COMMENTS AND OPINIONS

Cytokines May Favor a Role for Human Papillomaviruses in the Pathogenesis of Psoriasis

In the March issue of the ARCHIVES, de Villiers and Ruhland reported that the proinflammatory cytokines interleukin 17 and interferon-γ activate in vitro the promoter of human papillomavirus (HPV) 20, a human papillomavirus associated with epidermodysplasia verruciformis (EV), which may induce replication of this virus. They conclude that EV-HPV infection (eg, HPV-5) does not play an active role in the pathogenesis of psoriasis, but that the virus, present latently in the skin, could become activated by cytokines.

The cytokines are indeed an important stimulus for keratinocyte proliferation, which is a prerequisite for activation of latent HPV infection. It is generally accepted that early (guttate) psoriatic lesions are induced by an influx of proinflammatory cytokines (ie, interferon-γ, interleukin 17, and others) produced by CD4+ lymphocytes activated polyclonally by microbial superantigens. The authors demonstrated in vitro an interesting mechanism of direct stimulation of the EV-HPV promoter by proinflammatory cytokines, and it is quite possible that this mechanism might contribute to activation of the latent infection in vivo. However, a most important factor for HPV activation is keratinocyte proliferation. In psoriasis, keratinocyte proliferation is continuous, and whether self-perpetuation of this phenomenon could be related to the expression of EV HPV in psoriatic epidermis is the matter of debate.

We agree that EV HPVs are not causative factors. However, they could be involved in the pathogenesis of psoriasis in several ways. Early proteins E6 and E7 are known to stimulate keratinocyte proliferation. These proteins and capsid proteins L1 and L2 could be recognized by preactivated CD4+ lymphocytes, which would lead to generation of specific antibodies. On the other hand, viral proteins could play a part in oligoclonal expansion of CD8+ lymphocytes detected in the epidermis of plaque psoriasis, which would suggest a classic pathway of antigen activation. Viral capsid proteins, expressed in the upper layers of psoriatic epidermis, could be a target for specific antibodies. The resulting autoimmune reaction might lead to activation of complement components, chemotraction of polymorphonuclear leukocytes, and formation of Munro abscesses, a most characteristic feature of psoriasis. Thus, EV HPVs, although not a causative agent in psoriasis, could be involved in the pathogenesis of the disease, contributing both to epidermal hyperproliferation and its self-perpetuation and to autoimmune phenomena.

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The Changing Face of Syphilis: From Mimic to Disguise

We read with interest the study of syphilis incognito by Stratigos et al. The authors present interesting data of a changing pattern in the manifestation of syphilis in Greece. We would like to share information based on data collected over a 5-year period at the the sexually transmitted diseases (STDs) clinic of our center.

In India, besides screening patients with STDs for syphilis, we also use the venereal disease research laboratory (VDRL) test to screen pregnant women, under appropriate circumstances. Recently, latent syphilis (early or late) is being diagnosed more frequently than primary, secondary, or tertiary forms. Among 266 patients attending our STDs clinic, 40 had syphilis, an incidence of 15.04%. Among these 40 patients, 27 (67.5%) had latent syphilis, most (16 [39.3%]) of unknown duration and all diagnosed only at prenatal screening. Most of these women’s sexual partners were also infected.
None of the patients recalled any signs or symptoms of syphilis such as genital ulcers, rash, or lymph node enlargement at any time during the last 5 to 10 years. The findings of their clinical examination were normal, and they had no stigmata of past infection. The only evidence was a reactive VDRL finding (titers 1:2 to 1:128), subsequently confirmed with the Treponema pallidum hemagglutination test. Of the 27 patients with latent syphilis, 18 (66.7%) had titers of 1:8 or lower.

Many of these cases of syphilis may not be diagnosed because they are rendered noninfectious by the so-called “happenstance treatment” of syphilis with antibiotics taken for unrelated concomitant illnesses. In India, self-medication with drugs, including antibiotics, which are available without prescription, is a common phenomenon. Since these antibiotics are usually taken for only 5 to 7 days, the syphilis is not treated completely. Most of the currently used antibacterial drugs have some treponemical activity, with the possible exception of co-trimoxazole, gentamicin, and rifampin.

We believe that patients with latent syphilis and very low VDRL titers may not have an active syphilitic infection and may be noninfectious; the seropositive findings are probably due to partially treated self-resolved infection. Stratigos et al also observed a very high percentage (78.1%) of patients with low VDRL titers ranging from 1:2 to 1:8. Such patients are designated as serofast and, together with those patients with low T pallidum hemagglutination titers, may constitute the bulk of the so-called latent syphilitic or syphilis incognito population. Unfortunately, there is no way to detect these noninfectious and VDRL-reactive patients at the time of presentation. A presumptive treatment is of paramount importance in these patients, especially in women of reproductive age, to decrease the risk of vertical transmission of syphilis. Interestingly, with a widespread use of antibiotics that can mask the incubating disease, syphilis, once a great mimic of its time, is now undergoing a metamorphosis to an incognito form under the disguise of latency.

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tient’s total CD19+ (B-cell) subset. The results of this assay revealed a total B-cell deficiency, with a circulating total B-cell subset of 6% (reference range, 7%-23%). The patient was treated with 4 million units of penicillin G intravenously every 4 hours for 14 days. At 6-month follow-up, the lesions had completely resolved.

Comment. The clinical characteristics of syphilis may be altered among patients with HIV infection. For example, HIV-infected patients with syphilis are more likely to present with secondary syphilis, and those with secondary syphilis are more likely to have persistent chancres. Rarely, fulminant presentation, rapid progression, and treatment failures have also been reported. Our patient not only failed to develop nontreponemal antibodies, but also did not respond to antibiotic treatment with multiple doses of benzathine penicillin for secondary syphilis. Only after receiving a prolonged course of intravenous antibiotics did her skin lesions resolve.

This apparent treatment failure agrees with some but not all previous reports and suggests that the phenomenon of treatment failure may depend in part on the degree of HIV-related immunosuppression at the time of contact with Treponema pallidum. Our patient had a total B-cell subset deficiency, suggesting that her inability to express an adequate humoral response may have been due in part to low levels of circulating B cells. In this instance, the positive findings from Warthin-Starry stain, the characteristic histopathologic findings from the biopsies, and the complete response to intravenous penicillin therapy establish syphilis as the cause of the skin lesions.

This case underscores the need to maintain a high degree of suspicion for syphilis when caring for persons with HIV infection. Biopsies of skin lesions in HIV-infected persons should be done early if serologic tests are nondiagnostic to rule out this treatable cause of morbidity and mortality.

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The Handheld Dermatoscope Improves the Recognition of Wickham Striae and Capillaries in Lichen Planus Lesions

The surface of lichen planus lesions may show white lines in a variable configuration (Wickham striae). These are characteristic but not apparent in many patients. Their recognition has been traditionally improved by painting the lesions with oil. Bringing this old approach up-to-date, we consider it worthwhile to communicate our experience in an atypical patient for whom exploration with a handheld dermatoscope allowed easier recognition of Wickham striae and facilitated the diagnosis of lichen planus. Moreover, it also allowed direct observation of the adjoining microvasculature.

Report of a Case. A 35-year-old man was diagnosed in our department as having psoriasis vulgaris of 2 years’ duration. He had nonpruriginous, sharply demarcated, erythematous plaques covered with silvery scales on his elbows and knees. At one follow-up examination, he presented with new lesions on the flexor surface of forearms and wrists. The lesions were nonscaling, erythematous, violaceous, isolated, flat papules. They had appeared in the last 2 months without any previous drug intake and were diagnosed as psoriasis.

On the next follow-up, the new lesions were pruriginous, more elevated, and violaceous. There were no other lesions on skin or oral mucosa. After painting the lesions with oil, we examined those on the forearm with the handheld dermatoscope (Delta 10; Heine Optotechnik, Munich, Germany) with a fixed magnification ×10 and photographed them with Dermaphot photographic equipment (Heine Optotechnik). Reticular whitish striae could be easily observed on the surface of the lesions. Capillaries were seen surrounding the striae as radial, horizontally oriented red lines or red dots (Figure). A clinical diagnosis of lichen planus was made, this being confirmed by biopsy. The coexisting lesions of psoriasis did not present this dermatoscopic pattern but disclosed uniform rounded dilated red capillaries. Psoriasis was also confirmed histologically.

Comment. The handheld dermatoscope was developed by Braun-Falco in 1990 and renders results similar to more sophisticated instruments (eg, the stereomicroscope) in evaluating pigmented lesions. To the best of our knowledge, there are no previous studies reporting its value in diagnosing lichen planus. A few studies with the stereomicroscope have been done on this disease,2,4 but they were focused on capillary microscopy. Our observations with the handheld dermatoscope agree with the results of those studies, but it is important to emphasize that this device is simpler, lower cost, and generally available in daily office practice, unlike the stereomicroscope. We conclude that the dermatoscope may be of value not only for clinical recognition of Wickham striae of lichen planus, but also for the simultaneous observation of the adjoining vascular structures hidden on clinical examination, especially when lichen coexists with psoriasis, as in this case. This association is thought to be underreported.3 Nevertheless, further studies are necessary to confirm the long-standing statement of Oscar Gilje in 1953: “It seems that the differential diagnosis of lichen planus on the basis of capillary microscopy should not be difficult.”2

The ABCD Rule of Dermatoscopy Does Not Apply to Small Melanocytic Skin Lesions

One of the most relevant diagnostic methods used in dermatoscopy is the ABCD rule (A, asymmetry; B, borders; C, colors; D, differential structures) set forth by Stolz et al.1 Nachbar et al2 demonstrated the reproducibility of the ABCD rule in a prospective study, with 90% specificity and 93% sensitivity in the diagnosis of melanoma. However, 2 recent studies revealed controversial results regarding the validity of the ABCD rule.3,4 To investigate interobserver reliability and diagnostic validity of the ABCD rule in the diagnosis of melanoma, 129 small (≤5-mm) melanocytic skin lesions were evaluated by 6 observers in a retrospective study.

Mean total dermatoscopic score (TDS) of 129 small melanocytic skin lesions, as determined by each of the 6 observers. Error bars indicate SD; numbers in parentheses, the observer number; and P values, the significance of the difference between the mean TDS values of benign lesions and the mean TDS values of melanomas for each observer (1, H.P.S.; 2, M.A.P.; 3, G.P.; 4, D.P.; 5, G.A.; and 6, T.B.; Wilcoxon test).

**Patients, Materials, and Methods.** The sample collection consisted of 129 small melanocytic skin lesions (median size, 4.0 mm; range, 1.2-5.0 mm) found in 123 patients (46 men, 83 women) who were seen at the National Cancer Institute, Aviano, Italy, between April 1996 and September 1998. Selection criteria were based on small dimension of the lesion (≤5 mm) and presence of an equivocal dermatoscopic diagnosis. A single pathologist (A.C.) made the histopathologic diagnoses of all specimens, finding either melanoma (5 cases) or benign melanocytic nevus (124 cases). Five of the melanocytic nevi were further specified as Spitz-Reed nevus.

Dermatoscopic images obtained during routine patient care were examined independently by 6 observers using the ABCD rule to calculate the total dermatoscopic score (TDS). All observers were blinded to the diagnosis.

Using the diagnosis of the senior observer (H.P.S.) as the standard, we used the \( \kappa \) test to determine interobserver agreement as follows: unsatisfactory (<=0.20); barely sufficient (0.21-0.40); moderately good (0.41-0.60); good (0.61-0.80); and excellent (>0.80). A nonparametric test (Wilcoxon test) was used to compare median scores between 2 observers. Results were considered statistically significant when \( P \leq 0.05 \) (2-tailed).

**Results.** The Table gives the \( \kappa \) results (interobserver agreement) for the 6 observers. For each of the ABCD criteria, the median values for \( \kappa \) and for TDS emerged as “barely sufficient.” Comparison of the mean TDS values of benign lesions to the mean TDS values of melanomas (Figure) showed a significant difference in only 1 observer.

**Comment.** In our study of small melanocytic skin lesions, the \( \kappa \) values of agreement for all individual dermatoscopic criteria of the ABCD rule were either barely sufficient or only moderately good. The low to moderate interobserver reliability might be regarded as a serious methodological drawback of the ABCD rule; however, the results may have been skewed by the small number of melanomas (5 [4%] of 129) in the sample collection. Comparable data on interobserver reliability of the individual ABCD criteria have not been published even for larger melanocytic skin lesions.

The ABCD rule does not seem useful in managing small melanocytic skin lesions. The question remains whether small melanocytic skin lesions that are histologically negative and have a TDS of 5.45 or greater are true negatives and constitute a limit of the ABCD rule. For small melanocytic skin lesions, however, the histopathologic criteria for the diagnosis of melanoma are not well established and may also be subject to critical interpretation.

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Blood dyscrasias include a variety of malignant and premalignant conditions of blood or bone marrow such as leukemias, myelodysplasia, and myeloproliferative disorders. These disorders are associated with a broad range of cutaneous findings, ranging from recurrent cutaneous infections to malignant cell invasion. However, these eruptions are not associated with tissue eosinophilia, as seen in immunobullous diseases, parasitic infections, drug reactions, and cutaneous T-cell lymphoma. We describe 4 patients with blood dyscrasias who presented with a persistent, erythematous, papulonodular eruption characterized by dermal lymphocytic and eosinophilic infiltrates. As our patients share many features with patients described elsewhere,1–7 we have named this unique eruption eosinophilic dermatosis of myeloproliferative disease.

Report of Cases. The histories and clinical courses of our patients are summarized in Table 1. All were men, with hematologic disorders and a persistent, pruritic, papulonodular dermatosis characterized by prominent dermal eosinophilia. None of them reported an associated drug exposure, insect bite, parasitic infection, or collagen-vascular disease. On examination, the cutaneous lesions were erythematous papules and nodules distributed on the face, scalp, torso, extremities, and buttocks (Figure 1). No vesicles or bullae were present. In 2 cases, the eruption developed before the hematologic neoplasm was diagnosed; in 1 case, the eruption developed after the initiation of chemotherapy for chronic lymphocytic leukemia. In general, the lesions and associated pruritus were difficult to treat, being recalcitrant to numerous therapies. Two patients experienced complete clearing after systemic chemotherapy for leukemia, with prompt reappearance of the papulonodular eruption on discontinuation of the chemotherapy. In these 2 patients, chemotherapy was later reinstituted specifically to control the skin eruption. Recently, 2 patients have responded to narrowband UV-B phototherapy.

Skin biopsy specimens were obtained from each patient (1–6 per patient). Fifteen specimens were blindly reviewed by a dermatopathologist (M.L.C.) to evaluate qualitatively the extent and nature of the infiltrates. All specimens showed a superficial and deep lymphohistiocytic infiltrate that was perivascular in 15 (100%), perifollicular in 10 (67%), and periadnexal in 14 (93%). Diffuse dermal eosinophilia was noted in all specimens (Figure 2).

Comment. The differential diagnosis of the eosinophilic dermatosis seen in our 4 patients includes leukemia cutis and various reactive dermatoses. The most similar reactive process is eosinophilic pustular folliculitis, which has been associated with human immunodeficiency vi-

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**Table 1. Clinical Data on Index Cases of Eosinophilic Dermatosis of Myeloproliferative Disease**

<table>
<thead>
<tr>
<th>Age, y</th>
<th>Diagnosis/Treatment</th>
<th>Onset</th>
<th>Location/Morphologic Findings</th>
<th>Pathological Findings</th>
<th>Course of Pruritic Eruption</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>71</td>
<td>CLL (B cell)/ chemotherapy</td>
<td>8 y after CLL diagnosis</td>
<td>Face and scalp/erythematous nodules</td>
<td>Perivascular and periadnexal lymphocytic infiltrate with numerous eosinophils</td>
<td>Improved after chemotherapy; no response to topical or systemic steroids, antibiotics, antifungals, isotretinoin, or colchicine</td>
<td>Died of sepsis</td>
</tr>
<tr>
<td>53</td>
<td>CLL (B cell)/ chemotherapy</td>
<td>After first chemotherapy</td>
<td>Face, scalp, and torso/erythematous nodules</td>
<td>Perivascular and periadnexal lymphocytic infiltrate with numerous eosinophils</td>
<td>Improved after NBUVB; no response to antihistamines, topical steroids, or colchicine</td>
<td>Alive with active disease</td>
</tr>
<tr>
<td>81</td>
<td>AML/chemotherapy</td>
<td>2 y before diagnosis of AML</td>
<td>Trunk, buttock, and extremities/erythematous nodules</td>
<td>Perivascular and periadnexal lymphocytic infiltrate with numerous eosinophils</td>
<td>Improved after chemotherapy</td>
<td>Died of AML</td>
</tr>
<tr>
<td>71</td>
<td>MDS anemia with excess blasts/triple</td>
<td>Several months before diagnosis of MDS</td>
<td>Scalp and extremities/erythematous and hemorrhagic papules</td>
<td>Perivascular lymphocytic infiltrate with numerous eosinophils</td>
<td>Improved after NBUVB; no response to steroids, cyclosporine, hydroxyurea, or hydroxychloroquine sulfate</td>
<td>Alive with active disease</td>
</tr>
</tbody>
</table>

* CLL indicates chronic lymphocytic leukemia; AML, acute myeloid leukemia; MDS, myelodysplastic syndrome; and NBUVB, narrowband UV-B. 

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rus, myelodysplastic syndrome, bone marrow transplantation, leukemia, and lymphoma. However, the characteristic lesions of eosinophilic pustular folliculitis are follicular pustules and erythematous papules, differing morphologically from the lesions in our patients. In addition, most patients with eosinophilic pustular folliculitis experience spontaneous relapse, and although no definitive therapy has been established, numerous modalities have been reported as effective.

Wells syndrome has also been reported in association with myelodysplastic disorders. This disease remits spontaneously. At clinical presentation, large, edematous plaques and characteristic flame figures are seen on histopathologic examination.

Arthropod bites and stings are associated with tissue and peripheral eosinophilia, and exaggerated responses to insect bites have been recognized in association with hematologic malignancies (Table 2). For unknown reasons, some patients with hematologic disorders appear to have an abnormal cutaneous response that manifests in 2 distinct clinical presentations. The first is seen in patients with a history of antecedent insect bite(s), who exhibit an exaggerated response to insect antigen and follow an acute course with rapid resolution (2-14 days) requiring minimal therapy. The second presentation, resembling that of our patients, follows a chronic course that is resistant to

![Figure 1. Erythematous, discrete papules on left cheek and neck in patient 1.](image1)

![Figure 2. Biopsy specimen from patient 1 showing the eosinophil-rich perivascular and interstitial lymphohistiocytic infiltrate (hematoxylin-eosin, original magnification ×20).](image2)

<table>
<thead>
<tr>
<th>Reference</th>
<th>No. of Patients With Known Insect Bite</th>
<th>Associated Hematologic Condition</th>
<th>Descriptive Terms</th>
<th>Course</th>
<th>Response to Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weed5</td>
<td>8/8</td>
<td>CLL (8/8)</td>
<td>Exaggerated, delayed hypersensitivity to mosquito bites</td>
<td>Spontaneous resolution, 2-14 d</td>
<td>NA</td>
</tr>
<tr>
<td>Houston and Keene7</td>
<td>1/1</td>
<td>Non-Hodgkin lymphoma</td>
<td>Exaggerated, delayed hypersensitivity to mosquito venom</td>
<td>Spontaneous resolution, 2-3 wk</td>
<td>NA</td>
</tr>
<tr>
<td>Kolbusz et al6</td>
<td>1/1</td>
<td>CLL</td>
<td>Exaggerated response to insect bites</td>
<td>Resolution, 10 d</td>
<td>NA</td>
</tr>
<tr>
<td>Rosen et al3</td>
<td>0/10</td>
<td>CLL (10/10)</td>
<td>Characteristic vesiculobullous eruption</td>
<td>Intermittent and recurrent</td>
<td>NA</td>
</tr>
<tr>
<td>Pedersen et al2</td>
<td>1/3</td>
<td>CLL (3/3)</td>
<td>Exaggerated response to insect bites</td>
<td>Persistent and recurrent</td>
<td>Partial response to chemotherapy and systemic steroids</td>
</tr>
<tr>
<td>Davis et al1</td>
<td>2/8</td>
<td>CLL (8/8)</td>
<td>Exaggerated arthropod-bite lesions</td>
<td>Persistent and recurrent</td>
<td>Partial response to chemotherapy and systemic steroids</td>
</tr>
<tr>
<td>Barzilai et al4</td>
<td>0/8</td>
<td>CLL (3/8), ALL (1/8), myelofibrosis (1/8), mantle cell lymphoma (1/8), AMOL (1/8)</td>
<td>Insect bite–like reaction</td>
<td>Persistent and recurrent</td>
<td>Partial response to chemotherapy and systemic steroids</td>
</tr>
</tbody>
</table>

*AMOL indicates acute monocytic leukemia; NA, not available. Other abbreviations are given in the footnote to Table 1.
conservative treatment. In these patients, history of insect bite can rarely be elicited (Table 2).

We have chosen to call this latter syndrome eosinophilic dermatosis of myeloproliferative disease. This term best encompasses the clinical and histopathologic findings in our patients and those reported by others.\(^1,7\) We propose the following criteria for the diagnosis: (1) pruritic papules, nodules, and/or vesiculobullous eruption resistant to conservative treatment; (2) eosinophil-rich dermal lymphohistiocytic infiltrate (superficial and deep) on histopathologic examination; (3) exclusion of other causes of tissue eosinophilia, including immunobullous diseases, parasitic infections, known insect bite, or drug reactions; and (4) preexisting diagnosis of a hematologic malignancy or dyscrasia or its subsequent development.

Although the pathogenesis of this unique eruption remains unknown, no evidence of clonal T-cell proliferation was noted in our patients’ tissue samples. Reactive T cells might produce higher levels of interleukin 5, stimulating tissue eosinophilia and subsequent pruritus. This would be consistent with the suggestions of Davis et al\(^2\) and the findings of Simon et al,\(^9\) where idiopathic eosinophilia was associated with pruritic skin lesions in a few patients.

In summary, we present 4 cases and a review of related reports that suggest the existence of a unique syndrome. We propose the name eosinophilic dermatosis of myeloproliferative disease for these therapeutically resistant, pruritic papulonodules occurring in patients with blood dyscrasias. Diagnostic criteria, including the specific exclusion of other eosinophilic processes, are also proposed. This syndrome is important to identify in patients with hematologic neoplasia, as it may be the principle symptom complex that leads to chemotherapeutic intervention. Also encouraging is improvement after narrowband UV-B phototherapy, which should be considered as a therapeutic option in these patients.

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**Correction**

Error in Dose Calculation. In the Vignette titled “Single-Dose and Steady-State Administration of Hypericum perforatum Extract (St John’s Wort) Does Not Influence Skin Sensitivity to UV Radiation, Visible Light, and Solar-Simulated Radiation,” published in the April issue of the ARCHIVES (2001;137:512-513), an error was made in dose calculation. Each LI 160 tablet contained 900 µg of hypericins, and so the correct dose, as detailed on page 512, should have been “6 tablets (5400 µg).”