Archives of Dermatology

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Archives Feature
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 to deliver original 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 therapies 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 clinicopathologic correlations; clinical disorders of unique didactic value; pharmacologic, medical and surgical therapeutics; and ethical, moral, socioeconomic, and political issues.

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Multiple Primary Melanomas in a CDKN2A Mutation Carrier Exposed to Ionizing Radiation

In addition to environmental insults, family history represents a significant risk factor for malignant melanoma. Melanoma is associated with a complex genetic heterogeneity, with cyclin-dependent kinase inhibitor 2A (CDKN2A or p16) and melanocortin-1 receptor (MC1R) gene mutations contributing to melanoma risk. In this case report, Eliason et al describe a patient from a familial melanoma pedigree with 7 primary melanomas on the right side of her body, the first occurring 5 years after atmospheric testing in the 1950s during which that side of her body was exposed to ionizing radiation. Genetic testing revealed deleterious homozygous CDKN2A and MC1R mutations. In this case, multiple primary melanomas were likely the result of environmental exposures superimposed on a highly vulnerable genetic predisposition.

See page 1409

Association of Androgenetic Alopecia With Smoking and Its Prevalence Among Asian Men: A Community-Based Survey

The pathogenesis of androgenetic alopecia (AGA) involves androgens and a genetic predisposition. In this population-based cross-sectional survey in Taiwan, Su and Chen investigate whether environmental factors such as smoking may play a role. The prevalence of AGA increased steadily with advancing age, regardless of family history. Smoking status, current amount of cigarette smoking, and smoking intensity were significantly associated with AGA, suggesting that patients with early onset of AGA may well receive smoking cessation advice to prevent further worsening.

See page 1401

Dermoscopic Changes in Acral Melanocytic Nevi During Digital Follow-up

Even for experienced dermatologists, acral melanocytic nevi may be difficult to differentiate from early acral melanoma by clinical evaluation alone. Acral melanocytic nevi present unique dermoscopic features, including the parallel furrow pattern and its globular and double-lined variants, the latticelike pattern, the fibrillar pattern, and the nontypical pattern. Digital dermoscopic surveillance with short-term monitoring is a valuable tool for early detection of melanoma. In this retrospective analysis of digital dermoscopic follow-up of 230 nevi located on acral volar skin, Altamura et al classified the type and frequency of dermoscopic changes over time. The parallel furrow pattern was the most frequent and the most dynamic dermoscopic pattern of acral melanocytic nevi.

See page 1372

Predictors of Skin-Related Quality of Life After Treatment of Cutaneous Basal Cell Carcinoma and Squamous Cell Carcinoma

Health-related quality of life is a crucial outcome in cancer research and clinical care, particularly for nonfatal cancers for which alternative therapies exist. Cutaneous basal cell and squamous cell carcinomas are typically nonfatal. In this prospective cohort study of consecutive patients with nonmelanoma skin cancer, Chen et al identified predictors of skin-related quality of life after treatment of nonmelanoma skin cancer. The strongest independent predictor of skin-related quality of life after therapy was skin-related quality of life before therapy. Mental health status, comorbidity, and race were the only other independent predictors of quality of life. Tumor characteristics were not related to quality-of-life outcomes.

See page 1386

Skin Disorders Among Construction Workers Following Hurricane Katrina and Hurricane Rita: An Outbreak Investigation in New Orleans, Louisiana

Outbreaks of dermatologic diseases such as staphylococcal infections, tinea corporis, and arthropod bites occur frequently after hurricanes and flooding. In this retrospective cohort study, Noe et al determined the extent and scope of an outbreak of skin eruptions that affected civilian construction workers living and working on a New Orleans military base after hurricanes Katrina and Rita made landfall. Four clinical entities were identified. Most common was papular urticaria, followed by bacterial folliculitis, fiberglass dermatitis, and brachioradial photodermatitis. People working and living in posthurricane environments may be at increased risk of arthropod exposure, and the authors offer strategies for avoiding dermatologic diseases.

See page 1393
BOOK REVIEW


This pamphlet contains several short papers describing a hanging apparatus for various therapeutic purposes, and some newer improvements in the technical application of the Finsen light by A. Jungmann, also a report on some experiments made on animals to show the effects of the X-rays on the ovaries during pregnancy. The principal part is taken up by Dr. Jungmann’s report on the working of the Vienna Institute for the treatment of patients affected with lupus, during the year 1905. Among 694 patients treated there were 460 cases of lupus and 234 of chronic skin diseases. They were partly treated by operation after the method used so successfully by Prof. Lang (52). With the Finsen light 160 were treated, among them 146 affected with lupus, and 12 cases of lupus erythematous; 82 were treated with X-rays and 28 with applications of radium. The results of the operations were as satisfactory as in other series published before; the Finsen treatment has given very different results: 20 practically cured, 32 very much improved, 18 improved, in some the treatment could not be continued long enough and in small number it was entirely unsuccessful. Patients with severe complications in the lungs or the larynx, or with affections of the glands, ought not to be subjected to the long-continued Finsen treatment, because the lupus is the least important part of their troubles; glandular swellings ought to be treated first with X-rays, which have a much more powerful influence on the same, also very severe and very extensive lesions in which, at best, only improvement can be expected. Often local treatment has to precede the Finsen treatment. Careful attention is given to the indications for operation and for the combination of operations with the Finsen light or other methods. Lupus erythematous gave satisfactory results in some cases, but in others proved as ineffective as other methods. The X-rays are of value in some conditions preparatory to the light-treatment, partly favorable in some hypertrophic forms, but only in few cases is a practical cure obtained. With radium no definite results have so far been obtained. Short histories of all the cases and numerous illustrations showing the conditions before and after treatment accompany the report.

H. G. K.

J Cutan Dis.
November 1907;25(11);528.

Six Degrees of Separation: Eduard Lang Edition

Eduard Lang—one of the leading physicians in turn-of-the-century Vienna—was the chief proponent for surgical treatment of lupus vulgaris. Given his stature and area of expertise, it is not surprising that Dr Lang was familiar with the pioneering studies using UV light against tuberculosis. Indeed, it was Dr Lang who first proposed that the 1903 Nobel Prize for Medicine be awarded to Nils Finsen for his research on the phototherapy of tuberculosis. Unfortunately, Dr Finsen succumbed to restrictive pericarditis within a year of his laureate. Though Finsen revolutionized medicine with his therapeutic light treatment, it wasn’t until 1942 that a way to block the deleterious effects of UV light was uncovered. The experiments conducted by Stephen Rothman and J. Rubin demonstrated that an ointment containing para-aminobenzoic acid (PABA) blocked short-wave UV light. Some 20 years later, the clinical studies performed by M. Pathak, E. Frenck, and Thomas Fitzpatrick confirmed the superiority of PABA-containing sunscreens. Perhaps the most influential dermatologist of his day, Dr Fitzpatrick assured his legacy with the host of trainees who ascended to prominent positions in academia. Among the most successful of his intellectual progeny was Kenneth Arndt, an outstanding clinician, teacher, researcher, and author. Dr Arndt was also editor par excellence of the Archives of Dermatology from 1984 to 2003. When Dr Arndt relinquished the editorial reins of this journal to June Robinson, it was by her grace and favor that yours truly, Mark Bernhardt, was granted permission to continue cultivating his small, dusty patch here at the Archives.

Okay. Your turn.
Successful Treatment of the Erythema and Flushing of Rosacea Using a Topically Applied Selective α1-Adrenergic Receptor Agonist, Oxymetazoline

Stuart D. Shanler, MD; Andrew L. Ondo, MD; School of Medicine, University of New Mexico, Albuquerque (Dr Ondo). Dr Shanler is in private practice in New York, New York.

The Cutting Edge: Challenges in Medical and Surgical Therapeutics

The erythematotelangiectatic (ETR) subtype of rosacea is characterized by frequent episodes of facial flushing and persistent centrofacial erythema and may be accompanied by telangiectasias, facial edema, burning, or stinging. The pathophysiologic cause of the erythema is uncertain, and there are currently no satisfactory treatments for this common form of rosacea.

REPORT OF CASES

CASE 1

A 55-year-old man presented with a long history of ETR rosacea manifesting with prolonged facial flushing provoked by multiple stimuli including heat, exercise, sun exposure, and the consumption of alcoholic beverages. He confided that he was particularly disturbed that, for many years, people frequently asked him: “Why is your face so red?” His condition had progressed over the last 15 years to include persistent facial erythema. In addition to his usual triggers, he had noted that during his workday in an air conditioned office the erythema worsened, usually peaking in early afternoon, sometimes with concurrent facial stinging or burning. He had previously been treated with several oral antibiotics, multiple topical therapies including metronidazole, and most recently azelaic acid gel, with no effect. He asked if there was anything that might help the erythema and symptoms.

CASE 2

A 70-year-old woman presented with a history of ETR rosacea, progressively worsening throughout her adult life. Although she had endured episodic flushing for decades, her erythema had become persistent in recent years. She had used numerous topical antibiotics for decades, including metronidazole, clindamycin phosphate, and combination sodium sulfacetamide, 10%, and precipitated sulfur, 5%, in an attempt to alleviate the erythema. She noted no improvement with the use of any of these agents and stated that she had continued using them “more out of hope” than because the medications had any effect. She had also used topical tretinoin with no improvement and had considered pulsed-dye laser therapy but had decided against it.

SOLUTION

An attempt to treat ETR rosacea using an over-the-counter drug known to possess vasoconstrictive properties was undertaken. A commercially available preparation of oxymetazoline hydrochloride, 0.05%, solution was applied once daily to the affected area of the face.

Patient 1 and her physician (1 of us) (A.L.O.) noted a decrease in facial erythema within 1 hour of drug application, and a dramatic improvement within 2 to 3 hours. This effect was sustained throughout the entire day. After a 7:30 AM application of the drug, the patient noted an improvement in the chronic “baseline” erythema, and experienced a marked reduction in his transient flares. His erythema continued to be controlled in the early afternoon, at his normal time of peak erythema, and he experienced no stinging or burning (Figure).
Patient 2 reported a similar improvement in her appearance and symptoms. Two weeks after initiating therapy, she was so pleased with the response that she sent her physician (1 of us) (A.L.O.) a letter of thanks indicating that the treatment was still effective and that she had discontinued use of topical metronidazole, her most current treatment. She returned 3 months after initiating therapy and continued to evidence marked improvement in the erythema and had experienced no episodic flares of flushing.

Both patients were counseled that this treatment was “off label” and that even though the medication was over the counter, adverse effects could occur and could include the listed adverse effects of underlying heart disease, hypertension, thyroid disease, diabetes mellitus, and urinary retention. Both patients elected to continue treatment on their own. Patient 1 stated that “This is the first time my face has been normal in decades.” Six weeks after initiating once-daily application, patient 1 demonstrated continued control of the erythema and had complete relief of his facial stinging and burning. Neither patient experienced any adverse effects, has evidenced any rebound flares in erythema or other symptoms, or has demonstrated any tachyphylaxis to the current regimen. At the last follow-up examination, patient 1 had continued treatment for 8 months and patient 2 for 17 months, with sustained effects. Both patients had discontinued all other therapies directed toward their rosacea other than sunscreen use.

Rosacea is a common, chronic cutaneous disorder, the clinical manifestations and subtypes of which have been very well described and recently reviewed.1-3 Erythematotelangiectatic rosacea is the subtype of rosacea most characterized by its frequent episodes of transient facial erythema (flushing) and nontransient, or persistent, erythema. It may be accompanied by facial edema, burning, or stinging.4 While rosacea remains a disorder of uncertain etiology and pathogenesis, the abnormal flushing and persistent erythema have usually been theorized to arise from a dysregulation in the cutaneous vasomotor response, which, whether triggered by neurogenic, hormonal, thermal, topical, or other stimuli, has as its end result an abnormal and persistent dilation of facial blood vessels.1,2,4-7

The regulation of the cutaneous circulation is of paramount importance and is extremely complex. It is mediated by the sympathetic nervous system both locally, through the release of catecholamines from the sympathetic nerve terminals, and systemically, through their release into the general circulation by the adrenal medulla. In recent years, and with newer molecular genetic techniques, the simple model of 2 adrenergic receptors (adrenoceptors) that mediate the vascular response to catecholamines6 has been replaced. The concept of “generic” α-adrenergic receptors, responsible mostly for “excitatory” functions such as vasoconstriction and uterine and urethral contraction, and “generic” β-adrenergic receptors, responsible mostly for “inhibitory” functions such as vasodilatation, bronchodilation, and uterine and urethral relaxation (though notably inotropic for the heart) has been further refined and specific receptor subtypes, localizations, and functions have been elucidated. The current model is that of a complex family of structurally related receptors consisting of at least 6 α-receptor subtypes (α1A [α1A/1B/1D], α1B, α1D, α2A [α2A/2B], α2B, and α2C) and at least 3 β-receptor subtypes (β1, β2, and β3),8-13 with additional conformational variants such as α1H and β1, bringing the total number of functional adrenoceptor conformations to at least 11.

These adrenergic receptors are all members of the G-protein–coupled receptor superfamily of proteins and modulate their effects through a classic 7-transmembrane protein second-messenger system. Their final local and systemic effects, however, are myriad, as noted previously, including vasoactive effects ranging from vasoconstriction to vasodilatation, and occur through a wide variety of intracellular mechanisms12 that are governed by local receptor subtype concentration, relative receptor subtype distribution throughout the body, ligand-binding characteristics, and other factors (eg, local temperature and hypoxia), the full discussion of which is beyond the scope of this article.9-13 Elegant in vitro, in vivo, and ex vivo studies in a variety of vascular tissues and species reveal that the contraction of peripheral vascular smooth muscle is primarily mediated by α1A- and α1D-receptor subtypes, although it varies in different vas-
ular regions. Studies of α2-receptor suggest that α2A/D and α2B effects are also of importance, particularly on the arterial side, and that the α2A, and α2C effects are of importance on the venular side, although variations based on the experimental model used are well reported.

The actual physiologic and clinical responses to stimulating or inhibiting these receptors selectively is, however, difficult to predict.

Oxymetazoline is a synthetic, direct-acting, imidazoline-type sympathomimetic agonist that is highly selective for the α1A, adrenoceptor and is a partially selective α2A-receptor agonist as well. It is a potent vasoconstrictor. Locally applied α1-receptor agonists such as phenylephrine hydrochloride, naphazoline hydrochloride, tetrahydrozoline hydrochloride, oxymetazoline hydrochloride, and xylometazoline hydrochloride are well known for their ability to clinically “get the red out” and have been used as vasoconstrictive agents in over-the-counter preparations for decades. These drugs have been used as decongestants on nasal and ocular mucous membranes for the treatment of conditions such as allergic rhinitis and conjunctivitis and decrease erythema and edema of the mucous membranes with safety and excellent efficacy. Selective α2A-receptor agonists such as brimonidine tartrate and apraclonidine hydrochloride have similarly been applied to the ocular mucosa to take advantage of their vasoconstrictive (and other) actions to treat ocular hypertension and open-angle glaucoma, also with great efficacy. However, drugs of these classes have never been used for topical application to the skin.

Although it was initially believed that their effects were modulated purely through their vasoconstrictive properties, it has been demonstrated in recent years that several of the α-adrenergic receptor vasoconstrictors also exhibit significant anti-inflammatory properties. In upper respiratory tract infections, oxymetazoline and xylometazoline have been shown to inhibit neutrophilic phagocytosis and oxidative burst, resulting in a decrease in microbial killing, decreased generation of proinflammatory cytokines, and decreased inflammation. Oxymetazoline has also recently been shown to have significant effects on the arachidonic acid cascade, strongly inhibiting 5-lipoxygenase activity and thus decreasing the synthesis of the highly proinflammatory leukotriene B4. A potential clinical role for oxymetazoline, or other agents of this class, as inhibitors of inflammation and oxidative-stress dependent reactions in inflammatory and/or infectious skin conditions is intriguing but has yet to be investigated.

Two major concerns of therapy with intranasal α-agonist decongestants are those of a loss of efficacy with prolonged use due to desensitization (tachyphylaxis) and rebound vasodilation with a flare of erythema and edema. Neither of our patients exhibited either problem with the application of oxymetazoline to the skin. While the laboratory induction of receptor desensitization cannot yet be perfectly correlated with actual physiologic response, recent laboratory studies indicate that agonists that are more selective for α1A, adrenoceptors are less prone to induce receptor desensitization than are α1A or α1B agonists. The clinical significance of this may be an important consideration in contemplating any potential future use of these drug classes on the skin because agonists with certain receptor subtype binding profiles may retain their clinically desirable effects while minimizing their adverse effect.

In these 2 patients with treatment-resistant ETR rosacea, we report that topically administering a selective α1-agonist has resulted in a positive clinical response. This was evidenced as a durable improvement in the erythema, a marked decrease of erythematous flares, relief from the symptoms of stinging and burning, and no adverse effects. It seems plausible that the erythema and flushing of ETR may be due, at least in part, to an abnormal expression, function, distribution, or responsiveness of α-adrenergic receptors, likely of an α1-receptor subtype, and that these clinical manifestations may be successfully treated by the topical application of agonists selective for α1-adrenergic receptors such as oxymetazoline.

Accepted for Publication: May 7, 2007.
Correspondence: Stuart D. Shanler, MD, 100 Winston Dr, Apt 17E North, Cliffside Park, NJ 07010 (sdsmd@aspectpharma.com).

Financial Disclosure: Drs Shanler and Ondo are principal owners and corporate officers in Aspect Pharmaceuticals LLC, Las Cruces, New Mexico, a privately held corporation that owns the rights to patent applications regarding the use of topically applied selective α1-agonists to the skin.

REFERENCES

Objective: To investigate changes in dermoscopic patterns of acquired acral melanocytic nevi (AAMN) over time.

Design: Retrospective analysis of digital dermoscopic follow-up of 230 AAMN located on acral volar skin.

Setting: Outpatient clinics at university dermatology departments.

Patients: A total of 230 AAMN located on the soles (n=149), fingers (n=62), and palms (n=19), of 230 white subjects 14 years or younger (n=81), 15 to 30 years (n=72), and older than 30 years (n=77).

Main Outcome Measure: Comparison of baseline and follow-up dermoscopic patterns.

Results: Individual AAMN had a digital follow-up of 6 months (n=59), 12 months (n=74), 18 months (n=44), and 24 months (n=53). Baseline dermoscopic images showed the following patterns: parallel furrow (48.8%), latticelike (16.1%), fibrillar (10.9%), nontypical (10.9%), homogeneous (4.8%), globular (3.5%), transition (3.5%), and reticular (2.6%). Dermoscopic changes over time were observed in 42 of the 230 AAMN (18.3%), with the greatest frequency of changes occurring in patients 14 years or younger (23 of 81 lesions; 28.4%) (P=.005). The parallel furrow pattern (25.9%) showed more variations over time than other dermoscopic patterns (11.0%) (P=.004). The frequency of change increased linearly over time (P=.001). Four of 7 clinically regressing nevi showed a homogeneous pattern at the last examination.

Conclusions: Dermoscopic changes of AAMN are most common in subjects younger than 14 years. The parallel furrow pattern appears to be the dermoscopic pattern most subject to change, while the homogeneous pattern may be seen also in AAMN showing clinical and dermoscopic involution.

Arch Dermatol. 2007;143(11):1372-1376
Table 1. Distribution of Global Dermoscopic Variations of Acral Melanocytic Nevi

<table>
<thead>
<tr>
<th>Patient Age, y</th>
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<th>Nevi</th>
<th>Changed</th>
<th>Nevi</th>
<th>Changed</th>
<th>Nevi</th>
<th>Changed</th>
<th>Nevi</th>
<th>Changed</th>
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<th>Nevi</th>
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<td>18</td>
<td>4 (22.2)</td>
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<td>22</td>
<td>11 (50.0)</td>
<td>81</td>
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<td></td>
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<td></td>
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<tr>
<td>15-30</td>
<td>17</td>
<td>1 (5.9)</td>
<td>28</td>
<td>3 (10.7)</td>
<td>14</td>
<td>1 (7.1)</td>
<td>13</td>
<td>1 (7.7)</td>
<td>72</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>&gt;30</td>
<td>15</td>
<td>1 (6.7)</td>
<td>28</td>
<td>3 (10.7)</td>
<td>16</td>
<td>4 (25.0)</td>
<td>18</td>
<td>5 (27.8)</td>
<td>77</td>
<td>13 (16.9)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>59</td>
<td>5 (8.5)</td>
<td>74</td>
<td>10 (13.5)</td>
<td>44</td>
<td>10 (22.7)</td>
<td>53</td>
<td>17 (32.1)</td>
<td>230</td>
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</table>

*Unless otherwise indicated, data are reported as number of nevi or number (percentage) of nevi showing change.

Frequency of dermoscopic changes of melanocytic lesions located on acral volar skin have been not yet described.

In this study we analyze a series of acral melanocytic nevi to evaluate the dermoscopic patterns of such lesions and changes observed during digital dermoscopic follow-up.

**METHODS**

Dermoscopic images evaluated in this study had been entered in the databases of the outpatient clinics of the Departments of Dermatology of the University of L’Aquila, L’Aquila, Italy, and the Second University of Naples, Naples, Italy, between January 2002 and December 2005. We retrieved all images of acquired melanocytic lesions located on acral volar skin that included a digital dermoscopic follow-up and that did not show clear-cut dermoscopic criteria of malignancy at initial observation. The selected lesions had a follow-up period ranging from 6 to 24 months. The images had been obtained with a digital imaging dermoscopic system using a standardized balance of colors and light (Dermogenius, version 1.6-SP2; Linos AG, Göttingen, Germany [original magnification ×30]; or Videocap; DS Medica, Milan, Italy [original magnification ×20]).

Dermoscopic patterns of all images were classified according to the standard dermoscopic classification criteria for acral melanocytic nevi.1,4,6 The nontypical pattern was defined by both the presence of dermoscopic features not conforming to any of the typical patterns (parallel furrow pattern and other patterns). Associations between variations expressed as dichotomous variable (absent or present) and categorical variables were assessed with the χ² test calculated on contingency tables. The Fisher exact test was calculated when the expected count was less than 5. The same analysis was performed stratifying by maximum length of follow-up period (6, 12, 18, and 24 months). The χ² statistic for trend was used to test the null hypothesis of no association between proportion of variation and follow-up time.

**RESULTS**

**GENERAL DATA**

We analyzed the dermoscopic images of 230 melanocytic nevi located on acral volar skin of 230 subjects (135 female [58.7%] and 95 male [41.3%]) with a mean age of 24.4 years. At initial observation, 81 of 230 subjects were 14 years or younger (35.2%); 72 of 230 ranged in age from 15 to 30 years (31.3%), and 77 of 230 were older than 30 years (33.5%). All patients were white and of Italian descent.

Anatomic sites of the lesions were the soles (149 of 230; 64.8%), volar or lateral aspects of the fingers or toes (62 of 230; 27.0%), and palms (19 of 230; 8.2%). The mean follow-up period was 14.4 months. Digital follow-up was available at 6 months for 59 of 230 lesions (25.7%); at 12 months for 74 of 230 lesions (32.2%); at 18 months for 44 of 230 lesions (19.1%); and at 24 months for 53 of 230 lesions (23.0%).

**DERMOSCOPIC PATTERNS AT BASELINE AND FOLLOW-UP IMAGES**

The baseline images of the 230 lesions showed the following benign dermoscopic features: (1) parallel furrow pattern in 112 (48.7%), including 37 showing the globular variant and 20 showing the double-line variant; (2) latticelike pattern in 35 (15.2%); (3) fibrillar pattern in 25 (10.8%); (4) nontypical pattern in 25 (10.8%); (5) homogeneous pattern in 11 (4.8%); (6) globular pattern in 8 (3.5%); (7) transition pattern in 8 (3.5%); and (8) reticular pattern in 6 (2.6%).

Dermoscopic changes in the 230 lesions over time were observed in 42 acral melanocytic nevi (18.3%). A time-related linear increase in the frequency of changing nevi was found (P = .001 for trend). Dermoscopic patterns changed in 5 of 59 lesions (8.5%) after a maximum follow-up period of 6 months; in 10 of 74 (13.5%) after 12 months; in 10 of 44 (22.7%) after 18 months; and in 17 of 53 (32.1%) after 24 months.

The highest frequency of variation was found in acral nevi of patients 14 years or younger (23 of 81 lesions; 28.4%) followed by nevi of subjects older than 30 years (13 of 77 lesions; 16.9%) and those between 15 and 30 years (6 of 72 lesions; 8.3%) (P = .005) (Table 1). In subjects 14 years or younger and older than 30 years, the frequency of dermoscopic changes over time was related to...
the time of observation ($P = .002$ and $P = .05$ for trend, respectively), while this association was not found in patients aged between 15 and 30 years (Table 1).

Table 2 summarizes the numbers and percentages of acral melanocytic lesions that changed during dermoscopic follow-up. There was a higher frequency of change seen with the parallel furrow pattern (29 of 112 lesions; 25.9%) than with other dermoscopic patterns (13 of 118 lesions; 11.0%) ($P = .004$), although the rate of change increased over time for both dermoscopic features ($P = .008$ and $P = .04$, respectively, for trend).

Minimal variations in the parallel furrow pattern were the most common dermoscopic changes over time (10 of 42; 23.8%), followed by substantial variations in this pattern such as change into fibrillar (9 of 42; 21.4%), latticelike (6 of 42; 14.3%), and nontypical patterns (4 of 42; 9.5%) (Figure 1). None of the changing lesions exhibited significant increase in size or diffuse darkening appearance, while 1 of 42 showed a substantial reduction in diameter (2.4%). Table 3 summarizes the variations in dermoscopic patterns observed over time.

**HISTOPATHOLOGIC RESULTS OF NEVI**

Surgical excision was performed in 20 of 230 acral melanocytic nevi (8.7%). Among these 20 lesions, histopathologic examination allowed a diagnosis of compound nevus for 12 (60%), junctional nevus for 6 (30%), and dermal nevus for 2 (10%). Clinical records from follow-up examinations described morphologic changes in all of these lesions. In 13 of the 20 excised nevi (65.0%), the following dermoscopic features were detected: bluish areas in 5 (38.5%) (Figure 2A and B), irregular dots and/or globules in 3 (38.5%) (Figure 2C and D), and brown to black irregular pigmentation in 3 (23.0%). Dermoscopically irregular globules histopathologically correlated with nests of pigmented melanocytes at the dermoepidermal junction and in the dermis. The bluish areas corresponded to nests of heavily pigmented melanocytes and numerous melanophages in the medium and lower dermis, while irregular pigmentation was related to nests of heavily pigmented melanocytes at the dermoepidermal junction, and irregular dots corresponded to focal transepidermal elimination of melanin in the cornified layer.

Seven of the 20 excised lesions exhibited a clinically lighter appearance over time and decreased pigmentation by dermoscopic analysis (35.0%). Follow-up images revealed a homogeneous pattern in 4 of these 7 lesions (Figure 2E and F), while the remaining 3 nevi showed the same dermoscopic pattern observed at baseline (Figure 2G and H). Histopathologic examination of these 7 lesions showed predominantly intradermal melanocytes with no evidence of regression areas.

**COMMENT**

Benign melanocytic lesions located on acral volar skin are “dynamic” lesions. In our series of 230 acquired acral melanocytic nevi, we observed morphologic changes in 18.3%
of the lesions over a follow-up period ranging from 6 to 24 months. However, the rate of dermoscopic change observed in our series of nevi cannot be compared directly with rates seen in follow-up studies with different inclusion criteria or in studies evaluating melanocytic nevi located on nonglabrous skin.11,17,21,22 Kittler et al11 observed substantial dermoscopic change over time in 5.9% of common nevi and in 9.1% of atypical nevi after a median follow-up of 12.6 months. In a subsequent study,17 researchers showed that nearly 80% of nevi with a peripheral rim of brown globules enlarged during a median follow-up period of 11.4 months. In contrast, Braun et al22 reported a 69% rate of dermoscopic variations over time in 150 melanocytic lesions, including common and Spitz nevi, that were observed over 2 years.

In our series of acral melanocytic nevi, the frequency of dermoscopic modifications linearly increased over time ($P = .001$), with changes observed in 8.5% of nevi after 6 months of follow-up; 13.5% after 12 months; 22.7% after 18 months; and in 32.1% of lesions after 24 months. Dermoscopic changes of acral nevi were significantly more frequent in subjects 14 years or younger ($P = .005$), with approximately 55% of the changes we observed over time seen in this age group. Notably, in patients 14 years or younger changes were found in 50% of nevi after a follow-up of 24 months.

An earlier study indicated that dysplastic melanocytic nevi located on nonglabrous skin become more stable with increasing age of subjects.23 Banky et al24 recently reported that the incidence of changed nevi in patients at high risk for melanoma significantly decreased with increasing age, with more than a 2-fold higher incidence in subjects younger than 30 years compared with older subjects. In our study, the parallel furrow pattern was the most frequent and the most changing dermoscopic pattern of acral melanocytic nevi. In fact, although the rate of pattern modifications linearly increased over time for all dermoscopic features, we found a higher frequency of variations of the parallel furrow pattern (25.9%) than with other dermoscopic patterns (11.0%) ($P = .004$).

During a mean follow-up period of 14.4 months, none of the 230 nevi in our series showed the parallel ridge pattern or diffuse irregular pigmentation, which are the most typical dermoscopic features of acral melanoma.1,6,10 Furthermore, histopathologic examination of the 20 surgically excised nevi showed no signs of melanoma. These findings support the view that the only acral lesions that require surgical excision are those that exhibit clear-cut dermoscopic features suggestive of malignancy.1,4,6

A few studies have reported that the number of nevi decreases with age, suggesting that the lesions regress.25,26 Seven of the 230 acral nevi in our series showed decreased pigmentation over time by clinical and dermoscopic examination (3.1%), but none of these lesions displayed histopathologic features of regression. In addition, 4 of these 7 nevi showed a light brown, unstructured, homogeneous pigmentation at the follow-up dermoscopic examination. This finding suggests that the homogeneous pattern, which has been described as a distinct dermoscopic pattern of acral nevi,5,6 may also be seen in acral melanocytic nevi exhibiting clinical and dermoscopic involution.

### Table 3. Changes in Dermoscopic Patterns Observed in Acral Melanocytic Nevi During Digital Follow-up

<table>
<thead>
<tr>
<th>Dermoscopic Pattern</th>
<th>Nevi With Dermoscopic Changes, No. (%)</th>
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<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td>Final</td>
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<tr>
<td>Parallel furrow</td>
<td>Minimal change</td>
</tr>
<tr>
<td>Parallel furrow</td>
<td>Fibrillar</td>
</tr>
<tr>
<td>Parallel furrow</td>
<td>Latticelike</td>
</tr>
<tr>
<td>Parallel furrow</td>
<td>Nontypical</td>
</tr>
<tr>
<td>Fibrillar</td>
<td>Parallel furrow</td>
</tr>
<tr>
<td>Fibrillar</td>
<td>Homogeneous</td>
</tr>
<tr>
<td>Latticelike</td>
<td>Parallel furrow</td>
</tr>
<tr>
<td>Latticelike</td>
<td>Fibrillar</td>
</tr>
<tr>
<td>Latticelike</td>
<td>Nontypical</td>
</tr>
<tr>
<td>Latticelike</td>
<td>Homogeneous</td>
</tr>
<tr>
<td>Nontypical</td>
<td>Homogeneous</td>
</tr>
<tr>
<td>Nontypical</td>
<td>Globular</td>
</tr>
<tr>
<td>Globular</td>
<td>Nontypical</td>
</tr>
<tr>
<td>Reticular</td>
<td>Parallel furrow</td>
</tr>
<tr>
<td>Total</td>
<td>42 (100)</td>
</tr>
</tbody>
</table>

Figure 2. Excised lesions showed dermoscopic changes during dermoscopic follow-up. The images on the left represent the nevi at baseline (A, C, E, and G); those on the right, later follow-up images (B, D, F, and H). Changes included irregular increase of focal blue pigmentation (A and B) or peripheral irregular globules (C and D); dermoscopically lighter appearance in a homogeneous pattern (E and F); or no change in pattern from baseline (G and H).
REFERENCES


Variations in the Dermoscopic Features of Acquired Acral Melanocytic Nevi

Fezal Ozdemir, MD; Isil Kilinc Karaarslan, MD; Taner Akalin, MD

Objective: To investigate the dermoscopic features of acquired acral melanocytic nevi (AAMN) in a white population in Turkey.

Design: Prospective population-based study.

Setting: University dermatology department dermoscopy unit.

Patients: A total of 2625 patients admitted to our dermoscopy unit.

Interventions: Patients were examined for AAMN clinically and dermoscopically with a digital imaging system, and AAMN larger than 7 mm and dermoscopically suggestive lesions were excised and examined histopathologically. For other nevi, digital dermoscopic follow-up at 6-month intervals was recommended.

Results: A total of 188 AAMN were observed in 138 patients. The most common dermoscopic pattern was the parallel furrow pattern (58.5%). The other patterns seen were fibrillar (12.2%), latticelike (6.4%), homogeneous (6.4%), globulostreaklike (5.3%), reticular (4.3%), globular (2.1%), nontypical (3.2%), and the pattern suggestive of malignancy (1.6%). All 39 excised lesions (20.7%) were benign. In addition, within 1 year, some changes in dermoscopic features were observed in 24 of the 33 lesions observed on digital dermoscopic follow-up (73%).

Conclusions: There may be many variations in AAMN. In our population, although the parallel furrow pattern is the most common pattern, as reported in Japanese populations, fibrillar and latticelike patterns occurred in lower proportions. Conversely the homogeneous pattern is more frequent and may be considered one of the major patterns in the white population. In addition, changes in the dermoscopic features of AAMN may occur, even during short-term follow-up.

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DERMOSCOPY IS A NONINVASIVE tool for the evaluation of pigmented skin lesions. Acral pigmented lesions have special dermoscopic features due to the regional anatomy. In people of color, the acral area is the most common site of melanoma; therefore, dermoscopy has become useful to enhance the diagnosis of acral lesions in the Japanese population.1-5 Others have studied acral nevi in the predominantly white populations of Spain and Italy.6,7 In the present study, we investigate the dermoscopic features of acquired acral melanocytic nevi (AAMN) in the white population of Turkey.

METHODS

We examined the palms and soles of all patients admitted to our dermoscopy unit from May 2003 to July 2005 (n=2625). All the AAMN were included in the study. The patients were from the Aegean region, the west of Turkey. All of them were white and of Turkish origin. The region was defined according to the participant’s cities of residence. The patients’ race and ethnicity were defined by the investigator. These were assessed in the study because, to our knowledge, the reports on acral nevi in the white population are limited.

See also pages 1372 and 1423

Lentigo simplex was classified as an acquired melanocytic nevus. Acral nevi on dorsal and subungual locations and lesions with congenital anamnesis were excluded. Dermoscopic images of all the lesions were stored in a digital imaging system (Molemax; Derma Instruments LP, Vienna, Austria) at 30-fold magnification, with a maximum field of 1 cm, and also with a digital camera (Dermlight FOTO; 3Gen LLC, San Juan Capistrano, California). According to the criteria established by Saida,4 lesions larger than 7 mm and dermoscopi-
Patients with 33 lesions

This study was planned and conducted in accordance with the Helsinki Declaration of 1975, as revised in 1983, as well as the Principles of Ethics Committee of Ege University Medical Faculty.

A total of 188 AAMN in 138 patients were evaluated. The patients and the clinical features of the nevi are summarized in Table 1, and the different dermoscopic patterns observed and their ratios are summarized in Table 2. The most common pattern was the parallel furrow pattern (110 lesions; 58.5%). Among those, single-line parallel furrow pattern was seen in 57 lesions (51.8%), of which 24 were prototypical (Figure 2A), 15 were associated with homogeneous pigmentation (Figure 2B), 12 were associated with dots (Figure 2C), and 6 were associated with a fine reticulated background (Figure 2D). Variants of the parallel furrow pattern included double dotted line (27 lesions; 24.5%) (Figure 2E), single dotted line (23 lesions; 21%) (Figure 2F), and double line (3 lesions; 2.7%) (Figure 2G).

A fibularr pattern was observed in 23 lesions (12.2%) (Figure 2H). In 3 of these, the fibular pattern was accompanied by dots and/or globules (Figure 2I). The latticelike pattern was observed in 12 lesions (6.4%) (Figure 2J). In 5 of these, the latticelike pattern was associated with dots and/or globules distributed on the ridges near the openings of the eccrine ducts in a regular fashion. The homogeneous pattern was seen also in 12 lesions (6.4%) (Figure 2L). Three of these were papular lesions. Ten lesions exhibited dark brown globules and brown linear or curvilinear streaklike structures (5.3%) (Figure 3A) similar to pattern type 2 described by Akasu et al. We called this pattern globulostreaklike.

The reticular pattern was observed in 8 lesions (4.3%). Six of these were located on the skin folds (plicae) of the palms, and the reticular pigmentation was not associated with any other pattern (Figure 3B). The other 2 lesions were located on the sole, but not on the skin folds. In 1 of these, the reticular pigmentation was partially associated with a linear pigmentation suggesting a parallel furrow pattern in the upper part (Figure 3C). In the other lesion, on a background of reticulare pigmentation, regular globules were located on the ridges suggesting the “crista dotted pattern” (Figure 3D). The crista dotted pattern is composed of dots and globules distributed on the ridges near the openings of the eccrine ducts in a regular fashion.

---

**Table 1. Patient and AAMN Clinical Characteristics**

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<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
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<td>Fitzpatrick skin type,%</td>
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<td>II</td>
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<tr>
<td>III</td>
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</tr>
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<td>IV</td>
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**Table 2. Different Dermoscopic Patterns Found in AAMN**

<table>
<thead>
<tr>
<th>Dermoscopic Pattern</th>
<th>Lesions, No. (%)</th>
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<tr>
<td>Parallel furrow</td>
<td>110 (58.5)</td>
</tr>
<tr>
<td>Fibrillar</td>
<td>23 (12.2)</td>
</tr>
<tr>
<td>Latticelike</td>
<td>12 (6.4)</td>
</tr>
<tr>
<td>Homogeneous</td>
<td>12 (6.4)</td>
</tr>
<tr>
<td>Globulostreaklike</td>
<td>10 (5.3)</td>
</tr>
<tr>
<td>Reticular</td>
<td>8 (4.3)</td>
</tr>
<tr>
<td>Globular</td>
<td>4 (2.1)</td>
</tr>
<tr>
<td>Nontypical</td>
<td>6 (3.2)</td>
</tr>
<tr>
<td>Suspect for malignancy</td>
<td>3 (1.6)</td>
</tr>
<tr>
<td>Total</td>
<td>188 (100)</td>
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</table>

Abbreviation: AAMN, acquired acral melanocytic nevi.
The globular pattern was observed in 4 lesions (2.1%). This pattern was composed of dots and/or globules on a diffuse, light brown pigmentation. However, in 1 of the lesions, the globules were observed in a random, nonparallel distribution, while the other 3 lesions were associated with a parallel pattern. Of these 3 lesions with the parallel pattern, 1 showed dots and globules distributed evenly all through the lesion on a background of light brown pigmentation; the second exhibited a similar appearance, but the dots and globules were distributed more heavily and especially spared the openings of the eccrine ducts; and the third showed the crista dotted pattern.

Six lesions that could not be classified into any of these patterns and were not suggestive of malignancy either clinically or dermoscopically were diagnosed as having a nontypical pattern (3.2%). These were all papular lesions. Four of them were excised and diagnosed histopathologically as compound or intradermal nevi. There was no cytologic atypia in any of them, but 2 of them showed fibrosis.

Three lesions were clinically and dermoscopically suggestive of malignancy (1.6%). In 1 of them, a blue-white structure was observed (Figure 4A). This symmetric, grayish-brown papular lesion was an intradermal nevus histopathologically (Figure 4B). The second suggestive lesion showed atypical features with black pigmentation filling the ridges and the sulci, forming a kind of irregular blotch (Figure 4C); however, it was a compound nevus histopathologically (Figure 4D). The third suggestive lesion was dark with a diameter of 7 mm; it exhibited an atypical pigmented networklike area (Figure 4E), and histopathologic examination revealed a dysplastic nevus (Figure 4F).

A total of 39 lesions were excised (20.7%), including the ones excised after a follow-up period. All of these lesions were histopathologically benign (3 lentigo simplex, 12 junctional nevi, 18 compound nevi, 5 intradermal nevi, and 1 dysplastic nevus). The relationship between the dermoscopic patterns and the histopathologic diagnoses is detailed in Table 3. In all dermoscopic patterns, junctional nevi (including lentigo simplex) or compound nevi outnumbered intradermal types (32 of 36; 88.9%) except the pattern suggestive of malignancy. The 3 lesions that showed the suggestive pattern were compound nevus, intradermal nevus, and dysplastic nevus.

In all patients whose lesions did not require excision, digital follow-up was recommended; only 22 of these (with 33 lesions) have continued follow-up. The images taken during those visits (range, 1-3) were stored.
mean follow-up time was 11 months (range, 6-21 months). No change occurred in 9 of these lesions (27%). Evolution in the pigmentation was seen in 20 lesions, 14 becoming lighter and 6 becoming darker. Evaluation of the lesion size showed that 12 lesions enlarged and 7 became smaller. In 1 lesion, the enlargement and the darkening were seen together in the summertime (Figure 5A and B), and that same lesion regressed during the winter and became even smaller and lighter than it was in the baseline image (Figure 5C). As for the dermoscopic structures, only 3 lesions showed a decrease in the number of dots, and 1 lesion (on an 8-year-old patient) that originally showed the fibrillar pattern changed after 6 months into a parallel furrow pattern, double dotted-line variant (Figure 5D and E).

**COMMENT**

The major dermoscopic patterns seen in acral melanocytic lesions are the parallel furrow pattern, the lattice-like pattern, and the fibrillar pattern. The parallel furrow pattern is reported to be the most common, found in proportions of 44%, 42%, 42.1%, and 52.9% by Saida et al, Saida et al, Altamura et al, and Malvehy and Puig, respectively. Oguchi et al have also reported this pattern to be the most common in their series of 108 acral lesions in which 90.7% were acquired and the rest were congenital acral melanocytic nevi. The proportion was 58.5% in the present study.

The single-line parallel furrow pattern serves as the parallel furrow pattern prototype. Single dotted-line, double-line, double dotted-line, fine reticulated background, and associated with dots and/or globules are the other reported variations of the parallel furrow pattern. Our findings were similar: the parallel furrow pattern was the most common pattern found in our white population also. However, in addition to the previously reported variations, we found that this pattern was also accompanied by homogeneous brown pigmentation in 15 of 110 lesions (13.6%) (Figure 5B). The single-line parallel furrow pattern was the most common pattern found in our white population also. However, in addition to the previously reported variations, we found that this pattern was also accompanied by homogeneous brown pigmentation in 15 of 110 lesions (13.6%) (Figure 5B), and all of these variations were seen in association with only the single-line type of the parallel furrow pattern in our study. The percentage of lesions with the fibrillar pattern has been reported as 12%, 33%, 6.2%, and 10.8% by Saida et al, Saida et al, Malvehy and Puig, and Altamura et al, respectively. Akasu et al have described this pattern as type 1. This pattern was observed in 12.2% in our study,
and it was accompanied by dots and globules in a few cases (Figure 2I). To our knowledge, only Saida et al\(^1\) have reported this association with brown globules.

The latticelike pattern was reported to be 27%, 19%, 12.4%, and 14.9% by Saida et al\(^1\), Saida et al\(^4\), Malvehy and Puig\(^6\), and Altamura et al\(^7\) respectively. Akasu et al\(^2\) have described this pattern as type 5. This proportion was 6.4% in our study. Saida et al\(^4\) reported this pattern to be accompanied by dots and globules in some cases, but we did not observe this association. However, we observed that in 5 of the 12 latticelike lesions (41.7%), the latticelike pattern was partially joined together with the parallel furrow pattern in small areas (Figure 2K); that is, the pattern was only partially formed. This is not an unexpected finding because the latticelike pattern is considered a variant of the parallel furrow pattern.\(^1,3\)

The homogeneous pattern, globular pattern, and acral network pattern were described as 3 novel, minor, benign patterns by Malvehy and Puig.\(^6\) The homogeneous pattern was observed in 7.1% of lesions by these authors\(^6\) and in 9.3% by Altamura et al.\(^7\) This pattern was described by Saida et al\(^4\) as the most prevalent nontypical pattern. In the present study, 6.4% of the lesions exhibited this pattern.

The major benign dermoscopic patterns in our series are similar to those reported in Japanese studies,\(^1,3,4\) the parallel furrow pattern being the most common. However, the fibrillar pattern (12.2%) and the latticelike pattern (6.4%) were less common in our study than in the Japanese studies, in agreement with the reports of Malvehy and Puig\(^6\) and Altamura et al.\(^7\)

We also found that the homogeneous pattern occurred in equal proportion to the latticelike pattern, which is one of the major patterns. Although Malvehy and Puig\(^6\) considered the homogeneous pattern one of the minor patterns, the frequency of occurrence of the homogeneous pattern in their series (7.1%) was greater than that of one of their major patterns, the fibrillar pattern (6.2%).\(^6\) Probably related to their cohort selection of patients with atypical mole syndrome, Malvehy and Puig\(^6\) preferred not to report the homogeneous pattern as a major one. Altamura et al\(^7\) observed the homogeneous pattern in 9.3% of the examined lesions, which is very close to another major pattern, the fibrillar pattern (10.8%). According to these 3 studies, we can conclude that in the white population, the homogeneous pattern is seen more frequently than in Japanese people and perhaps may be considered a major dermoscopic pattern in the acral area.

The globular pattern was described by Malvehy and Puig\(^6\) (5.2%), Altamura et al\(^7\) (5.4%), Saida et al,\(^4\) and Akasu et al.\(^2\) Among the lesions showing a globular pattern in the present study (2.1%), 1 showed globules with nonparallel distribution, similar to the cases reported by Malvehy and Puig\(^6\); however, 3 lesions showing the parallel pattern supported the findings of Saida et al\(^4\) and

<p>| Table 3. The Relationship Between AAMN Dermoscopic Patterns and Histopathologic Diagnoses |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>Dermoscopic Pattern</th>
<th>Lesions, No.</th>
<th>Lentigo Simplex</th>
<th>Junctional</th>
<th>Compound</th>
<th>Intradermal</th>
<th>Dysplastic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parallel furrow</td>
<td>13</td>
<td>1</td>
<td>3</td>
<td>8</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Fibrillar</td>
<td>4</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Latticelike</td>
<td>4</td>
<td>0</td>
<td>1</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Homogeneous</td>
<td>3</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Globulostreaklike</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Reticular</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Globular</td>
<td>3</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Nontypical</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Suspect for malignancy</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>39</td>
<td>3</td>
<td>12</td>
<td>18</td>
<td>5</td>
<td>1</td>
</tr>
</tbody>
</table>

Abbreviation: AAMN, acquired acral melanocytic nevi.
Akasu et al.² Akasu et al² included the crista dotted pattern as a type 4 nevus.

Malvehy and Puig⁶ found the acral reticular pattern—a reticulated pigmentation similar to the pigment network of nonglabrous skin without any association with parallel furrow, fibrillar, or latticelike pattern—in 2.4% of the lesions in their series. However, Saida et al⁴ observed this reticulated pigmentation as a background in 5.8% of the parallel furrow patterns in their study of 121 melanocytic acral nevi.⁴ Altamura et al⁷ reported this pattern in 2.1% and a combination of reticular pigmentation with parallel furrow pattern or latticelike pattern in 1.8%. This latter combination was reported as a novel dermoscopic pattern and designated as transition pattern because it was seen on the lateral aspect of the fingers where volar skin converted into nonglabrous skin.

We observed the reticular pattern in 4.3% of the lesions in the present study. Two of the lesions with the reticular pattern, which were not located on the skin folds, were associated partially with the parallel furrow pattern (Figure 3C) (similar to the transition pattern described by Altamura et al⁷) or associated with the crista dotted pattern (Figure 3D). However, the former lesion was not located on the transition point between the glabrous and nonglabrous skin, as reported by Altamura et al.⁷ The remaining 6 lesions in our study located on the skin folds (plicae) showed pure reticular pigmentation without any association with other patterns (Figure 3B). This observation of pure reticular pigmentation on skin plicae only, all of which were on the palms, is noteworthy; perhaps it results from special anatomic features.

Akasu et al² described 5 different patterns in 500 nevi. Type 2 showed a mottled appearance with round to oval bluish pigmented spots attached to irregular brownish pigmentation. This pigmentation was annular or in some cases dotted and unrelated to the sulcus or crista superficialis. In our study, a pattern similar to that of the type 2 with annular pigmentation was observed in 5.3% of the lesions (Figure 3A). However these bluish pigmented spots appeared as dark brown globules in our cases. We called this pattern globulostreaklike to be more descriptive and practical in daily use.

Dermoscopic features that could not be classified into any of the typical patterns have been described as nontypical pattern and reported at proportions of approximately 17%,¹ 6%,⁴ 13.8%,⁶ and 13.7%⁷ of observed acral melanocytic nevi. It was suggested that a nontypical pattern could be explained by the normal evolution of the lesions into mature nevi, the presence of fibrosis in some lesions being responsible for the loss of acral structures,⁶ or by the existence of histologic atypia.² We observed this feature in 3.2% of the lesions in our study. No histologic atypia was observed in these lesions; however, 2 of them showed fibrosis. This lower proportion of 3.2% in our study is probably owing to our identifying the globulostreaklike pattern as a separate pattern. Probably such cases were considered nontypical pattern in other studies.₄,₆,⁷ However, we believe that the globulostreaklike pattern should be considered a distinct minor pattern because it is typical and not exceptional, with an incidence of 5.3% in the present study.

Some dermoscopic features were reported to be suggestive of melanoma.¹ 3.⁵⁻⁷ In the present study, 3 lesions were considered suggestive of malignancy because of the presence of a blue-white structure (Figure 4A), irregular pigmentation (Figure 4C), and an atypical pigment networklike area (Figure 4E). None of them was malignant histopathologically, but 1 showed melanocytic proliferation with cytologic atypia and was diagnosed as a dysplastic nevus. This lesion was the one with the atypi-
cases disappeared completely. Similarly, in our study, a parallel furrow pattern to a homogeneous pattern and in some pigmentation evolved from a fibrillar, filamentous, or par-
ported that some of the lesions with homogeneous patterns besides the 3 well-known major patterns.
Importantly, we also observed changes in the dermoscopic appearance of lesions over time. We observed differences in 73% of the studied lesions on follow-up within a year, including darkening or fading in pigmentation, enlargement or decrease in size, and changes in dermoscopic structure and dermoscopic pattern. Short-term changes may occur in acral nevi without necessarily signaling a real evolution in either direction (toward malignancy or disappearance). Malvehy and Puig reported that some of the lesions with homogeneous pigmentation evolved from a fibrillar, filamentous, or parallel furrow pattern to a homogeneous pattern and in some cases disappeared completely. Similarly, in our study, a fibrillar pattern lesion on an 8-year-old patient was replaced over a 6-month period by a parallel furrow pattern, double-line variant (Figure 5D and E). As reported by Miyazaki et al, melanocytic nevi with the fibrillar pattern show a tendency to appear on the sites directly pressed by the body’s weight, and in these nevi, the cornified layer shows a slanting arrangement. Therefore, moving the skin surface in a horizontal direction with the probe may change the fibrillar pattern to a parallel furrow pattern. In the case of the nevi evolution in our 8-year-old patient, this may also be a possibility. Further studies with digital follow-up of AAMN are needed to clarify their evolution.

CONCLUSIONS

1. There may be some variations in acral nevi patterns besides the 3 well-known major patterns.
2. Of the major patterns seen in AAMN, the parallel furrow pattern is the most common in white and Japanese populations; while the fibrillar and latticelike patterns occur in lower proportions in both races, they are less common in white patients than in Japanese patients.
3. The homogeneous pattern is seen more frequently in white patients than in Japanese patients and may be considered one of the major patterns in the white population.
4. The globulostreaklike pattern may be considered a minor pattern because it is typical and not exceptional (5.3%) compared with the other minor patterns (homogeneous, globular, and reticular patterns showing proportions of 7.1%, 5.2%, and 2.4%, respectively, in the study by Malvehy and Puig, and 9.3%, 5.4%, and 2.1%, respectively, in the study by Altamura et al; in the present study, the proportions were 6.4%, 2.1%, and 4.3%, respectively).
5. The acral reticular pattern seen in the present study exhibiting pure reticular pigmentation only on the skin plicae, without any association with other patterns, was noteworthy.
6. Changes may occur in dermoscopic features of AAMN, even over a short-term follow-up period.

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Author Contributions: Study concept and design: Ozdemir and Kilinc Karaarslan. Acquisition of data: Ozdemir, Kilinc Karaarslan, and Akalin. Analysis and interpretation of data: Ozdemir, Kilinc Karaarslan, and Akalin. Drafting of the manuscript: Kilinc Karaarslan and Akalin. Critical revision of the manuscript for important intellectual content: Ozdemir. Administrative, technical, and material support: Ozdemir, Kilinc Karaarslan, and Akalin. Study supervision: Ozdemir.

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REFERENCES

Predictors of Skin-Related Quality of Life After Treatment of Cutaneous Basal Cell Carcinoma and Squamous Cell Carcinoma

Tina Chen, MD; Daniel Bertenthal, MPH; Anju Sahay, PhD; Saunak Sen, PhD; Mary-Margaret Chren, MD

Objective: To identify predictors of skin-related quality of life (QOL) after treatment of nonmelanoma skin cancer (NMSC).


Setting: University-affiliated private practice and a Veterans Affairs clinic.

Patients: A total of 633 patients who responded to a questionnaire before treatment.

Main Outcome Measure: Skin-related QOL, measured with the 16-item version of Skindex-16, a validated measure. Skindex-16 scores vary from 0 (best QOL) to 100 (worst QOL) and are reported in 3 domains: symptoms, emotional effects, and effects on functioning.

Results: Controlling for treatment group, the strongest independent predictor of skin-related QOL after treatment of NMSC was pretreatment skin-related QOL. Other patient characteristics that predicted better QOL included less comorbidity and better mental health status. No tumor or care characteristic (including location of tumor, size of tumor, site of therapy, or training level of treating clinician [attending physician, resident, or nurse practitioner]) was found to predict better skin-related QOL after treatment of NMSC.

Conclusions: Patients with better pretreatment skin-related QOL, less comorbidity, and better mental health status had better skin-related QOL after treatment of NMSC. These findings may be useful for pretreatment assessment and counseling.

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Health-related quality of life (QOL)—the impact of illness on a patient’s functioning and physical, psychological, emotional, and social well-being—is a crucial outcome in cancer research and clinical care, particularly for typically nonfatal cancers for which alternative therapies exist. Understanding QOL effects of nonfatal cancers is important for informing clinician-patient interactions and decisions about choice of therapy (hereinafter, “clinician” refers to attending physicians, residents, and nurse practitioners).

Cutaneous basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) are typically nonfatal, but lesions grow locally and can jeopardize adjacent structures such as eyes or ears. Treatment for these cancers is common and expensive, among the top 5 most costly cancers to treat within the Medicare population.1 Moreover, the risk of subsequent skin cancer approaches 50% in the 5 years after a tumor is diagnosed,2 highlighting that the care of patients with skin cancer is often lifelong. However, despite the prevalence and chronic nature of these cancers, their effects on patients’ experiences are poorly understood.

For editorial comment see page 1429

We have previously shown that skin-related QOL was similarly improved after Mohs surgery and excision and was unchanged after tumor destruction.3 We used the skin-related QOL measure Skindex-16 (hereinafter, Skindex) and determined that patients treated with excision or Mohs surgery improved in all QOL domains, with approximately 10-point and 20-point improvements in symptoms and emotional effects, respectively (improvements that are clinically meaningful).3 The purpose of this study was to determine pretreatment patient, tumor, and care characteristics that are associated with better skin-related QOL after treatment for nonmelanoma skin cancer (NMSC), control-
ling for treatment type. Based on our clinical impressions and previous studies, we hypothesized that skin-related QOL after treatment would be related to pretreatment QOL and would be better in men, in patients with smaller tumors, in patients with tumors that were not located on the head or neck, and in patients treated in a private setting compared with those treated at a Veterans Affairs (VA) Medical Center.

### METHODS

#### DESIGN, SETTING, AND SUBJECTS

This study was part of an ongoing prospective study of consecutive patients with cutaneous BCC or SCC diagnosed in 1999 and 2000 and treated at a university-affiliated private dermatology practice or the dermatology clinic at the VA Medical Center affiliated with the university. The study was approved by the institutional review boards of both institutions.

All treatments were available at both sites. Decisions regarding treatment choice were made by the clinician who performed the biopsy after histopathological results were known. The most common treatments were electrodesiccation and curettage (EDC), excision, and Mohs surgery. Residents and attending physicians performed biopsies at both sites; in addition, nurse practitioners also performed biopsies at the VA Medical Center. Most often, the treating clinician was not the same clinician who performed the biopsy. All clinicians performed EDC, residents and attending physicians performed tumor excision. Mohs surgery was performed only by attending physicians.

Patients with BCC or SCC (including SCC in situ) were identified by daily review of dermatopathology records at both hospitals. All patients were considered eligible for inclusion in the study; however, individuals were excluded if they were younger than 18 years, if the medical record was protected because the patient was an employee, or if the patient had already been diagnosed with a prior BCC or SCC during the study period. Because recurrent cancers are believed to be at higher risk for further recurrence, we eliminated from the sample 222 patients whose tumors were described in the medical record as "recurrent" or "possibly recurrent."

Patients with tumors were enrolled if they had a current mailing address and if they had responded to a pretreatment questionnaire about their health and QOL. If a patient had multiple tumors, he or she was asked to respond only about the effects of the tumor that caused recurrent cancers are believed to be at higher risk for further recurrence. Besides QOL, we also calculated a composite QOL score as the mean of the 3 Skindex subscale scores. Based on our previous work with patients with BCC or SCC, the minimal clinically meaningful difference in all Skindex subscales is 10 points. Health status was measured with an adapted version of the 12-Item Short-Form Health Survey (SF-12) instrument. Scores on the SF-12 are reported as a Physical Component Summary (PCS) score and a Mental Component Summary (MCS) score; a higher score reflects a better health status, and the median value is designed to be 50 points. Comorbid illnesses were recorded using an adapted version of the Charlson Comorbidity Index.

#### Tumor Characteristics

Data obtained from the medical records included the histologic type, location (specifically, whether the tumor involved the head and neck and areas that are more difficult to treat, such as the area of midface and ear known as the H-zone), and the diameter of the tumor, as well as the presence of histologic risk factors for recurrence (ie, whether the tumor was infiltrative, morpheaform, sclerosing, adenoid, poorly differentiated, anaplastic, or neurotropic).

#### Care Characteristics

Data included the site (VA Medical Center or private hospital), type of treatment, and the training level of the treating clinician (attending physician, resident, or nurse practitioner).

#### DATA ANALYSIS

We first described patient, tumor, and care characteristics in patients grouped according to tertiles of pretreatment composite QOL scores. Differences among the groups were evaluated using χ² or Fisher exact tests if the variable was dichotomous and with analysis of variance if the variable was continuous.

Next, we determined the bivariable association of pretreatment patient, tumor, and care characteristics with follow-up skin-related QOL, while adjusting for pretreatment Skindex scores. Because Skindex scores are not normally distributed, conventionally calculated P values are not appropriate to assess statistical significance. Instead, we calculated P values with permutation tests, using 40,000 random permutations to ensure that the P values are correct to at least 2 decimal places. For the bivariable analyses only, we divided age and diameter into categorical variables in order to have groups for comparison. We chose the age of 65 years because it is the typical age for Medicare eligibility, and chose a tumor diameter of 10 mm because tumors with diameters greater than 10 mm are conventionally regarded as larger. We performed these calculations for composite Skindex scores, as well as each of the 3 Skindex subscales.
Furthermore, to determine the independent association of pretreatment characteristics with QOL after therapy, we performed a sequential regression analysis by creating multivariable linear regression models in a stepwise fashion, including first the baseline QOL, followed by patient, tumor, and care characteristics in subsequent steps. In these models, we adjusted for treatment type and incorporated a random effect for treating clinician. Dependent variables were the composite and subscale Skindex scores. Independent variables were those significant \((P < .10)\) characteristics in bivariable analyses, type of treatment, and other characteristics that we reasoned may be important: pretreatment QOL, age, sex, histologic type of tumor, and tumor diameter. To accommodate the nonstandard distribution of the outcome, Skindex scores, we computed confidence intervals for the regression coefficients using nonparametric bootstrap analyses with 40,000 repetitions.\(^{12}\) \(P\) values for the hypothesis tests were obtained by inverting the confidence interval obtained from the bootstrap procedure.\(^{11}\) We used Stata statistical software (release 9.2; StataCorp, College Station, Texas) for all statistical analyses.

**RESULTS**

**ASSOCIATION OF PRETREATMENT QOL WITH OTHER CHARACTERISTICS**

Pretreatment QOL was associated with several patient, tumor, and care characteristics (Table 1). Patients who were married, who had completed at least some graduate school or professional school education, who had an annual income of greater than $30,000, who had fewer comorbidities, or who had better physical and mental health status had better skin-related QOL. Before treatment, QOL was not

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**Table 1. Patient, Tumor, and Care Characteristics Before Treatment of 633 Patients With Nonrecurrent NMSC, Grouped by Skin-Related QOL\(^a\)**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Best QOL (n = 211) Patients</th>
<th>Middle-Level QOL (n = 211) Patients</th>
<th>Worst QOL (n = 211) Patients</th>
<th>(P) Value(^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient Characteristics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, mean ± SD, y</td>
<td>67 ± 14</td>
<td>66 ± 15</td>
<td>65 ± 15</td>
<td>.31</td>
</tr>
<tr>
<td>Female sex</td>
<td>26</td>
<td>23</td>
<td>21</td>
<td>.58</td>
</tr>
<tr>
<td>Married</td>
<td>56</td>
<td>46</td>
<td>38</td>
<td>.001</td>
</tr>
<tr>
<td>White race</td>
<td>96</td>
<td>93</td>
<td>93</td>
<td>.46</td>
</tr>
<tr>
<td>Education level completed</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High school or less</td>
<td>38</td>
<td>35</td>
<td>43</td>
<td>.22</td>
</tr>
<tr>
<td>College</td>
<td>25</td>
<td>29</td>
<td>29</td>
<td>.56</td>
</tr>
<tr>
<td>Graduate or professional school</td>
<td>36</td>
<td>32</td>
<td>24</td>
<td>.02</td>
</tr>
<tr>
<td>Employment, work for pay</td>
<td>38</td>
<td>35</td>
<td>27</td>
<td>.06</td>
</tr>
<tr>
<td>Annual income &lt; $30,000</td>
<td>41</td>
<td>50</td>
<td>65</td>
<td>&lt;.001</td>
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<tr>
<td>History of previous NMSC</td>
<td>56</td>
<td>55</td>
<td>50</td>
<td>.47</td>
</tr>
<tr>
<td>Charlson Comorbidity Index, mean ± SD(^d)</td>
<td>1.8 ± 2.6</td>
<td>2.1 ± 2.8</td>
<td>2.6 ± 3.1</td>
<td>.02</td>
</tr>
<tr>
<td>Health status, SF-12 score, mean ± SD(^e)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCS</td>
<td>48.8 ± 10.6</td>
<td>46.5 ± 11.0</td>
<td>42.7 ± 12.2</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>MCS</td>
<td>52.4 ± 9.2</td>
<td>50.0 ± 10.0</td>
<td>43.6 ± 11.4</td>
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<tr>
<td><strong>Skin-related QOL, Skindex-16 subscale score, mean ± SD</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Symptoms</td>
<td>3.4 ± 5.8</td>
<td>17.0 ± 8.7</td>
<td>42.9 ± 23.3</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Emotional effects</td>
<td>10.4 ± 8.7</td>
<td>39.3 ± 17.1</td>
<td>70.4 ± 18.5</td>
<td>&lt;.001</td>
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<tr>
<td>Functioning</td>
<td>0.7 ± 2.3</td>
<td>5.1 ± 8.1</td>
<td>35.4 ± 27.4</td>
<td>&lt;.001</td>
</tr>
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<td><strong>Tumor Characteristics</strong></td>
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<td>Histologic type, BCC</td>
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<td>80</td>
<td>69</td>
<td>.02</td>
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<tr>
<td>Location of tumor on head and neck</td>
<td>59</td>
<td>70</td>
<td>70</td>
<td>.02</td>
</tr>
<tr>
<td>Tumor diameter, mean ± SD, mm</td>
<td>8.7 ± 5.7</td>
<td>9.7 ± 6.6</td>
<td>12.1 ± 14.1</td>
<td>.003</td>
</tr>
<tr>
<td>Noted histologic risk factors for recurrence</td>
<td>13</td>
<td>18</td>
<td>11</td>
<td>.09</td>
</tr>
<tr>
<td><strong>Care Characteristics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Location of treatment, private hospital</td>
<td>56</td>
<td>55</td>
<td>45</td>
<td>.04</td>
</tr>
<tr>
<td>Attending physician</td>
<td>71</td>
<td>70</td>
<td>70</td>
<td>.99</td>
</tr>
<tr>
<td>Resident</td>
<td>27</td>
<td>27</td>
<td>29</td>
<td>.92</td>
</tr>
<tr>
<td>Nurse practitioner</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>.94</td>
</tr>
</tbody>
</table>

Abbreviations: BCC, basal cell carcinoma; MCS, Mental Component Summary; NMSC, nonmelanoma skin cancer; PCS, Physical Component Summary; SF-12, 12-Item Short-Form Health Survey.

\(^a\) Data are given as percentages except where indicated. Data are complete except for the following characteristics (number of missing values in parentheses): marital status (25), race (30), education (33), employment (43), income (43), PCS (43), MCS (43), tumor diameter (87), and clinician who administered treatment (15).

\(^b\) As defined by the composite Skindex-16\(^{12}\) score, which is equal to the mean of the 3 Skindex subscales: symptoms, emotional effects, and effects on functioning.

\(^c\) \(P\) value compares the 3 QOL groups.

\(^d\) Using an adaptation of Charlson Comorbidity Index.\(^{12}\) A higher score indicates more comorbid illness.

\(^e\) The SF-12 instrument\(^6\) measures patient health status in terms of PCS and MCS scores; a higher score reflects better health status.
found to correlate with age, race, or history of a previous BCC or SCC.

Regarding characteristics of the tumor itself, patients with BCCs, tumors not located on the head or neck, and smaller tumors had notably better pretreatment QOL. With respect to care characteristics, patients who were treated at the private hospital had better QOL before treatment vs those treated at the VA Medical Center.

**TREATMENT FREQUENCIES AND RESPONSES ABOUT FOLLOW-UP QOL**

Therapies used to treat skin cancers of patients in the cohort were EDC in 132 cases (21%), surgical excision in 245 (39%), Mohs surgery in 238 (37%), and a variety of other, less common therapies in 18 (3%). Of the 633 enrolled patients, 514 (81%) responded at 12, 18, or 24 months after therapy. Patients who responded were similar to those who did not respond following treatment in most patient, tumor, and care characteristics. Compared with those who responded, those who did not respond were, however, more likely to have been separated, divorced, or widowed (42.4% vs 31.5% of those who responded; \( P = .02 \)), to have more comorbidities (Charlson Comorbidity Index, 2.8 vs 2.0; \( P = .01 \)), to have smaller tumors (9.6 vs 10.3 mm; \( P < .001 \)), to have been treated with therapy other than EDC, excision, or Mohs surgery (5.8% vs 2.3%; \( P = .04 \)), and to have been treated at the private hospital (59.7% vs 50.7%; \( P = .04 \)).

**BIVARIABLE ANALYSES**

After adjusting for pretreatment QOL, relatively few characteristics were related to QOL after treatment (Table 2). With respect to patient characteristics, those who considered themselves “white (not of Hispanic origin),” with annual incomes greater than $30,000, with fewer comorbidities, or with better physical or mental health had better QOL after therapy. Tumors located on the head and neck were associated with better QOL after therapy. No other tumor characteristic, however, was associated with better QOL after therapy. Finally, the treatment site (VA Medical Center or private hospital) was not associated with QOL after treatment. Similar results were found in analyses of each Skindex subscale.

**MULTIVARIABLE ANALYSES**

Adjusting for treatment, better pretreatment QOL, white race, fewer comorbidities, and better mental health status independently correlated with better QOL after therapy. No other patient, tumor, or care characteristic was independently associated with QOL after treatment. Similar results were found in multivariable analyses of each Skindex subscale.

Table 3 provides the coefficients and probabilities from the sequential regression analysis and describes the overall relationship of pretreatment characteristics and QOL after therapy in terms of change in the level of each characteristic. For an improvement in pretreatment Skindex score of 10 points, the Skindex score after therapy improved roughly 5 points. For every 10-point improve-
Table 2. Skin-Related QOL Before and After Treatment for 633 Patients With Nonrecurrent NMSC

<table>
<thead>
<tr>
<th>Pretreatment Characteristic</th>
<th>Patients, No.</th>
<th>Skin-Related QOL, Median Skindex-16 Score (Interquartile Range)</th>
<th>P Value&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient Characteristics</strong></td>
<td></td>
<td>Before Treatment</td>
<td>After Treatment</td>
</tr>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65</td>
<td>266</td>
<td>19.4 (8.3-40.1)</td>
<td>7.4 (2.1-21.7)</td>
</tr>
<tr>
<td>≥65</td>
<td>367</td>
<td>21.2 (8.1-38.0)</td>
<td>8.6 (1.5-22.4)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>485</td>
<td>21.8 (8.3-39.1)</td>
<td>8.1 (2.0-22.5)</td>
</tr>
<tr>
<td>Female</td>
<td>148</td>
<td>17.1 (8.2-34.9)</td>
<td>7.5 (1.8-22.3)</td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>111</td>
<td>25.0 (9.5-38.8)</td>
<td>8.4 (2.0-21.5)</td>
</tr>
<tr>
<td>Married or living with partner</td>
<td>295</td>
<td>15.7 (6.3-34.7)</td>
<td>7.1 (1.6-19.2)</td>
</tr>
<tr>
<td>Separated, divorced, or widowed</td>
<td>202</td>
<td>23.0 (10.4-42.1)</td>
<td>10.2 (2.0-27.5)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>566</td>
<td>19.8 (7.9-36.9)</td>
<td>7.5 (1.9-21.2)</td>
</tr>
<tr>
<td>Other</td>
<td>37</td>
<td>25.6 (11.1-42.9)</td>
<td>16.4 (4.0-38.0)</td>
</tr>
<tr>
<td>Education level completed</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High school or less</td>
<td>231</td>
<td>22.6 (7.5-41.9)</td>
<td>9.4 (1.9-22.4)</td>
</tr>
<tr>
<td>College</td>
<td>176</td>
<td>21.4 (9.2-36.9)</td>
<td>9.4 (2.3-21.8)</td>
</tr>
<tr>
<td>Graduate or professional school</td>
<td>194</td>
<td>17.2 (6.3-31.1)</td>
<td>8.2 (1.5-22.8)</td>
</tr>
<tr>
<td>Employment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Work full time or part time for pay</td>
<td>198</td>
<td>17.0 (7.1-32.0)</td>
<td>6.3 (2.1-15.0)</td>
</tr>
<tr>
<td>Other</td>
<td>392</td>
<td>22.3 (8.5-41.6)</td>
<td>9.4 (1.8-25.9)</td>
</tr>
<tr>
<td>Annual income, $</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;30 000</td>
<td>308</td>
<td>25.6 (10.7-44.5)</td>
<td>12.9 (2.2-28.4)</td>
</tr>
<tr>
<td>31 000-75 000</td>
<td>142</td>
<td>15.4 (6.5-32.8)</td>
<td>6.2 (1.3-14.8)</td>
</tr>
<tr>
<td>&gt;75 000</td>
<td>139</td>
<td>15.5 (6.8-28.4)</td>
<td>4.9 (1.4-13.5)</td>
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<tr>
<td>History of previous NMSC</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Yes</td>
<td>339</td>
<td>19.8 (7.9-38.0)</td>
<td>8.5 (2.0-21.8)</td>
</tr>
<tr>
<td>No</td>
<td>294</td>
<td>21.4 (8.7-38.8)</td>
<td>7.5 (1.6-23.7)</td>
</tr>
<tr>
<td>Charlson Comorbidity Index&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>240</td>
<td>15.8 (6.4-31.1)</td>
<td>5.6 (1.5-17.8)</td>
</tr>
<tr>
<td>1</td>
<td>149</td>
<td>22.9 (8.3-40.9)</td>
<td>7.1 (1.7-15.9)</td>
</tr>
<tr>
<td>2-4</td>
<td>122</td>
<td>25.1 (11.4-47.0)</td>
<td>13.2 (3.3-27.0)</td>
</tr>
<tr>
<td>&gt;5</td>
<td>122</td>
<td>24.2 (8.4-44.0)</td>
<td>11.6 (2.4-30.6)</td>
</tr>
<tr>
<td>PCS&lt;sup&gt;d&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50</td>
<td>301</td>
<td>25.7 (11.4-45.8)</td>
<td>12.3 (2.9-28.4)</td>
</tr>
<tr>
<td>≥50</td>
<td>332</td>
<td>15.0 (5.8-30.5)</td>
<td>4.9 (1.3-15.9)</td>
</tr>
<tr>
<td>MCS&lt;sup&gt;d&lt;/sup&gt;</td>
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<td></td>
<td></td>
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<tr>
<td>&lt;50</td>
<td>263</td>
<td>30.2 (13.3-49.6)</td>
<td>15.0 (3.3-34.5)</td>
</tr>
<tr>
<td>≥50</td>
<td>370</td>
<td>15.0 (6.2-28.6)</td>
<td>4.9 (1.3-14.2)</td>
</tr>
<tr>
<td>Tumor Characteristics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Histologic type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BCC</td>
<td>487</td>
<td>18.6 (7.9-36.0)</td>
<td>7.1 (1.9-20.8)</td>
</tr>
<tr>
<td>SCC</td>
<td>146</td>
<td>28.9 (10.9-47.3)</td>
<td>11.1 (2.1-29.1)</td>
</tr>
<tr>
<td>Location of lesion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Head and neck</td>
<td>421</td>
<td>22.2 (9.5-41.6)</td>
<td>7.5 (2.0-21.8)</td>
</tr>
<tr>
<td>Other</td>
<td>212</td>
<td>15.8 (6.4-33.6)</td>
<td>9.4 (1.9-23.5)</td>
</tr>
<tr>
<td>Tumor diameter, mm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤10</td>
<td>380</td>
<td>18.5 (7.5-36.7)</td>
<td>5.5 (1.5-18.4)</td>
</tr>
<tr>
<td>&gt;10</td>
<td>253</td>
<td>24.1 (9.2-41.8)</td>
<td>10.9 (2.8-28.9)</td>
</tr>
<tr>
<td>Histologic risk factor for recurrence</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>90</td>
<td>18.7 (9.1-31.2)</td>
<td>4.3 (1.7-21.2)</td>
</tr>
<tr>
<td>No</td>
<td>543</td>
<td>21.2 (8.1-40.5)</td>
<td>8.5 (2.0-22.9)</td>
</tr>
<tr>
<td>Care Characteristics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Location of treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VA Medical Center</td>
<td>304</td>
<td>24.2 (8.8-42.6)</td>
<td>9.9 (2.2-24.8)</td>
</tr>
<tr>
<td>Private hospital</td>
<td>329</td>
<td>17.3 (7.9-33.8)</td>
<td>6.1 (1.4-17.9)</td>
</tr>
<tr>
<td>Clinician who administered treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Attending physician</td>
<td>436</td>
<td>20.1 (8.3-38.4)</td>
<td>7.1 (1.4-21.0)</td>
</tr>
<tr>
<td>Resident</td>
<td>169</td>
<td>20.1 (7.8-38.0)</td>
<td>10.0 (2.4-23.1)</td>
</tr>
<tr>
<td>Nurse practitioner</td>
<td>13</td>
<td>18.8 (8.6-32.1)</td>
<td>10.6 (2.6-23.1)</td>
</tr>
</tbody>
</table>

Abbreviations: BCC, basal cell carcinoma; MCS, Mental Component Summary; NMSC, nonmelanoma skin cancer; PCS, Physical Component Summary; QOL, quality of life; SCC, squamous cell carcinoma.

<sup>a</sup> As defined by the composite Skindex-16 score, defined as the mean of the 3 Skindex subscales: symptoms, emotional effects, and effects on functioning. A higher score indicates worse QOL.

<sup>b</sup> The P values refer to the comparison of QOL after therapy in the different groups, after adjusting for baseline QOL.

<sup>c</sup> Using an adaptation of the Charlson Comorbidity Index. A higher score indicates more comorbid illness.

<sup>d</sup> The 12-Item Short-Form Health Survey measures patient health status in terms of PCS and MCS scores; a higher score reflects a better health status.
of Cancer Therapy-General (FACT-G) measures. However, they found an improvement in the SF-36 mental health subscale as well as in the FACT-G emotional well-being subscale, particularly for employed patients younger than 65 years. In our larger study with longer follow-up and an instrument that specifically measures skin-related QOL, however, we found that age and employment did not predict skin-related QOL after treatment. These investigators also found no demographic or tumor characteristics to be associated with change in QOL. Our results are similar in that, with the exception of race, we found that no demographic or tumor characteristic independently predicted better QOL. Furthermore, our finding that QOL after treatment is most strongly associated with a patient’s well-being and health status before therapy and not with features of the skin cancer itself is supported by studies of other conditions.18-20

The finding that white race was associated with better QOL after treatment of BCC and SCC is difficult to interpret. Most of the sample was white (94%), and the total number of nonwhite patients was very small (n = 37). The confidence interval around the point estimate in the multivariable model is also wide, indicating substantial uncertainty about the value, and the variable did not reach statistical significance (P = .05) until the final model in sequential regression analyses. Although nonwhite patients have been shown to have worse QOL in other conditions,21,22 our study does not provide enough information to validate or understand the effect of race on outcomes. These results may be useful for pretreatment assessment and counseling because they help clinicians identify patients who are at higher risk for poor QOL outcomes. For example, clinicians may focus on improving mental health status (ie, treating depression) or improving the status of comorbidities prior to therapy. Further studies should address whether QOL outcomes can be improved by interventions that target remediable pretreatment characteristics.

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

Financial Disclosure: None reported.

Additional Contributions: Leah Maddock, MPH, contributed data collection and management.

REFERENCES


Table 3. Independent Relationship of Differences in Pretreatment Characteristics and QOL After Therapy for NMSC

<table>
<thead>
<tr>
<th>Difference in Pretreatment Characteristics</th>
<th>Coefficients (Probability) From Sequential Regression Analysis</th>
<th>Improvement in Skin-Related QOL After Treatment (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>10-Point difference in pretreatment skin-related QOL score</td>
<td>5.4 (.001)</td>
<td>4.6 (.001)</td>
<td>4.6 (.001)</td>
</tr>
<tr>
<td>10-Point difference in pretreatment mental health status score</td>
<td>NA</td>
<td>3.0 (.001)</td>
<td>2.9 (.001)</td>
</tr>
<tr>
<td>1-Point difference in pretreatment comorbidity index</td>
<td>NA</td>
<td>0.7 (.03)</td>
<td>0.7 (.04)</td>
</tr>
<tr>
<td>White race (vs nonwhite race)</td>
<td>NA</td>
<td>6.1 (.07)</td>
<td>6.3 (.06)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; MCS, Mental Component Summary; NA, not applicable; NMSC, nonmelanoma skin cancer; PCS, Physical Component Summary; QOL, quality of life.

a From left to right, the columns report the coefficients in cumulative step-wise fashion including (A) baseline QOL, followed by patient (B), tumor (C), and care (D) characteristics in subsequent steps; 95% CIs are reported only for the analysis that included baseline quality of life, patient, tumor, and care characteristics.

b As defined by the composite Skindex-16 score, which is equal to the mean of the 3 Skindex subscales: symptoms, emotional effects, and effects on functioning.

c The MGS of the 12-Item Short-Form Health Survey.

d Measured with the Charlson Comorbidity Index.

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**Manuscript Submission**

- Before preparing a manuscript authors should review the Instructions for Authors available at http://www.archdermatol.com.
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Skin Disorders Among Construction Workers Following Hurricane Katrina and Hurricane Rita

An Outbreak Investigation in New Orleans, Louisiana

Rebecca Noe, MPH; Adam L. Cohen, MD; Edith Lederman, MD; L. Hannah Gould, PhD; Hannah Alsdurf, MPH; Peter Vranken, DPH; Raoul Ratard, MD; Juliette Morgan, MD; Scott A. Norton, MD, MPH; Joshua Mott, PhD

Objectives: To determine the extent and scope of the outbreak of skin eruptions, to identify the causes of the acute skin diseases, to identify risk factors for the conditions, and to reduce the dermatologic morbidity among workers repairing buildings damaged by Hurricane Katrina and Hurricane Rita.

Design: Retrospective cohort study.

Setting: Military base in New Orleans, Louisiana.

Participants: Civilian construction workers living and working at a New Orleans military base between August 30, 2005, and October 3, 2005. Living conditions were mainly wooden huts and tents with limited sanitation facilities.

Main Outcome Measures: Survey of risk factors, physical examination, skin biopsy specimens, and environmental investigation of the occupational and domiciliary exposures.

Results: Of 136 workers, 58 reported rash, yielding an attack rate of 42.6%. The following 4 clinical entities were diagnosed among 41 workers who had a physical examination (some had >1 diagnosis): 27 (65.9%) having papular urticaria, 8 (19.5%) having bacterial folliculitis, 6 (14.6%) having fiberglass dermatitis, and 2 (4.9%) having brachioradial photodermatitis. All diagnoses except brachioradial photodermatitis were confirmed by histopathologic examination. After adjusting for race/ethnicity and occupation, sleeping in previously flooded huts was statistically significantly (adjusted odds ratio, 20.4; 95% confidence interval, 5.9-70.2) associated with developing papular urticaria, the most common cause of rash in this cluster.

Conclusions: We identified 4 distinct clinical entities, although most workers were diagnosed as having papular urticaria. Huts previously flooded as a result of the hurricanes and used for sleeping may have harbored mites, a likely source of papular urticaria. To reduce the morbidity of hurricane-related skin diseases, we suggest avoiding flooded areas, fumigating with an acaricide, and wearing protective clothing.

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Outbreaks of dermatologic diseases occur frequently after hurricanes and flooding; however, few of these outbreaks have been systematically investigated. The causes of dermatologic problems after recent hurricanes in the United States have included staphylococcal infections, tinea corporis, and arthropod bites. Hurricane Katrina made landfall on August 29, 2005, and Hurricane Rita on September 24, 2005. Syndromic surveillance in New Orleans, Louisiana, following these hurricanes indicated that 22% of diseases treated were dermatologic conditions (ie, skin or wound infections and rashes).

On September 30, 2005, members of the Centers for Disease Control and Prevention Greater New Orleans Public Health Support Epidemiology and Surveillance team were approached by officials from a New Orleans hospital to assist in the investigation of an outbreak of dermatologic disease among construction workers. The objectives of the investigation were to determine the extent and scope of the outbreak, to identify the causes of the acute skin diseases, to identify risk factors for the conditions, and to reduce the dermatologic morbidity among these workers.
METHODS

EPIDEMIOLOGICAL INVESTIGATION

The construction workers were living and working together at a military base in northern Plaquemines Parish, Louisiana. Living quarters consisted of an encampment on the base that had 11 screened-in wooden huts raised above the ground, several personal tents on the ground, trailers, and limited sanitation facilities (Figure 1). Work duties mainly entailed repairing roofs of buildings on the base damaged by the recent hurricanes. Base authorities and the construction company’s supervisory staff became concerned when several workers were unable to participate in routine work activities because of the severity of their rashes.

We defined a case as any worker living or working at the encampment who had a self-reported rash with onset from August 30, 2005, the date of entry into the camp, to October 3, 2005, the date of our investigation. All employees living in the encampment were interviewed using a standardized questionnaire. The questionnaire asked about typical risk factors for acute skin diseases such as poor personal hygiene, occupational exposures to fiberglass and other building materials, sleeping location and conditions, exposure to animals and arthropods, and preexisting medical conditions. Respondents were asked to identify their primary sleeping location during the week before rash onset on a map of the encampment (Figure 1).

Univariate and bivariate analyses were performed to determine risk factors associated with the development of specific dermatologic conditions. Multivariate logistic regression models were constructed using all variables statistically significant on univariate analysis; the comparison group was the rest of the cohort. In addition, we assessed colinearity using condition indexes. Data were analyzed using Epi Info (Centers for Disease Control and Prevention, Atlanta, Georgia) and SAS 9.0 (SAS Institute, Cary, North Carolina).

DERMATOLOGIC AND HISTOPATHOLOGIC EXAMINATION

All patients with self-reported rash were offered an on-site physical examination by a board-certified dermatologist (S.A.N.). Skin biopsy specimens of representative cases were obtained and sent to Ochsner Medical Center (New Orleans) and to Walter Reed Army Medical Center (Washington, DC) for histopathologic examination.

ENVIRONMENTAL INVESTIGATION

All wooden huts and several tents were evaluated for weather and flood damage. Soil and leaf litter around the wooden huts were collected for desiccation and microscopic examination for arthropods of clinical significance. A work site evaluation was

Table 1. Demographic Characteristics of Workers With Self-Reported Rash

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Self-reported Rash (n = 58)</th>
<th>No Rash (n = 78)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median, y</td>
<td>34 (100.0)</td>
<td>42 (100.0)</td>
<td>&lt; .01</td>
</tr>
<tr>
<td>Male sex</td>
<td>58 (100.0)</td>
<td>78 (100.0)</td>
<td></td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>22 (37.9)</td>
<td>46 (58.9)</td>
<td>.02b</td>
</tr>
<tr>
<td>Native American</td>
<td>24 (41.4)</td>
<td>10 (12.8)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Black</td>
<td>8 (13.8)</td>
<td>12 (15.4)</td>
<td>.79</td>
</tr>
<tr>
<td>Mexican/Hispanic</td>
<td>4 (6.9)</td>
<td>8 (10.3)</td>
<td>.49</td>
</tr>
<tr>
<td>Other</td>
<td>0</td>
<td>2 (2.6)</td>
<td>.22</td>
</tr>
</tbody>
</table>

aWilcoxon rank sum test.
bχ² Test.
Conducted by a team from the National Institute for Occupational Safety and Health (NIOSH). The NIOSH investigators collected air and roofing samples for composition analysis.

RESULTS

All 136 employees living in the encampment on October 3, 2005, were interviewed. All were male, with a median age of 39 years (age range, 18-64 years). Half of the workers identified themselves as being of white race/ethnicity and a quarter as Native American (Table 1). Of 136 employees, 58 reported rash or pruritus, yielding a crude attack rate of 42.6%. Forty-one of 58 individuals (70.7%) were examined, and the following 4 distinct clinical entities were diagnosed (some had >1 diagnosis): 27 (65.9%) having papular urticaria (Figure 2), 8 (19.5%) having bacterial folliculitis (Figure 3), 6 (14.6%) having fiberglass dermatitis (Figure 4), and 2 (4.9%) having brachioradial photodermatitis. Ten workers had more than 1 condition (Figure 5).

Twenty-nine of 58 workers (50.0%) with self-reported rash slept in huts 7 through 10 (Figure 1), statistically significantly more than those who slept in the other huts (relative risk [RR], 3.7; 95% confidence interval [CI], 2.6-5.2). Of those workers sleeping in huts 7 through 10, 68.9% were identified as Native American. Most (79.3%) of the workers with a self-reported rash identified their occupation as roofer, whereas the remaining 20.7% held various occupations such as carpenters, forklift operators, and insulators. In addition, 84.5% of this group reported showering daily, and 34.5% used insect repellent daily. Insects reported at the encampment by the workers included flies, gnats, mosquitoes, and fleas; however, only 6 of those with self-reported rash associated their skin lesions with mosquito bites. The military base was treated with aerial spraying of an insecticide after Hurricane Katrina, and insect monitoring was maintained by military leadership.3,6

INVESTIGATIONS OF SPECIFIC DERMATOLOGIC CONDITIONS

Papular Urticaria

Of 41 workers examined, 27 (65.9%) were diagnosed as having papular urticaria (Figure 2A). The diagnosis of papular urticaria was made in the field by the board-certified dermatologist (S.A.N.) based on clinical findings of multiple edematous erythematous papules, often with a minute central punctum or hemorrhage, and was confirmed by histopathologic presence of eosinophilic infiltrate in the superficial and deep dermis (Figure 2B). Workers having papular urticaria had a dense rash, particularly on their upper and lower extremities and chest, and more than one-third of cases had between 50 and 200 papules.

Of the workers having papular urticaria, all were male, and the median age was 26 years, which was statistically significantly younger than the rest of the workers (P < .01). Seventy percent of those with papular urticaria were Native American, and Native American race/ethnicity was statistically significantly associated with the development of papular urticaria (RR, 7.1; 95% CI, 3.4-14.8) (Table 2). Ninety-three percent described their occupation as roofer, which was also statistically significantly associated with the development of papular urticaria (RR, 7.3; 95% CI, 1.8-29.4). Having slept in huts 7...
through 10 was statistically significantly associated with the development of papular urticaria (RR, 16.8; 95% CI, 6.3-45.1) compared with all other sleep locations. After adjusting for the effects of sleeping location, Native American race/ethnicity, and occupation as roofer, only sleeping in huts 7 through 10 remained statistically significantly associated with the development of papular urticaria (adjusted OR, 20.4; 95% CI, 5.9-70.2). We found no evidence of collinearity between the variables in our regression model using condition indexes. All workers sleeping in huts 7 through 10 relocated to other sleep locations; the use of repellent and the fumigation of huts were recommended.

**Bacterial Folliculitis**

Eight workers (median age, 27 years) were diagnosed clinically as having bacterial folliculitis (Figure 3). Half of these workers were Native American, 7 were roofers, and 3 had slept in huts 7 through 10. Compared with those without rash, none of the risk factors (race/ethnicity, occupation, or sleeping in huts 7-10) were statistically significant in the development of folliculitis. Histopathologic examination showed folliculitis. If clinically indicated, patients were treated with oral antibiotics.

**Fiberglass Dermatitis**

Six workers (median age, 28 years) were diagnosed as having fiberglass dermatitis (Figure 4A). This diagnosis was made among those workers who manifested poorly demarcated diffuse erythema with urticarial, sandpapery, or morbilliform texture, predominantly on the volar aspects of the forearms, with intense pruritus that began within 4 hours of exposure of handling fiberglass.

Four of 6 were Native American, all were roofers, and 3 had slept in huts 7 through 10. Only Native American race/ethnicity (RR, 6.0; 95% CI, 1.2-31.3) was statistically significant on univariate analysis. We obtained punch biopsy specimens from 2 patients with suspected fiberglass dermatitis, both of which had a histopathologic appearance consistent with fiberglass irritation (Figure 4B). Treatment with topical corticosteroids was prescribed to those with fiberglass dermatitis; the use of personal protective measures was stressed as well.

**Brachioradial Photodermatitis**

Two workers (median age, 44 years) were diagnosed as having brachioradial photodermatitis.7 One was Native American and the other of white race/ethnicity, 1 was a roofer, and 1 had slept in huts 7 through 10. Because of the small sample size, none of these risk factors could be analyzed.

**ENVIRONMENTAL AND SITE INVESTIGATION**

Although the interiors of huts 7 through 10 and the surrounding grounds were dry at the time of the investigation, the environmental investigation revealed that these huts had sustained flooding during Hurricane Katrina as evidenced by a remaining waterline (Figure 1). Shower and laundry facilities were available on-site, although the main shower trailer at the time of the investigation was out of order. The soil and leaf litter samples collected from around the huts were processed using a Berlese funnel but did not yield any arthropod species.

The work site evaluation by NIOSH included air and material sampling. Three personal breathing zone air samples were collected over approximately 4 hours during which old rooftops were removed. The roofing materials contained fiberglass, and 1 of the air samples detected a fiberglass concentration of 0.01 fiber/cm$^3$, which is below the NIOSH recommended exposure limit of 3 fibers/cm$^3$. Therefore, this exposure was not clinically or occupationally important, but it confirmed the presence of fiberglass at the work site. All other air samples were below the analytical detection limit. Two bulk samples of roofing material were tested for asbestos; none were detected in either sample.
In this posthurricane outbreak investigation, we identified the following 4 clinical entities: papular urticaria, bacterial folliculitis, fiberglass dermatitis, and brachioradial photodermatitis. Although most of the workers were diagnosed as having papular urticaria, this outbreak demonstrates the importance of a multidisciplinary team suited to evaluate skin disease in a setting with environmental and occupational exposures. The delineation of the different dermatologic entities allowed us to implement appropriate treatment and preventive measures, as well as to allay fears of epidemic skin disease.

Various skin diseases have been associated with hurricanes. Infestations with mites may occur when there is a disturbance to the ecosystem such as flooding. This causes displacement of rodents or birds, leaving mites to seek alternate hosts such as humans. Infections caused by such as *Vibrio vulnificus* and leptospirosis should be considered in ill patients with open wounds that were exposed to posthurricane floodwaters. *Vibrio vulnificus* is common in the warm waters (>20°C) of the Gulf of Mexico, and several wound-associated cases were documented after Hurricane Katrina. Leptospirosis wound infections occur when persons are exposed to freshwater or mud contaminated by the urine of animals infected with leptospires. Floodwaters have been associated with outbreaks of leptospirosis. Other dermatologic conditions associated with occupational and chemical exposures in postflooding cleanup activities have been documented.

We found that workers with a self-reported rash were 4 times more likely to be sleeping in huts that had sustained flooding at the time of rash onset. Similarly, those with papular urticaria were 20 times more likely to be sleeping in the previously flooded huts. One or 2 days before this investigation, the workers living in huts 7 through 10 relocated to tents. A follow-up with the safety officer 2 weeks after the investigation revealed that workers’ rashes were improving and that huts 7 through 10 remained unoccupied. Therefore, the arthropod bites were clearly associated with the flooded huts. Papular urticaria is a reaction caused by bites from mosquitoes, fleas, bedbugs, and various species of mites. We suspect that the source may have been mites whose natural hosts such as rodents or birds may have been displaced by the flooding in these huts. Mosquitoes were less likely the source because of spraying that occurred at the base and because the bites resolved once the workers relocated out of the contaminated huts. Likewise, bedbugs and fleas were never seen by the workers with self-reported rashes in the huts, and they used the same bedding without further experiencing bites. No specific arthropod could be identified from the environmental sampling. Receding floodwaters, the return of arthropods to their natural habitat and hosts, and nocturnal behavior of the offending arthropod could explain our inability to identify the causative organism.

Construction workers living and working at this military base came from all parts of the United States, including several Native American reservations. Initial reports suggested that the skin problems were primarily in Native American workers. Our investigation found that Native American race/ethnicity was associated with the risk of papular urticaria on univariate analysis; however, this finding did not persist on multivariate analysis. The workers racially/ethnically self-segregated in the encampment (eg, 68.9% of the Native Americans slept in huts 7-10), which may have led to confounding among these variables. Once we controlled for these variables, only sleeping in huts 7 through 10 remained a statistically significant risk factor. Most of the cases were in Native Americans, and racial/ethnic self-segregation into specific sleeping huts may have played a role in this focal environmental exposure.

Our investigation has several limitations. Before our investigation, 53 employees had left the compound as part of normal work rotations. These workers were primarily Mexican and Mexican American, and they had lived in tents in the encampment area since August 30, 2005. None had reported rashes, and we did not have access to their contact information. Therefore, inclusion of this group would have most likely biased our results toward the null. The few workers with bacterial folliculitis, fiberglass dermatitis, and brachioradial photodermatitis prevented adequate analysis of risk factors for these conditions.

A multidisciplinary team, including epidemiologists (R.N., A.L.C., E.L., and L.H.G.), a dermatologist, and an entomologist, were able to discern 4 separate clinical entities among cases originally reported as a rash cluster and to provide appropriate clinical and preventive recommendations. A suspected mite infestation of flooded housing units is the most plausible hypothesis, although we were unable to identify the arthropod source. Our immediate recommendations to the construction company and to the military leadership were to relocate all workers sleeping in huts 7 through 10 to other sleep quarters, to improve the accessible laundry services for workers’ clothes, to encourage workers to shower daily and to use insect repellent, and to enforce Occupational Safety and Health Administration guidelines when removing fiberglass roofing, including wearing long-sleeved shirts and gloves.

People working and living in posthurricane environments where flooding has occurred may be at an increased risk of exposure to arthropods. To reduce dermatologic morbidity, we suggest avoiding flooded areas, fumigating with an acaricide, wearing protective clothing, and using arthropod repellent.

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**Correspondence:** Rebecca Noe, MPH, Centers for Disease Control and Prevention, 1600 Clifton Rd NE, Atlanta, GA 30333 (RNoe@cdc.gov).

**Author Contributions:** All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. **Study concept and design:** Noe, Cohen, Lederman, Morgan, Norton, and Mott. **Acquisition of data:** Noe, Cohen,
Financial Disclosure: None reported.

Disclaimer: The findings and conclusions in this study are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention, the US Army, or the US Navy.

Previous Presentation: This study was presented in part at the Epidemic Intelligence Service Conference; March 21, 2006; Atlanta, Georgia.

Additional Contributions: The Centers for Disease Control and Prevention Greater New Orleans Public Health Response team, Michele Pearson, MD, Elizabeth Javernick, MD, John Faught, MD, Jeffrey W. Clark, MS, Stephen J. Krivda, MD, Jennifer Lincoln, PhD, and Gary Mullen, PhD, provided additional contributions.

REFERENCES


Association of Androgenetic Alopecia With Smoking and Its Prevalence Among Asian Men

A Community-Based Survey

Lin-Hui Su, MD, MSc; Tony Hsiu-Hsi Chen, DDS, PhD

Objectives: To evaluate the association of androgenetic alopecia (AGA) with smoking and to estimate its prevalence among Asian men.


Setting: Tainan County, Taiwan.

Participants: The eligible population consisted of all male residents 40 years or older in Tainan County. A total of 740 subjects aged 40 to 91 years participated in the survey between April 10, 2005, and June 12, 2005.

Main Outcome Measures: Norwood and Ludwig classifications were used to assess the degree of hair loss. Information on smoking, together with other possible risk factors and age at onset of AGA, was collected using a questionnaire interview.

Results: After controlling for age and family history, statistically significant positive associations were noted between moderate or severe AGA (Norwood types I-IV) and smoking status (odds ratio [OR], 1.77; 95% confidence interval [CI], 1.14-2.76), current cigarette smoking of 20 cigarettes or more per day (OR, 2.34; 95% CI, 1.19-4.59), and smoking intensity (OR, 1.78; 95% CI, 1.03-3.07). The OR of early-onset history for AGA grades increased in a dose-response pattern. Risk for moderate or severe AGA increased for family history of first-degree and second-degree relatives, as well as for paternal relatives.

Conclusions: The age-specific prevalence of AGA in Taiwan was compatible to that among Korean men but was lower than that among persons of white race/ethnicity. Smoking status, current amount of cigarette smoking, and smoking intensity were statistically significant factors responsible for AGA after controlling for age and family history. Patients with early-onset AGA should receive advice early to prevent more advanced progression.

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Androgenetic alopecia (AGA), a hereditary androgen-dependent disorder, is characterized by progressive thinning of the scalp hair defined by various patterns. It is the most common type of hair loss in men. Lower prevalence has been seen among Asian, Native American, and African American men, whereas high prevalence has been found among men of white race/ethnicity.

The changes of AGA are androgen dependent and follow an inheritance mode with gene polymorphisms. To our knowledge, only 1 gene that encodes the androgen receptor has been identified. While prerequisites are androgens and a genetic predisposition, clinical practice has shown that simply blocking androgens does not result in the conversion of miniaturized follicles to terminal ones in advanced alopecia. Some environmental factors such as smoking may play a role in the pathogenesis of AGA. The association between smoking and AGA has been addressed in 3 studies with inconsistent results. One study showed a positive association, one study failed to demonstrate a statistically significant positive association, and another study showed the opposite findings, albeit statistically nonsignificant.

The first objective of this study was to estimate the prevalence and types of AGA among Taiwanese men and to compare our findings with those in other countries. The second objective was to investigate the association between smoking, family history, and other potential risk factors and AGA.

STUDY SUBJECTS AND DESIGN

Eligible subjects in this study consisted of male residents 40 years or older in Tainan County, Taiwan. Our study was part of a community-based integrated screening program that invited residents 30 years or older. The details of a screening program similar to ours in Tainan County.
Norwood type IV of AGA represents the starting grade of severe frontal AGA concurrent with vertex AGA. Therefore, we divided AGA into 2 categories (mild AGA [Norwood types I-III] and moderate or severe AGA [Norwood types IV-VIII]) to assess its association with smoking and other potential risk factors.

SMOKING AND OTHER POSSIBLE RISK FACTORS

In addition to classification of AGA, we collected information on age at onset of AGA together with smoking and other possible risk factors using a face-to-face questionnaire interview. Smoking status (never, quit, or current); age at start of smoking; and quantity, duration, and frequency of smoking were collected using a structured questionnaire administered by trained staff members. In addition to smoking status, we categorized cigarette smoking into 4 groups (never, quit, current smoker of <20 cigarettes per day, or current smoker of ≥20 cigarettes per day) for comparison. Regarding anthropometric measures, body weight, body height, waist circumference, and hip circumference were measured. Body mass index was calculated as weight in kilograms divided by height in meters squared. Blood pressure was measured twice with at least a 5-minute interval between measurements. Hypertension was defined as a systolic blood pressure of 140 mm Hg or higher and a diastolic blood pressure of 90 mm Hg or higher or as taking antihypertensive medication.

To collect biochemical markers, a venous blood sample was obtained after 12-hour fasting to check blood glucose, triglycerides, total cholesterol, and high-density lipoprotein cholesterol levels. Low-density lipoprotein cholesterol level was calculated in accord with the following formula: low-density lipoprotein cholesterol level = [(total cholesterol level−high-density lipoprotein cholesterol level−(triglyceride level/5)]. If the triglyceride level was greater than 400 mg/dL (to convert to millimoles per liter, multiply by 0.0113), the low-density lipoprotein cholesterol level was set as a missing value. Abnormal status for these biochemical markers included hypertriglyceridemia (triglyceride level, >160 mg/dL), hypercholesterolemia (total cholesterol level, >220 mg/dL [to convert to millimoles per liter, multiply by 0.0259]), low high-density lipoprotein cholesterol level (<42 mg/dL), high low-density lipoprotein cholesterol level (≥140 mg/dL), and high fasting glucose level (>110 mg/dL [to convert to millimoles per liter, multiply by 0.0555]). Dyslipidemia was defined as abnormal serum triglyceride, total cholesterol, high-density lipoprotein cholesterol, or low-density lipoprotein cholesterol level or as taking lipid-lowering drugs.

In each subject, a questionnaire regarding diagnoses of chronic diseases such as hypertension, diabetes mellitus, cardiovascular disease, antihypertensive and lipid-lowering drug use, timing of growth spurt in puberty, socioeconomic factors, alcoholic beverage consumption, and betel nut chewing history was completed. The socioeconomic factors included age, occupation, and level of education. Age was defined as the age at study enrollment. Information about baldness among the first-degree, second-degree, and third-degree relatives was also collected using a structured questionnaire administered by trained staff members. The degree of hair loss was recalled by the study subjects.

STATISTICAL ANALYSIS

The age-specific prevalence of AGA (Norwood types ≥III) was expressed as a percentage. A multivariate logistic regression model was used to assess the relationships of each possible risk factor such as smoking and degrees of relative relationships for family history of AGA (first-degree, second-degree, and third-

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Table 1. Age-Specific Types of Androgenetic Alopecia

<table>
<thead>
<tr>
<th>Age Group, y.</th>
<th>40-49</th>
<th>50-59</th>
<th>60-69</th>
<th>≥70</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norwood</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>65 (65.7)</td>
<td>55 (57.8)</td>
<td>106 (42.7)</td>
<td>131 (44.0)</td>
<td>357</td>
</tr>
<tr>
<td>II</td>
<td>14 (14.1)</td>
<td>18 (19.5)</td>
<td>43 (17.3)</td>
<td>37 (12.4)</td>
<td>112</td>
</tr>
<tr>
<td>III</td>
<td>3 (3.0)</td>
<td>1 (1.1)</td>
<td>12 (4.8)</td>
<td>10 (3.4)</td>
<td>26</td>
</tr>
<tr>
<td>IV</td>
<td>5 (5.1)</td>
<td>6 (6.3)</td>
<td>12 (4.8)</td>
<td>19 (6.4)</td>
<td>42</td>
</tr>
<tr>
<td>V</td>
<td>2 (2.0)</td>
<td>1 (1.1)</td>
<td>12 (4.8)</td>
<td>14 (4.9)</td>
<td>27</td>
</tr>
<tr>
<td>VI</td>
<td>1 (1.0)</td>
<td>0</td>
<td>5 (2.0)</td>
<td>6 (2.0)</td>
<td>12</td>
</tr>
<tr>
<td>VII</td>
<td>6 (6.1)</td>
<td>5 (5.3)</td>
<td>21 (8.5)</td>
<td>20 (6.7)</td>
<td>52</td>
</tr>
<tr>
<td>Va</td>
<td>1 (1.0)</td>
<td>0</td>
<td>1 (0.4)</td>
<td>3 (1.0)</td>
<td>5</td>
</tr>
<tr>
<td>V</td>
<td>1 (1.0)</td>
<td>3 (3.2)</td>
<td>12 (4.8)</td>
<td>14 (4.7)</td>
<td>30</td>
</tr>
<tr>
<td>Va</td>
<td>0</td>
<td>0</td>
<td>2 (0.8)</td>
<td>3 (1.0)</td>
<td>5</td>
</tr>
<tr>
<td>VI</td>
<td>1 (1.0)</td>
<td>2 (2.1)</td>
<td>10 (4.0)</td>
<td>23 (7.7)</td>
<td>36</td>
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<tr>
<td>VII</td>
<td>0</td>
<td>2 (2.1)</td>
<td>8 (3.2)</td>
<td>13 (4.4)</td>
<td>23</td>
</tr>
</tbody>
</table>

Ludwig       |       |       |       |     |       |
| L-I          | 0 | 0 | 4 (1.6) | 6 (2.0) | 10 |
| L-II         | 0 | 2 (2.1) | 0 (0.3) | 3 |
| L-III        | 0 | 0 | 0 | 0 | 0 |
| Total        | 99 | 95 | 248 | 298 | 740 |

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County have been published elsewhere. A community-based survey on prevalence of AGA was added to this integrated community-based screening program between April 10, 2005, and June 12, 2005, by inviting 929 residents who were selected from a population household registry of Tainan County in light of different screening criteria based on evidence-based medicine. Most participants were 40 years or older; this age group is subsidized by the local government. Only 5 subjects were aged 30 to 39 years, and they were excluded from the study. Of the remaining 924 subjects invited, the overall response rate to participate in our survey on AGA was 80.1% (740 of 924). The age-specific response rates were 83.9% for those aged 40 to 49 years (99 of 118), 81.9% for those aged 50 to 59 years (95 of 116), 84.9% for those aged 60 to 69 years (248 of 292), and 74.9% for those aged 70 years and older (298 of 398). There was a similar distribution with respect to age between respondents and nonrespondents. Therefore, the study population for age-specific prevalence in the AGA survey is representative of the underlying population invited to attend the screening. The study protocol was approved by the ethics committee of the Bureau of Tainan County, and informed consent was obtained from all participants.

CLASSIFICATION OF AGA

The diagnosis of AGA was based on the pattern of hair loss of the participants. Assessment of the degree of hair loss was obtained by independent public health nurses trained by a dermatologist. To classify the degree of AGA for each subject, the classification by Norwood, a standard classification scheme with good test-retest reliability, was used. Some men with “female pattern hair loss” (noninvolvement of the frontal hairline) were assessed separately using the classification by Ludwig. Androgenetic alopecia among men with cosmetically significant male pattern baldness was defined as type III or greater (types III [including IIIv and IIIa], IV [including IVa], V [including Va], VI, and VII) according to the Norwood classification. The prevalence of more advanced degrees of alopecia characterized by only a remaining horseshoe fringe of hair (Norwood types V, Va, VI, and VII) was also estimated. The prevalence of AGA with female pattern hair loss was reported separately.
degree relatives) to moderate or severe AGA (Norwood types ≥IV). A cumulative logits model was used to assess the incremental effect of age at onset of AGA (≤40 vs >40 years) on AGA severity (Norwood types I-VII) with ordinal properties. The proportional odds assumption was checked for the 7 AGA grades. In addition, the association between family history of AGA and age at onset of AGA was assessed. Because age and family history of AGA were 2 established factors for AGA, they were retained in the model in the multivariate analysis. All odds ratios (ORs) and their 95% confidence intervals (CIs) were computed using statistical software (SAS version 8; SAS Institute, Inc, Cary, North Carolina).

RESULTS

Of 924 invited men, 740 participated in this survey. The mean ± SD age of participants was 65.2 ± 11.2 (age range, 40-91 years).

PREVALENCE

The age-specific number and percentage of different AGA types are given in Table 1. Figure 1 shows that the age-specific prevalence of AGA (Norwood types III [including IIIv and IIIa], IV [including IVa], V [including Va], VI, and VII) increased with advancing age. The age-specific prevalence of severe hair loss (Norwood types V, Va, VI, and VII) was low. In Figure 2, the age-specific prevalence of AGA (Norwood types ≥III) is compared with the results of previous studies.

Of 740 men examined, 48 (6.5%) were Norwood type A variants, higher than that reported in the study by Norwood (3%), and 13 (1.8%) manifested female pattern AGA. The prevalence did not increase with age for Norwood type A variants or for Ludwig grades L-I to L-III. For the groups aged 40 to 49, 50 to 59, 60 to 69, and 70 years or older, the age–specific prevalences of Norwood type A variants were 5.1%, 1.1%, 8.1%, and 7.4%, respectively, and those of female pattern AGA were 0.0%, 2.1%, 1.6%, and 2.4%, respectively (Table 1).

ASSOCIATION

In the univariate analysis, smokers were at increased risk of having moderate or severe AGA (Norwood types ≥IV) (OR, 1.61; 95% CI, 1.05-2.46). However, no statistically significant associations were found for intensity or duration of smoking (Table 2).

There were statistically significant positive associations between moderate or severe AGA and smoking status (OR, 1.77; 95% CI, 1.14-2.76), current cigarette smoking of 20 cigarettes or more per day (OR, 2.34; 95% CI, 1.19-4.59), smoking intensity (OR, 1.78; 95% CI, 1.03-3.07), and dyslipidemia (OR, 1.47; 95% CI, 1.01-2.14) after adjusting for age and family history of AGA (Table 2).

Smoking status and other statistically significant variables (age, family history of AGA, dyslipidemia, and betel nut chewing) were retained in the model and were adjusted for each other. A statistically significant association between smoking status and moderate or severe AGA (OR, 1.63; 95% CI, 1.00-2.63) still remained.

EARLY-ONSET AGA AND AGA GRADES

The incremental effect of early-onset on severity of AGA was demonstrated by using the cumulative logits model. Findings suggest that earlier onset of AGA was associated with severe AGA. In those with early-onset AGA, AGA grades were statistically significantly worse (OR, 2.09; 95% CI, 1.14-3.85). Early-onset AGA was also related to family history of AGA (OR, 2.89; 95% CI, 1.42-5.88) using the logistic regression model.

Risk for moderate or severe AGA increased with degree of relationship for family history (first degree [OR, 13.38; 95% CI, 4.80-37.27], second degree [OR, 6.33; 95% CI, 2.00-20.07]).
CI, 2.37-16.91], and third degree [OR, 5.32; 95% CI, 0.80-35.48]) (Table 3). The association between moderate or severe AGA and family history of AGA from paternal relatives was statistically significant (OR, 12.69; 95% CI, 4.65-34.60), whereas the corresponding association from maternal relatives was not (OR, 3.07; 95% CI, 0.30-35.48).

Table 2. Univariate and Multivariate Analyses of Risk Factors

<table>
<thead>
<tr>
<th>Variable</th>
<th>Norwood Type, No.</th>
<th>Univariate Analysis</th>
<th>Multivariate Analysisa</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>I-III</td>
<td>IV-VII</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Never</td>
<td>446</td>
<td>103</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>Quit and current</td>
<td>105</td>
<td>39</td>
<td>1.61 (1.05-2.46)</td>
</tr>
<tr>
<td>Cigarette smoking</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>471</td>
<td>112</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>Quit</td>
<td>27</td>
<td>12</td>
<td>1.92 (0.94-3.93)</td>
</tr>
<tr>
<td>Current, &lt;20 cigarettes/d</td>
<td>43</td>
<td>12</td>
<td>1.21 (0.62-2.37)</td>
</tr>
<tr>
<td>Current, ≥20 cigarettes/d</td>
<td>35</td>
<td>15</td>
<td>1.86 (0.98-3.53)</td>
</tr>
<tr>
<td>Smoking intensity, duration × amount per day</td>
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<td></td>
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</tr>
<tr>
<td>&lt;350</td>
<td>24</td>
<td>5</td>
<td>1 [Reference]</td>
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<tr>
<td>≥350</td>
<td>63</td>
<td>23</td>
<td>1.75 (0.60-5.14)</td>
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<td>Duration of smoking, y</td>
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<td></td>
</tr>
<tr>
<td>&lt;25</td>
<td>14</td>
<td>3</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>≥25</td>
<td>76</td>
<td>27</td>
<td>1.66 (0.44-6.22)</td>
</tr>
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<td>Age, continuous variable, y</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Family history of androgenetic alopecia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>548</td>
<td>125</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>Yes</td>
<td>28</td>
<td>26</td>
<td>4.07 (2.31-7.18)</td>
</tr>
<tr>
<td>Educational achievement</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ College</td>
<td>29</td>
<td>11</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>&lt; College</td>
<td>538</td>
<td>140</td>
<td>0.69 (0.33-1.41)</td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>≤90</td>
<td>397</td>
<td>103</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>&gt;90</td>
<td>176</td>
<td>48</td>
<td>1.05 (0.72-1.55)</td>
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<tr>
<td>Hip circumference, cm</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>≤100</td>
<td>409</td>
<td>121</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>&gt;100</td>
<td>110</td>
<td>29</td>
<td>0.89 (0.56-1.41)</td>
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<tr>
<td>Body mass indexb</td>
<td></td>
<td></td>
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<tr>
<td>≤27</td>
<td>457</td>
<td>122</td>
<td>1 [Reference]</td>
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<tr>
<td>&gt;27</td>
<td>116</td>
<td>29</td>
<td>0.94 (0.60-1.47)</td>
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<td>Hypertension</td>
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<td></td>
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<tr>
<td>No</td>
<td>261</td>
<td>57</td>
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<tr>
<td>Yes</td>
<td>152</td>
<td>50</td>
<td>1.51 (0.98-2.31)</td>
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<tr>
<td>Diabetes mellitus</td>
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<td></td>
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<tr>
<td>No</td>
<td>493</td>
<td>131</td>
<td>1 [Reference]</td>
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<tr>
<td>Yes</td>
<td>82</td>
<td>20</td>
<td>0.92 (0.54-1.55)</td>
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<td>Cardiovascular disease</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>No</td>
<td>64</td>
<td>16</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>Yes</td>
<td>39</td>
<td>18</td>
<td>1.85 (0.84-4.04)</td>
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<td>Dyslipidemia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>293</td>
<td>66</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>Yes</td>
<td>283</td>
<td>85</td>
<td>1.33 (0.93-1.91)</td>
</tr>
<tr>
<td>Benign prostatic hypertrophy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>414</td>
<td>109</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>Yes</td>
<td>98</td>
<td>35</td>
<td>1.36 (0.87-2.11)</td>
</tr>
<tr>
<td>Alcohol drinking</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>492</td>
<td>122</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>Yes</td>
<td>56</td>
<td>18</td>
<td>1.30 (0.74-2.30)</td>
</tr>
<tr>
<td>Betel nut chewing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>514</td>
<td>130</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>Yes</td>
<td>30</td>
<td>11</td>
<td>1.45 (0.71-2.97)</td>
</tr>
<tr>
<td>Pubertal growth spurt, y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;16</td>
<td>270</td>
<td>75</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>≤16</td>
<td>291</td>
<td>70</td>
<td>0.87 (0.60-1.25)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; NA, not available; OR, odds ratio.

a Adjusted for age and family history.

b Calculated as weight in kilograms divided by height in meters squared.
In our study, the age-specific prevalence of male pattern AGA was comparable with that among Korean men. Compared with the results of another Asian study conducted in Singapore, our prevalence rate of AGA was lower. However, the comparison should be interpreted with caution because the definition of cosmetically significant AGA by Tang et al was Norwood type I or greater, which was different from the definition (Norwood types ≥III) used in our study. This may also explain why the age-specific prevalence of AGA in their study was much higher than that in our study. The age-specific prevalence of AGA in another Asian study conducted in Thailand was also higher than that in our study. However, race/ethnicity in Taiwan is different from that in Thailand.

The prevalence of AGA increased steadily with advancing age but was lower than that among persons of white race/ethnicity. An increase in risk of AGA with age reflects the natural progression of this condition. Advancing age is a risk factor for AGA in all men, irrespective of their family history. In addition, female pattern hair loss was observed in 13 of 740 men (1.8%) examined. Because AGA in some men may follow the female (Ludwig) pattern, we suggest that the female pattern should be included in the classification of AGA in men.

A positive association between smoking and AGA was demonstrated in our study. Our results were consistent with findings by Mosley and Gibbs using a cross-sectional survey in a general surgical outpatient clinic in the United Kingdom. Unlike our study that was based on the general population, the generalizability of their study may be limited because respondents came from a general surgical outpatient clinic. In addition, no confounders were considered, and the dose-response relationship to AGA with respect to amount and duration of smoking was not elucidated.

Our positive results were not comparable with the findings from 2 studies. Severi et al reported a lower risk of AGA among current smokers (OR, 0.86; 95% CI, 0.54-1.38) and exsmokers (OR, 0.91; 95% CI, 0.65-1.29), although the results were not statistically significant. Nevertheless, details of smoking history were lacking, and the age at onset of AGA was unknown. In addition, different AGA classification categories instead of the Norwood classification were used. Therefore, it was difficult to compare their results with those of other studies. Matilainen et al found that the prevalence of current smoking among women with extensive hair loss (Ludwig grades ≥L-II to L-III) did not differ from those with normal or minimal hair loss (P = .92). However, the main objective of the study was not tailored to smoking history, and no definition of smoking was addressed.

The mechanisms by which smoking causes hair loss may be multifactorial. First, cigarette smoking may be deleterious to the microvasculature of the dermal hair papilla. Second, smoke genotoxics may do damage to DNA of the hair follicle. Third, smoking may lead to an imbalance in the follicular protease or antiprotease system. Smoking-induced oxidative stress may lead to the release of proinflammatory cytokines that, in turn, results in follicular microinflammation and fibrosis. Fourth, cigarette smoking may yield a relative hypoestrogenic state by inducing increased hydroxylation of estradiol and inhibition of aromatase.

Although the genetic basis of AGA is well documented in the medical community and among the general population, there are few studies investigating the familial aggregation of AGA. Chumlea et al reported that the risk of AGA increased among men with a positive maternal grandfather history and even more with a history of hair loss in their father. In our study, moderate or severe AGA was statistically significantly associated with family history of AGA among the first-degree and second-degree relatives but not among the third-degree relatives after adjusting for age. The highest OR was associated with a family history among first-degree relatives. In addition, family history of AGA among paternal relatives was statistically significantly predictive of moderate or severe AGA after adjusting for age. Our findings do not support an association between moderate or severe AGA and family history of AGA among maternal relatives. The effect of family history among both paternal and maternal older relatives could not be assessed because no case was found among subjects without AGA.

Moreover, we found that family history of AGA is statistically significantly associated with the risk of early-onset AGA. This implies that those with a family history of AGA have a higher risk of early-onset AGA and a higher risk of developing severe AGA. Most important, early-onset AGA (age at onset ≤40 years) showed a statistically significant dose-dependent association with AGA grade after adjusting for age and family history. From the clinical point of view, this suggests that patients with early-onset AGA should receive early advice to prevent the deterioration of AGA.

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>1 [Reference]</td>
<td></td>
</tr>
<tr>
<td>Third-degree relatives</td>
<td>5.32 (0.80-35.48)</td>
<td>.08</td>
</tr>
<tr>
<td>Second-degree relatives</td>
<td>6.33 (2.37-16.91)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>First-degree relatives</td>
<td>13.38 (4.80-37.27)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Parental family history of AGA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>1 [Reference]</td>
<td></td>
</tr>
<tr>
<td>Paternal family history positive</td>
<td>12.69 (4.65-34.60)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Maternal family history positive</td>
<td>3.07 (0.30-31.32)</td>
<td>.34</td>
</tr>
<tr>
<td>Both positive</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; NA, not available; OR, odds ratio.
In conclusion, our study showed that the prevalence of AGA among men in Taiwan was lower than that among persons of white race/ethnicity. The severity of AGA was also milder in Taiwan. We suggest that a female pattern should be included in the classification because AGA in some men may follow this Ludwig pattern. We also confirmed that smoking status, current amount of cigarette smoking, and smoking intensity play important roles in the development of moderate or severe AGA.

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Correspondence: Tony Hsiu-Hsi Chen, DDS, PhD, Division of Biostatistics, Institute of Preventive Medicine, College of Public Health, National Taiwan University, Room 521, Fifth Floor, 17 Suchow Rd, Taipei 100, Taiwan (chenlin@ntu.edu.tw).

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

Financial Disclosure: None reported.

Additional Contributions: Yao-Der Chen, MS, and other colleagues helped with data collection, and Min-Shu Hsu, BSc, performed data management.

REFERENCES

Multiple Primary Melanomas in a CDKN2A Mutation Carrier Exposed to Ionizing Radiation

Mark J. Eliason, MD; Chris B. Hansen, MD; Marybeth Hart, MS; Patricia Porter-Gill, BS; Wei Chen, BM, MD; Richard A. Sturm, PhD; Glen Bowen, MD; Scott R. Florell, MD; Ronald M. Harris, MD, MBA; Lisa A. Cannon-Albright, PhD; Leonard Swinyer, MD; Sancy A. Leachman, MD, PhD

Background: Recent research has shown a possible causal relationship between ionizing radiation exposure and melanoma. Individuals with mutations in CDKN2A (cyclin-dependent kinase inhibitor 2A), the major melanoma predisposition gene, have an increased susceptibility to melanoma-promoting exposures, such as UV light. We describe a patient from a familial melanoma pedigree with 7 primary melanomas on the right side of her body, the first occurring 5 years after exposure to atmospheric nuclear bomb testing in the 1950s.

Observations: Physical examination revealed photo-type I skin, red hair, and 26 nevi (14 on the right and 12 on the left side of her body). One nevus was larger than 5 mm, and 2 were clinically atypical. Sequence analysis demonstrated a known deleterious mutation in CDKN2A (G→34T) and homozygosity for a red hair color variant in MC1R (melanocortin 1 receptor) (R151C). Fluorescence in situ hybridization analysis of blood, fibroblasts, and melanocytes from both upper extremities ruled out mosaicism.

Conclusions: Individuals such as this patient, who has CDKN2A and MC1R mutations, are likely to be more susceptible to environmental insults. A careful review of environmental exposures in these vulnerable cases may reveal cancer-promoting agents, such as ionizing radiation, that go unnoticed in less susceptible populations.

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The patient is a white woman who underwent investigation for a history of MPM. Medical records and blood and tissue samples were collected for investigation.

Her medical history was remarkable for the development of a melanoma on her right ear at 28 years of age, treated by excision and a radical neck lymph node dissection (Figure 1). She subsequently developed 6 additional primary melanomas. Of the 7 total melanomas, 6 were found on the right side of her body and 1 was in the midline (Figure 2). A squamous cell carcinoma of her right upper lip was diagnosed in 1997. Other pertinent medical history includes a 46-year history of smoking, coronary artery disease with placement of 3 coronary artery stents, and polycythemia vera diagnosed at 63 years of age.

Her environmental exposure history was significant for 1 blistering sunburn before 20 years of age, with minimal sunbathing and no subsequent sunburns. She also reports 1 episode of intense exposure to ionizing radiation at 27 years of age that occurred in October 1958 in southern Utah and Nevada. The patient and her husband left the car in which they were traveling to observe an atmospheric nuclear detonation from an undetermined distance for 20 to 30 minutes. After leaving the blast site, the patient sat in the passenger side of the car, the side oriented toward the test site, riding with her arm outside the car. They noted a fine, sticky dust on the top of the car when they arrived home, consistent with nuclear fallout. The patient denies the development of nausea or other acute symptoms the day of the exposure.

Her family history includes a cousin with melanoma and melanoma in the children of another cousin. Multiple other cancer types were also described in her extended family.

**PHYSICAL EXAMINATION**

Pertinent findings included phototype I skin, green eyes, red hair, and mild freckling. On the right side of her body, the patient had 14 moles, 1 of which was atypical. No nevi were larger than 5 mm. She also had 12 well-healed biopsy and treatment scars. On the left side of her body, the patient had 12 moles, 1 larger than 5 mm and 1 with atypical features, and 5 well-healed biopsy scars.

**LABORATORY TESTS**

Results of routine laboratory tests, including complete blood cell count, liver function tests, and a lipid panel, were unremarkable other than an elevated hematocrit consistent with polycythemia vera. Sequencing of the CDKN2A gene and promoter region revealed a G−34T 5’ UTR mutation known to be deleterious. No additional mutations were found within the coding region. The alternate reading frame gene was also sequenced and had no mutations. Sequencing of MC1R demonstrated that the patient was homozygous for the R151C mutation. Chromosomal studies were performed on melanocytes, peripheral blood, and fibroblasts. Tissue specimens were collected from both sides of the body. Metaphase cells analyzed from cultures of all these tissues revealed a nor-
This is a unique case report of ionizing radiation exposure in an individual with a deleterious CDKN2A mutation and MPM. The patient had 7 primary melanomas during a course of about 30 years, starting late in her third decade of life. Her laboratory studies are significant for a deleterious CDKN2A mutation, homozygosity for an MC1R red hair color variant, and fluorescence in situ hybridization results that were negative for chromosomal aberrancy on either side of her body. Her physical examination revealed skin phototype I, red hair, numerous biopsy excisional scars, and a random distribution of 26 nevi, 2 of which had atypical features. Most of her melanomas occurred in traditionally sun-protected areas. Her family history is consistent with hereditary melanoma.

Many groups have investigated the correlation between MPM and CDKN2A mutations (Table). Collectively, these groups have described 467 individuals with MPM, 70 of them (15.0%) with CDKN2A mutations. Not all groups specified the number of primary melanomas for each individual. Of the studies that did specify the number of primary melanomas, 14,18-24 5 of 311 cases (1.6%) had at least 7 primary melanomas. Even among individuals with CDKN2A mutations, it is rare to have 7 primary melanomas. Puig et al14 reported that among their 104 patients with MPM, only 3 had a second primary melanoma appear in proximity (defined as on the same extremity as the first melanoma).14 Our patient was initially seen with a grouping of 4 independent melanomas on the right side, 1 on the inner left thigh, and 3 melanomas close to one another on the right ear, right shoulder, and upper back area (Figure 2).

Her exposure history is significant for 1 blistering sunburn and her report of observing an above-ground nuclear test while traveling in Utah and Nevada. The time of the exposure she describes is chronologically consistent with Operation Hardtack II (September 12 to October 30, 1958), during which atmospheric nuclear testing took place in southern Nevada.25,26

Previous studies have linked exposure to ionizing radiation and nonmelanoma skin carcinomas, including leukemia and thyroid, breast, and lung cancers.9,27,28 There are also several brief reports that have described an excess rate of polycythemia rubra vera in subjects exposed to the fallout of nuclear tests.29,30 Ionizing radiation has not been historically considered a promoting agent for melanoma, because many of the original studies that reviewed the cancer in atomic blast survivors in Japan did not identify melanoma as an outcome of interest.
The studies reviewed by Fink and Bates collectively totaled hundreds of thousands of individuals who were predominantly white, the population most susceptible to melanoma. In addition to the rates of melanoma, the authors reported which of these studies demonstrated an excess rate of leukemia as a means to distinguish which cohorts received a significant radiation exposure. Five of the 7 cohorts had elevated rates of leukemia and melanoma. The remaining 2 cohorts did not have excess melanoma or excess leukemia, suggesting that both did not receive sufficient irradiation to induce any malignancy. They conclude that melanoma has not always been considered a significant end point in epidemiological studies on ionizing radiation, which may have hampered identifying a potentially causal relationship between ionizing radiation and melanoma. They also recommend that future epidemiological studies of ionizing radiation consider inclusion of melanoma as an outcome of interest.  

It is not clearly understood why some patients with CDKN2A mutations never develop melanoma, whereas others with the same mutation and even in the same family may have been a result of the superimposition of environmental exposures (ionizing radiation) on her highly vulnerable genetic predisposition. The careful examination of phenotypic and environmental risk factors in the very vulnerable subgroup of CDKN2A mutation carriers may be a strategy to identify and clinically verify risk factors less obvious in the general population.

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Author Contributions: Dr Leachman had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Hansen, Bowen, Cannon-Albright, and Leachman. Acquisition of data: Eliason, Hart, Florell, Harris, Swinney, and Leachman. Analysis and interpretation of data: Eliason, Porter-Gill, Chen, Sturm, and Leachman. Drafting of the manuscript: Eliason, Hansen, Hart, and Leachman. Critical revision of the manuscript for important intellectual content: Eliason, Hansen, Hart, Porter-Gill, Chen, Sturm, Bowen, Florell, Harris, Cannon-Albright, Swinney, and Leachman. Administrative, technical or material support: Chen and Sturm. Study supervision: Leachman.

Financial Disclosure: None reported.

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Additional Contributions: April Alexander Larson provided the pedi- gree and Population Resource (with funding from the Huntsman Cancer Foundation) provided data and contributed support related to the Utah Population Database.

REFERENCES

**OBSERVATION**

### Functional Dysregulation of Dendritic Cells in Patients With Papular Urticaria Caused by Fleabite

Adriana Cue´llar, MSc; Elizabeth Garcı´a, MD; Adriana Rodrı´guez, MSc; Evelyne Halpert, MD, MSc; Alberto Go´mez, PhD

#### Background:
Papular urticaria is a chronic allergic disease caused by fleabite. The presence of eosinophils, predominance of CD4-positive T cells in lesions, and IgE response suggest a Th2 immune response to flea proteins in patients with papular urticaria caused by fleabite (PUFB). Although PUFB is defined as an allergic reaction, the immunological mechanisms and the role of dendritic cells (DCs) have not been established.

#### Observations:
Flea body extract did not induce the maturation of monocyte-derived DCs in 10 patients with PUFB and in 10 healthy children. Simultaneous exposure of DCs to flea extract and lipopolysaccharide induced increased expression of CD83 ($P < .01$), CD86 ($P < .01$), and HLA-DR ($P < .05$), which was statistically significantly greater in patients’ cells. Dendritic cells from patients stimulated with lipopolysaccharide secreted less interleukin 6 (IL-6) and IL-10 than DCs from control subjects.

#### Conclusions:
Results of this study indicate that the involvement of DCs in an immune response produced in the disease is mediated through the altered expression of membrane molecules. This may be related to constitutive impairment in the production of regulatory cytokines such as IL-6 and IL-10 in these patients.

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**See also page 1393**

### METHODS

**SAMPLE**

The sample included 10 patients aged 1 to 15 years clinically diagnosed as having papular urticaria for no longer than 5 years. From this group, 4 children reported a personal history and 9 children a family history of atopy (asthma, allergic rhinitis, and atopic dermatitis). They attended the pediatric dermatology and allergy services at the Fundación Santa Fe de Bogotá, Bogotá, Colombia. Exclusion criteria included the presentation of secondary infected lesions, immunosuppression by sys-
The diagnosis of PUFB was made according to clinical characteristics. Patients had lesions that appeared usually as groups of papules or nodules; in some patients, exposed areas of the extremities were affected. In some patients, lesions appeared intermittently in a chronic course and left hypopigmented areas. The diagnosis of PUFB was made according to clinical characteristics. Patients had lesions that appeared usually as groups of papules or nodules; in some patients, exposed areas of the extremities were affected. In some patients, lesions appeared intermittently in a chronic course and left hypopigmented areas. The diagnosis of PUFB was made according to clinical characteristics. Patients had lesions that appeared usually as groups of papules or nodules; in some patients, exposed areas of the extremities were affected. In some patients, lesions appeared intermittently in a chronic course and left hypopigmented areas.

OBTAINING ANTIGEN FROM FLEAS

A complete *Ctenocephalides felis* (Greer Laboratories, Lenoir, North Carolina) flea aqueous extract (10% weight per volume) was prepared by maceration in a phosphate-buffered saline solution, with constant shaking for 2 hours at room temperature. It was centrifuged at 15,000 rpm for 15 minutes at 4°C and was filtered through a 0.22-µm membrane. The protein concentration, determined by Bradford technique, was 1.3 mg/dL. The extract was aliquoted and stored at −70°C.

OBTAINING AND STIMULATING DCs

After obtaining informed consent from the child’s legal guardian, 10 to 15 mL of heparin-anticoagulated blood was drawn from each child. Peripheral blood mononuclear cells were obtained using Ficoll-Hypaque gradients. Monocytes were separated with anti-CD14 monoclonal antibodies coupled to magnetic pearls using a commercially available system (MiniMACS; Miltenyi Biotec, Auburn, California). The cells obtained were washed in base medium (RPMI 1640) with 2% fetal calf serum. Viability was evaluated using trypan blue stain, and then cells were counted. The purity of the population was determined by flow cytometry using an anti-CD14, PE antibody. CD14-positive cell populations demonstrated greater than 94% purity in all cases.

CD14-positive cells were cultured in complete medium (RPMI 1640, antibiotics, nonessential amino acids, sodium pyruvate, and 10% fetal calf serum) in 48-well plates at a density of 3 × 10^6/mL in the presence of 1000-U/mL interleukin 4 (IL-4) and 30-ng/mL granulocyte-macrophage colony-stimulating factor (GM-CSF) (R and D Systems, Minneapolis, Minnesota) for 7 days to obtain iDCs. In the last 48 hours, 1-µg/mL lipopolysaccharide (LPS) was added to obtain mDCs or 10 µg of flea extract in the presence or absence of LPS to evaluate the effect of the flea extract.

A DC culture was exposed to flea extract in the presence or absence of polymyxin B sulfate at concentrations inhibiting LPS activity to establish the presence of small amounts of LPS in the flea extract that might have altered cell behavior. No difference was found regarding marker expression or cytokine secretion (data not shown). All reagents used in the culture were negative for detectable LPS levels (*Lymulus* species amoebocytes kit; BioWhittaker, Walkersville, Maryland), with a sensitivity of 0.1 endotoxin unit per milliliter.

FLOW CYTOMETRY

The presence of mDC markers was evaluated by flow cytometry with anti-CD14, APC (BD Biosciences, San Jose, California), anti-CD83, FITC (Pharmingen, San Diego, California), anti-CD86, PE (Pharmingen), and anti-HLA-DR, PerCP (BD Biosciences) antibodies with IgG1, FITC (Pharmingen), IgG2a, PE (Pharmingen), and IgG2a, PerCP (BD Biosciences) isotype controls. A kit (Cytometric Bead Array, BD Biosciences) was used for quantifying cytokines in supernatant using antibodies having different fluorescence intensity with peridinin chlorophyll protein, covered with capture antibodies fluorescent with R-phycocerythrin, for IL-1B, IL-6, IL-8, IL-10, IL-12p70, and tumor necrosis factor (TNF) α. Concentration was calculated using different cytokine patterns in known concentrations. Data were acquired using a flow cytometer (FACSCalibur, BD Biosciences) and were then analyzed using commercially available software (Cell Quest; BD Biosciences).

ANALYZING THE RESULTS

The results are presented as mean±SE. Statistically significant differences between means were established using the Mann-Whitney test.
EFFECT OF FLEA EXTRACT ON DC CULTURES

There was no statistically significant difference between patient and control DCs exposed to flea extract, as both showed a phenotype similar to that of iDCs (Figure 2). Flea extract alone did not induce monocyte-derived DC maturation.

EFFECT OF FLEA EXTRACT PLUS LPS ON DC CULTURE

Simultaneous stimulation with flea extract and LPS increased the levels of CD83 (P < .01), CD86 (P < .01), and HLA-DR (P < .05) in patients’ DCs compared with those of healthy controls. These results are shown in Figure 3.

CYTOKINES SECRETED BY DCs

Cytokine secretion by iDCs in culture medium alone showed no difference compared with cytokine secretion by iDCs exposed to flea extract, indicating that in the extract used, no molecules were able to induce functional changes in cells. Patients’ mDCs showed a statistically significant reduction in IL-6 and IL-10 (P < .05 for both) compared with cells obtained from healthy controls (Figure 4). The IL-1β, IL-8, and TNF-α levels did not show statistically significant differences in any of the conditions studied. There was a reduction of IL-12p70 levels in patients compared with controls when cells were exposed to LPS or flea extract, although this difference was not statistically significant.

COMMENT

There are many important factors in determining a Th1/Th2 response, including antigen type and dose, the exposure route, the host’s genetic background, the microenvironment of the cytokines found during antigen presentation, and the type of DCs involved and its interaction with the T cells and with the costimulatory molecules expressed. Flea body extract did not induce the maturation of iDCs by itself, and this inability to induce reactivity has been previously proposed; however, when oral antigens are combined with Freund complete adjuvant, hypersensitivity is induced. Therefore, flea oral secretion seems to contain a particular substance able to induce hypersensitivity in the presence of an adjuvant, and molecules having allergenic potential can be found in a complete extract.

This effect revealed by Freund complete adjuvant in vivo experiments was similar to that observed in vitro when DCs exposed to flea extract in the presence of LPS increased expression of molecules related to antigen presentation such as HLA-DR, CD83, and CD86. The adjuvant action of LPS has also been observed with aeroallergens. Low inhaled LPS levels are needed for inducing a Th2 response to inhaled antigens in a murine model of allergic sensitization involving DC activation. Lipopolysaccharide may not be a relevant factor at the moment of the bite. Although not demonstrated, it is probable that some molecules on the skin such as collagen in the presence of flea antigen may act as adjuvants for a susceptible individual to develop hypersensitivity.

The expression of CD86 in DCs is important for the induction of a Th2 response. Mice with this molecule blocked that were exposed to albumin aerosols did not develop an allergic reaction. In atopic dermatitis, the use of anti-CD86 antibodies inhibits the proliferation of T cells stimulated with mite extract. In addition, increased expression of CD86 in patients with allergic
Asthma has been demonstrated, which is related to IgE synthesis.\textsuperscript{21} The statistically significant increase in the expression of CD83, CD86, and HLA-DR observed in DCs obtained from patients experiencing PUFB demonstrated the specific effect of flea extract on patients' DCs compared with cells from healthy controls.

Interleukin 10 is considered to be an anti-inflammatory molecule because of its ability to inhibit the production of a large number of cytokines such as IL-2, IL-3, IL-12, TNF, GM-CSF, and interferon gamma,\textsuperscript{23} and IL-10 lessens allergic inflammation because of its ability to inhibit the synthesis of proinflammatory cytokines such as IL-1, IL-4, IL-5, IL-6, and TNF-\(\alpha\). The effect of IL-10 on allergic disease has also been shown, as it has a tolerance-inducing effect on allergens by T cells,\textsuperscript{24} inhibiting eosinophil survival\textsuperscript{25} and IgE synthesis.\textsuperscript{26} A statistically significant reduction of IL-6 and IL-10 was found in our patients' DCs with a maturing stimulus such as LPS, indicating a functional change in cells from patients compared with those of healthy controls. The differences found regarding surface molecule expression and levels of secreted cytokines by DCs in patients with PUFB indicate that these cells may play an active role in immunological mechanisms on which the development of the disease is based. The results show that the specific involvement of DCs in the immune response of papular urticaria is mediated by the altered expression of membrane molecules such as CD86 and HLA-DR. This finding may be related to a constitutive impairment in the production of regulatory cytokines such as IL-6 and IL-10 in patients with PUFB. Although this effect is abrogated with flea extract in the presence of LPS in vitro, this does not mean that the patients would not have active disease, because the inflammatory process involves the activation of not only the regulatory response but also the effector response. This modulating effect in the immune response generated by an adjuvant coupled with an antigen in vitro has been shown with other molecules.\textsuperscript{29}

Dendritic cells from patients with PUFB manifest a dysregulated immune response similar to that of other allergic diseases such as asthma, allergic rhinitis, and atopic dermatitis. Therefore, we hypothesize that the immunological response of PUFB has an allergenic origin.

The differences found regarding surface molecule expression and levels of secreted cytokines by DCs in patients with PUFB indicate that these cells may play an active role in immunological mechanisms on which the development of the disease is based. The results show that the specific involvement of DCs in the immune response of papular urticaria is mediated by the altered expression of membrane molecules such as CD86 and HLA-DR. This finding may be related to a constitutive impairment in the production of regulatory cytokines such as IL-6 and IL-10 in patients with PUFB. Although this effect is abrogated with flea extract in the presence of LPS in vitro, this does not mean that the patients would not have active disease, because the inflammatory process involves the activation of not only the regulatory response but also the effector response. This modulating effect in the immune response generated by an adjuvant coupled with an antigen in vitro has been shown with other molecules.\textsuperscript{29}

Dendritic cells from patients with PUFB manifest a dysregulated immune response similar to that of other allergic diseases such as asthma, allergic rhinitis, and atopic dermatitis. Therefore, we hypothesize that the immunological response of PUFB has an allergenic origin.

The immunopathologic mechanism of PUFB may be summarized by considering the following findings. The activation of the skin's DCs takes place under the influence of mediators secreted by local microenvironment cells. In atopic individuals, these mediators induce a functional change that affects not only the skin's resident cells but also the type of cytokines secreted by T cells. Accordingly, based on results of this research, patients with papular urticaria have increased expression of mol-
ecules related to antigen presentation and lower levels of regulatory cytokines. This scenario may favor the secretion of Th2 proinflammatory cytokines that contributes to the generation and maintenance of allergic reaction in skin caused by fleabite during childhood.

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DERMOSCOPY HAS OPENED A NEW MORPHOLOGIC DIMENSION IN CLINICAL DERMATOLOGY. USING THIS NONINVASIVE METHOD, WE CAN RECOGNIZE VARIOUS KINDS OF NOVEL MORPHOLOGIC CHARACTERISTICS UNRECOGNIZABLE WITH THE NAKED EYE. DERMOSCOPY IS PARTICULARLY USEFUL IN EVALUATING PIGMENTED LESIONS ON ACRAL VOLAR SKIN BECAUSE DERMOSCOPIC PATTERNS DETECTED IN PIGMENTED LESIONS AFFECTING THIS UNIQUE ANATOMIC SITE ARE RATHER SIMPLE AND EASY TO INTERPRET. ACRAL VOLAR SKIN IS THE MOST PREVALENT SITE OF MALIGNANT MELANOMA IN NONWHITE POPULATIONS; ABOUT HALF OF ALL CUTANEOUS MELANOMAS IN JAPANESE PATIENTS ARE SEEN IN ACRAL SKIN.1 MELANOCYTIC NEVI ARE ALSO PREVALENT IN ACRAL SKIN, FOUND IN ABOUT 7% TO 9% OF THE JAPANESE GENERAL POPULATION.2 DERMATOLOGISTS OFTEN EXPERIENCE DIFFICULTY IN CLINICALLY DIFFERENTIATING EARLY ACRAL MELANOMA FROM ACRAL NEVI BECAUSE BOTH LESIONS ARE SEEN AS BROWNISH-BLACK MACULES. OUR RECENT STUDIES HAVE REVEALED THAT DERMOSCOPY IS IMMINENTLY HELPFUL IN THIS DIFFERENTIATION. THE 2 BIOLOGICALLY DISTINCT MELANOCYTIC ENTITIES SHOW COMpletely DIFFERENT DERMOSCOPIC PATTERNS IN ACRAL VOLAR SKIN.3

VARIATIONS OF DERMOSCOPIC PATTERNS OF ACRAL MELANOCYTIC NEVI

Our research group has reported that the major dermoscopic patterns seen in acral nevi are the (1) parallel furrow, (2) latticelike, and (3) fibrillar patterns.4,6 The parallel furrow pattern shows brownish linear pigmentation along the sulci of the surface skin markings. Although there are several variants of the parallel furrow pattern, such as dotted-line and double-line variants, in our estimation, single solid lines on the sulci are the basic type of the parallel furrow pattern.6 The latticelike pattern is composed of parallel, pigmented lines along the sulci as well as lines crossing the parallel lines. The fibrillar pattern shows densely packed, fine, pigmented lines, usually arranged in the direction crossing the skin markings. In the first report from our group in 1995,4 we lumped together all the dermoscopic patterns not conforming to any of these 3 typical patterns under the term nontypical pattern. The prevalence of these patterns is shown in the Table. The parallel furrow pattern was most prevalent, followed by the latticelike pattern, and then by the fibrillar pattern. Later studies including white populations confirmed that these were the major dermoscopic patterns in acral nevi.7,8

In later studies, a few other dermoscopic patterns were described in acral nevi. In 2004, Malvehy and Puig7 identified 3 novel patterns in acral nevi seen in a Spanish population: the globular, homogeneous, and reticular patterns. According to the researchers, the globular pattern, composed of dots and/or globules distributed in a nonparallel fashion, was seen in 5.2% of acral nevi. The homogeneous pattern showing structureless, light brown pigmentation was detected in 7.1%, and the reticular pat-

<table>
<thead>
<tr>
<th>Dermoscopic Pattern</th>
<th>Saida et al4 (n=66)</th>
<th>Saida and Koga (Present Article) (n=97)</th>
<th>Malvehy and Puig7 (n=210)</th>
<th>Altamura et al8 (n=723)</th>
<th>Ozdemir et al9 (n=188)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parallel furrow</td>
<td>28 (44)</td>
<td>40 (42)</td>
<td>111 (53)</td>
<td>304 (42)</td>
<td>110 (59)</td>
</tr>
<tr>
<td>Latticelike</td>
<td>18 (27)</td>
<td>13 (13)</td>
<td>26 (13)</td>
<td>108 (15)</td>
<td>12 (7)</td>
</tr>
<tr>
<td>Fibrillar</td>
<td>8 (12)</td>
<td>20 (21)</td>
<td>13 (6)</td>
<td>78 (11)</td>
<td>23 (12)</td>
</tr>
<tr>
<td>Homogeneous</td>
<td>NE</td>
<td>2 (2)</td>
<td>15 (7)</td>
<td>67 (9)</td>
<td>12 (7)</td>
</tr>
<tr>
<td>Globular</td>
<td>NE</td>
<td>5 (5)</td>
<td>11 (5)</td>
<td>15 (2)</td>
<td>4 (2)</td>
</tr>
<tr>
<td>Reticular</td>
<td>NE</td>
<td>3 (3)</td>
<td>5 (2)</td>
<td>39 (5)</td>
<td>8 (4)</td>
</tr>
<tr>
<td>Transition</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
<td>13 (2)</td>
<td>NE</td>
</tr>
<tr>
<td>Globulostreaklike</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
<td>10 (5)</td>
</tr>
<tr>
<td>Nontypical</td>
<td>11 (17)</td>
<td>14 (14)</td>
<td>29 (14)</td>
<td>99 (14)</td>
<td>9 (5)c</td>
</tr>
</tbody>
</table>

Abbreviation: NE, not evaluated.
4 Only biopsied and histopathologically diagnosed lesions included.
5 All acral nevi included regardless of biopsy performance.
6 Three of the 9 lesions showed dermoscopic patterns suggestive of acral melanoma.
tern showing network pigmentation was detected in 2.4% of the observed acral nevi. In 2006, Altamura et al., who analyzed an Italian population, added a new pattern, termed the transition pattern, showing a combination parallel furrow/latticelike pattern in 1 area and pigment-network pattern in the other area. This pattern was mainly seen in acral nevi located on the sites where volar skin converted into nonglabrous skin. In this issue of the Archives, Ozdemir et al, describe a new pattern called the globulostreaklike pattern detected in 5.3% of their series of acral nevi in a Turkish population. This pattern was composed of dark brown globules and linear or curvilinear streaks.

The prevalence of these dermoscopic patterns seen in acral nevi is summarized in the Table. Note that our group’s study in 1995 analyzed only acral nevi biopsied and diagnosed histopathologically, thus producing selection bias. On the other hand, our own unpublished data compiled in 2007 includes all the acral nevi seen at our dermatology clinic. Based on the data in the Table, the parallel furrow pattern is the major dermoscopic pattern most frequently seen in acral nevi, ranging from 42% to 59%. The prevalence of the latticelike pattern was approximately 13% to 15% in Japanese, Spanish, and Italian populations; however, this pattern was lower (7%) in the Turkish population. Although the fibrillar pattern was the second most prevalent pattern in the Japanese population, accounting for 21%, the prevalence was lower in white populations, ranging from 6% to 12%.

What is the reason for the different prevalence of dermoscopic patterns among populations? It may reflect real ethnic difference. However, it is our opinion that the most important reason for the different prevalence is arbitrary criteria for the differentiation of the 3 major dermoscopic patterns. In fact, acral nevi not infrequently show a combination of 2 or 3 of these patterns, as shown in Figure 1. In such a case, we evaluate which is the main or predominant pattern among the dermoscopic patterns and then determine the pattern of the lesion. However, this determination is arbitrary, and different interpretations may be possible, which results in substantial differences in the prevalence of the pattern.

Regarding classification of the major 3 patterns, we must consider why these dermoscopic patterns are produced. As our group has reported previously, the parallel furrow pattern is caused by melanin pigment produced by nevus cells (melanocytes) residing in the crista profunda limitans, an epidermal rete ridge underlying the surface sulcus. Acral nevi of the latticelike pattern are concentrated in the arch areas of the sole, where the skin markings show the criss-cross pattern, and pigmentation is seen along the sulci of the criss-cross skin markings. This pattern is common to the parallel furrow pattern in the selective pigmentation along the sulci. Thus, the latticelike pattern can be considered a variant of the parallel furrow pattern.

We have found that the fibrillar pattern is caused by an oblique arrangement of melanin pigment in the slanting cornified layer. The slanting is considered to be produced by mechanical pressure from the body weight. Of note, even in the fibrillar pattern, the nests of nevus cells are mainly located in the crista profunda limitans, as they are in the parallel furrow pattern. Therefore, the fibrillar pattern can be regarded as an artifactual expression of the parallel furrow pattern. These are the reasons why we insist that the parallel furrow pattern is the prototype of...
the major dermoscopic patterns seen in acral nevi. From our viewpoint, the 3 major dermoscopic patterns seen in acral nevi are essentially the same. Therefore, we think that the different prevalence of the 3 major patterns among different populations is unremarkable.

What are the meanings of the minor dermoscopic patterns of acral nevi, such as homogeneous, globular, reticular, transition, and globulostreaklike patterns? Some of these patterns can be explained by the anatomic locations of the nevi. For example, the transition pattern is found in nevi located on borderline sites between glabrous and nonglabrous skin. Acral nevi with the globulostreaklike pattern are small, ranging in diameter from 1 to 3 mm (Fezal Ozdemir, MD, written communication, March 19, 2007), and thus we suppose that this pattern may represent an evolving stage of any of the major or minor patterns. Frequency and significance of these minor patterns may be an interesting subject of investigation. However, we are concerned that too much detailed and complicated classification may produce confusion in the interpretation. What is essentially important is that we recognize that the parallel furrow pattern is the major, prototypical dermoscopic pattern in acral nevi.

**DIGITAL FOLLOW-UP AND CHANGES OF THE DERMOSCOPIC PATTERNS IN ACRAL NEVI**

In contrast to melanocytic nevi of nonglabrous skin, to our knowledge there have been almost no articles describing changes in dermoscopic patterns of acral nevi over time. In this issue of the *Archives*, Altamura et al report their follow-up data of dermoscopic patterns of acral nevi. In their study, they defined any change from a given benign pattern at baseline into a different pattern at the follow-up visit as substantial variation. However, changes over time in the parallel furrow pattern into its globular or double-line variants, and vice versa, were considered minimal variations. A total of 230 acquired acral melanocytic nevi had a digital follow-up of 6, 12, 18, and 24 months. Dermoscopic changes over time were observed in 42 of the 230 acral nevi (18.3%), and the frequency of change increased linearly over time. The parallel furrow pattern showed more variations over time than the other dermoscopic patterns. Minimal variations in the parallel furrow pattern were the most common changes (10 of 42), followed by substantial variations in this pattern such as changes into fibrillar (9 of 42), latticelike (6 of 42), and nontypical patterns (4 of 42).

Changes in the dermoscopic features were also described in the article by Ozdemir et al. A total of 33 acral nevi were observed for a mean of 11 months. During this period, 24 of the 33 acral nevi showed changes (73%); however, most of them were changes in color and/or size. As for the dermoscopic structures, the number of dots decreased in 3 lesions. A change of the dermoscopic pattern was seen in only 1 acral nevus, in an 8-year-old patient: the fibrillar pattern changed into the parallel furrow pattern (double dotted-line variant) after a 6-month follow-up period.

These data indicate that acral nevi are dynamic and that their dermoscopic patterns often change over time. These changes may be expected because the parallel furrow pattern is the prototype, and most other patterns can be considered its variations. In these studies, no acral nevi showed changes from benign to malignant dermoscopic patterns.

**A 3-STEP ALGORITHM FOR THE MANAGEMENT OF ACRAL MELANOCYTIC LESIONS**

To improve the prognosis of acral melanoma, it is important to establish a method for effective screening of early acral melanoma from a large number of acral nevi. In 1990, our research group first proposed clinical guidelines for the early detection of plantar malignant melanoma, which recommended excision and histopathologic evaluation of plantar melanocytic lesions larger than 7 mm in maximum diameter. This was based on our analysis of the distribution of melanocytic nevi and acral melanoma affecting the sole. Then the use of dermoscopy was introduced into the diagnosis of pigmented lesions affecting acral volar skin. Our group has found that the parallel ridge dermoscopic pattern is highly specific to early acral melanoma. In 2000, our group revised the guidelines for the early detection of acral melanoma by recommending that small lesions, 7 mm or smaller, should be biopsied when they showed the parallel ridge pattern on dermoscopy.

Our group’s further dermoscopic studies have confirmed the diagnostic significance of dermoscopic patterns in acral melanocytic lesions. In acral melanoma in situ, diagnostic sensitivity and specificity of the parallel ridge pattern were 86% and 99%, respectively. In contrast, in acral nevi, diagnostic specificity and positive predictive value of the parallel furrow pattern and/or the latticelike pattern were 93% and 98%, respectively. Moreover, we investigated cyclin D1 amplification in clinically and histopathologically ambiguous acral melanocytic lesions. Four of 9 lesions with the dermoscopic features of the parallel ridge pattern showed the amplification of cyclin D1. In contrast, all 7 of the acral lesions with the benign dermoscopic patterns (the parallel furrow, latticelike, or regular fibrillar pattern) did not show the amplification. These data certainly support the diagnostic significance of these dermoscopic patterns.

Based on these findings, we now propose a 3-step algorithm for the management of acquired acral melanocytic lesions, illustrated in Figure 2. In the first step, we evaluate the dermoscopic pattern of a lesion. If it exhibits the parallel ridge pattern, regardless of the size, we excise the lesion for histopathologic evaluation. If it does not show the parallel ridge pattern, in the second step, we measure the maximum diameter of the lesion. If it is 7 mm or less in diameter, we might just observe the course of the lesion. If it is more than 7 mm, we go to the third step and reevaluate the lesion dermoscopically. If it shows the typical benign pattern (parallel furrow, latticelike, or regular fibrillar pattern), we might just observe it. However, if it does not conform to any of the benign dermoscopic patterns, we biopsy the lesion for histopathologic evaluation. Our preliminary study using the data at our clinic seems to verify the validity of this algorithm. We believe that this
3-step algorithm not only aids in effective detection of early acral melanoma but also reduces unnecessary biopsy of benign lesions.

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Question the Obvious

In the evaluation of therapies, the physician-based clinical model (e.g., global assessment by a physician, change in affected body surface area, index scores, disease-free interval, and survival and recurrence rates) alone is no longer sufficient. In addition to traditional methods of evaluating disease, regulatory agencies now require the assessment of the patient-reported outcomes (PROs). These outcomes are pivotal in dermatology because most dermatological diseases are chronic, intermittent, nonfatal, and very visible; cause no permanent physical damage; and their disease activity cannot be measured using serological markers. Initially, PROs focused on inflammatory dermatoses, but they now also include noninflammatory diseases and (benign and malignant) neoplasms, which are associated with different and specific issues (to some extent).

**IMPORTANCE OF PROS**

Because nonmelanoma skin cancers (NMSCs) rarely metastasize and cause few symptoms and treatment is often local, interest in patients’ perspectives on their skin cancers and treatments has been very recent. However, NMSCs are cancers, often located on the face. Surgery may be associated with substantial fear and functional and cosmetic morbidity, and the risk of subsequent skin cancer is close to 50%, making this a chronic disease. These issues are troubling to patients and should be incorporated into the assessment of global disease severity and evaluation of skin cancer therapy. A better understanding and documentation of patients’ views is helpful in improving patient-physician interaction, skin cancer care, treatment outcome, and the selection of patients in need of additional pretreatment counseling.

**HRQOL IN PATIENTS WITH SKIN CANCER**

Of the available generic or dermatology-specific HRQOL instruments, the Short Form (SF)-36, Sickness Impact Profile, Dermatology Life Questionnaire Index, and Skin-dex-16 have been used to assess the impact of basal cell carcinoma (BCC) on patients’ lives and demonstrated a minimal to small impact of this disease. This can, in part, be explained by the fact that these instruments lack specificity (i.e., asking about concepts relevant to patients with skin cancer), sensitivity (i.e., detecting small impairments), and responsiveness (i.e., detecting HRQOL changes after improving or worsening of health status) in patients with NMSC. These nonspecific instruments are likely to suffer from “floor” effects (i.e., a substantial proportion of respondents will tick off the lowest response category). Summed scores are likely to be in the lowest quartile of the instrument’s range because several pivotal concepts, such as susceptibility of skin cancer, worry about (facial) health problems, appearances

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**See also page 1386**

In clinical studies, there are 3 obvious “players” that should be evaluated separately (i.e., disease, patient, and treatment) (Figure). The disease is evaluated using traditional clinical methods, the effect of the intervention on patients’ lives is captured by health-related quality-of-life (HRQOL) and symptom assessment, and treatment is evaluated by assessing its adverse events and satisfaction with medication or intervention. Physicians assess clinical measures, but patients are more and more actively involved in judging the other aspects of therapy,

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**Figure.** The 3 key players and corresponding outcomes in the evaluation of a treatment.
(eg, scars and dysmorphism), and fear of recurrence, new skin cancer, or surgery, are not assessed in detail. The skewed distribution of item responses and total scores to the low levels makes it difficult for these tools to differentiate within the range of limited impairment and to detect changes over time. Therefore, skin cancer–specific HRQOL questionnaires, such as the Skin Cancer Index, which have been introduced recently, should be validated before they can be used in conjunction with dermatology-specific, cancer-specific, and/or generic tools.

Recently, Chen et al used HRQOL as a primary outcome in a comparative cohort study in the treatment of NMSC. This very interesting study showed that the emotional impact of NMSC was almost 3-fold that of functional impact. This very interesting study showed that the emotional impact of NMSC was almost 3-fold that of functional impact. NMSC. Moreover, from a theoretical perspective, the use of different disease on their lives, or a lack of the sensitivity of the measurement is not yet clear. But again, this population is in extra need of counseling prior to NMSC therapy to optimize its outcome.

The primary outcome of the study in this issue of the Archives12 is the mean Skinflex-16 score of multiple assessments, and each Skinflex-16 score obtained at the time of assessment is the mean of its 3 scales. This approach was chosen to minimize loss of data and is based on the assumption that Skinflex-16 scores did not change after 12 months, which is in contrast with other dermatological HRQOL studies that suggest that some concepts change over time as patients learn to cope with and adjust to chronic conditions. Also, the proportions of patients who responded 1, 2, or 3 times is unclear, and a substantial number of patients who were lost to follow-up may have affected the results of this study. Although it is stated throughout the “Results” section of the article by Chen et al that similar trends were detected for the 3 scales, the presentation of a total Skinflex-16 score is unfortunate because it does not allow assessment of the effect of therapy on the emotion scale. That scale represents most NMSC-induced variance of the Skinflex-16 scores because it includes 2 items that are highly relevant to patients with skin cancer (ie, how often patients have been bothered by “the persistence and recurrence” and “worry about their skin condition spreading, getting worse, scarring, and being unpredictable”). The latter item is a composite question that assesses multiple issues simultaneously, providing important but nonspecific information about the impact of NMSC. Moreover, from a theoretical perspective, the use of a total score is inappropriate because it has no face validity, it was not formally tested, and factor analyses have shown that the structure of the Skinflex-16 is multidimensional. This implies that each dimension should be presented with a separate scale score and that an overall score is suboptimal and should not be used as an interval measurement.

**PREDICTORS OF HRQOL IMPROVEMENT**

In a study presented in this issue of the Archives, the same group (Chen et al) investigated the predictors of this observed HRQOL improvement after skin cancer therapy to understand why NMSC therapy affects people in different ways and to identify individuals who are at higher risk of not experiencing a therapeutic benefit after a “successful” therapy. The authors have used a heterogeneous cohort of 663 patients with new BCC (77.3%) and squamous cell carcinoma (SCC) (32.7%) who received therapy at VA hospitals or private practices. For multiple patients, tumor and care characteristics, pretreatment skin-related HRQOL, comorbidity, health status (ie, SF-12 scores), and white race significantly improved post-treatment Skinflex-16 scores after adjusting for confounding factors in a multivariate model. The strongest independent predictor of skin-related HRQOL posttreatment was pretreatment skin-related HRQOL. This is in accordance with a previous study showing that individuals’ preoperative health beliefs (eg, worry, fear, and susceptibility) determine in large part the extent to which patients respond to BCC therapy.

Therefore, physicians should gauge patients’ perceptions of NMSC and its treatment and inform patients about both before therapy is administered, especially those who express higher levels of worry and fear. This may seem obvious, but physicians may have an ambiguous attitude toward BCC and to a lesser extent toward SCC. On the one hand, NMSC is considered to be a malignant neoplasm that requires an oncological approach (eg, the cosmetic and functional outcome is inferior to complete removal); on the other hand, it may be trivialized because it is so common and rarely metastasizes. This subconscious attitude may result in physicians telling patients that “it is skin cancer, but it is not a malignancy,” “BCC is the ‘best’ of the bunch,” or “it is cancer, but it is not serious,” which is confusing to patients. People with skin cancer should be informed about the necessity to treat NMSC adequately (including a long-term follow-up), the risk of metastases (exceptional in cases of BCC and up to a 10% risk for cases of SCC), and ways to actively participate in the prevention of skin cancer (eg, skin self-examination, sun protection, and chemoprevention). They should be reassured at the same time about the behavior of most NMSCs.

Another predictor of skin-related HRQOL after therapy was the general health of the treated individuals (measured by a comorbidity index and the SF-12). The importance of respondents’ health status on their HRQOL is recognized in the development of some HRQOL assessments (eg, the visual analog scale for general health of the EuroQOL-5D). This importance is also confirmed by observations demonstrating that the presence of comorbidity affects the fear of developing a new BCC and is an important predictor of HRQOL impairment in patients with psoriasis. Patients with a high comorbidity index score or those who indicate that health has a large impact on their QOL (ie, low SF-12 scores) are less likely to notice an effect of skin cancer therapy than those who are in better health. Whether this is caused by item bias (patients with the same level of skin-related HRQOL impairment who are in poor health score differently in several Skinflex-16 items than those in better health), patients’ inability to differentiate the impact of different diseases on their lives, or a lack of the sensitivity of the measurement is not yet clear. But again, this population is in extra need of counseling prior to NMSC therapy to optimize its outcome.
Although it is comprehensible from a methodological perspective that Chen et al. included only patients with new NMSCs, the study results are not generalizable for all patients with NMSC. A substantial proportion of patients with NMSC have a history of multiple (pre)malignant skin tumors, and it would be interesting to investigate whether these patients experience NMSC differently than those with their first NMSC. Does a history of several NMSCs enhance patients’ anxiety about recurrence and subsequent cancers, or are they more likely to psychologically adapt to living with NMSC than those with a first NMSC? Another interesting issue is the effect of patient education about NMSC on HRQOL and treatment satisfaction. It could be that patients appreciate more detailed information—or that the saying “let sleeping dogs lie” applies and that it increases their worry and fear.

INTERPRETATION OF COMPARISONS

Statistical comparisons between HRQOL scores before and after an intervention should be interpreted with caution because a statistically significant difference does not always equal a clinically significant difference. The requisites of comparing HRQOL scores are that nonparametric statistical techniques are used, that the measure is reliable (ie, that it provides similar scores in patients with unchanged disease status at different time points) and responsive to clinical change, and that the meaning of obtained scores and differences are known. An aid in interpreting HRQOL scores is categorization of a continuous score in different levels of impairment. Chen et al. have created categories based on the tertile distribution of the mean scores, which is helpful in presenting data but is not a formal way of categorizing PROs such as distribution-based or banding techniques. The minimal clinically important difference informs physicians that a difference in HRQOL scores observed after therapy is likely to have at least some clinical relevance to most patients. Chen et al. assumed that the minimal clinically important difference of the total Skindex-16 score is 10 points because it was estimated to be about 10 points for each of the 3 scales. The authors have presented the HRQOL data in such a way that statistical and clinical significances are likely to overlap, although they have done so with some limitations.

ADVANTAGES OF NEW TREATMENTS

No statistical difference in HRQOL changes was detected between traditional excision and Mohs surgery of NMSC, suggesting that patients’ primary concern is the excision of the malignant neoplasm. Although it is expected that a detailed examination of tumor margins in Mohs surgery would result in a more satisfied and reassured patient, which would be reflected in an improvement of HRQOL, the work by Chen et al. suggests that patients do not appreciate that examination as much as expected. Also, undergoing a more complicated procedure, such as Mohs surgery, may affect patients’ perception about NMSC differently than a traditional excision or electrodesiccation and coagulation. For now, the theoretical advantages of Mohs surgery compared with traditional excision (eg, a reduced recurrence rate, improved cosmetic outcome, detailed examination of tumor margins, and cost-effectiveness) have not (yet) been confirmed from the perspectives of physicians, patients, and regulatory agencies. The advantage of Mohs surgery for NMSC concerning recurrence rate and HRQOL improvement may be more pronounced for patients with high-risk facial NMSCs, such as micronodular, morpheaform, or recurrent BCC in the H-zone, and after long-term follow-up (ie, 5 years). This implies that there is no evidence to treat every (facial) BCC with Mohs surgery and that a strict patient selection is appropriate. The recent trend in the care of NMSC is to use noninvasive or minimally invasive treatments such as photodynamic therapy and treatment with imiquimod cream. The primary advantage of these options is to reduce the functional and cosmetic morbidity associated with the treatment of skin cancer. Interestingly, Chren et al. demonstrated that electrodesiccation and coagulation, which can be considered to be a minimally invasive technique that may scar, did not notably improve HRQOL in patients with NMSC. In part, this may be explained by the fact that patients’ worry and fear do not substantially improve after therapies that do not “physically” remove the skin cancer. Although the new minimally invasive techniques focus on the benefit of avoiding scars, patients’ perceptions about the efficacy and safety of these therapies is not well documented and may not reassure patients as much as surgical excisions. Patients’ beliefs about therapies warrant further investigation.

SENSIBLE RESOURCE ALLOCATION

Nonmelanoma skin cancer is one of the top 5 most costly cancers to treat, and therapy consumes about half a billion dollars annually in the United States. The costs of NMSCs are likely to continue to grow owing to an increasing incidence of NMSCs in the coming decades. In addition to clinical guidance, the effect of therapy on HRQOL can be used to justify the societal costs associated with NMSC therapy. Preference-based HRQOL measures, such as the EuroQOL-5D and the SF-6D, are expressed in quality-adjusted life-years (QALYs); a QALY combines information about the level of HRQOL impairment and its duration (ie, 1 QALY equals 1 year of full quality). Because of the relatively limited mortality of NMSC and impact on HRQOL, the costs per QALY for NMSC therapy may be high, especially for Mohs surgery. The high incidence of NMSC warrants the development and use of cost-effective therapies to control the impact of NMSC on national health care budgets. To make an evidence-based decision in NMSC treatment, well-performed HRQOL and pharmacoconomic studies, along with randomized clinical trials, are needed.

In conclusion, demonstrating HRQOL improvements after NMSC therapy and its predictors is important because it may affect treatment choice and outcome, identification of patients in need of additional information, and allocation of health care budget. For now, the obvious advantages of Mohs surgery have not yet been
confirmed from the perspectives of physicians, patients, and regulatory agencies; additional studies are warranted to study the effect of NMSC therapies.

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**Financial Disclosure:** None reported.

**REFERENCES**


The Monthly Final Page: skINsight

In the July 2003 issue of the Archives, the skINsight section was introduced. It was the idea of the editor at that time, Kenneth A. Arndt, MD. When Dr Arndt first called me about his idea, he described an interest in using the last page of the journal for something different, something brief in text but loaded with imagery. He pointed out that dermatology was a visual specialty and the last page should be a National Geographic, if you will, for dermatology. Our hope was that the imagery presented would encourage thought and potentially motivate research. The name of the section was not immediately clear, but after much pondering, skINsight came into being. Conceptually, “sight” worked because the section was to be visual. “Skin” worked for obvious reasons. But it was “insight” that was the key, in that we hoped the reader would be enlightened to some degree. Thus, skINsight was born.

The section continues to be dynamic. Over more than 4 years, 50 skINsights have been published (including one this month). Images revealing consistent patterns across patients have been encouraged, whereas single-patient case reports have been discouraged. Images of dermoscopic patterns took the early lead (35 of the skINsights essentially form a dermoscopy atlas). The dermoscopic patterns displayed are reproducible and consistent, but we still lack a fundamental understanding of the specific mutation (or environmental conditions) responsible for each pattern. Hopefully, with research the answers will be forthcoming. Seven of the skINsights included clinical human images, introducing us to new descriptors for dermatology (diverging from the food theme) including the “louse blouse” and the “igneous rock sign.” Two of the skINsights included clinical animal images, introducing us to dermatoses of dogs and horses. Others have included confocal microscopic images of scabies mites, light microscopic art in the surgery clinic, and radiographic images underlying dermatologic conditions. It has been a good run, and hopefully we will be able to include an ever-expanding array of visual images as we move forward.

Last month, we presented the first skINsight to include video, a visual display of the actions of Langerhans cells in the presence of dinitrofluorobenzene. Images with corresponding videos are tagged with a video symbol, and the videos are readily accessible for viewing on the Archives web site (http://www.archdermatol.com). In this issue, we present videos in a skINsight on optical coherence tomography.

The introduction of video to the section is a result of the vision of the current editor, June K. Robinson, MD. She has noted that videos are a natural extension of the original goal of the skINsight section. Dermatology is dynamic, and we need a forum for the display of high-quality videos of dynamic dermatologic phenomena. In anticipation of an increased number of images needed to convey the sense of motion, the section will be increased as needed to 2 pages and will remain the final insightful page in each issue.

We encourage submission of high-quality images and videos of dermatologic phenomena to the skINsight section. We are particularly interested in demonstrable and repeatable phenomena across patients (not single-
patient case reports). Examples include confocal microscopic videos slicing down through the epidermis, revealing pagetoid cells in the early phase of benign nevus growth in several patients; cutaneous ultrasonography videos displaying their value in determining thickness of several tumors; video demonstrations of repeatable dynamic clinical signs (ie, umbilication, blanching, or dermato graphism); and dynamic clinical findings (ie, movement in myiasis or time-lapse photography).

With the expansion of the section, we are also expanding the skINsight team and are pleased to welcome 2 new assistant section editors, Ashfaq A. Marghoob, MD, and Alon Scope, MD.

We hope the skINsight section will continue to provide a forum for the publication and sharing of visual information.

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Financial Disclosure: Dr Grichnik is a founder and major shareholder of Digital Derm Inc, manufacturer of MoleMapCD (total body photography). He is also a consultant for and has received funding from Electro-Optical-Systems Inc, manufacturer of Melafind (a melanoma detection device).

REFERENCES


The Role of Filaggrin Mutations as an Etiologic Factor in Atopic Dermatitis

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Common Loss-of-Function Variants of the Epidermal Barrier Protein Filaggrin Are a Major Predisposing Factor for Atopic Dermatitis
Palmer CN, Irvine AD, Terron-Kwiatkowski A, et al
Nat Genet. 2006;38(4):441-446

Atopic disease, including atopic dermatitis (eczema), allergy and asthma, has increased in frequency in recent decades and now affects 20% of the population in the developed world. Twin and family studies have shown that predisposition to atopic disease is highly heritable. Although most genetic studies have focused on immunological mechanisms, a primary epithelial barrier defect has been anticipated. Filaggrin is a key protein that facilitates terminal differentiation of the epidermis and formation of the skin barrier. Here we show that two independent loss-of-function genetic variants (R510X and 2282del4) in the gene encoding filaggrin (FLG) are very strong predisposing factors for atopic dermatitis. These variants are carried by 9% of people of European origin. These variants also show highly significant association with asthma occurring in the context of atopic dermatitis. This work establishes a key role for impaired skin barrier function in the development of atopic disease.

COMMENT

Cutaneous inflammation and defects in the epidermal barrier function are the 2 hallmarks of atopic dermatitis (AD). In a classic which came first, the chicken or the egg? situation, though, it has been difficult to determine if cutaneous inflammation causes barrier impairment or if impaired barrier function leads to cutaneous inflammation.

Palmer et al have provided at least a partial answer to this question. Their group produced strong evidence that 2 loss-of-function mutations in the filaggrin gene are the primary cause of AD in a sizable portion of patients of European descent. They found a clear, reproducible, semidominant pattern of inheritance with incomplete penetrance by which filaggrin loss-of-function mutations cause AD. Their results have been confirmed in several additional studies in different European populations. Based on these studies, it is estimated that these 2 alleles are directly responsible for the AD of 11% of patients of European descent. Although these 2 alleles appear to be the most prevalent, there are additional alleles that account for an additional portion of AD cases.

Filaggrin plays a major role in the production of the epidermal barrier function. It is initially produced as pro-filaggrin in the granular layer and is then processed to filaggrin at the junction of the granular and corneal layers of the epidermis. Filaggrin functions to aggregate keratin filaments so that effective corneocytes are produced (the “bricks” of the “brick and mortar” stratum corneum). Filaggrin is then degraded into individual amino acids, becoming the natural moisturizing factor of the stratum corneum. Filaggrin deficiency has obvious adverse effects on stratum corneum function.

These studies have also demonstrated that filaggrin loss-of-function alleles confer a risk for asthma associated with AD but do not increase the risk for asthma in the absence of AD. In other words, a patient with both a filaggrin loss-of-function allele and AD has a markedly increased risk of asthma compared with either (1) a patient with AD but no filaggrin loss-of-function alleles or (2) a patient with a filaggrin loss-of-function allele but no AD. This finding may help explain the atopic march, the observation that AD often precedes asthma and/or allergic rhinitis. It suggests that a defective epidermal barrier allows external protein allergens to gain access to the immunocompetent portions of the epidermis. This mechanism of exposure is a highly efficient mechanism for developing Th2-type responses to these allergens, which classically involves production of IgE. When these same allergens later gain access to respiratory epithelium, the IgE that was generated as a result of cutaneous exposure is able to induce allergen-related asthma or allergic rhinitis.

Overall, these findings suggest the following: (1) In many patients with AD, the underlying cause is an abnormal epidermal barrier related to filaggrin deficiency; (2) this abnormal epidermal barrier predisposes these patients with AD to asthma; and (3) repairing the barrier or preventing barrier dysfunction may be an effective strategy for preventing asthma in patients with AD.
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Financial Disclosure: Dr Zirwas has served on the speakers bureaus of Coria Laboratories Ltd, Fort Worth, Texas, the manufacturer of a skin moisturizer and a topical steroid, and Astellas Pharma, Tokyo, Japan, the manufacturer of Protopic.

REFERENCES


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]).

Correction

Error in Video Access Web Address. In the skinSight feature titled “Epidermal Langerhans Cell Movement In Situ: A Model for Understanding Immunologic Function in the Skin” by Mohr and Takashima, published in the October issue of the Archives (2007;143[10]:1352), the Web address cited to access the associated video was incorrect. The correct Web address is www.archdermatol.com.
Brown and Black Scaly Patches on the Lower Leg

Romily L. Soederberg, MD; Misty Sharp, MD; Patrick E. Curtsinger, MD; Central Arkansas Veterans Healthcare System and the University of Arkansas for Medical Sciences, Little Rock

REPORT OF A CASE

A 68-year-old man presented to the dermatology clinic with chronic swelling of the lower legs accompanied by pruritus and scaling. He had noticed a gradual increase in pigmentation of the lower part of his left leg. His medical history included congestive heart failure, hypertension, and protein C deficiency with deep venous thrombosis of the lower part of the left leg.

Physical examination revealed bilateral (1/2) pitting edema of the legs extending proximally to his knees. The lower left leg was erythematous and edematous, with scale overlying an ulcer. The patient had undergone a surgical operation to treat a fracture of his right femur. Subsequently, an infection of the right knee prostheses developed. Treatment with 500 mg/d of oral levofloxacin was begun. One month into this treatment regimen, she started to notice a blue-black discoloration of the thighs and dorsum of the legs and later to the forearms. The patient denied the external application of any product or the ingestion of other drugs. She had not been sunbathing. The results of blood and urine tests were normal.

Physical examination disclosed a blue-black pigmentation of the legs, thighs, and surface area of the forearms (Figures 1 and 2). There were no other skin findings. A diagnosis of traumatic or idiopathic cutaneous calcification was made. A complete serum analysis demonstrated no abnormalities, and there was no evidence of an immune disease or metastatic calcification.

A slowly progressing papule on the gluteal fold that had appeared a few months earlier. Physical examination revealed a smooth, firm, skin-colored, exophytic papule, situated more than 2.5 cm from the anal verge, measuring 0.5 cm in diameter. The lesion was excised, and microscopic examination showed irregular deep-blue basophilic masses with fine scale admixed with speckled black pigment (Figures 1 and 2). There were no other skin findings. A punch biopsy specimen was obtained from both lower parts of the legs and stained with hematoxylin-eosin, melanin, and von Kossa technique (Figures 3 and 4).

What is your diagnosis?

Blue-Black Pigmentation of Legs and Arms in a 68-Year-Old Woman

Anne Cecilia Patrizi, MD; Paola Giacomin, MD; Paola Biscaldi, MD; Cosimo Misciali, MD; Iria Neri, MD; University of Bologna, Bologna, Italy

REPORT OF A CASE

A 68-year-old white woman requested consultation for the progressive blue-black pigmentation of both legs and arms (Figures 1 and 2). The ear candidacy (1/2) pitting edema of the legs extending proximally to his knees. The lower left leg was erythematous and edematous, with scale overlying an ulcer. The patient had undergone a surgical operation to treat a fracture of his right femur. Subsequently, an infection of the right knee prostheses developed. Treatment with 500 mg/d of oral levofloxacin was begun. One month into this treatment regimen, she started to notice a blue-black discoloration of the thighs and dorsum of the legs and later to the forearms. The patient denied the external application of any product or the ingestion of other drugs. She had not been sunbathing. The results of blood and urine tests were normal.

Physical examination disclosed a blue-black pigmentation of the legs, thighs, and surface area of the forearms (Figures 1 and 2). There were no other skin findings. A diagnosis of traumatic or idiopathic cutaneous calcification was made. A complete serum analysis demonstrated no abnormalities, and there was no evidence of an immune disease or metastatic calcification.

A slowly progressing papule on the gluteal fold that had appeared a few months earlier. Physical examination revealed a smooth, firm, skin-colored, exophytic papule, situated more than 2.5 cm from the anal verge, measuring 0.5 cm in diameter. The lesion was excised, and microscopic examination showed irregular deep-blue basophilic masses with fine scale admixed with speckled black pigment (Figures 1 and 2). There were no other skin findings. A punch biopsy specimen was obtained from both lower parts of the legs and stained with hematoxylin-eosin, melanin, and von Kossa technique (Figures 3 and 4).

What is your diagnosis?

Recurrent Calcified Cutaneous Nodule of the Perianal Region

Annalisa Patrizi, MD; Paola Giacomin, MD; Paola Biscaldi, MD; Cosimo Misciali, MD; Iria Neri, MD; University of Bologna, Bologna, Italy

REPORT OF A CASE

A 14-year-old immunocompetent boy who had been receiving growth hormone therapy for 2 years presented with recurrent painful, swollen, and mildly pruritic nodules on the lower limbs. He had noticed a gradual increase in pigmentation of his left leg, but no other skin findings. A diagnosis of traumatic or idiopathic cutaneous calcification was made. A complete serum analysis demonstrated no abnormalities, and there was no evidence of an immune disease or metastatic calcification.

A slowly progressing papule on the gluteal fold that had appeared a few months earlier. Physical examination revealed a smooth, firm, skin-colored, exophytic papule, situated more than 2.5 cm from the anal verge, measuring 0.5 cm in diameter. The lesion was excised, and microscopic examination showed irregular deep-blue basophilic masses with fine scale admixed with speckled black pigment (Figures 1 and 2). There were no other skin findings. A punch biopsy specimen was obtained from both lower parts of the legs and stained with hematoxylin-eosin, melanin, and von Kossa technique (Figures 3 and 4).

What is your diagnosis?

Auricular Erythema With Nodules and Scale

Mark Batchik, MD; Carol Chenoweth, MD; Linglei Ma, MD, PhD; Kelly McClean, MD; University of Michigan, Ann Arbor

REPORT OF A CASE

A 68-year-old woman presented with a 4-month history of a painful, swollen left ear. Her problems began with a small pimplelike lesion in the mid portion of the ear, and she subsequently developed multiple nodules in the surrounding area. The left ear became progressively more painful, swollen, and mildly pruritic. She denied a history of fever, chills, or night sweats. The patient was treated unsuccessfully with multiple courses of antibiotics, including ciprofloxacin, doxycycline, cephalexin, rifampin, and topical metronidazole. Her medical history was notable for acne, dermatitis but was otherwise unremarkable.

On physical examination, the superior portion of the ear was erythematous and edematous with scale overlying several fluctuant nodules (Figure 1). The ear canal was 3 mm in diameter. The lesion was excised, and microscopic examination showed irregular deep-blue basophilic masses with fine scale admixed with speckled black pigment (Figures 1 and 2). There were no other skin findings. A punch biopsy specimen was obtained from both lower parts of the legs and stained with hematoxylin-eosin, melanin, and von Kossa technique (Figures 3 and 4).

What is your diagnosis?
inflammation develops when the skin shows clinical signs of inflammation, such as erythema, edema, or vesicles. Microscopically, the key feature is the presence of histiocytes containing lysosomes filled with lipofuscin, which gives the tissue a characteristic orange-brown appearance.

**REFERENCES**

A Practice Brochure: Complement to, Not Supplement for, Good Physician-Patient Interaction

Patient satisfaction affects patients' compliance with prescribed regimens and their clinical outcomes. Based on the results of patient satisfaction surveys, we suspected that providing an informational brochure to patients regarding their physician's qualifications and desires to provide high-quality care would improve patient satisfaction.

Methods. We surveyed 50 new adult patients attending a dermatology clinic visit for various dermatologic conditions. The 25 patients in the intervention group received a short brochure containing information about their dermatologist's training, desire to provide high-quality health care, and contact information; 25 control patients did not receive the brochure. Both groups completed a postvisit survey of 6 questions related to patient demographics, including age, sex, ethnicity, education, payment source, and reason for their office visit. They also completed 11 items related to their experience, satisfaction, and comfort level during their visit, each item rated on a numerical scale on which 0 indicated "strongly disagree" and 10, "strongly agree." The survey was analyzed using t tests and corresponding means; P values were then calculated.

Results. The mean overall satisfaction of the control group, which did not receive an informational brochure, was 8.6 vs 8.4 for the intervention group. Most questions were answered more favorably by the control group, although none of the differences were statistically significant. For example, the control group agreed more strongly than the intervention group with the statement "I know who to contact if I have a question or concern regarding my treatment or appointment" (P = .06). The control group mean scores were also slightly higher for the statements "I am satisfied with the care my dermatologist provides"; "my dermatologist is concerned about the skin care I receive"; "I am comfortable speaking to my dermatologist about my questions and concerns"; "my questions about skin care were answered during my office visit"; and "I am confident about my treatment plan." No statistical difference was found demographically between the 2 groups except that slightly more Medicare patients were included in the intervention group.

Comment. A dermatologist's interpersonal skills are the most relevant factor in determining patient satisfaction. To the extent that patients who received the brochure had higher expectations than those who did not, the dermatologist may have been more likely to disappoint them with the service provided. The small size of our sample population was a limiting factor in our study. In addition, we did not account for disease severity. It may be easier to please patients with more severe disease where even small improvements may significantly affect the quality of life.

Patient satisfaction is an integral aspect of providing optimal patient care: high patient satisfaction helps lead to improved health outcomes. Patients generally view their dermatologist as the primary source for information about their skin, and they desire a genuine concern from their physician as well as answers to their questions. A supplemental brochure provided to new patients at the check-in counter did not improve patient satisfaction to a statistically significant degree and is not a substitute for quality time with the physician.

A Randomized Double-Blind Study of the Effect of Botox and Dysport/Reloxin on Forehead Wrinkles and Electromyographic Activity

The difference between the potency units of the 2 main botulinum toxin A products, Botox (Allergan, Irvine, California) and Dysport/Reloxin (Ipsen Ltd, Slough, England), is still a subject of discussion even after 15 years of clinical use. The manufacturer of Botox recommends higher ratios than does the manufacturer of Dysport/Reloxin. Herein, we report the findings of a randomized, double-blind, split-face study of forehead wrinkles and electromyographic (EMG) activity following application of the 2 products at a 3:1 dose ratio, independent of the support of either manufacturer.

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Financial Disclosure: Dr Feldman owns stock in www.DrScore.com, an online patient satisfaction survey service.

Funding/Support: The Center for Dermatology Research is supported by an educational grant from Galderma Laboratories LP, Fort Worth, Texas.

We recommend this model as a relatively simple and accessible way of obtaining quantitative comparative data in a clinical treatment situation.

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Financial Disclosure: None reported.

Additional Contributions: Jochen Hirsch, MD, PhD, provided expert statistical assistance.


COMMENTS AND OPINIONS

Infliximab-Induced Palmoplantar Pustulosis in a Patient With Crohn Disease

We read with interest the recent accounts in the Archives of paradoxical induction of psoriasis-like disease in patients undergoing therapy with tumor necrosis factor α (TNF-α) inhibitors.1-3 Similar reports have been published elsewhere in the dermatologic4-5 and rheumatologic literature.6-8

Report of a Case. We report the case of a 37-year-old woman with Crohn disease who developed palmoplantar pustulosis (PPP) during treatment with infliximab. Palmoplantar pustulosis has not previously been reported in cases of Crohn disease treated with TNF-α inhibitors. Our patient was diagnosed as having Crohn disease in November 2005, had no history of psoriasis, and was otherwise healthy. A regimen of infliximab was begun at 5 mg/kg, and the patient had 3 infusions, January, June, and July 2006, resulting in complete remission of her bowel symptoms.

One month later, she developed classic PPP together with a mild psoriasiform eruption on the lower legs. In particular, the patient’s feet were painful, which adversely affected her mobility. We prescribed betamethasone dipropionate in optimized vehicle ointment twice daily, polyethylene occlusion at night, and soap-free wash and moisturizer. Over the following 3 to 4 weeks, the patient improved clinically and symptomatically and did not need additional psoriasi treatment. By February 2007, the PPP had cleared, presumably due to the diminishing effects of infliximab, but there was a corresponding slight relapse of Crohn disease. The patient began treatment with azathioprine, and the Crohn disease again passed into remission. However, if this treatment does not provide adequate control in the future, we will reintroduce infliximab therapy and treat any skin changes with aggressive topical therapy, oral agents such as methotrexate, or switch to another anti–TNF-α agent such as adalimumab.

Comment. All anti–TNF-α agents, paradoxically, induce or exacerbate psoriasis, albeit rarely.9 Although this is considered a class effect,10 1 case of etanercept-induced psoriatic lesions did not occur after switching to infliximab.6 Usually, the skin changes are self-limiting,10 but in some cases they have been sufficiently severe to discontinue treatment.10 The cause is unknown, although hypotheses include the cross-regulation between TNF-α and interferon1 or the abnormal expression of TNF-α in eccrine sweat glands.2 Understanding this paradox may help in our further understanding of the mechanisms, causes, and treatment of psoriasis.10

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Financial Disclosure: None reported.


Suppression of the HPA Axis in Pediatric Patients With Atopic Dermatitis

We read with interest the recent article by Schlessinger et al1 that assessed the potential of the topical corticosteroid fluticasone to suppress the hypothalamic-pituitary-adrenal...
(HPA) axis. In this study, fluocinonide cream was applied for 2 weeks to 126 patients aged 3 months to 18 years with atopic dermatitis. The authors defined HPA axis suppression as serum cortisol levels of 18 µg/dL or lower (to convert serum cortisol to nanomoles per liter, multiply by 27.588) 30 minutes after intravenous (IV) cosyntropin stimulation. Using this cut-off cortisol level, they found that 3 patients (2%) showed evidence of HPA axis suppression. However, the authors did not specify the cosyntropin dose that they used. They merely mentioned that they used cosyntropin as directed in the package insert. Because the manufacturer suggests collecting blood samples before and 30 minutes after IV injection of 250 µg of corticotropin (or 125 µg in children 2 years or younger), we assume that the authors used this conventional dose of corticotropin.

Whereas the standard-dose test (SDT) for corticotropin (250 µg) is clearly intended for the diagnosis of primary adrenal insufficiency, it is lacking sensitivity in the evaluation of secondary adrenal insufficiency. During the SDT, pharmacologic serum corticotropin levels are achieved, resulting in overstimulation of the adrenal cortex and hypersecretion of cortisol. In comparison with the cortisol response to hypoglycemia on the insulin tolerance test, a similar cortisol response was obtained with the LDT and the SDT (mean ± SE serum cortisol levels were 25.7 ± 4.3 µg/dL and 30.2 ± 5.1 µg/dL, respectively). However, after 30 minutes, serum cortisol levels continued to rise with the SDT, although not significantly, whereas a decline was seen in the LDT. Thus, peak cortisol levels during the LDT observed 30 minutes after injection compared with peak cortisol levels at 60 minutes during the SDT.

The LDT provided a 94.7% sensitivity and 90% specificity, with an overall diagnostic accuracy of 90%, in contrast with the 6.2% sensitivity for the SDT. Thus, the SDT fails to recognize secondary adrenocortical insufficiency in patients undergoing treatment with topical steroids. We suggest that children treated with topical steroids, with uncertain risk of HPA axis impairment, may benefit from the enhanced sensitivity of the LDT screening for adrenal insufficiency.

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VIGNETTES
Fractional Photothermolysis: A Novel Treatment for Disseminated Superficial Actinic Porokeratosis

D isseminated superficial actinic porokeratosis (DSAP) occurs diffusely in sun-exposed areas, notably the legs and forearms. The exposed nature of the lesions can cause emotional distress among patients. Additionally, these lesions present a risk of transformation into invasive squamous cell carcinoma. Treatments for DSAP have had mixed results, especially for extensive lesions. We report 2 cases of DSAP responding to treatment with fractional photothermolysis.

Report of Cases. Case 1. A 47-year-old woman with Fitzpatrick skin type II presented with multiple, pruritic, scattered, red-brown macules with peripheral scale covering her lower extremities, clinically consistent with DSAP. Biopsy findings confirmed the diagnosis. Previous treat-
ments included cryotherapy, topical diclofenac, tazarotene, and intralesional triamcinolone.

The patient underwent 3 treatment sessions at 4-week intervals with fractional photothermolysis to the anterior surfaces of both legs and thighs with a 1550-nm erbium-doped fiber fractional photothermolysis laser (Fraxel SR 750; Reliant Technologies, Mountain View, California). Topical anesthetic containing benzocaine, 10%, lidocaine, 6%, and tetracaine, 4% (Triple Anesthetic; New England Compounding Center, Framingham, Massachusetts) was applied under occlusion 1 hour before treatment and was then removed with a dry gauze immediately before the procedure. Ten passes were performed, for a final treatment density of 2500 microthermal treatment zones (MTZ)/cm² (pulse energy, 10 mJ; density, 250 MTZ/cm² per pass). A Zimmer Elektromedizin Cryo 5 skin cooling device (Zimmer MedizinSystems, Irvine, California) was used during treatment to cool the skin and mitigate patient discomfort (fan power 2, 10-15 cm from the skin surface).

Postprocedure erythema was observed for 1 to 2 days. Four weeks after the third treatment, the patient and an independent physician noted moderate to marked improvement of lesions (50%-75% improvement) (Figure 1A and B and Figure 2A and B). The patient reported a 50% improvement of skin texture along with resolution of associated pruritus. Eight months after 3 fractional photothermolysis treatments, the patient had

Figure 1. Areas of disseminated superficial actinic porokeratosis (ovals) during the fractional photothermolysis treatment course on the thigh of patient 1. A, Red, scaly, slightly elevated papules and plaques at baseline. B, After 3 treatments to the entire thigh, a moderate to marked flattening and fading of the lesions has occurred. (Note the bruise on the medial knee and thigh.) These results were maintained for 8 months. C, After 6 treatments to the anterior surface of the thigh, the lesions have improved further. The patient reported resolution of pruritus and a marked improvement of skin texture. These results were maintained for 1 year after the last treatment. There is a bruise on the lateral thigh.

Figure 2. Area of disseminated superficial actinic porokeratosis (DSAP) (rectangle) and DSAP lesion of interest (arrow) during the fractional photothermolysis treatment course on the lower leg of patient 1. A, Baseline. B, After 3 treatments to the entire leg. C, After 6 treatments to the leg, a marked reduction in the number, color, and scaliness of the lesions is evident. Note the fading and flattening of the lesion demarcated by the arrow. Clinically, the smoothness of the skin increased. Note the decrease in the number of lesions within the marked rectangle as well as the fading and flattening of the large lesions within the rectangle.
sustained improvement. At that time, the patient decided to undergo 3 additional treatments. Independent physician assessment 1 year after the sixth treatment revealed a greater than 50% improvement in DSAP lesions from baseline (Figure 1C and Figure 2C). The patient was extremely satisfied with the improvement of lesions and skin texture (evenness of color and skin smoothness) and reported that the lesions continued to be free of pruritus.

Case 2. A 48-year-old woman with Fitzpatrick skin type II presented with scattered red-brown macules with peripheral scale on both forearms clinically consistent with DSAP. The forearms were treated with 3 fractional photothermolysis treatments spaced 1 month apart. Topical anesthetic was applied as in case 1, and the patient received 8 passes for a final treatment density of 2000 MTZ/cm² for the first 2 treatments and 2250 MTZ/cm² for the third treatment (pulse energy, 8 mJ; density, 250 MTZ/cm² per pass for the first 2 treatments and pulse energy, 9 mJ; density, 250 MTZ/cm² per pass for the third treatment). During the third treatment, the energy was increased to maximize the depth of laser penetration. The energy level was determined by the patient’s pain threshold. The Zimmer Elektromedizin Cryo 5 cold-air cooling system was used to cool the skin during the treatment and mitigate patient discomfort (fan power, 2; distance from the skin surface, 10-15 cm).

After the patient’s second treatment, greater than 50% improvement of her lesions was noted. The patient was satisfied with the results after the third treatment and reported continued improvement of skin texture and a reduction in number of lesions 12 months after treatment.

Comment. Fractional resurfacing creates hundreds of MTZ at controlled depths while sparing the surrounding tissue. This technique allows for faster wound healing owing to small injury regions and short migratory paths for keratinocytes. Its other advantages over ablative skin resurfacing (carbon dioxide laser or erbium: YAG) include less severe adverse effects (erythema and pain), shorter duration of recovery time, and safety of application to treat facial and nonfacial lesions.1-3

These cases illustrate moderate to marked decreases in the size of DSAP lesions as well as improvement of skin texture (evenness of color and skin smoothness) after 3 to 6 treatments of fractional photothermolysis. Improvement was maintained 1 year after 3 to 6 treatment sessions. The stimulatory effects of fractional resurfacing on dermal collagen remodeling and epidermal regeneration, in addition to the reversal effects on photodamaged skin, are mechanisms that might explain the successful treatment of DSAP. One limitation of our report is the lack of histologic confirmation of resolution of the skin lesions. It would be useful to prove histologically that existing lesions resolved after fractional photothermolysis in future reports because this resolution would reduce the risk for squamous cell carcinoma in these patients.

To our knowledge, this is the first reported use of fractional resurfacing for the treatment of DSAP. Additional studies with greater numbers of patients, different skin types, and greater duration of follow-up are needed to thoroughly evaluate efficacy of the erbium-doped 1550-nm laser in the treatment of DSAP.

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Comparison of Treatment Options for a Monsel Tattoo

Monsel solution is a hemostatic agent used in minor surgical procedures. It scleroses blood vessels by depositing ferric salts that precipitate proteins. Rarely, these deposits remain visible in the skin creating a Monsel tattoo. Herein we compare 3 methods used to treat a Monsel tattoo.

Report of a Case. A 34-year-old man underwent a shave biopsy on his back. Monsel solution was applied for hemostasis. Histologic analysis showed an intradermal nevocellular nevus with clear margins. Two months later, the patient presented with a 1.2 × 1.0-cm brown patch over the entire biopsy scar.

The Monsel tattoo was divided into 3 treatment quadrants and 1 control quadrant. Treatments included a liquid nitrogen spray gun; a Q-switched Nd:YAG 532-nm laser (at 1.0 J/cm² with a 2-mm spot size); and a Q-switched Nd:YAG 1064-nm laser (3.5 J/cm² with a 2-mm spot size).

Two cycles of cryotherapy with 15-second thaw times were administered while covering the other quadrants. Lasers were targeted to their respective quadrants. Treatments were performed at 17 and 23 weeks after the biopsy. Outcomes were assessed at 30 weeks. At 44 weeks, punch biopsy specimens were obtained from each quadrant.

At 17 weeks there was mottled pigment throughout the scar with a darker continuous rim at the edge (Figure A). Six weeks after the first treatment, fading was evident in all quadrants (Figure B). Improvement in the control quadrant suggests that the tattoo was fading with time. Seven weeks after the second treatment, additional fading was evident (Figure C). The base of the scar had lost...
most of its pigment, but the darker rim remained in the untreated quadrant. The laser-treated rim areas were slightly more faded than the control rim. The 532-nm Nd:YAG–treated area was focally more faded than the 1064-nm Nd:YAG quadrant. The greatest response was seen in the cryotherapy quadrant, where minimal pigment remained. After 2 years, no pigment could be detected clinically in any quadrant. All treatments were well tolerated.

At 44 weeks, tissue from the control quadrant had noticeable dermal iron deposits (Figure, D). The 1064-nm Nd:YAG quadrant had less iron than the control but more than the other 2 treatment sites. The 532-nm Nd:YAG treatment resulted in minimal residual iron deposits; and cryotherapy appeared to reduce the amount of iron in the most.

Comment. Monsel solution has proven hemostatic effect and no negative effect on epidermal regeneration. The infrequent complication of a Monsel tattoo can be clinically and histologically confused with recurrent melanotic lesions. Furthermore, Monsel deposits are radiographically opaque, and the altered radiographic appearance under a biopsy site of a malignant neoplasm might erroneously suggest bony involvement. Alternative agents such as aluminum chloride solution lack a tattoo risk but are thought to be less effective at hemostasis.

Many options exist for the treatment of Monsel tattoo. This study evaluates the uses of cryotherapy and Q-switched Nd:YAG lasers. While time alone caused some fading, cryotherapy accelerated tattoo resolution. We found the Nd:YAG laser to be less effective, but additional treatments or higher fluences might have improved the laser’s performance. In this 1 case, all treatments reduced the amount of histologically detectable pigment, while cryotherapy had superior clinical efficacy in reducing the visible Monsel tattoo.

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Dermatoscopic Changes in Acquired Melanocytic Nevi and Seborrheic Keratoses After the Application of a Self-tanning Airbrush

Report of a Case. A 39-year-old woman with multiple acquired melanocytic nevi was regularly evaluated in our Department of Dermatology using digital dermoscopy. In one of her routine visits, dermoscopy revealed that many of her nevi and seborrheic keratoses had changed since her last visit. Multiple yellow-brownish blotches now appeared in almost all the lesions, and these blotches varied greatly in size. In the flat lesions, a few small globules of yellow-brownish pigment were noted scattered over the nevi, while in the raised lesions appeared multiple larger blotches of the same color, similar to, but larger than, comedolike or pseudofollicular openings (Figure 1). However, no clinical changes were noted.

To improve her physical appearance for a special event, she had air-brushed a sunless tanning solution onto her body 20 days before. We decided on observation and follow-up for the patient. Three months later, almost all of the globules and blotches had completely disappeared, although multiple comedolike openings in 1 pruriginous lesion on the chest remained (Figure 1, top right panel, marked with a black square), and we removed it.

Histologically, a compound melanocytic nevus was found that showed strikingly large and numerous horn pseudocysts containing multiple concentric keratin lamellae. These lamellae and the overlying horny layer included bands of black or brownish pigment all over the lesion. Slight epidermal spongiosis was also noted (Figure 2).
Comment. Sunless self-tanning preparations contain dihydroxyacetone (DHA), an active agent that produces a temporary staining of the skin, and other additive agents such as bronzers and moisturizers. A 3-carbon sugar, DHA preferentially reacts with basic amino acids found in abundance in the keratinized stratum corneum and forms brown-black chromophore compounds called melanosins, resulting in the simulation of a tan. Color change should be apparent within 1 hour, but maximum darkening occurs between 8 and 24 hours after application.

Figure 1. Dermoscopic images of 6 lesions (rows 1-6) prior to airbrush application of self-tanning product (left column) and 2 weeks (center column) and 3 months (right column) after application. (Rows 3 and 5 show seborrheic keratoses; all others show nevi.) Notice the presence of multiple globules and comedolike pseudofollicular openings after the application of the self-tanning product. The nevus photograph at the top right, marked with the black square, represents an excised lesion.
Most individuals report the disappearance of the color over 5 to 7 days, although in the present case, histologic residue of the pigmentation remained 3 months later.

In the excised lesion, multiple comedolike pseudo-follicular openings were the most notable dermoscopic feature. Histopathologically, the prominent hyperkeratosis in the form of large horn pseudocysts and large amounts of pigment in the overlying horny layer might constitute an epidermal reaction to DHA. The epidermis in this case showed a tendency to produce large globules of concentric keratin lamellae in transition with parallel keratin lamellae on the surface. In addition, the histologic findings suggest that the reaction did not only affect the stratum corneum, as is currently attributed to DHA. Dermoscopically, the reaction was more evident in the raised lesions, those with a more thickened epidermis and stratum corneum, than in the flat lesions.

To our knowledge, no previous reports describe morphologic changes in melanocytic nevi and seborrheic keratoses after exposure to self-tanning preparations. Although self-tanning lotions are considered a safe method to induce a tanned appearance of the skin, further investigations are needed to evaluate the behavioral implications and the potential risks of widely endorsing artificial tanning products.

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Diabetic Muscle Infarction

Diabetic muscle infarction (DMI) is a frequently misdiagnosed, rare event complicating poorly controlled diabetes. It typically presents with acute, unilateral pain and swelling of the leg. We report a patient diagnosed as having DMI by the dermatology consultation service after that service was called to evaluate for nephrogenic systemic fibrosis (NSF) in a patient with diabetic nephropathy undergoing hemodialysis.

Report of a Case. A 51-year-old man undergoing hemodialysis for diabetic nephropathy was admitted for left thigh pain and subjective fevers for several weeks. He had been treated the previous month with vancomycin and amikacin for a polymicrobial fistula infection. He had no history of recent trauma. On admission, he was afebrile. The medial left thigh was tender to deep palpation with an ill-defined masslike swelling and induration (Figure 1) but minimal overlying erythema. No pitting edema was present.

Laboratory evaluation revealed a white blood cell count of 9500 cells/µL (to convert white blood cells to number of cells × 10⁹/L, multiply by 0.001) with neutrophils at a proportion of 0.82. The erythrocyte sedimentation rate was 106 mm/h, and the creatine kinase level was normal. Magnetic resonance imaging (MRI) demonstrated enhanced T2 signaling of the left adductor muscles as well as edema between fascial planes and in the subcutaneous tissue (Figure 2). There was no radiographic evidence of fibrosis, abscess, or neoplasm. Lower extremity ultrasound findings were negative for deep venous thrombosis. No muscle biopsy was performed, and the pain resolved with rest, elevation, and analgesics.

Comment. First described by Angervall and Stener in 1965 as tumoriform focal muscular degeneration, skeletal muscle infarction occurs in patients with diabetes and coexisting microvascular complications, including nephropathy, retinopathy, and neuropathy. It is thought to result from a combination of microangiopathy and occlusive peripheral vascular disease.

Diabetic muscle infarction presents as acute, severe muscle pain and tenderness, followed by deep swelling and varying severity of induration and erythema. A palpable mass may develop in several days to weeks. The most common sites of involvement are the quadriceps and hamstrings, although iliofemoral, calf, and upper extremity infarcts have been reported. The patients are usually afebrile and have normal to slightly elevated white blood cell counts. The creatine kinase level may initially be elevated but usually drops to normal values within 1 week of the onset of symptoms. The erythrocyte sedimentation rate is characteristically very high.

Kattapuram et al reviewed the MRI characteristics of 14 patients with skeletal myonecrosis and described high signal intensity within a muscle group on T2-weighted images, often with central, streaky nonenhancing areas. Muscle biopsy, when performed, demonstrates areas of hemorrhagic necrosis of myocytes with varying levels of inflammation, fibrosis, and atrophy of surrounding fibers.

This entity should be considered in the differential diagnosis for any patient with diabetes presenting with a painful extremity. Diabetic muscle infarction can be differentiated from eosinophilic fasciitis, scleromyxedema, and NSF by the relative lack of cutaneous erythema, woody induration, and hyperesthesia. Furthermore, NSF with skeletal muscle involvement typically has associated cutaneous features with varying severity of myopathy and fibrosis found on muscle biopsy specimens. However, imaging characteristics of skeletal muscle NSF are poorly defined. Patients with pyomyositis are usually febrile and have leukocytosis, positive blood cultures, and a well-defined enhancing abscess or fluid collection on radiographic imaging.

Fortunately, the short-term prognosis of DMI is favorable. Conservative management with analgesics, rest,
and immobilization usually leads to resolution within 8 weeks. Rarely, a compartment syndrome develops necessitating surgical intervention.

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Eruptive Keratoacanthomas in a New Tattoo

Report of a Case. A 56-year-old white man with a history of diabetes, hypertension, smoking, and multiple, long-standing, multicolored tattoos obtained a new tattoo on his left forearm with red, black, and yellow pigments. He had a history of 2 basal cell carcinomas (BCCs) of the head and neck. Within 3 weeks of getting this new tattoo, 4 crusted nodules developed within it, ranging in size from 0.6 to 2.6 cm (Figure 1). Biopsy specimens of all 4 lesions indicated keratoacanthomas (KAs), and the lesions were excised. Microscopically, invasive broad tongues of atypical glassy keratinocytes extended into the dermis with tattoo pigment both free in the dermis as well as in scattered histiocytes (Figure 2). No additional tumors developed in the 6 months following surgery.

Comment. There have been 5 to 10 reports of melanoma1 and BCC2 developing within tattoos, and 3 reports of squamous cell carcinoma (SCC)3,4 arising in a tattoo. In 1 case,3 the SCC developed within the red portion of a tattoo that had been inflamed for 10 years. In 2 recently described cases,4 SCCs developed within the black portions of the tattoos 10 months in the one case, and 10 years in the other, after tattoo application. In the present case, KA development was not limited to a particular tattoo color.

Multiple factors have been associated with KA development, including immunosuppression, UV light, genetic predisposition, acute trauma, chemical carcinogenesis, and human papillomavirus infection.5-9 In the present case, the trauma of the tattoo was likely the precipitating factor leading to the eruptive KAs. Other tumors such as melanoma and BCCs take years to develop within a tattoo and probably have a different pathogenesis. These differences in lag times are seen in other forms of trauma such as thermal burns, where KAs develop in weeks,7 whereas the other types of tumors develop over years.8 The mechanism by which trauma stimulates these different types of cutaneous neoplasias is unknown, but cellular hyperplasia and localized immunosuppression are considerations. Indeed, 2 reports describe epidermal hyperplasia occurring within a tattoo,9,10 although in 1 of these,9 a regressing KA was considered.

Finally, it must be noted that in the present case, the occurrence of the eruptive KAs may be coincidental rather than related to the patient's new tattoo, but clearly the chronology of events and the specific location of the four KAs within the new tattoo suggest that the tattoo served as some form of acute trigger.

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ucleopads (KPs) are benign, asymptomatic, well-circumscribed, freely movable, skin-colored, wartlike, solitary or multiple nodules and plaques up to 40 mm in diameter located in the skin overlying the dorsal aspects of the hands and feet. However, any skin site subjected to constant pressure or friction could develop lesions similar to KPs, and in such cases, terms such as heloderma, subcutaneous fibromas, tylositas articuli, and discrete keratodermas are more suitable. No KP differences are found between races, sexes, or age groups. Across all groups, lesions resemble scars, keloids, calluses, clavi, verrucae vulgaris, fibromas, granulomas annulare, gouty tophi, xanthomas, rheumatoid nodules, foreign body reactions, and erythema elevatum diutinum. The diagnosis is clinical. Histopathologic analysis helps to exclude other diagnoses. There are 2 patterns: (1) epidermal, with hyperkeratosis, acanthosis, discrete fibroblast proliferation; and (2) dermal, with marked fibroblast proliferation, thickened collagen fibers, and sometimes hyperkeratosis.

A review of the literature gives us a KP classification system summarized as follows: Primary KPs are seen in children and young adults, can be idiopathic or sporadic, not associated with other conditions or inherited in a familial (autosomal dominant) pattern, associated with palmar plantar keratoderma (with or without ichthyosis vulgaris), acrokeratolastoidosis costa, keratoderma hereditaria mutilans, and pseudoxanthoma elasticum. The association of KPs, mixed sensorineural and conductive deafness, and leukonychia is known as Bart-Pumphrey syndrome. In older patients, KPs are associated with fibrosing conditions such as Dupuytren contracture, Ledderhose disease, and Peyronie disease.

Secondary (acquired) KPs, also known as pseudo-KPs, are seen in (1) patients with obsessive-compulsive disorder who apply repeated friction, trauma, or pressure and produce “chewing pads” or “cuticles,” (2) bulimic patients who traumatize their fingers as an adverse effect of inducing emesis; (3) patients in certain professions, such as plumbers, carpet layers, mechanics, tailors, textile workers, plasterers, and live-chicken hangers; and (4) patients involved in sports or athletic activities, such as football players, surfers (surfer nodules), boxers, and athletes in general (athlete nodules).

Knuckle pads grow progressively and gradually over months or years until reaching full size. Eventual disappearance, indefinite persistence, spontaneous decrease in size without disappearance, subsidence after discontinuation of occupation, and subsidence of surfer nodules when surfing season ends have been reported. Several medical and surgical treatments have been reported, usually performed for cosmetic reasons or to relieve discomfort, and they have achieved limited success. No response was achieved with the application of salicylic acid gel under occlusion for 3 months or fluocinolone acetonide cream, 0.025%, twice daily for 2 months. However, use of urea lotion, 25%, for 1 month resulted in softening and flattening of the lesions. Some reduction in size was achieved with intralesional corticosteroids, although this treatment is very painful and inappropriate for younger children. Size reduction was also seen with solid carbon dioxide treatment, but once again, great discomfort is an adverse effect, causing unwillingness on the part of the patient to repeat it. Occlusive dressings with silicone gel have shown improvements in hypertrophic scars and keloids.

Simple excision and excision with skin grafting can be effective but should be done with dermofasciectomy to prevent recurrences. Scarring and keloids have been reported after surgery. Another report showed excellent healing and cosmetic and functional results with no recurrences 9 months after simple excision.

The best response has been obtained in posttraumatic KPs by behavior modification. Avoiding the source of the trauma, changing the sport or occupation, and psychiatric consultation have resulted in great improvement.

**Report of Cases.** Case 1. A 27-year-old woman, Fitzpatrick skin type III, presented with traumatic (shoe-related) KPs on the fourth and fifth proximal interphalangeal joints of both feet (Figure 1A). She was treated with intralesional fluorouracil in a concentration of 50 mg/mL (0.9 mL of fluorouracil with 0.1 mL of triamcinolone acetonide [Kenalog; Bristol-Meyers Squibb, Princeton, New Jersey] at 10 mg/mL). At 9 months after 1 treatment, she showed almost complete remission of the lesions, no sign of relapse, and no adverse effects (Figure 1B).

Case 2. A 23-year-old man, Fitzpatrick skin type IV, presented with traumatic (occupational-related) KPs on his third, fourth, and fifth metacarpophalangeal joints of both hands (Figure 2A). He was treated with fluorouracil. At 2 months after 1 treatment, he showed almost complete remission with no relapses and no adverse effects (Figure 2B).

**Comment.** Fluorouracil is an antimetabolite drug (pyrimidine analogue) that inhibits fibroblast proliferation in vitro and in vivo. Its efficacy and safety have been described many times as a monotherapy or in combination with other drugs for the treatment of keloids and hypertrophic scars and for adverse foreign body reaction and sarcoidal granulomatous complications caused by soft tissue fillers.

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Knuckle pads are the result of fibroblast proliferation or at least develop some degree of it. We treated our patients based on this premise. To our knowledge, this is the first time fluorouracil has been reported as a treatment for KP.

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**Figure 1.** Knuckle pads on the dorsal aspect of the left foot. A, Pretreatment. B, Nine months after 1 treatment with intralesional fluorouracil.

**Figure 2.** Knuckle pads on the dorsal aspect of the left hand. A, Pretreatment. B, Two months after 1 treatment with intralesional fluorouracil.
Perioral Dermatitis Associated With an Inhaled Corticosteroid

Perioral dermatitis is a papulopustular eruption involving the nasolabial folds, chin, and perioral region, sparing the vermillion border. Proposed causes include infectious agents, hormonal factors, topical corticosteroids, inhaled corticosteroids, and personal care products. Herein, we report perioral dermatitis in a woman with asthma coinciding with the inadvertent perioral contact of fluticasone powder from a steroid inhaler. To our knowledge, this is the first report of perioral dermatitis caused by a steroid inhaler in an adult.

Report of a Case. A 39-year-old woman developed a pruritic rash on the chin 2 months after initiating treatment with a fluticasone/salmeterol inhaler. Following mouth rinsing after inhalation to prevent oral thrush, dried medication residue remained on the chin region. Medical history was significant for asthma, seasonal allergies, and childhood eczema.

An acneiform rash with background erythema and scaling was present in a perioral distribution (Figure), consistent with perioral dermatitis. The patient was advised to (1) minimize inhaled steroid powder contact with the skin and (2) wash the perioral region with mild soap and water after each dose. Treatment was initiated with 100 mg/d of oral doxycycline hyclate and topical 1% clindamycin hydrochloride lotion. Within 2 months, the condition had completely cleared.

Comment. The association of topical corticosteroids and perioral dermatitis has been well documented. In addition, Held et al and Dubus et al described the development of perioral dermatitis in children with asthma following use of inhaled corticosteroid. The latter study was a prospective, cross-sectional, multicenter study of 639 children with asthma treated with either inhaled beclomethasone dipropionate or budesonide. They found that the inhaler or nebulizer combined with the spacer and face mask increased the deposition and direct local effects of corticosteroid on perioral skin, thereby causing perioral dermatitis. The present case is a classic case of perioral dermatitis associated with a novel method of corticosteroid exposure. It appears that the cutaneous exposure to the corticosteroid occurred following oral rinsing to prevent candidiasis. Dermatologists can expect to see such cases because asthma is a common illness and is frequently treated with inhaled steroids.

The patient's history of seasonal allergies, asthma, and eczema suggested that this case of perioral dermatitis might be associated with atopy as proposed previously. Dirschka et al explored features of atopy and skin barrier function in perioral dermatitis and rosacea. Patients with perioral dermatitis had significantly greater clinical signs for atopic diathesis and higher specific IgE levels against aeroallergens than both the rosacea and control groups. Transepidermal water loss was increased in the perioral dermatitis group along with an impairment of epidermal barrier function. Though atopic eczema may be a contributing factor, the onset of this process, location at the site of the steroid powder residue, clearing with antibiotic therapy, and lack of recurrence all point to topical corticosteroids as a primary cause.

In summary, physicians must be vigilant in counseling patients to properly use steroid inhalers to optimize drug delivery while minimizing adverse events. In addition to oral rinsing after each steroid inhalant dose to prevent thrush, washing the perioral area with mild soap and water may serve to minimize perioral dermatitis.

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Bleomycin-Induced "Flagellate Dermatitis"

Report of a Case. A 45-year-old woman with stage IA nodular sclerosing Hodgkin lymphoma began a regimen of doxorubicin, bleomycin, vinblastine, and dacarbazine chemotherapy. Seventy-two hours later, she developed intensely itchy, erythematous, linear lesions affecting the arms, back, neck, occipital scalp, and hands. She was prescribed clobetasone propionate ointment, 0.05%, twice daily (Dermovate; GlaxoSmithKline, Brentford, Middlesex, England) because the pruritic eruption was suggestive clinically of a lichenoid dermatitis, and the rash subsided following the completion of the first course of chemotherapy.

Forty-eight hours after commencement of the second course of chemotherapy, the rash recurred in the same sites affected initially and extending to other areas. Examination revealed multiple, erythematous, urticarial, linearly arranged lesions on the shoulders (Figure 1), hands, abdominal wall, and left thigh in addition to erythematous nodules on her fingers. A diagnostic biopsy specimen taken from a lesion on the anterior abdominal wall revealed a moderate, predominantly dermal, perivascular infiltrate consisting of lymphocytes and many eosinophils. Blood vessels displayed reactive endothelial swelling and patchy perivascular hemorrhage. A mild degree of leukocytoclasia was observed. Frequent eosinophils were noted within the interstitial collagen, many with features of degranulation (Figure 2). The appearances were those of a florid inflammatory dermatitis with both urticarial and vasculitic components, the abundant eosinophils being in keeping with a drug-induced cause.

Findings from immunofluorescence studies were negative, and electron microscopy results were unremarkable. The patient had normal creatine kinase levels and tested negative for anti-Jo antibodies and negative or inconclusive for antinuclear antibodies. She was treated with clobetasone propionate ointment, 0.05%, twice daily followed by mometasone furoate ointment, 0.01%, once daily (Elocon; Schering-Plough, Kenilworth, New Jersey), and symptomatic and clinical improvement was noted. Bleomycin was subsequently omitted from her chemotherapy regimen, and the dermatitis gradually subsided, leaving residual postinflammatory hyperpigmentation. Postchemotherapy contrast tomodography scanning revealed complete remission of the lymphoma, and the patient underwent a 2-week course of consolidation radiotherapy.

Comment. Bleomycin, a sulfur-containing antineoplastic polypeptide isolated from a strain of *Streptomyces verticipillus*, is used to treat a variety of malignant neoplasms.1 Bleomycin-induced flagellate dermatitis was described initially by Moulin et al2 in 1970. This eruption, reminiscent of self-inflicted skin lesions of “flagellantes” of medieval times, is known to occur between 1 day and 9 weeks after bleomycin administration, and occurrence of the eruption within 24 hours of rechallenge has been documented.3 A similar eruption has been reported following the use of the bleomycin-derivative peptomycin, in systemic inflammatory disease and adult-onset Still disease, in dermatomyositis, secondary to cutaneous deposits from a breast carcinoma, and following *Lentinus edodes* (shiitake mushroom) ingestion.4 Histologically, flagellate dermatitis is associated with hyperkeratosis, parakeratosis, acanthosis, spongiosis, and dermal sclerosis; ultrastructurally, epidermal hypermelanosisis, enhanced melanocyte activity, and transfer of melanosomes to keratinocytes have been noted.5

![Figure 1. Bleomycin-induced flagellate dermatitis manifesting as multiple, erythematous, indurated, linear lesions on the left shoulder.](image1)

![Figure 2. Histopathologic appearance of flagellate dermatitis. Perivascular cuffing of a small dermal blood vessel, a dilated lymphatic vessel, and many eosinophils in the interstitial space, some showing degranulation (arrow) (hematoxylin-eosin, original magnification ×200).](image2)
Treatment consists of potent topical steroids as well as antihistamines to relieve the intense itch. Postinflammatory melanoderma, as a result of bleomycin-induced increase in local melanogenesis, is a potential complication. We highlight the importance of a detailed drug history in patients presenting with pruritic, digitate rashes, particularly because bleomycin has its applications in the field of dermatology.

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OPTICAL COHERENCE TOMOGRAPHY (OCT) is an emerging technology in dermatology. Translating the principles of ultrasound to use with light waves, OCT captures in vivo images allowing for 3-dimensional reconstruction and Doppler flow measurements. Compared with confocal microscopy, standard OCT has a greater depth of penetration but lower resolution. This places the technology between traditional ultrasound and confocal microscopy in the trade-off between depth penetration and surface resolution (Figure 1). Optical coherence tomography creates an image by splitting an infrared laser into a reference arm and a sample arm (Figure 2). The sample arm scans a designated region of skin, and an interferometer then compares the signal from the skin with a reference arm. Mathematical processing of the differences results in image creation. The depth of penetration and resolution of OCT is determined by the light wavelength and hardware and software processing capabilities. We used a 1310-nm
laser system with a lateral resolution of 20 µm and a penetration depth of approximately 1.8 mm. Given the current improvements in handheld probes and software, OCT images can now be readily captured and viewed in the clinical setting. The photographs in Figures 3A, 4A, and 5A reveal the visible light surface features of a hemangioma, a telangiectasia, and a psoriatic lesion, respectively. With institutional review board approval and patient consent, we also obtained OCT images of these 3 lesions (Figures 3B, 4B, and 5B, respectively). Paired with vessel-rendering software, OCT may be useful in elucidating vessel angiogenesis and patterns in vascular lesions as shown in Figure 4B. Optical coherence tomography has Doppler capabilities, and it has superior sensitivity to ultrasound Doppler. Additionally, it can determine flow in a single vessel. The use of OCT in the clinical setting is increasing. Recent studies showed excellent correlation between the margins of basal cell carcinoma visualized by OCT and standard histopathologic analysis. Optical coherence tomography also successfully visualizes wound reepithelialization in studies. Furthermore, OCT appears useful for investigating the cutaneous penetration of light-scattering contrast agents. Optical coherence tomographic technology is likely to play a significant role in future bedside dermatologic diagnostics.

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Additional Information: Supplemental videos of the OCT images are available at http://www.archdermatol.com and are reproduced with permission from Ms Thomas.