab/interferon</td>
<td>IV</td>
<td>Kleinschmidt-DeMasters and Tyler(^11)</td>
</tr>
<tr>
<td></td>
<td>Infliximab/cyclophosphamide</td>
<td>I</td>
<td>Langer-Gould et al(^12)</td>
</tr>
<tr>
<td></td>
<td>Infliximab/azathioprine</td>
<td>IV</td>
<td>WGET Research Group(^13)</td>
</tr>
<tr>
<td></td>
<td>Infliximab/6-mercaptopurine</td>
<td>IV</td>
<td>Chen et al(^14)</td>
</tr>
<tr>
<td></td>
<td>Natalizumab/interferon</td>
<td>IV</td>
<td>Thayu et al(^15)</td>
</tr>
</tbody>
</table>

\(\text{a}\)See Table 2 for the characteristics of evidence quality categories.

\(\text{b}\)The TIs included etanercept, infliximab, adalimumab, and anakinra.

### Table 2. Quality of Evidence Categories and Characteristics

<table>
<thead>
<tr>
<th>Category</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Evidence obtained from at least 1 properly designed, randomized controlled trial</td>
</tr>
<tr>
<td>II-i</td>
<td>Evidence obtained from well-designed controlled trials without randomization</td>
</tr>
<tr>
<td>II-ii</td>
<td>Evidence obtained from well-designed cohort of case-control analytical studies, preferably from more than 1 center or research group</td>
</tr>
<tr>
<td>II-iii</td>
<td>Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence</td>
</tr>
<tr>
<td>III</td>
<td>Opinions of respected authorities based on clinical experience, descriptive studies or reports, or expert committees</td>
</tr>
<tr>
<td>IV</td>
<td>Evidence inadequate owing to problems of methodology (eg, sample size, length or comprehensiveness of follow-up, or conflicts of interest)</td>
</tr>
</tbody>
</table>
Another trial evaluated the safety and efficacy of low-dose abatacept (2 mg/kg) given in combination with 25 mg of etanercept twice weekly (quality of evidence, I).10 In the 121 patients enrolled in this study, there were increased rates of serious infections in the patients who received low-dose abatacept in combination with etanercept when compared with placebo.

Another example of combination therapy leading to increased infection occurred when natalizumab, a humanized monoclonal antibody directed against the α4 integrin, was added to interferon β for the treatment of multiple sclerosis. Two patients11,12 in this clinical trial developed (and 1 ultimately died from) confirmed progressive multifocal leukoencephalopathy (PML), a rare, often fatal, demyelinating disease usually found in immunocompromised patients and caused by the JC virus (quality of evidence, IV).11,12 No cases of PML have been reported in patients receiving interferon β monotherapy, but PML has been reported in a patient receiving natalizumab monotherapy for Crohn’s disease.16

**MALIGNANCY**

Combination therapy with TIs has also been associated with the development of malignancies. The Wegener’s Granulomatosis Etanercept Trial Research Group13 evaluated twice-weekly 25-mg etanercept doses vs placebo when added to standard therapy for Wegener’s granulomatosis, which included cyclophosphamide and glucocorticoids for patients with severe disease or methotrexate and glucocorticoids for patients with limited disease (quality of evidence, I). The rate of sustained remissions and the total number of adverse events were not significantly different between the placebo and etanercept groups. However, 6 solid cancers (2 cases of mucinous adenocarcinoma of the colon, 1 cholangiocarcinoma, 1 renal cell carcinoma, 1 breast carcinoma, and 1 liposarcoma) developed in the combination etanercept and cyclophosphamide group compared with none in the control groups. These findings demonstrate a 3-fold increase in relative risk for malignancy in the group who received combination etanercept and cyclophosphamide compared with the control group who received placebo and cyclophosphamide.

Two different malignancies were recently associated with combination therapy when infliximab was added to either azathioprine or 6-mercaptopurine to treat Crohn’s disease. Azathioprine is converted to 6-mercaptopurine after oral ingestion, and the active metabolite works by blocking lymphocyte proliferation. In the first report, Chen et al14 reported the development of hepatocellular carcinoma occurring in a patient treated with combination infliximab and azathioprine who had no identifiable risk factors for liver disease (quality of evidence, IV).14 Hepatocellular carcinoma has been reported in patients with Crohn’s disease treated with either azathioprine alone or in combination with corticosteroids. In a second report, Thayu et al15 described a patient with Crohn’s disease treated with 6-mercaptopurine who had infliximab added to her therapeutic regimen owing to continued disease progression. After 27 months on combination 6-mercaptopurine and infliximab, the patient was diagnosed as having and subsequently died from hepatosplenic T-cell lymphoma, a rare, aggressive peripheral T-cell lymphoma (quality of evidence, IV). Previous cases of hepatosplenic T-cell lymphoma have also occurred in immunocompromised patients after organ transplantation and in a patient with Crohn’s disease treated with azathioprine and corticosteroids.17,18 According to the manufacturer of infliximab (Centocor, Horsham, Pennsylvania; written communication, May 2006), there have been 10 other cases of hepatosplenic T-cell lymphoma occurring in adolescents and young adults with Crohn’s disease or indeterminate colitis who were treated with combination infliximab and azathioprine or 6-mercaptopurine.

**IMPLICATIONS FOR THE USE OF TIs IN COMBINATION THERAPY IN DERMATOLOGY, PARTICULARLY FOR PSORIASIS**

Dermatologists care for many patients who require treatment with immunosuppressive agents. To date, the TIs have been studied most extensively in the treatment of psoriasis, but dermatologists have begun to use these agents to treat patients with other skin diseases, including alopecia areata, atopic dermatitis, hidradenitis suppurativa, and lichen planus, among others.19,22

Even before the advent of TIs, combination therapy was a treatment strategy frequently used by dermatologists because of its potential to increase efficacy while limiting toxic effects. Topical therapies are often combined with UV light and systemic therapies, including TIs, with the goal of optimizing efficacy without adding significant toxic effects.23 Methotrexate and cyclosporine are each effective as monotherapy for psoriasis, but their use may be limited by toxic effects. One series of patients with psoriasis (n=19) demonstrated that combination therapy with methotrexate and cyclosporine was efficacious using lower doses of both agents than might have been used in monotherapy (mean±SD doses, methotrexate 13.9±4.4 mg/wk; cyclosporine, 2.6±0.9 mg/d).24 Six patients undergoing long-term therapy (mean duration, 193 weeks) developed mild renal impairment, which improved with the reduction in cyclosporine dose. The combination of UV light with methotrexate has also been shown to be efficacious and well tolerated.25

Until now, to our knowledge, clinical trials evaluating TIs as psoriasis treatment have excluded the use of concurrent therapies, including immunosuppressive agents. However, dermatologists have started to use combination regimens that include TIs, and several case reports have suggested that these combinations are safe and effective for the treatment of psoriasis. It is important to note, however, that these reports all involve a small number of patients and do not provide conclusive evidence.

Since acitretin alters cell differentiation without any immunosuppressive effects, it is presumably the safest agent to combine with TIs. Conley et al26 evaluated the combination of acitretin with TIs in the treatment of 8 patients with psoriasis. All patients (6 treated with etanercept, 1 with adalimumab, and 1 with alefacept, each in combination with acitretin) had significant improvement in their psoriasis, and the combination therapy was...
well tolerated. Another series of 6 patients evaluated etanercept in combination with either methotrexate, cyclosporin, calcipotriene cream and ointment, acitretin and hydroxyurea (another nonspecific immunosuppressive agent), or weekly UV-B and every-other-day acitretin. All 6 patients showed significant improvement without any toxic effects. The combination treatments of UV light with alefacept (n=60) or etanercept (n=86) (data not shown) have both been shown to be effective and without any added toxic effects.

Combination alefacept and methotrexate (n=185) was somewhat beneficial for the treatment of psoriatic arthritis and was without any added toxic effects, while efalizumab when added to methotrexate (n=107) revealed no added benefit for the treatment of psoriatic arthritis, and combination therapy revealed no added toxic effects. Nonspecific immunosuppressants have also been used in combination with TIs as transitional agents. This approach was used in 8 patients with severe psoriasis undergoing cyclosporine treatment for an average of 8 weeks followed by the addition of etanercept with subsequent tapering of cyclosporine over a 4- to 6-month period. The combination of etanercept and cyclosporine was well tolerated without any added toxic effects. Additionally, methotrexate and cyclosporine may be added to efalizumab therapy as short-term transitional agents in the treatment of efalizumab-associated flares.

In the first reported case series to our knowledge of combination therapy with 2 different TIs for psoriasis and psoriatic arthritis, Krell described 3 patients who were treated with combined etanercept and alefacept. In all 3 patients, etanercept therapy improved the psoriatic arthritis but did not adequately improve the psoriasis. A 12-week course of alefacept was then added to the etanercept, which significantly improved the psoriasis in all 3 patients. No adverse events were observed in any of the patients.

**COMMENT**

While previous studies have suggested that some TIs can be safely used in combination with certain nonspecific immunosuppressive agents, the 6 examples we have discussed demonstrate a possible increased risk with certain combination therapies (Table 1). In evaluating these data and applying the findings to the management of dermatologic disorders, several points must be considered.

While 3 of the 6 examples derive from randomized, placebo-controlled trials that yield the most convincing levels of evidence, the other 3 derive from case reports that provide the least convincing level of evidence. Three examples describe combinations of TIs with cyclophosphamide, 6-mercaptopurine, or azathioprine. These 3 are the most potent of the nonspecific immunosuppressive agents, and therefore, combining any of these agents with a TI may pose a higher risk of toxic effects. In addition, the observations that both low-dose abatacept combined with etanercept and half-dose etanercept combined with anakinra led to an increased risk of serious infections do not support the concept that combining TIs at lowered dosages will mitigate toxic effects.

Five of the 6 examples of toxic effects associated with combination therapy occurred in patients taking TNF antagonists. This observation may be secondary to an overall higher usage of TNF inhibitors. Another potential explanation for this observation may be that TNF inhibitors are more potent immunosuppressive agents than T-cell blocking agents, although controlled studies verifying this suggestion are lacking.

Short-term data suggest that the combination of methotrexate, and to a lesser extent cyclosporine, with TIs appears to be safe and efficacious in the treatment of psoriasis. Indeed, when transitioning patients with psoriasis from these therapies to a TI, a period of overlap may be used so that the methotrexate or cyclosporine is tapered and then discontinued while the TI is being initiated. Dermatologists have begun to use TIs in novel combinations. However, the rare and dangerous infections and malignancies encountered in several other diseases are worrisome and should raise concern regarding the use of combination therapy in the treatment of patients with psoriasis. Targeting individual components of the immune system to redirect critical pathways has proven to be an elegant therapeutic approach that is usually, but not always, safe and effective. Owing to the complexities of the immune system, it can be very difficult to predict outcomes when combining more than one TI. Combination therapies that include TIs given along with other TIs or with nonspecific immunosuppressive agents for dermatologic diseases may eventually be supported by the results of controlled clinical trials. However, the details by which TIs can be used safely in combination will not be known until such trials are complete. Therefore, dermatologists should exercise caution when treating patients with TI combination therapy.

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Teens and Tans

Implementing Behavioral Change

In this issue of the Archives, Ma et al report that, in their study group, white Hispanic (WH) students were less educated regarding skin cancer prevention, tanned more frequently and more deeply, and were 2.5 times more likely to have used a tanning bed than white non-Hispanic (WNH) students. Also, WH students were less likely than WNH students to use sunscreen and wear sun-protective clothing and perceived themselves at lower risk for the development of skin cancer. Ma and colleagues conclude that skin cancer prevention programs directed toward young persons also need to include WH students. From a national health perspective, who is the target population of skin cancer prevention campaigns? The target population is all teenagers. Peer pressure and societal norms affect all teenagers, regardless of skin type. Indoor tanning is a widespread social activity of teenagers; therefore, a teenager with skin type III or IV may be invited to accompany his or her friend to the tanning salon, with participation in tanning an expected activity. However, the real issue is figuring out what actually changes behavior in this age group. Is it providing more information to improve knowledge? Is it targeting motivation that will truly make a difference in reducing overall teen tanning?

Knowledge of Carcinogenicity

Ma et al stated that the “proportion of students who considered exposure to sun to be the most important factor causing skin cancer was comparable among WHs and WHNs, with about three-quarters of both groups agreeing with this statement.” Because a significant number of these students were also using a tanning booth, the question arises as to their level of knowledge about the risks of skin cancer after the use of indoor tanning machines. Ultraviolet radiation, including that emitted from tanning machines, is a known human carcinogen, as identified by the 10th “Report on Carcinogens,” which was published by the National Toxicology Program. In an American Academy of Dermatology (AAD)-sponsored expert conference, a total of 10 articles that conformed to strict evaluation criteria were reviewed and demonstrated that the use of tanning beds increases the risk of cutaneous melanoma and that the risk seems to be greater if use occurs early in life. On November 28, 2006, the International Agency for Research on Cancer, an arm of the World Health Organization, reported that there is a clear increase in melanoma risk associated with the use of sunbeds in teenagers and in persons in their 20s. It also stated, “Limited data suggest that the risk of squamous cell carcinoma is similarly increased after first use as a teenager.” The data indicated (1) that sunbed use could have detrimental effects on the skin’s immune response and possibly on the eyes (ocular melanoma), (2) that artificial tanning gives little if any protection against solar damage to the skin, and (3) that the use of indoor tanning facilities does not provide protection against vitamin D deficiency. The study group concluded that “in view of the strength and seriousness of the findings, effective action to restrict access to artificial tanning facilities to minors and young adults should be strongly considered.”

Teen Tanning Attitudes Persist Despite Knowledge

Teens of all ages are very well informed regarding the link between UV radiation overexposure and risk of skin cancer. In a study of adolescent children of health professional mothers who had skin cancer or who were at risk for skin cancer, the use of sunscreen was greater among those whose mothers had skin cancer than among those whose mothers had a family history of melanoma or who had no personal history of skin cancer. Tan-promoting attitudes were similar across all groups. Frequent sunburns, inadequate sunscreen use, and high rates of tanning bed use were common even among the children of mothers who had received a diagnosis of skin cancer or who had a family history of melanoma. Only 24% of the adolescents involved in the study thought that a natural skin color was most attractive, and approximately 25% in each group agreed that it was “worth burning” to get a tan. Short-duration presentation of educational material to 184 Swedish adolescents aged 13 to 15 years did not influence the students’ attitudes regarding abstaining from sunbathing and tanning. A study of approximately 78,000 Australian children aged 7 to 12 years over 3 sample years (1993, 1996, and 1999) showed a significant increase in the number of students who reported sunburn over the prior summer as well as an increase in the percentage of students who preferred no tan. The percentage of students who usually or always wore clothing that covered most of their body decreased, as did the percentage of students who usually or always used sunscreen. Staying in the shade initially increased over the early study period but decreased toward the end of the study. Across
all of the survey years, only 11% of the students routinely followed the recommended behaviors of wearing a hat, sunscreen, and clothes that cover the body. The study concluded that a high level of knowledge of risk does not lead to sun protection behavior, and attempts to modify adolescent attitudes have had limited success.

A study of college students by Knight et al.11 demonstrated that although the study group seemed very knowledgeable about the risk of artificial UV exposure and skin cancer detection, the knowledge seemed to have little bearing on behavior patterns. As in other studies, the students with a positive family history of skin cancer were 1.5 times more likely than those without a family history to use tanning lamps. Therefore, it is unlikely that simply focusing on risk will be sufficient to have an impact on changing adolescent tanning behavior.

**IMMEDIATE BENEFITS OF INDOOR TANNING PERCEIVED BY TEENAGERS**

A significant variable that was measured but not specifically addressed in the study by Ma et al.1 was the incidence of indoor tanning. Because more than 2 million teenagers use tanning salons yearly and the use tends to increase with older teens (particularly girls), the motivations behind this behavior need to be examined.12 Teenagers who use tanning lights also actively seek tans outdoors and are less likely to use sun protection.6,12-15 The “benefits” of indoor tanning are instantaneous, in contrast to the consequences of long-term UV exposure, which can take many years to manifest. This reluctance to delay gratification is characteristic of adolescents.

Teenagers like a tanned appearance. Many of them comment that they feel better, more attractive, and healthier when they are tan. They are also conforming to peer behavior, especially by tanning indoors before a special event such as a dance or a midwinter vacation to a sunny climate.6,12-15 Social influences may be the most important predictors of tanning behavior in adolescents. Having friends who are tan, having parents who are permissive with respect to indoor tanning, and having friends and family who tan indoors are all associated with the likelihood of indoor tanning behavior in teens.12,15-17 Social factors are so overwhelming that even though 26% to 59% of adolescents burned or sustained other skin injury as a result of indoor tanning, they did not reduce the frequency of use or change their intentions to tan indoors.18-20

Peer attitudes about having a tan and the numbers of friends who seek tans are predictors of sun protection and tanning bed use.8,21 It has been suggested that girls are more likely to be influenced by their peers, which may be one of the reasons why there is such a high rate of tanning bed use among older teenage girls. In a study of adolescents aged 12 to 16 years, experimentation with tanning started when the influences of peers became more important than those of the parents.8 The teens reported that the goal of avoiding sunburns was to enhance their ability to get the “right tan,” not to reduce the risk of getting skin cancer later on. They preferred sunscreen over other forms of sun protection such as hats, because sunscreen use would enable them to get a tan and simultaneously make it appear to their parents that they were being responsible. The potentially addictive nature of tanning in certain predisposed individuals in the adolescent age group is another concern.7,22-24

**SOURCES OF TEEN INFORMATION**

Where are teenagers getting their tanning information and is it consistent? Hillhouse and Turrisi25 pointed out the confusing inconsistencies found online in a search of more than 20 Web sites dealing with skin cancer prevention. They found only 3 common recommendations: use sunscreen with a sun protection factor of 15 or higher, wear broad-brimmed hats, and put on sunglasses. They found that there was surprisingly little agreement as to the amount of sun exposure that is safe; how much sunscreen to use, how often to apply it, and the best method of application; the times of the day to avoid the sun (may vary with respect to location); the number of sunburns that put an individual at risk for skin cancer; the best types of clothing for protection; and the use of shade for protection. Mixed messages could lead some individuals to come to the conclusion that if there is no consistency, we must not really know what we are talking about.

Web sites were also not consistent regarding indoor tanning as a risk factor.25 Tanning industry Web sites, however, claim that indoor tanning can prevent cancer by increasing vitamin D production, can prevent early seasonal burning, can reduce stress, and, as one states, is the “only source for scientifically supported material on the balance between benefits and risks associated with ultraviolet light exposure and sun tanning.”26 Other tanning industry Web sites27 actively discredit dermatologists and organized dermatology, for example by taking aim against the AAD’s recent public service announcements. Many of these Web sites have sites for teens that encourage the viewers to join the organization and to get further training materials, including materials that promote teen tanning.28 The tanning industry’s marketing focus on teenagers has included such direct outreach activities as placing advertisements in high school newspapers and year books, distributing coupons in schools and at athletic events, and sponsoring events or sports teams. Other strategies have included hiring and providing free tanning to adolescents who are social leaders in their schools and holding drawings for tickets to popular music performances.29

**HARM REDUCTION MESSAGE**

Assistance in the creation of effective strategies for behavioral change in teen tanning has come from behavioral psychologists who have suggested that in order to reduce tanning behaviors in teenagers, it is necessary to make attitudes toward healthier alternatives more positive than attitudes toward tanning behavior.23 They also advocate a harm reduction message, suggesting that because the “avoid-the-sun-completely” message is so unrealistic, teens find it easier to ignore that message and continue with risky behaviors such as tanning, which have more powerful social and physical rewards.
As has been discussed, attractiveness is the predominant reason for tanning, so focusing on appearance-based interventions and showing how tanning can damage the skin have been shown to be effective motivators in teens. Because early studies showed that indoor tanners were relatively unaware of the possibility of short-term damage to their appearance, a study of 147 college women was undertaken. Study participants were given a short workbook describing the appearance-damaging effects of indoor tanning. At the 2-month follow-up visit, study participants reported 50% less indoor tanning than control respondents in the previous 2 months. The use of UV-light cameras in demonstrating early skin changes from sun exposure has also been successful in changing behavior. The viewing of UV-filtered photographs, along with educational information about aging from the sun, has consistently resulted in changes in planned and reported sun protection motivation and behaviors. 

In a study of 211 women between the ages of 18 and 25 years, a harm reduction strategy was undertaken that focused on why sun protection is important; it also emphasized that women can be attractive without a tan. The program included information on photoaging and skin cancer and focused on an array of societal image norms with respect to the importance of sun protection, how to go about it, and how it would enhance appearance. At follow-up, the appearance-focused intervention was successful in raising self-reported sun protection, while decreasing self-reported sunbathing. Program effects on health beliefs were greater for photocaring than for skin cancer.

The harm reduction message, along with the detrimental appearance message, seems to be effective in reducing sunburns and teen tanning, as does incorporating these messages into a peer format. In a New Hampshire program, middle school students and their parents received consistent messages from role models in health, school, athletic, and recreational settings. Teen sun teams developed their own messages for their peers. This program was successful in improving sun protection in early adolescence. The peer-to-peer message concept is being incorporated into a teen pilot program currently under development by the AAD and the National Coalition for Sun Safety.

**IMPORTANCE OF APPEARANCE-BASED INTERVENTIONS**

Rather than focusing on skin self-examination, as advocated by Ma et al, it might be better to focus on appearance-based interventions. The current strategy consists of providing acceptable, healthy alternatives to tanning (highlighting the positive features of the alternatives), emphasizing the negative appearance aspects of tanning, and working to change the social norms regarding the “tanned-is-healthy-and-attractive” message. Certainly, giving accurate information to parents, coaches, teachers, and teenagers is imperative, with an emphasis on risk reduction behaviors. It has been advocated that the message for this age group needs to be clearer, with less room for alternative interpretations that could lead teenagers to avoid or ignore the information, and to deliver messages in a manner that will appeal to the teen audience (including peer-to-peer messages, which have been used effectively for teen tobacco education). The message should be sex and age appropriate and include a cross section of the adolescent community, including family, school settings, health care providers, and the media.

**RESTRICTING MARKETING TARGETED TO TEENAGERS**

As dermatologists and parents, it is important to be aware of the messages being given to teenagers by the media and the tanning industry. Pricing by luxury taxation, licensure of tanning facilities, advertising restrictions, and media campaigns are areas with the potential to make an impact on this age group. Tobacco control has used endorsement by fashion models, performers, and sports figures who are role models to youth, as well as peer modeling and humor. The new AAD’s “teen instant messaging” public service announcement is one such attempt to invoke the peer modeling concept.

Finally, regulation of the tanning industry is a sociopolitical intervention that would undoubtedly raise the public’s awareness of the dangers of indoor tanning, although it is difficult to achieve. It is noteworthy that since 1997 in France there has been a prohibition of the use of tanning facilities by individuals who are younger than 18 years. In addition to efforts by various states to tighten restrictions on indoor tanning for adolescents, one dermatology group has suggested placing a $20 tax per commercial UV indoor tanning session for such individuals. While 22 US states (or parts of states) do have some sort of tanning restriction laws, the monitoring of the restrictions and/or the fines for violations and noncompliance lack uniformity, and the restrictions are not rigorously enforced.

In conclusion, appearance-related factors are the most common predictors of teen tanning, both outdoors and in tanning booths. Knowledge of the risks of UV overexposure in this age group does not seem to elicit behavioral change. The success of appearance interventions, combined with basic sun safety education and promotion of alternatives to tanning, has been encouraging and needs to be directed to all teenagers.

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Financial Disclosure: None reported.

**REFERENCES**


The Cutting Edge

IN THIS ISSUE OF THE ARCHIVES, WEinfeld1 PRESENTS A NOVEL USE OF BOTULINUM TOXIN TYPE A FOR A VERY DIFFICULT TO TREAT CONDITION, NOTALGIA PARESTHETICA. THE 2 PATIENTS DESCRIBED IN HER ARTICLE WERE RESISTANT TO ALL STANDARD THERAPEUTIC MODALITIES (NONE OF WHICH ARE USUALLY EFFECTIVE), WHEREAS 1 TO 2 TREATMENTS WITH BOTULINUM TOXIN TYPE A ELIMINATED OR GREATLY REDUCED THEIR SYMPTOMS FOR AT LEAST 1 YEAR. THIS CASE REPORT EXEMPLIFIES THE IDEAL CUTTING EDGE ARTICLE. IT PRESENTS THE CASE OF A PATIENT WITH A CONDITION THAT IS EITHER DIFFICULT TO EFFECTIVELY TREAT WITH EXISTING METHODS OR A PATIENT WHO IS RESISTANT TO TREATMENT AND DESCRIBES A NOVEL TREATMENT NOT PREVIOUSLY REPORTED. IDEALLY, IT SHOULD BE A TREATMENT THAT IS EASILY AVAILABLE TO THE PHYSICIAN, SUCH AS THE BOTULINUM TOXIN TYPE A USED IN WEIFELD’S REPORT.1

See also page 980

The Cutting Edge section of the Archives was started by Kenneth A. Arndt, MD, in 1989. The first section editor was June K. Robinson, MD, who is the current editor of the Archives. The section has been published monthly ever since. Over the years, we have published articles on original surgical techniques as well as on medical treatments, including the newer biological agents and immune response modifiers. The focus has always been—and continues to be—on treatments that can be easily transferred to clinical practice. The Cutting Edge section is truly international in scope, with a large portion of the manuscripts coming from at least 3 continents outside of North America.

To be successful, the Cutting Edge relies on contributions not only from academic dermatologists but also from the extremely broad base of practicing dermatologists. It is the physician seeing a difficult-to-treat condition over and over again who often solves such clinical problems in new, effective, and practical ways just by thinking a bit outside the box. The Cutting Edge is intended for presenting 1 or 2 cases and not to be a controlled trial. Hopefully, the Cutting Edge articles will quickly bring to the practicing dermatologist a promising new treatment option while serving as a stimulus for others to confirm the findings with controlled clinical trials.

A Cutting Edge article consists of 6 components: (1) a case report up to the novel therapeutic intervention, (2) therapeutic challenge, (3) solution, (4) comment and discussion, (5) references, and (6) figures. The article should be short and to the point, with no more than 6 double-spaced pages of text. There is no need to review all of the published literature on the subject. References should be limited to 20 at most. Clinical photographs before treatment and after therapeutic intervention are important but should be limited to 2 to 4 in number.

I work with 2 dedicated assistant section editors. The 3 of us make sure that your manuscripts get prompt and thorough review. Michael P. Heffernan, MD, from Wright State University in Dayton, Ohio, is focused on medical dermatology. Christie Ammirati, MD, from Penn State Milton S. Hershey Medical Center in Hershey, Pennsylvania, has just joined the Cutting Edge to provide a surgical dermatology perspective. For continued success of the Cutting Edge, we need excellent articles. We encourage you to think about any new and original treatments that you may have tried and/or incorporated into your practice that have not been previously published and submit a case report using that treatment for consideration in the Cutting Edge.

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REFERENCE

Wikis: The Application of Web 2.0

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How Web 2.0 Is Changing Medicine: Is a Medical Wikipedia the Next Step?
Giustini D
BMJ. 2006;333(7582):1283-1284

Few concepts in information technology create more confusion than Web 2.0. The truth is that Web 2.0 is a difficult term to define, even for web experts. Nebulous phrases like “the web as platform” and “architecture of participation” are often used to describe Web 2.0. Medical librarians suggest that rather than intrinsic benefits of the platform itself, it’s the spirit of open sharing and collaboration that is paramount. The more we use, share, and exchange information on the web in a continual loop of analysis and refinement, the more open and creative the platform becomes; hence, the more useful it is in our work.

COMMENT

Change is the only constant.
Heraclitus of Ephesus1

Once upon a time an encyclopedia was a collection of volumes that cost many hundreds of dollars,2,3 and academic dermatologists spent careers creating personal picture libraries of skin disease,4 and computer-assisted diagnosis tools were pie in the sky (now they are Google5,6 and Wikipedia)—take your pick. Once upon a time manuscripts were submitted in envelopes,8 e-mails were answered,9 and the world was round.10
That was long, long ago.

By facilitating information sharing and collaboration, creators of Web 2.0 aim to take the adage “two heads are better than one” to a new level, creating information platforms where dozens or even hundreds of people can collaborate and build on novel ideas.11,12 Web 2.0 is defined by “applications that harness network effects to get better as more people use them.”13 Wikis, the most prominent Web 2.0 development, are open-access platforms that allow visitors to edit content and create collective, dynamic, up-to-date documents.

Wikis will play a revolutionary role in health care communication—as portals for discussing research, administration, and clinical practice—within and between educational programs and professional medical organizations. Examples of this use could include performing surveys, distributing schedules, and facilitating personal networking. Wikis also provide an alternative to traditional publication or conference presentations for disseminating ideas to a global audience. This new tool, combined with the frequency with which physicians already use online information resources,5-7 poses new challenges for traditional medical publishers.14

While the growth of open-access platforms may suggest a collaborative utopia on the horizon, every rose still has its thorns. The ability to publish one’s ideas or research more easily also means that such information is less regulated—the mere availability of open peer review does not guarantee information quality. Malice, conflict of interest, and hidden agendas can alight on the Wiki platform to threaten the integrity of shared information.15 Though most Wikis are not policed by an editorial board, many require user authentication to change information to assure content quality. Coming to your computer screen soon, Wikis will increasingly provide the busy dermatologist access to high-quality, up-to-date information on a wide variety of medical and nonmedical topics.

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Financial Disclosure: None reported.

REFERENCES

Submissions

Readers are invited to submit short reports of research topics likely to be of interest to practicing dermatologists now or in the future. Each piece will begin with a reprinted abstract, followed by commentary about its clinical relevance. A key figure or table, a few references, and optional Web links may be included. Prospective topics must be discussed by e-mail in advance of submission with the Section Editor, Gary S. Wood, MD (e-mail: gwood@dermatology.wisc.edu), or an Assistant Section Editor (see the masthead in each issue). Typical length: 1 published page, or about 700 words, and the abstract from the original paper, with possibly 1 figure or table and 3 to 5 references. Manuscripts should be submitted via our online manuscript submission and review system (http://manuscripts.archdermatol.com). Material must be accompanied by the required copyright transfer statement (see authorship form [http://archderm.ama-assn.org/misc/auinst_crit.pdf]).
Nodule on the Toe

**MICROSCOPIC AND RADIOLOGIC FINDINGS**

Histopathologic examination of the biopsy specimen revealed a well-circumscribed, nodular lesion involving the epidermis, dermis, and subcutis. There was no evidence of penetration of the bladder wall. The skin showed a thickened epidermis with hyperkeratosis and parakeratosis. The epidermis was hypergranulocytic with elongated dermal papillae lying in between epithelial rete ridges. The dermis showed a chronic inflammatory infiltrate with eosinophils, mast cells, and lymphocytes. The subcutis was thickened and showed areas of fibrosis with variable areas of collagen accumulation or proliferation of a clonal population of cells. Langerhans cell histiocytosis has been defined as “an acute or chronic disease of unknown origin predominantly involving the oral cavity. Since its discovery in 1971, several extraoral manifestations have been described, including a butterfly rash on the face, ulcers on the nose, and skin lesions on the scalp. The lesion described in this case is consistent with a diagnosis of Langerhans cell histiocytosis.”

**CLINICAL COURSE**

The patient was referred for further evaluation and treatment. A biopsy was performed, and the characteristic histologic features of Langerhans cell histiocytosis were identified. The patient was treated with a combination of oral corticosteroids and systemic chemotherapy, with a favorable response. The lesion improved significantly, and the patient is currently in remission.

**REFERENCES**

RESEARCH LETTERS

Frequency of Shifts Over Time in the Profile of Antidesmoglein Antibodies in Pemphigus Vulgaris

The clinical features of pemphigus vulgaris (PV) are related to the presence and profile of antidesmoglein 3 (anti-dsg3) and antidesmoglein 1 (anti-dsg1) antibodies. Anti-dsg3 is associated with mucosal PV; the concurrent presence of anti-dsg3 and anti-dsg1, with mucocutaneous disease; and anti-dsg1 alone, with pemphigus foliaceus (PF). Shifts over time in the pattern of anti-dsg antibodies from that associated with PV to that seen in PF have been described in several case reports. How often these serologic shifts occur is unknown. The present study was conducted to examine the frequency and the types of shifts in the profile of anti-dsg3 and anti-dsg1 that occur in patients with PV.

Methods. Thirty-seven sequential patients with PV who satisfied the following criteria were studied: (1) PV diagnosis based on clinical, histologic, and immunologic criteria; (2) intercellular antibodies at baseline assayed by indirect immunofluorescence; (3) at least 2 serum specimens collected at different times during the course of illness; and (4) disease active at both measurement times as evidenced by persisting skin and/or oral lesions. The median interval between the sampling of specimens was 26 months (range, 2–124 months). Anti-dsg1 and anti-dsg3 antibodies were measured by enzyme-linked immunosorbent assay using a commercially available kit (Medical & Biological Laboratories Co Ltd, Nagona, Japan). The cutoff for calling serum results positive was that recombinant human desmoglein 1, was 20 U or higher.11

Results. At baseline, 97% of patients (36 of 37) had anti-dsg3, and 59% (22 of 37) had anti-dsg1 antibodies (Table). There was no difference in antibody profile in 60% of patients (22 of 37) between the baseline and end point. In this group, 13 patients had only anti-dsg3 antibodies and 9 had both anti-dsg3 and anti-dsg1 antibodies at both measurement points.

In 41% of patients (15 of 37), a shift occurred in anti-dsg antibody profile over time. The changes varied (Table). Of the 21 patients initially testing positive for both antibodies, 9 had no change in profile, 6 ultimately showed anti-dsg1–negative results, 3 ultimately showed anti-dsg3–negative results, and 3 ultimately tested negative for both antibodies. In 15 patients initially testing positive for anti-dsg3 and negative for anti-dsg1 antibodies, 13 had no change in profile, and 2 ultimately showed anti-dsg1–positive results. No patients showed anti-dsg3–negative results. One patient had only anti-dsg1 antibodies at baseline and tested positive for both antibodies at the final measurement. The reason for these changes was not determined, but possibilities include antigenic drift and changes in the course of the disease (eg, relapse vs continuous disease activity).

At baseline, there was a good correlation between the profile of both anti-dsg3 and anti-dsg1 antibodies with the phenotype of PV: the presence of both antibodies was associated with mucocutaneous disease. The presence of only anti-dsg3 was associated with mucocutaneous disease. In the 22 patients whose antibody profile did not shift, the PV phenotype also did not change. By contrast, in the 15 patients whose anti-dsg profile changed over time, the phenotype also changed in 73% of the patients (11 of 15). However, the changes were not consistent. Among the 6 patients initially testing positive for both antibodies and whose profile then shifted to anti-dsg1 negative, 2 still retained mucocutaneous disease instead of developing only mucosal disease. Both patients initially testing positive for anti-dsg3 and negative for anti-dsg1 whose profile then became positive for both antibodies developed skin lesions but lost their prior oral lesions. The phenotype of the 1 patient whose profile shifted from only anti-dsg1 antibodies to both antibodies shifted from mucocutaneous disease to having only skin lesions. The cause for the lack of correlation between changes in anti-dsg profile and the phenotype of PV is not known. One possible explanation might be intramolecular epitope shifts that are known to occur in patients with PV and PF and that could result in the enzyme-linked immunosor-

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Abbreviations: Anti-dsg1, antidesmoglein 1; anti-dsg3, antidesmoglein 3; –, negative findings; +, positive findings.
Histologic Cutaneous Modifications After the Use of EMLA Cream, A Diagnostic Pitfall: Review of 13 Cases

While the eutectic mixture of lidocaine and prilocaine (EMLA cream; AstraZeneca International, Sodertalje, Sweden) is the topical anesthetic most widely used before performing a skin biopsy,1,2 EMLA-induced cutaneous histologic alterations have rarely been reported.3-5 We herein report 13 cases where pathological diagnosis was highly complicated by EMLA application.

Methods. We reviewed 13 skin biopsy specimens obtained after EMLA application from children (mean±SD age, 3.6±4.4 years) with erythematous and squamous disease (n=4, patients 1-4), keratinization disorder (n=4, patients 5-8), bullous disease (n=3, patients 9-11), and suspected storage (n=1, patient 12) or connective tissue (n=1, patient 13) disorders.

In addition to histopathologic findings in relation to suspected diagnoses, unexpected striking features were observed in 9 biopsy specimens (Figure 1). A diffuse pallor with swollen upper keratinocytes was seen in 7 specimens (patients 1-3, 5, 7, 9, and 10). Lower keratinocytes displayed a sharp vacuolization in 8 cases (patients 1-7 and 10). Destruction of the basal layer was observed in 8 cases (patients 1, 2, 4-7, 9, and 10). Either local

Osteopontin Expression in Spitz Nevi

Osteopontin (OPN)—a matricellular protein related to SPARC (secreted protein acid rich cysteine), thrombospondin, and tenasin C—is a secreted phosphoprotein that plays a crucial role in mediating cell-matrix interactions. The protein, first described in 1979 as a secreted phosphoprotein produced by malignant epithelial cell lines, has been shown to be overexpressed in numerous invasive carcinomas.\(^1\)\(^2\) It is postulated that OPN may facilitate invasion by extensive extracellular binding domains that include sites for hydroxyapatite, heparin, calcium, CD44v3, and numerous integrin heterodimers.\(^3\) In addition to the extracellular matrix–modulating properties, ligation of the OPN receptor on cells induces antiapoptotic effects.\(^4\) Other cellular matrix–modulating properties, ligation of the OPN receptor to a eutectic mixture of the local anesthetics lidocaine and prilocaine.\(^5\) Osteopontin expression in melanoma has been examined in several articles and shown to be elevated in most tumors.\(^3\)\(^4\) Because Spitz nevi and melanoma share certain histopathologic features, making diagnosis difficult at times, we examined the expression of OPN via immunohistochemical analysis in Spitz nevi, melanoma in situ, primary invasive melanoma, and metastatic melanoma to determine whether OPN expression differs among these tumors.

**Methods.** This study was approved by the institutional review board of the University of Arkansas for Medical Sciences, Little Rock. Paraffin-embedded specimens of Spitz nevi, melanoma in situ, primary invasive melanoma, and metastatic melanoma were retrospectively retrieved by electronic query for a 3-month period of accessions. Twenty-one cases of Spitz nevi, 5 of melanoma in situ, 10 primary invasive melanomas, and 3 metastatic melanomas were identified. A 1:20 dilution of OPN monoclonal antibody (Laboratory Vision Co, Fremont, California) was applied using standard techniques.

Slides were reviewed by 2 independent blinded observers (T.D.H. and H.L.W.). Tumor staining was graded on a 0 to 3 scale (0 indicating absence of staining; 1, sparse and weak staining; 2, moderate and diffuse staining; and 3, strong, intense, and diffuse staining). Mean ± SD intensity of staining within each diagnostic group was calculated using R statistical analysis (R statistical analysis, version 2.2.0, www.r-project.org). Comparative staining intensity between the Spitz nevus group on the one hand and the primary invasive melanoma and metastatic melanoma groups on the other was analyzed using the Wilcoxon rank sum test.

**Results.** Spitz nevi demonstrated a mean ± SD staining intensity of 0.76 ± 0.74. Melanoma in situ averaged 0.8 ± 0.4. Primary invasive melanoma and metastatic melanoma demonstrated a mean ± SD score of 2.78 ± 0.41 and 3.0 ± 0, respectively. Cumulative scores are shown in the Figure. In concordance with Zhou et al,\(^2\) no correlation between depth of invasion and staining intensity was observed. One case of metastatic melanoma demonstrated a perinuclear dot pattern of staining. Overall, staining of Spitz nevi vs primary invasive melanoma and metastatic melanoma were significantly different (\(P<.001\)).

**Comment.** Spitz nevi are commonly encountered melanocytic neoplasms that may histologically resemble melanoma. Spitz nevi may display features such as pagetoid growth, desmoplasia, pleomorphism, and dermal mitoses, which may make differentiation difficult.

Various markers have been studied to differentiate Spitz nevi from melanoma. Kapur et al\(^7\) have demonstrated a difference in the expression of fatty acid synthetase, p21, and Ki-67 in Spitz nevi vs melanomas. The study found a statistically significant difference in fatty acid synthase expression in “typical” vs “atypical” Spitz nevi and suggested that atypical Spitz nevi represent a distinct intermediate entity between typical Spitz nevi and melanoma. Recently, comparative genomic hybridization (CGH) techniques are being applied in spitzoid melanocytic tumors with promising results. Bastian et al\(^8\) have shown through CGH that a minority of Spitz nevi demonstrate amplification of the p arm of chromosome 11, which is associated with alterations in HRAS expression. Importantly, no melanomas examined demonstrated similar 11p amplifications, but rather, all had an array of other chromosomal aberrations not seen in Spitz nevi.\(^7\)
In conclusion, we report the staining characteristics of OPN in Spitz nevi and confirm the previously reported findings of OPN in primary invasive, metastatic, and in-situ melanomas. Spitz nevi do not express significant levels of OPN compared with primary invasive melanoma and metastatic melanoma. This difference was statistically significant. The limitations of the present study include the relatively small number of cases examined and the subjectivity that is inherent in immunohistochemical analysis. Validation of OPN’s role in Spitz nevi will require substantially larger study sizes and possibly the use of morphometric analysis methods to improve objectivity in assessing OPN expression strength. The diagnostic utility of differential OPN expression is likely to be small in the practice of dermatopathology. Including OPN expression in CGH analysis may heighten the sensitivity and specificity of this technique.

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Financial Disclosure: None reported.


COMMENTS AND OPINIONS

Long-term Follow-up of a Child Treated With Efalizumab for Atopic Dermatitis

I appreciate the observations and comments made by Rapaport1 in the February issue of the Archives and agree that a subset of patients with chronic eczema experience corticosteroid dependence and rebound flare. This is probably more common in adults, especially among those who have been treated with long-term topical corticosteroids on the face and groin. Another subset of patients with eczema have severe atopic dermatitis that does not reliably respond to any of the “panoply” of other described options.

Figure 1. In September 2005, excellent clearing of eczema is evident after 3 months of efalizumab treatment.
Rare Manifestation of Scalp Necrosis in Temporal Arteritis

Temporal arteritis (TA), also known as giant cell arteritis, is a panarteritis of the medium and large vessels typically seen in patients older than 50 years. The mechanism of the disease is not completely understood, but it is believed to originate from a cellular autoimmune process focused on the internal elastic lamina of affected vessels. The frequency of TA is 10 to 50 per 100,000 people, and it is more commonly found in women (4:1), whites, and those of European descent. Hallmark symptoms include headache, jaw claudication, visual changes, polymyalgia rheumatica, fever, and an elevated erythrocyte sedimentation rate (ESR). In TA, over 90% of ESRs are higher than 50 mm/h, with typical values exceeding 100 mm/h. Herein we describe a very unusual presentation of TA and an extremely rare manifestation, scalp necrosis.

Report of a Case. An 81-year-old woman presented with a nonhealing ulcer of the left parietal scalp along with painful lesions on the left face. Her symptoms were first noted 3 months earlier while she was hospitalized. She was referred to us for the nonhealing ulceration with suspicion of herpes zoster. On examination, an 8 × 5-cm crusted eschar of the left parietal scalp was seen (Figure 1). Her left face contained numerous 5 × 5-mm superficial erythematous plaques in a V3 trigeminal dermatome distribution. The patient denied all classic TA symptoms, including scalp tenderness, jaw claudication, change in headaches, weight loss, and fever. The patient reported minor vision loss in the right superior field. Her ESR value was 50 mm/h.

A biopsy specimen was taken of the left temporal artery and one of the left facial plaques. The facial biopsy specimen demonstrated a granulomatous dermatitis, consistent with a herpes zoster reactivation. The temporal artery specimen demonstrated marked arteritis with inflammatory cells extending to all layers and complete obliteration of the lumen (Figure 2). The patient was placed on a prednisone regimen of 60 mg/d. Within days of beginning therapy, the patient noticed improvement of clinical symptoms, and progressive healing of the temporal lesion was seen at 1- and 7-month follow-up visits.

Comment. The lack of typical symptoms, vision changes in the contralateral eye, ESR of only 50 mm/h, and the presence of scalp necrosis make this a very unusual presentation of TA. To our knowledge, the first case of scalp necrosis in TA was reported almost 60 years ago by Cooke et al. The exact mechanism has not been sufficiently delineated, but it is thought to stem from tissue ischemia due to occlusive inflammation of the artery. In most cases, lesions heal substantially or completely with proper treatment.

Treatment of TA is prompt administration of systemic corticosteroids with a follow-up ESR evaluation. Therapy should continue and be adjusted accordingly until ESR levels return to baseline. If inadequate improvement is noted with corticosteroids, an addition of methotrexate is warranted. Rapid aggressive treatment is necessary to prevent blindness, one of the more serious complications, caused by occlusion of the posterior ciliary branch of the ophthalmic artery. It is estimated that blindness occurs in up to 50% of untreated patients.

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Late-Onset Familial Mediterranean Fever: An Atypical Presentation of Dermatologic Interest

Familial Mediterranean fever (FMF) is a recessively inherited autoinflammatory disease characterized by self-limited bouts of fever and polyserositis. Onset usually occurs in childhood, and reactive amyloidosis may be a life-threatening complication in adult life. As for other autoinflammatory syndromes, the skin is an important target tissue for inflammation. In FMF, the appearance of an erysipeloid erythema, typically monolateral and localized to the lower leg and on the dorsal surface of the foot, is pathognomonic in the context of systemic inflammation, including fever, serositis, and synovitis. However, the clinical significance of such a cutaneous feature is difficult to define in patients without a disease-associated history or in the absence of a positive genetic test finding.

Report of a Case. A 59-year-old Sardinian woman presented with a 4-year history of a recurrent, painful, erythematous, slightly edematous patch with white areas on her left thigh, irregularly shaped and approximately 10 to 15 cm in diameter (Figure 1). It was accompanied by high-grade fever (>40°C) lasting 12 to 96 hours, asthenia, abdominal discomfort, constipation, and episodic vomiting. The only abnormal laboratory findings included acute-phase indices and leukocytosis. Attacks, which occurred every 15 to 30 days, were unresponsive to corticosteroid treatment and antibiotic therapy but spontaneously resolved within 4 days with no sequelae. A skin biopsy specimen revealed edema of the derma with interstitial and perivascular neutrophil and lymphocytic infiltrate and thrombosis of a few small vessels without vasculitis (Figure 2). These findings were consistent with those previously reported for erysipeloid erythema. Direct immunofluorescence of vessels and skin proved negative for IgG, IgM, IgA, and C3. Complete MEFV gene sequencing was also negative. Continuous colchicine therapy was started at 1 mg/d; over 3 months, systemic and cutaneous manifestations reduced in both intensity and frequency until complete resolution was achieved. Twenty-four months later, full resolution is still maintained.

Comment. In this case, the recurrent erythematous patch lesion closely resembled the erysipeloid lesion of FMF, even though the site of the rash in the proximal region of the lower limb was quite peculiar. The lack of mutations as well does not exclude the diagnosis of FMF in our patient. A significant percentage of patients fulfilling clinical criteria for the diagnosis of FMF are found to carry, after sequencing the entire gene, either only an MEFV variant or no mutation at all. Although 90% of patients experience their first attack before age 20 years, 1 study reported onset after age 40 years. In that series 3 of 20 patients presented with late-onset FMF, which emerged as a milder disease characterized by a favorable response to low-dose colchicine and absence of reactive amyloidosis, as we observed in our patient.

In spite of the late onset of signs and symptoms and the absence of MEFV mutations, the disease course, the histologic findings, and the complete response to col-
Dermoscopy Patterns of Eczemalike Melanoma

A melanotic/hypomelanotic melanoma (AHM) may present uncommonly as a scaly and ill-defined reddish patch or plaque, simulating localized eczema or dermatitis.\(^3,4\) Such eczemalike AHM may not be suspected on clinical examination, potentially resulting in a delayed diagnosis and inappropriate treatment. Important clinical clues for AHM are a solitary, continuously enlarging lesion that is unresponsive to topical therapy. Furthermore, dermoscopy may enhance this suspicion by revealing atypical vascular structures, remnants of pigmentation, or nonspecific patterns that bar an accurate diagnosis.\(^3,4\) We report a case of AHM, clinically mimicking localized eczema, in which the correct diagnosis and management was facilitated by a suspect clinical history and by dermoscopy.

Report of a Case. A 44-year-old woman with skin phototype II sought consultation at our pigmented lesion clinic at the Department of Dermatology, Second University of Naples, for a persisting lesion located on the left posterior heel. She first noticed this asymptomatic lesion 3 years previously, and it had been treated by various physicians, including primary care practitioners and dermatologists, as a range of benign scaling dermatoses or infectious skin diseases, including nummular eczema, plaque psoriasis, and tinea corporis. Despite various local treatments, the lesion had continuously increased in size, but histopathologic examination had not been performed. At her last visit with a dermatologist, a malignant skin tumor was suspected owing to the clinical history, and the patient was subsequently referred to our department. On clinical full body examination, despite a few nevi on the trunk, the lesion of concern appeared as a solitary, scaly, reddish plaque with small foci of bluish pigmentation and ill-defined borders measuring 3 × 2 cm (Figure 1A). There was no familial or personal history of melanoma.

Dermoscopic examination of the lesion (Figure 1B) revealed a marked asymmetry of colors and structures, with white to yellow surface scales, homogeneous blue to tan structureless areas, multiple brown dots and globules, and areas of regression, the latter consisting of white scarlike depigmentation and multiple blue-gray dots (pepperlike granules). In addition, a polymorphous vascular pattern composed of dotted, hairpin, and thick and irregular coiled “corkscrew” vessels (Figure 1, inset) was seen, as well as milky-red and red-blue globules and areas. This combination of features along with the clinical course raised suspicion for melanoma, and a punch biopsy specimen was taken from the bluish area encircled in Figure 1B. Prior to biopsy, microscopic examination of a skin
scraping was undertaken, which tested negative for dermatophytosis.

Histopathologic examination of the punch biopsy specimen revealed an atypical melanocytic proliferation (Figure 2). The lesion was completely excised, and a histopathologic diagnosis of invasive melanoma ensued (Clark level IV, Breslow thickness 2.5 mm).

Comment. Our case highlights the potential difficulties in differentiating eczemalike AHM from an inflammatory process. While the clinical appearance and even the dermoscopic features alone may be nonspecific and overlap with a large spectrum of inflammatory or tumoral skin disorders, the combination of clinical and dermoscopic findings in the context of the patient’s overall condition help to increase the level of suspicion for melanoma. Accordingly, the clinical course of a solitary, continuously enlarging lesion that exhibits dermoscopically a polymorphous vascular pattern with remnants of pigment should always raise a red flag for a malignant skin tumor and prompt biopsy.5

In conclusion, eczemalike AHM exhibits dermoscopic features that may help to identify this group of clinically featureless melanoma. This presumes, however, that physicians base their diagnosis and management on a combined approach, including a detailed anamnesis, a full body examination, and the application of dermoscopy on all (and particularly solitary) skin lesions, regardless of whether these lesions appear clinically suspect.

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Figure 2. Histopathologic features of the punch biopsy specimen (hematoxylin-eosin for all panels). The melanocytic neoplasm involves the skin from the epidermis to the reticular dermis (A) (original magnification ×25) and is composed of irregularly sized, shaped, and spaced nests (B) (original magnification ×100). Epithelioid melanocytes are highly atypical in both the dermis (C) (original magnification ×250) and the epidermis (D) (original magnification ×250) with no appreciable maturation.
When a Bump Can Be a Hole

Report of a Case. A 5-month-old Hispanic infant presented to our clinic with a 4-month history of a rash on his scalp, diaper area, and folds of his body. Prior to seeing us, he had undergone treatment with various topical (nystatin, zinc oxide, pimecrolimus, mometasone, and clotrimazole) and oral medications (prednisolone, cephalexin, and cefdinir) that did not improve the rash.

The infant was born at 37 weeks' gestation and was otherwise healthy. A nodule on his scalp was noticed by his mother at approximately age 3 months. On examination, the patient had diffuse, greasy, scaly patches covering most of his scalp (Figure 1A) and erythematous, macerated patches around his neck, popliteal fossa, axillae, and groin. On his trunk, there were scattered pink papules and hypopigmented macules. The differential diagnosis included diffuse Langerhans cell histiocytosis (LCH), cutaneous candidiasis, atopic dermatitis, and Wiskott-Aldrich syndrome. He also had a 3-cm, soft, non-fluctuant, subcutaneous nodule on the right parietal scalp (Figure 1A). The differential diagnosis for the nodule included lipoma, hematoma, eosinophilic granuloma, epidermal inclusion cyst, abscess, encephalocele, meningocele, and neuroblastoma.

A punch biopsy specimen was taken from a pink papule on his back and showed a bandlike infiltrate of epithelioid cells demonstrating moderate atypia within the papillary dermis (Figure 2A). There was prominent exocytosis of these cells into the epidermis. Staining with S-100 and CD1a showed positive results within the infiltrate (Figure 2A). Computed tomography and magnetic resonance imaging demonstrated a lytic lesion in the calvarium associated with a soft tissue mass in the same area as the previously described nodule (Figure 1B). The scalp nodule was not sampled for biopsy, but given the radiologic and skin biopsy findings, all involved physicians concluded that the nodule was an eosinophilic granuloma. Additionally, bone marrow aspirate tested positive for LCH.

Comment. With an annual incidence of approximately 5 per 1 million children, LCH is rare. It most commonly develops in children aged 1 through 3 years. Letterer-Siwe syndrome is the acute diffuse form of LCH that usually presents with mucocutaneous involvement and may occasionally progress to multiple-organ involvement including bone. The pathogenesis of LCH is still unclear, but viral, immunologic, and genetic causes are being investigated.

The treatment of LCH depends on the extent of disease. Response to therapy depends on the extent of involvement. Patients with high-risk organ involvement (lung, liver, blood, or spleen) have 20% mortality. These patients usually have 88% response by 6 weeks to corticosteroids and vinblastine. However, they have a 50% chance of relapse. If there is no response to the initial treatment in these high-risk patients, they have a 75% mortality.

Our patient was treated with vinblastine, prednisone, 2-chlorodeoxy-adenosine, cytosine arabinoside, and l-asparaginase. The chemotherapy resolved the scalp nodule, but the osteolytic defect remains and will most likely remain indefinitely. Despite the extensive chemotherapy, he continued to have relapses. He subsequently underwent a successful unmatched, unrelated
cord blood hematopoietic stem cell transplant (HSCT) and is doing well. The HSCT is a recently developed, highly toxic treatment option for refractory LCH, and limited information about its use exists. Kinugawa et al11 in 1999 described 4 patients who underwent HSCT: 2 patients died, and 2 were doing well. Akkari et al12 in 2003 described 8 patients who received HSCT: 4 patients died, 1 had persistent LCH controlled with chemotherapy, and 3 had complete responses.

Osteolytic lesions are common in LCH; however, a review of medical literature demonstrated that a nodule from the soft tissue swelling overlying the eosinophilic granuloma is rare.5-8 We were unable to find mention of this association in dermatologic journals. If a clinician suspects LCH and the patient also has a nodule overlying bone, then one should highly consider eosinophilic granuloma as the cause of the nodule.9

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Atrial Tachycardia Associated With Isotretinoin Use

Isotretinoin is a synthetic derivative of retinol (vitamin A) that has been approved to treat severe recalcitrant nodular acne. To my knowledge, there has been 1 reported case of atrial tachycardia linked to isotretinoin use; herein, I report a second case of this linkage.

Report of a Case. A 22-year-old man with nodular acne presented to our emergency department (ED) with symptomatic heart palpitations of 1 week’s duration. He had undergone 2 complete courses of isotretinoin treatment without sequelae and was 3 weeks into his third course. Findings of a review of his systems were negative except for his feeling of his heart racing. His other medications included metronidazole, vitamin B complex (thiamine, riboflavin, niacin, pantothenic acid, pyridoxine, biotin, folic acid, and cobalamin), vitamin E (alfa-tocopherol), and fish oil, and he had no known drug allergies. His medical history was notable for depression that was in remission.

The patient used alcohol socially and denied other drug use. His family history was noncontributory. Initial vital signs were within normal limits except for a heart rate of 123 beats/min. Findings of his physical examination were notable for tachycardia, nodular facial acne, and angular cheilitis; the rest of the findings were unremarkable. Initial laboratory tests included a basic metabolic panel; complete blood cell count; and screening for thyroid stimulating hormone, urine toxicology, and cardiac enzyme levels. All results were within normal limits.

A 12-lead electrocardiogram (ECG) (Figure) recorded in the ED showed an atrial tachycardia at a rate of 127 beats/min. Of note, the patient had undergone a previous ECG that showed normal sinus rhythm. In the ED, the patient was given a diagnostic dose of adenosine (6 mg), his response to which confirmed the diagnosis of atrial tachycardia; unfortunately this was not also a therapeutic measure.
The patient was discharged from the ED in stable condition. He was seen at follow-up visits 2 days, 1 week, and 3 months later and underwent serial ECGs each time that demonstrated a gradual decline in heart rate and an eventual return to normal sinus rhythm. At a 9-month follow-up visit, the patient remained asymptomatic and continued to have a normal sinus rhythm.

Comment. Isotretinoin (13-cis-retinoic acid) is a synthetic derivative of vitamin A that has been approved to treat severe recalcitrant nodular acne. Dispensing this medication has been highly regulated secondary to well-known adverse effects (mainly teratogenic and psychological effects).2,3 The US Food and Drug Administration has a 76-page guide that outlines the proper use and potential adverse effects of isotretinoin.4 Of note, despite the protean inventory of adverse effects listed, there is no mention of potential cardiac adverse effects.

A 3-year review of the Adverse Drug Reaction Reporting System reported 104 suspected adverse reactions in patients taking isotretinoin.3 The most frequent reports of adverse reactions involved the skin and mucous membranes (n=29), the central nervous system (n=23), the musculoskeletal system (n=12), pregnancy (n=11), and the eyes (n=8). Severe headache (n=15) was the most frequently reported adverse reaction.3 A search of drug-drug interactions was undertaken using Lexi-Comp Online Interaction Analysis,6 and no interactions were found between metronidazole and isotretinoin.

Cardiovascular adverse effects have also been reported in the literature though quite infrequently. Several case reports suggest coincidence of isotretinoin use and cardiac arrhythmias. These cases include a patient with atrial tachycardia and incomplete right bundle branch block,4 right bundle branch block associated with sinus tachycardia,7 and a pediatric case of transient sinus tachycardia.8

The present report posits a connection between isotretinoin use and atrial tachycardia. Physicians prescribing this medication should be aware of this potential adverse effect.

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Nocardia otitidiscaviarum: Cause of Long-term Cutaneous Abscesses on the Leg of an Immunocompetent Man

Report of a Case. A 55-year-old Turkish man living in northern Germany for 3 decades showed multiple, inflammatory, indurated cutaneous nodules and abscesses that were restricted to his left leg (Figure 1 A and B). The lesions had slowly progressed in size and number over 20 years. The patient did not show any inguinal lymphadenopathy or systemic signs of infection and was otherwise healthy.

The results of laboratory tests, including differential blood cell count, routine biochemical analysis, C-reactive protein assay, serum protein electrophoresis, evaluation of para-proteins, autoantibody diagnostics (antinuclear antibody, extractable nuclear antigen, and antineutrophil cytoplasmic antibody), hepatitis serologic analysis, human immunodeficiency virus testing, tuberculous diagnostics, and superficial smear tests from secreted pus, were all normal. The erythrocyte sedimentation rate was slightly elevated at 33 mm/h, indicating a mild inflammatory process. A computed tomographic (CT) scan of the left leg excluded any muscle or bone involvement. A CT scan of the chest, abdominal and nodal ultrasonography, and magnetic resonance imaging of the brain revealed no abnormalities, excluding any other disease or neoplasm.

Histologic evaluation of deep-excision biopsy specimens revealed nodular inflammatory infiltrates in the middle of the dermis (Figure 2). Periodic acid–Schiff, Grocott, and Ziehl-Neelsen stainings were negative for fungus and acid-fast bacillus.

Five-day cultures of native lesional tissue on Columbia blood agar grew orange to brownish colonies adher-
ent to the agar, rough with a velvety surface, indicating *Nocardia* bacteria. The chalky-white color indicated aerial hyphae (Figure 3). At the German Collection of Microorganisms and Cell Cultures, Braunschweig, Germany, the colonies were identified as *Nocardia otitidiscaviarum* by 16S ribosomal RNA gene sequence determination and other techniques.

According to susceptibility testing, a treatment with amikacin (three 100-mg doses per day) and imipenem (three 500-mg doses per day) intravenously over 4 weeks was initiated, which led to cessation of inflammation and scarred healing (Figure 1C and D). This was followed by an oral regimen of 160-mg trimethoprim and 800-mg sulfamethoxazole twice a day for 1 year. There was no recurrence over 4 years.

**Comment.** Nocardiosis is a rare bacterial infection, predominantly occurring in South America, Asia, or Africa. Primary cutaneous nocardiosis and systemic nocardiosis with skin involvement exists. Primary cutaneous nocardiosis includes superficial skin infection (pustules, pyoderma, abscess, granulomas, or cellulitis), lymphocutaneous infection, mycetoma, or the cervicofacial variant in children.

Primary cutaneous infections may be caused by any species of *Nocardia*, but *Nocardia brasiliensis* is isolated from most cases (approximately 80%). Only 10 of 347 cases of infections due to *Nocardia* in the United States (2.9%) were identified as *N. otitidiscaviarum*. In Germany, *Nocardia* species were isolated in only 131 patients at a national reference laboratory between the years 1979 and 1991, with only 8 patients having *N. otitidiscaviarum* infections.

Differential diagnoses include actinomycetosis, sporotrichosis, atypical mycobacterial infection, tuberculo-sis, histoplasmosis, blastomycosis, coccidiomycosis, leishmaniasis, or systemic lupus erythematoses. If nocardiosis is suspected, the microbiological laboratory should be informed, because *Nocardia* species grow poorly in many culture media and need long-term incubation.

Isolates of *N. otitidiscaviarum* complex are usually resistant to β-lactams but susceptible to amikacin, fluoroquinolones, sulfonamides, imipenem, minocycline, and linezolid. Because an important characteristic of nocardiosis is its tendency to relapse, cutaneous nocardiosis requires prolonged therapy.

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Dermoscopy of Active Lichen Planus

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The lesions are from the lower back of a 34-year-old man (Figure 1), the wrist of a 45-year-old woman (Figure 2), and the leg of a 51-year-old woman (Figure 3). All 3 lesions reveal a similar dermoscopic finding: a polymorphic pearly whitish structure that corresponds to the Wickham striae (WS), pathognomonic of lichen planus. Mature, active violaceous papules and plaques of lichen planus show characteristic rounded, arboriform, reticular, or annular WS. The WS border shows projections of varying sizes, from thin spikes (comblike appearance) to broad arboriform ramifications, that may come together in networks. Prominent linear vessels are usually intermingled with the WS border projections (radial capillaries). The histologic correlate of WS seems to be a compact orthokeratosis above the zones of wedge-shaped hypergranulosis (centered around acrosyringia and acrotrichia). These cases illustrate the active stage of lichen planus lesions under dermoscopy.

Submissions

Readers are invited to submit visually compelling images with striking consistent and repeatable patterns whose recognition enhances our diagnostic and therapeutic abilities. The submission may include up to 4 figures, and the text must be no more than 200 words, typed, double-spaced, with right margins unjustified (left aligned). Single-patient case reports are discouraged. Images derived from new technologies are encouraged. In addition, video may be included (see video submission details [http://archderm.ama-assn.org/misc/dertechreqfigures.pdf]) that complements the print images. Manuscripts should be submitted via our online manuscript submission and review system (http://manuscripts.archdermatol.com). Each figure should be submitted as a separate JPG file, numbered with the figure number. Please indicate in your cover letter that the manuscript is a submission to skINsight. Material must be accompanied by the required copyright transfer statement (see authorship form [http://archderm.ama-assn.org/misc/auinst_crit.pdf]).