

# Mimics of Cutaneous Lymphoma

## Report of the 2011 Society for Hematopathology/European Association for Haematopathology Workshop

George P. Sarantopoulos, MD,<sup>1</sup> Beth Palla, MD,<sup>1</sup> Jonathan Said, MD,<sup>1</sup> Marsha C. Kinney, MD,<sup>2</sup> Steven M. Swerdlow, MD,<sup>3</sup> Rein Willemze, MD, PhD,<sup>4</sup> and Scott W. Binder, MD<sup>1</sup>

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Upon completion of this activity you will be able to:

- identify benign mimics of lymphoma in skin.
- understand key histopathologic findings of benign lymphoma mimics in skin.
- understand what ancillary studies are used in the diagnosis of skin lymphohistiocytic proliferations.

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### Abstract

*The Society for Hematopathology and European Association for Haematopathology workshop, from October 27 to 29, 2011, in Los Angeles, CA, exhibited many exemplary skin biopsy specimens with interesting inflammatory changes mimicking features of cutaneous lymphoma. This article reviews features observed in cutaneous lymphoid hyperplasia, cutaneous drug reactions, lupus-associated panniculitis, pityriasis lichenoides, hypereosinophilic syndrome, histiocytic necrotizing lymphadenitis, traumatic ulcerative granuloma with stromal eosinophils, and pigmented purpuric dermatosis, as well as a brief review of the pertinent literature and discussion of submitted conference cases. For the pathologist, it is important to be aware of diagnostic pitfalls as well as the limitations of ancillary testing (eg, clonality studies). Finally, correlation with total clinical information, good communication with clinical colleagues, close clinical follow-up with rebiopsy, and prudent use of laboratory studies are vital and will likely offer the best path toward a correct diagnosis.*

The Society for Hematopathology and European Association for Hematopathology (SH/EAHP) Workshop convened at the Ritz-Carlton Hotel, Marina del Rey, CA, from October 27 to 29, 2011, and featured world-renowned experts in the fields of hematopathology, dermatopathology, and dermatology. Attendees were encouraged to submit difficult or interesting cases, of which 200 cases were selected by the expert panel and presented at the meeting. Cases submitted were of the following types: cutaneous B-cell lymphomas, mycosis fungoides (MF), nonmycosis fungoides, cutaneous T-cell lymphomas, other lymphohistiocytic malignancies of the skin, and reactive lymphoproliferations of the skin mimicking cutaneous lymphomas (as discussed in this article).


Although still relatively rare, skin is second only in frequency to the gastrointestinal tract as the most common extranodal non-Hodgkin primary lymphoma site.<sup>1,2</sup> There exists considerable histopathologic overlap between the features of B-cell and T-cell lymphoma and many of the inflammatory dermatoses. Therefore, distinguishing “reactive” histologic patterns from those of lymphoma is often very difficult. This article discusses several of the important mimics of cutaneous lymphoma as observed and highlighted within the 2011 SH/EAHP Workshop, their possible causes, and distinguishing clinical and histopathologic features, as well as submitted cases and a brief review of the current literature.

### Cutaneous Lymphoid Hyperplasia

Cutaneous lymphoid hyperplasia (CLH; aka lymphocytoma cutis, lymphadenoma benign cutis, and

pseudolymphoma) is most commonly assigned to those cases lacking a sufficient array of accepted malignant findings.<sup>3</sup> CLH is believed to be the result of some often unknown, outward cause (eg, tattoo, vaccination, arthropod bite/sting, drug, or infection).<sup>4,5</sup> Of note, 1 submitted workshop case showed the finding of reactive lymphoid hyperplasia following treatment with leeches (hirudotherapy)—a very uncommon but nonetheless reported phenomenon.<sup>6</sup>

Clinically, cases of CLH typically exhibit a range of findings that may mimic those seen in cutaneous lymphoma. Cases may present as nodules, plaques, or papules and are most often identified on the head, neck, trunk, and extremities.<sup>7</sup> Indeed, submitted cases labeled as CLH, reactive lymphoid hyperplasia, or atypical lymphoid proliferation by the expert panel revealed a similar body distribution, with the majority of cases identified in 1 or 2 body sites, including head and neck, extremities, and trunk. One submitted case showed lesions in all 3 regions. As expected, a range of clinical presentations was reported, including single nodules, plaques, multiple pruritic papules, or a rash-like presentation. Of note, 2 cases submitted as likely “reactive” lymphoid infiltrates, but subsequently labeled malignant by the expert panel, were described as more deep-seated masslike lesions at initial presentation.

Histologically, CLH is typically described as lymphocyte predominant (both B and T cells) with a nodular or diffuse pattern within the dermis, often with accompanying conspicuous inflammatory cells (including histiocytes, eosinophils, and plasma cells).<sup>7</sup> Additional features include an obvious grenz zone separating uninvolved epidermis from underlying inflammation, lymphoid follicles with or without a well-formed mantle zone, associated tingible-body macrophages, a wedge shape to the inflammatory infiltrate, sharp circumscription of lymphoid aggregates, and a “pushing” border.<sup>8</sup> Of note, however, some features classically suggestive of malignancy, including “epidermotropism” of lymphocytes and a more diffuse or “bottom-heavy” infiltrate, may also be observed in some cases of CLH .<sup>8,9</sup>

The majority of submitted workshop cases ultimately labeled as CLH, reactive lymphoid hyperplasia, or atypical lymphoid hyperplasia/proliferation showed many common findings of CLH, including a well-defined inflammatory infiltrate, an obvious grenz zone, and a polymorphous infiltrate. Of note, 1 case submitted as “florid cutaneous lymphoid infiltrate—favor reactive” and subsequently labeled by the expert panel as “primary cutaneous CD4+ small/medium pleomorphic T-cell lymphoma” revealed a combination of “benign” features, including sparing of epidermis and adnexa by a vaguely nodular infiltrate of predominantly small- to medium-sized lymphocytes admixed with conspicuous eosinophils. Similarly, another submitted case initially called “atypical lymphoid hyperplasia” and subsequently labeled by the expert panel as

“cutaneous lymphoid hyperplasia with progression to primary cutaneous follicle center lymphoma” showed a dense but fairly well-delineated lymphoid infiltrate with lymphoid follicles and a well-developed grenz zone, without epidermotropism or observed infiltration of the follicular epithelium. Therefore, changes historically suggestive of benignity may also be seen in cases of low-grade or evolving lymphoid malignancy.<sup>8</sup> Indeed, additional ancillary studies are most often required to arrive at the best diagnosis.

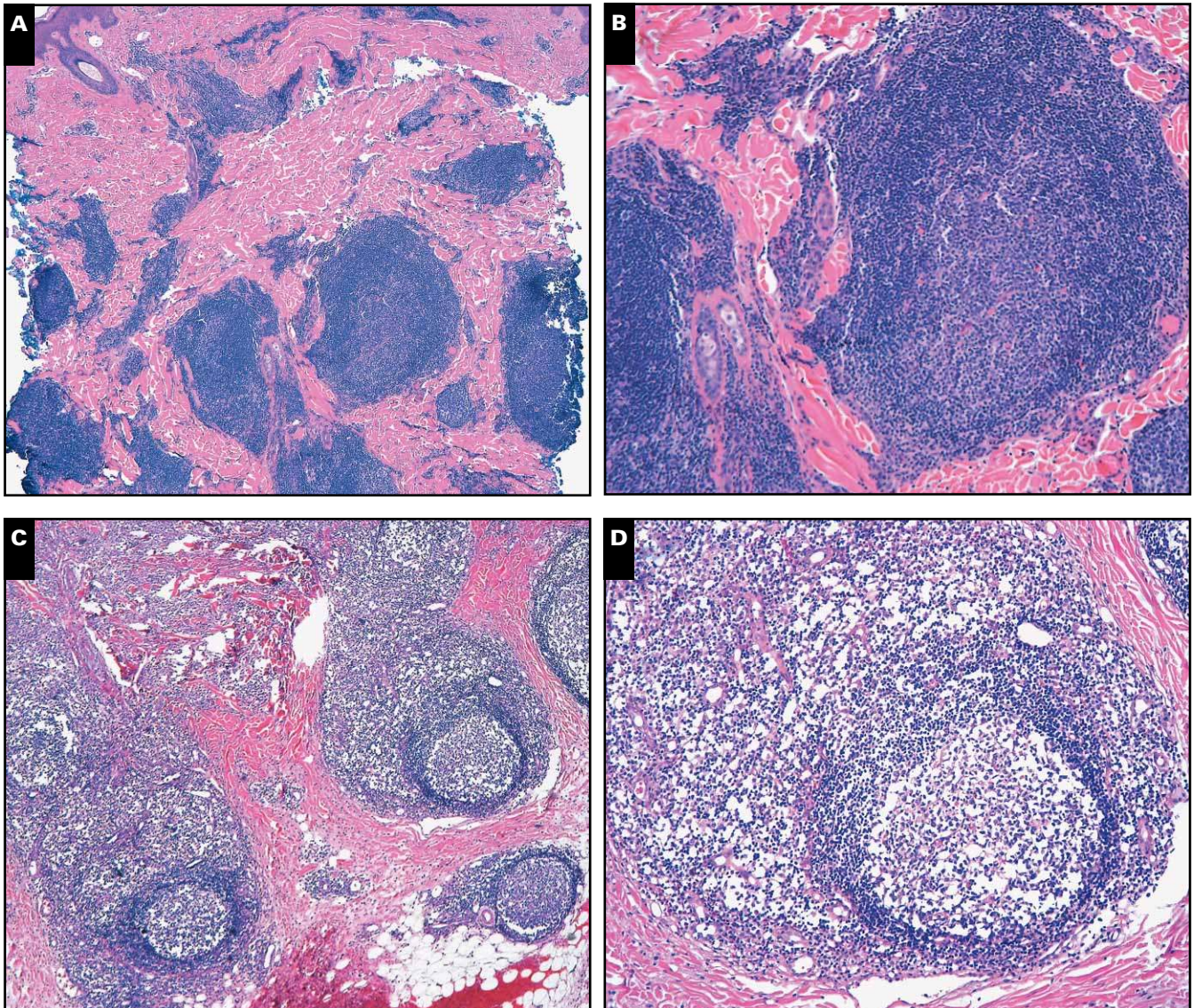
Immunohistochemistry typically reveals a predominance of CD3+ T lymphocytes and a subpopulation of associated CD20+ B lymphocytes. In cases with well-defined germinal centers, expected central zones of CD20+ B cells with surrounding CD3+ T cells are seen.<sup>7</sup> Well-formed germinal centers retain cells with positive staining for BCL6 and CD10.<sup>10</sup> CD68 will highlight associated tingible-body macrophages, and S-100 and/or CD1a will highlight well-dispersed dendritic cells. Associated plasma cells should not exhibit either  $\kappa$  or  $\lambda$  light chain restriction, and coexpression of CD20 and CD43 by constituent B cells is not expected.<sup>9,11</sup> Similarly, coexpression of BCL2 by germinal center cells is not seen.<sup>8</sup> Immunostaining for CD21 to highlight follicular dendritic meshworks in B-cell nodules may be useful in detecting aberrant patterns (eg, colonization or disruption).

Of note, CD7 may exhibit moderate loss despite other features of overall benignity.<sup>11</sup> Submitted workshop cases ultimately labeled as CLH by the expert panel showed similar benign staining patterns to those described earlier. Of note, 1 submitted case showed a somewhat peculiar pattern of predominantly CD8+ T cells on a middle-aged man’s ear for 6 months that simulated CD8+ cutaneous T-cell lymphoma; however, the lesion abated following biopsy without recurrence and was considered a form of rare “indolent CD8-positive lymphoproliferative disorder of the ear.”<sup>12</sup> (Note: this disorder is summarized in “Nonmycosis Fungoides Cutaneous T-Cell Lymphomas,” by Quintanilla-Martinez et al,<sup>13</sup> in this issue of the journal.)

Molecular testing to evaluate lymphocyte clonality has become fairly routine and may offer additional useful information. However, clonality may also be seen in a small subset of CLH cases.<sup>7,10,14</sup> Although not diagnostic of malignancy, demonstration of clonality has been correlated with evolution to lymphoma.<sup>14</sup> Of the submitted cases, most did not undergo molecular analysis or reveal a polyclonal population of constituent lymphocytes. Interestingly, 2 cases submitted initially as “likely reactive” and subsequently labeled as “primary cutaneous CD4+ small/medium pleomorphic T-cell lymphoma” and “CLH with progression to primary follicle center cell lymphoma” showed clonal lymphocyte populations per T-cell gene rearrangement studies.

Submitted cases ultimately labeled by the expert panel as “atypical lymphoid hyperplasia” or “atypical lymphoid





**Image 1** Histologic sections of cutaneous lymphoid hyperplasia typically reveal superficial and deep dermal perivascular and interstitial lymphocytic inflammation, including well-formed lymphoid follicles with germinal centers (**A** and **B**, H&E). (Case 265 courtesy of Gretchen Frieling, MD, Steven Tahan, MD, and Rajan Dewar, MD.) Usually, lymphoid follicles will also retain a well-formed mantle zone (**C** and **D**, H&E). (Case 211, courtesy of Gulsah Kaygusuz, MD, and Isinsu Kuzu, MD.)

proliferation” showed findings suggestive of evolving malignancy, including dense superficial and deep lymphoid infiltrates of small- to intermediate-sized lymphocytes with some atypia, as well as a positive T-cell gene rearrangement in 1 case. However, other supporting features of malignancy, including aberrant immunostaining patterns or systemic findings, were not apparent. In cases of uncertain malignancy, an overall air of caution was advised. In such cases, close clinical follow-up and rebiopsy are typically recommended. Of note, 1 submitted case was thought likely due to the patient’s long-standing phenytoin therapy, a well-known cause of cutaneous drug reactions (further discussion to follow).

### Cutaneous Drug Reactions

Cutaneous drug reactions are some of the most common inflammatory reactions observed in skin, with 10% to 20% of patients seen in the hospital setting and greater than 7% of the community outpatient population affected.<sup>15</sup> Adverse reactions to drugs include a range of clinical manifestations, including photosensitivity, urticarial reactions, morbilliform or diffuse rashes, and even marked erythroderma. Drug reactions may mimic the findings of cutaneous T-cell and B-cell lymphoma both clinically and histopathologically (termed *pseudolymphoma*) and, therefore, careful examination and correlation of all pertinent diagnostic and clinical information are paramount.<sup>16</sup>




The morbilliform or exanthematous type of drug reaction is the most common clinically reported drug-related eruption (>50%).<sup>17-19</sup> More prototypical histopathologic clues include (1) conspicuous eosinophils, (2) associated plasma cells (within some reactions), (3) associated necrotic keratinocytes/dyskeratosis, (4) urticarial-type dermal edema with mast cells, (5) extravasated erythrocytes, and (6) associated “activated” lymphocytes, which may appear cytologically atypical. Importantly, the array of histologic patterns observed with drug reactions is large and may mimic literally any inflammatory dermatosis—for example, pustular, eczematous, vesiculobullous, vasculitic, lichenoid, lymphomatous, and sclerodermoid (as reviewed in Justiniano et al<sup>17</sup> and Ramdial and Naidoo<sup>20</sup>).

One workshop case submitted as a possible drug or transfusion reaction, and subsequently labeled by the expert panel as “reactive CD30+ lymphoid proliferation associated with marrow reconstitution,” showed several key findings typically observed with the morbilliform-type drug reaction, including conspicuous eosinophils and associated, overlying epidermal acanthosis and spongiosis.<sup>21</sup> In fact, polyclonal infiltrates of enlarged CD30+ activated lymphocytes may be seen in a range of inflammatory or reactive conditions, including drug eruptions, arthropod bite reactions, and viral infections.<sup>22,23</sup> The presence of increased numbers of CD30+ lymphocytes should raise suspicion for the possibility of CD30+ lymphoproliferative disease (including the clinically benign variant lymphomatoid papulosis [LyP]). Although discussion of this group of diseases extends somewhat beyond the scope of this review, it is important to note that a diagnosis of LyP is typically accompanied by a fairly characteristic clinical picture of recurrent, regressing papules and nodules, often in crops, that often become necrotic and scar.<sup>24</sup> In addition, use of fascin immunohistochemistry has been shown to be more often positive in CD30 lymphoproliferative disease with a tendency to evolve to lymphoma (LyP type C) vs more indolent forms of the disease (LyP types A and B), which may add additional useful diagnostic information in difficult cases.<sup>25</sup>

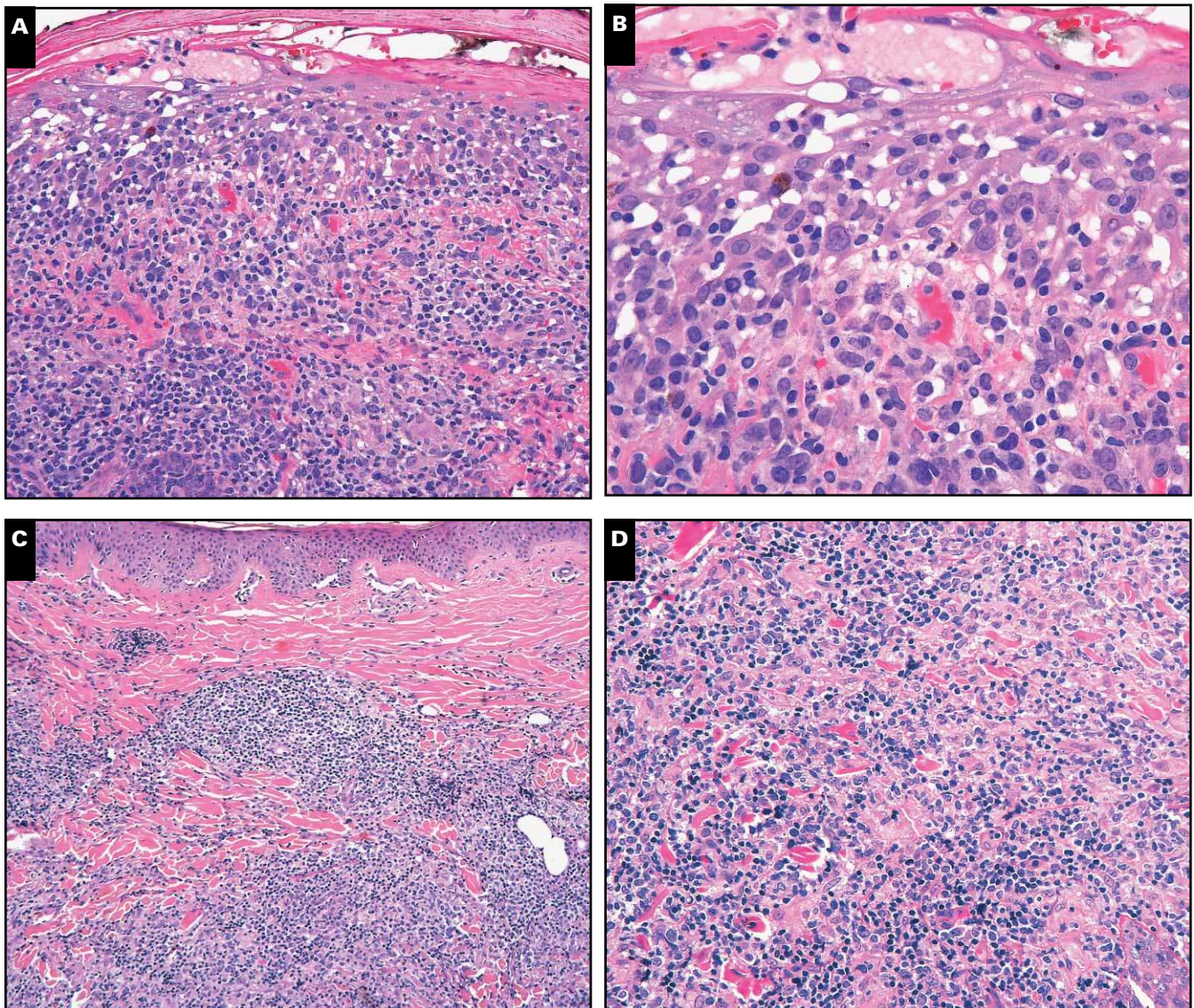
The lichenoid drug eruption, in which a lymphocytic infiltrate is observed within a fairly dense, band-like configuration in superficial dermal tissues and involving overlying epidermis, is common and may raise suspicion for lymphoma. In addition, mild epidermal spongiosis with parakeratosis, exocytosis of lymphocytes, dermal edema, and extravasated erythrocytes may be seen (as reviewed in Justiniano et al<sup>17</sup> and Ramdial and Naidoo<sup>20</sup>). Close examination of the superficial papillary dermis may show incontinent melanin pigment or even melanophages—the result of melanin release from damaged basilar keratinocytes. Associated dermal blood vessels may show perivascular lymphocytic inflammation with intramural lymphocytes and endothelial swelling (so-called lymphocytic vasculitis).<sup>26</sup>

As a result of the many similar histopathologic features, the lichenoid drug eruption is most apt to mimic cutaneous T-cell lymphoma/MF and prompt additional special studies, including immunohistochemistry, which often reveals a T-cell-rich superficial infiltrate. CD4+ T-helper lymphocytes with atypical cytomorphology may be seen within the overlying epidermis and may mimic the epidermotropism characteristic of MF. In addition, the CD4 to CD8 ratio (CD4:CD8) may be elevated, and loss of immunostaining for pan-T-cell marker CD7 may also be seen. To further confound matters, increased numbers of enlarged and activated CD30+ lymphocytes—occasionally in great numbers—may be seen in some cases<sup>27</sup> (and as reviewed in Ploysangam et al<sup>28</sup>).

Conventional wisdom has suggested that benign inflammatory conditions are composed of polyclonal aggregates of “reactive” lymphocytes. However, study in recent years has shown that clonal populations of lymphocytes (both B cell and T cell) may be demonstrated via gene rearrangement studies within cutaneous drug reactions. Debate persists as to whether the finding of clonality is an indicator of evolving lymphoid malignancy or a sort of “reactive lymphomatoid dermatitis,” as postulated by Magro and colleagues.<sup>27</sup> One difficult submitted case showed a dense lichenoid infiltrate with epidermotropism, associated spongiosis, and a somewhat mixed infiltrate (T cell > B cell, with admixed plasma cells and histiocytes), possibly due to an ingested or topical drug administration. The positive T-cell gene rearrangement study in this case, however, is of unknown significance, and the expert panel prudently labeled this lesion as an “atypical lymphoid proliferation” .

Indeed, pseudolymphoma may be caused by administering certain types of drugs, classically antiepileptic drugs such as phenytoin and carbamazepine (as reviewed by Harris et al<sup>29</sup>).<sup>30</sup> Other causative drugs include valproate, atenolol, griseofulvin, imatinib, angiotensin-converting enzyme (ACE) inhibitors, allopurinol, cyclosporine, levofloxacin, antihistamines, and analgesics.<sup>31,32</sup> Antidepressant drugs are especially associated with pseudolymphoma and may mimic B-cell lymphoma. In particular, fluoxetine may be associated with clonal B-cell lymphoid proliferations, and atypical lymphoid hyperplasia may progress to frank marginal zone lymphoma. Fluoxetine and other antidepressants may exert marked immune dysregulating effects, including a reduction in T-cell proliferation. This suppressive effect on T-cell function may lead to overresponsiveness of B cells to unknown antigens, which in turn may foster antigenically responding B-cell clones, possibly a critical event in B-cell lymphomagenesis.<sup>33,34</sup> Interestingly, 2 submitted cases dramatically illustrated a “lymphomatoid reaction” and “benign lymphoid hyperplasia,” most likely secondary to ongoing sertraline (Zoloft) therapy (Image 2). Ultimately, the diagnosis of drug-associated pseudolymphoma is established based on





**Image 2** Drug-related eruptions may show marked interface basal vacuolar degeneration, including intraepidermal lymphocytes mimicking epidermotropism of mycosis fungoides (**A**, H&E). Close examination, however, will typically reveal a more mixed inflammatory infiltrate, with Langerhans cells, eosinophils, and rare neutrophils. In addition, there is lack of cytologic atypia within epidermal lymphocytes (compared with dermal lymphocytes) and random exocytosis rather than lining up along the basal layer (**B**, H&E). (Case 124, courtesy of Jun Wang, MD, and Cassie Booth, MD.) On occasion, drug-related eruptions may show more dermal mixed inflammation, including lymphocytes, conspicuous histiocytes, and scattered enlarged lymphoid cells (**C** and **D**, H&E). (Case 108, courtesy of Karen Moser, MD, Glen Bowen, MD, Anneli Bowen, MD, and Rodney Miles, MD, PhD.)

the resolution of skin lesions with cessation of drug therapy, which may take weeks or even months.<sup>27,31,33</sup>

Finally, an inflammatory disorder may occur with reexposure following prior sensitization to a particular allergen. Rarely, contact dermatitis may simulate MF histologically (so-called lymphomatoid contact dermatitis).<sup>35,36</sup> As these lesions progress, psoriasiform change, often with spongiosis, dermal fibrosis, overlying scale crust, hyperkeratosis, and


parakeratosis, may be seen. Most cases result from contact with chemicals or metals, such as nickel or gold.<sup>37,38</sup> However, numerous offending agents have been reported that may produce lymphomatoid reactions, including such diverse items as resin in treated leather, constituents of ophthalmic preparations, ingredients in baby wipes, emulsifiers in shampoo, teak wood, and the striker portion of matchboxes.<sup>35,39-42</sup> Gene rearrangement studies often reveal a polyclonal population



of lymphocytes; however, rare clonal T-cell gene rearrangements have been reported.<sup>31</sup> Although long thought to be less frequent than irritant contact dermatitis, with use of better clinical studies (including more sensitive patch testing), an increasing prevalence of allergic contact dermatitis has been suggested.<sup>43</sup>

## Lupus-Associated Panniculitis

Lupus-associated panniculitis (LEP) is a rare variant form of lupus erythematosus, which affects predominantly middle-aged female patients (ages 30-60 years). Lesions consist primarily of plaques, typically observed on the upper trunk, face, and buttocks<sup>44</sup> (reviewed by Crowson and Magro<sup>45</sup>). Considerable overlap exists between the clinical presentation and susceptible patient populations of both LEP and subcutaneous panniculitis-like T-cell lymphoma (SPCTL), including the distribution and clinical appearance of lesions.<sup>46,47</sup>

Histopathologically, LEP typically shows a dense lobular infiltrate of lymphocytes, admixed with plasma cells and histiocytes, with thickened adjoining fibrous septa and hyalinized fat necrosis. Although some disagreement persists as to specific criteria used to diagnosis LEP, the findings of lymphocytic nuclear dust within the associated plasmalymphocytic infiltrate of involved fatty lobules, in addition to well-formed lymphoid follicles with germinal centers, are considered by some to be clues for the diagnosis of LEP (as reviewed by Crowson and Magro<sup>45</sup> and Requena and Sanchez Yus<sup>48</sup>). Of note, so-called rimming of adipocytes by lymphocytes—classically known as a distinguishing feature of SPCTL—may also be observed in cases of LEP; however, in contrast to only atypical lymphocytes in cases of SPCTL, Massone et al<sup>47</sup> observed adipocyte “rimming” in cases of LEP by lymphocytes, plasma cells, and histiocytes .<sup>47</sup> However, Crowson and Magro<sup>45</sup> warn that cases of LEP may show significant lymphocyte atypia, making distinction between LEP and SPCTL often very difficult. Associated interface dermatitis (characteristic of lupus) may be seen and offer additional supporting evidence of benignity; however, this finding may be absent in up to 50% of cases.<sup>47,49</sup>

Submitted cases subsequently labeled by the expert panel as consistent with LEP showed a range of findings, including the features of LEP as described above (Image 3). Of note, 1 submitted case showed extension of marked lobular inflammation into surrounding fibrous septa (deemed “mixed lobular and septal panniculitis”), which may be observed in established cases.<sup>47</sup> Similarly, although 1 patient was known to have Epstein-Barr virus (EBV)—positive diffuse large B-cell lymphoma, the expert panel concluded that the somewhat disparate findings observed in the subcutaneous biopsy specimen (including a mixture of T lymphocytes and histiocytes,

rimming of adipocytes by T cells, and virtual absence of associated B cells) were most suggestive of a reactive panniculitis, likely due to the patient’s ongoing EBV infection.

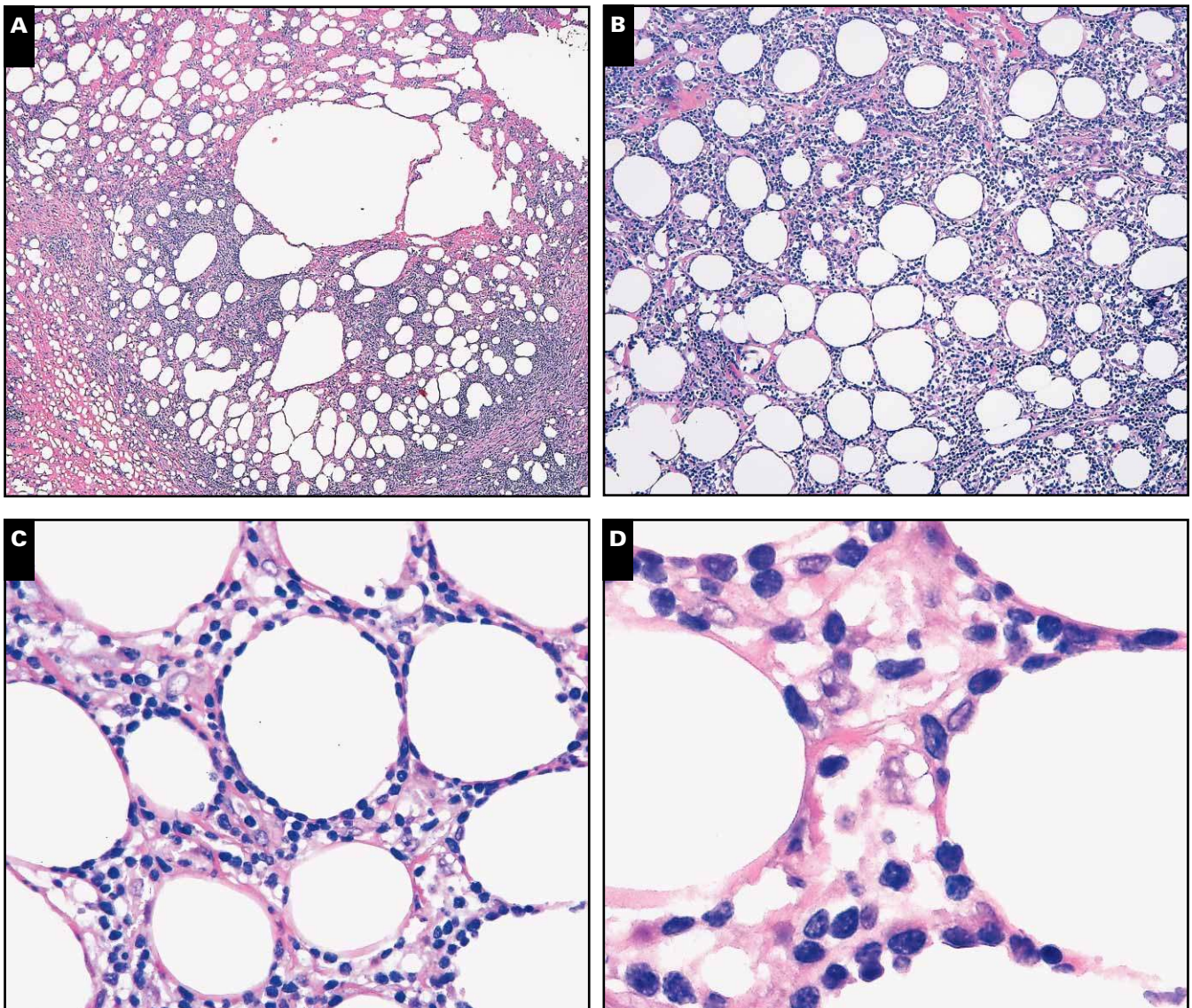
Immunohistochemical analysis is required when attempting to discern LEP from SPCTL. As in SPCTL, lymphocytes observed in LEP are typically CD8+; however, the number and extent of CD8+ T cells seen in LEP are typically not as great as in cases of SPCTL.<sup>47</sup> Staining for pan-T-cell markers CD5 and CD7 is observed and may be somewhat diminished.<sup>44</sup> CD20 will highlight small clusters or scattered B cells.<sup>46,50</sup> Ki-67 (MIB-1) may assess the degree of constituent lymphocyte proliferation, with higher rates (often exceeding >50% of cells) considered additional evidence for lymphoma.<sup>51</sup> Molecular studies may be employed to discern tumor cell clonality; however, LEP cases may exhibit clonal lymphoid populations in a minority of cases, and this result should be interpreted with caution.<sup>44</sup> Submitted workshop cases showed a T-lymphocyte–predominant infiltrate without evidence of clonality. Some cases showed typical CD8-predominant T-cell infiltrates, whereas others showed a CD4+ T-lymphocyte–predominant inflammatory response, perhaps due to the proposed EBV reaction or the mixed nature of the observed, ongoing panniculitis.

Finally, because of the considerable clinical and histopathologic overlap between LEP and SPCTL, studies by Magro and colleagues<sup>44,52</sup> support the notion that a continuum exists between these entities, with “atypical” variants and premalignant dyscrasias. In fact, a growing number of reported cases closely mimicking LEP, but ultimately demonstrating a malignant course, further highlight the likelihood of this proposition.<sup>51,53</sup> With that said, it is important to note that the coexistence of SPCTL and LEP has been reported as well.<sup>54</sup>

## Pityriasis Lichenoides

Pityriasis lichenoides (PL) is an uncommon, self-limited dermatosis of disputed histogenesis with a spectrum of clinical and histopathologic findings. Pityriasis lichenoides et varioliformis acuta (PLEVA) is an acute disorder with characteristic hemorrhagic papules that resolve to leave variably shaped scars. Pityriasis lichenoides chronica (PLC) is a subacute or chronic disorder characterized by small, scaly, red-brown maculopapules (as reviewed by Fernandes et al<sup>55</sup>). The distinction between PLEVA and PLC is not always clear-cut, and a continuum of findings with some degree of overlap is often observed.

PL exhibits a predilection for male patients in the second and third decades of life (although cases in children may also be seen). Crops of lesions, which vary in number, are most commonly identified on the trunk and/or flexor surfaces of the proximal extremities. The duration of disease is



**Image 3** Histologic sections of lupus-associated panniculitis reveal subcutaneous fibroadipose tissue with a dense lobular infiltrate of lymphocytes (**A** and **B**, H&E). Close examination often reveals adipocyte “rimming” by associated lymphocytes, as well as plasma cells and histiocytes (**C**, H&E). High magnification reveals some irregularity of lymphocyte nuclear membranes (**D**, H&E). (Case 261, courtesy of Thomas A. Summers Jr, MD, Mark Raffeld, MD, Stefania Pittaluga, MD, and Elaine S. Jaffe, MD.)

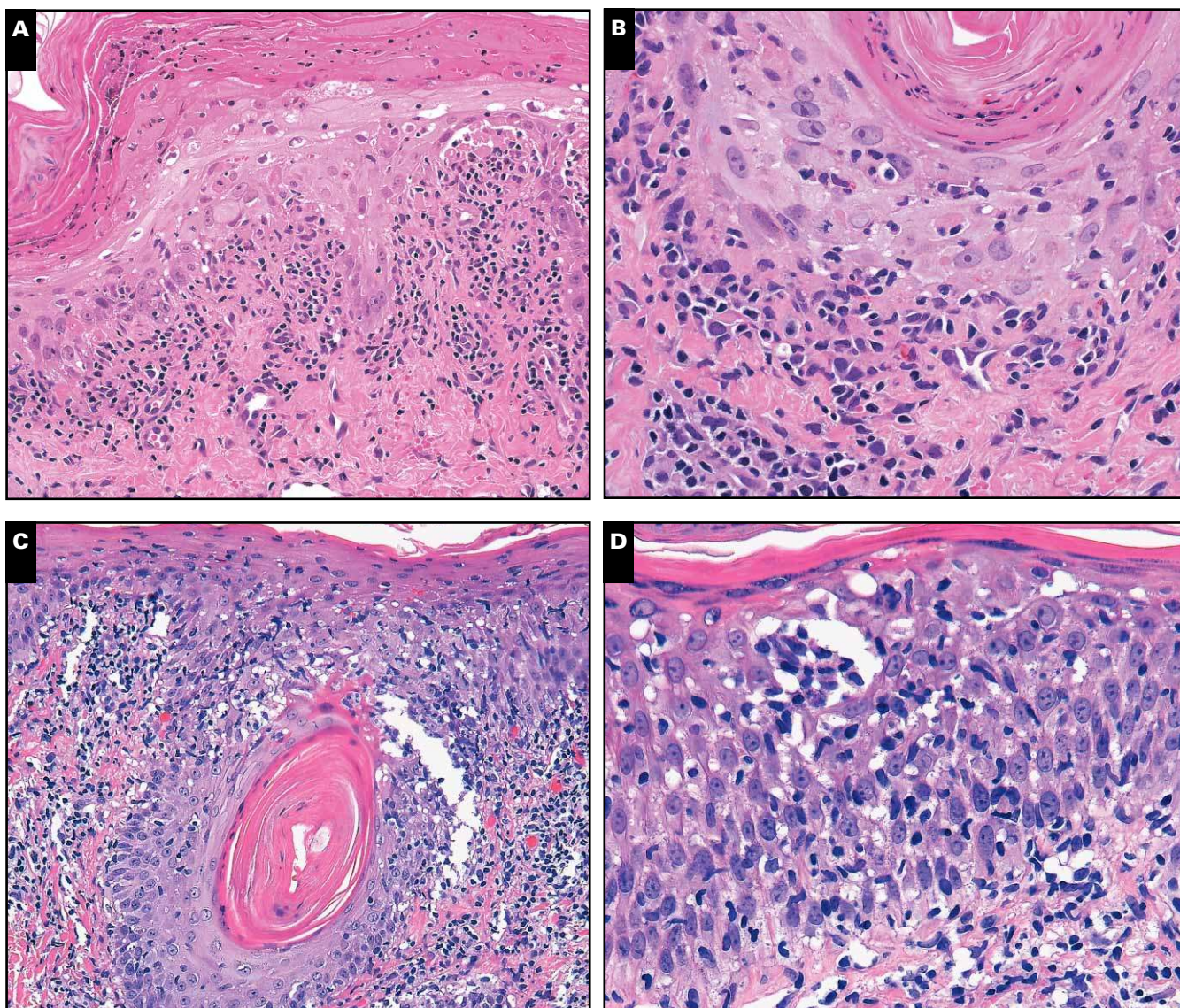
typically weeks to months and may recur.<sup>56-58</sup> Rare cases of PL will progress to lymphoma, and MF is the most common lymphoproliferative disorder to occur in association with PLEVA/PLC.<sup>59</sup>

The cause of PL is unknown. However, cell-mediated and/or immune complex-mediated causes are postulated, possibly related to viral or other infections. Proposed associations include EBV, parvovirus B19, toxoplasma, *Streptococcus*, *Staphylococcus*, herpes viruses, and HIV infections, among others (as reviewed by Fernandes et al<sup>55</sup>). A relationship of PL to LyP has been proposed but remains somewhat controversial;

however, these entities are more than likely pathogenically distinct.<sup>60</sup> In fact, Kempf et al<sup>61</sup> recently described what they believe to be a variant of PLEVA with a prominent CD30+ cell component. Some experts still believe, however, that PLEVA/PLC and LyP reside within a similar spectrum of often clonal T-cell lymphoproliferative disorders.<sup>62,63</sup>

The histologic changes of PLEVA include those of interface dermatitis, with basal vacuolar degeneration and a sparse to moderately dense lymphocyte-predominant, superficial, and, typically, deep perivascular inflammatory infiltrate.<sup>56-58,64</sup> Scattered necrotic keratinocytes within the epidermis, not seen





**Image 4** Pityriasis lichenoides et varioliformis acuta: marked exocytosis of lymphocytes, with many exhibiting irregular nuclear contours, is seen within the “reactive” and somewhat irregular epidermis. Overlying parakeratosis containing neutrophils is also seen (**A** and **B**, H&E). (From case collection of George P. Sarantopoulos, MD.) Pityriasis lichenoides chronica: there is marked exocytosis of lymphocytes into focally attenuated epidermis. Small groups of lymphocytes as well as some intraepidermal erythrocytes are also seen (**C**, H&E). Intraepidermal lymphocytes, many exhibiting irregular nuclear contours, may coalesce to mimic Pautrier microabscesses (aka pseudo-Pautrier abscesses) (**D**, H&E). (Case 227, courtesy of Scott Binder, MD.)

in direct association with atypical lymphocytes, are considered by some to be a feature that distinguishes inflammatory “reactive” dermatoses from lymphoproliferative disorders.<sup>57</sup> Both PLEVA and PLC may show scattered, enlarged atypical lymphocytes within the inflammatory infiltrate. Although cases of PLC typically exhibit less overall inflammation than PLEVA, a greater degree of lymphocyte atypia, as well as epidermotropism and Pautrier-like pseudo-abscesses, may be observed—all changes that mimic the findings of MF.<sup>58</sup> Of note, 1 submitted case showed histopathologic findings of MF, including apparent epidermotropism of lymphocytes.

Close examination, however, revealed additional histologic features that supported an inflammatory etiology, including rare necrotic keratinocytes, associated spongiosis, orthokeratosis/hyperkeratosis, parakeratosis with intracorneal neutrophils, and an overall lack of atypia among the epidermotropic lymphocytes **Image 4**.

Immunohistochemistry often reveals a T-cell–predominant dermal inflammatory infiltrate. Of note, a majority of CD8+ T-suppressor/cytotoxic cells are seen in cases of PLEVA, whereas CD4+ T-helper cells predominate in cases of PLC, particularly in those cases with progression to MF.<sup>57</sup>



In addition, loss of CD7 by the large majority of T cells—a fairly characteristic feature of MF—may be observed in cases of PL.<sup>57</sup> Scattered, enlarged CD30+ lymphoid cells may be seen as well and may further raise suspicion for CD30+ lymphoproliferative disorder.<sup>60</sup> One submitted workshop case showed a superficial and deep dermal lymphohistiocytic infiltrate, including some enlarged CD30+ lymphocytes within areas of crusting, ulceration, and marked reactive epidermal changes. T cells in this case were CD8 predominant with some aberrant loss of CD5 immunoreactivity. Of note, the most unusual finding in this case was the T-cell receptor  $\gamma$  positivity. Although the possibility of lymphoid malignancy was entertained, the pathologists in this case assessed all available clinical and pathologic information to arrive at the most prudent diagnosis of PLEVA.<sup>65</sup> Moreover, a diagnosis of LyP was considered for this case and is perhaps the most likely diagnosis.


Monoclonal populations of T cells may be observed in both PLEVA and PLC.<sup>57,58,63,66,67</sup> Observed monoclonality of constituent lymphocytes has been reported to be greater in cases of PLEVA vs PLC (approximately 60% vs 10%, respectively).<sup>67</sup> A subsequent study by Magro et al<sup>57</sup> examining only cases of PLC, however, found the number of clonal proliferations closer to that described for PLEVA (approximately 52%). Regardless of relative frequency, this fairly consistent finding of clonality within both PLEVA and PLC has led Magro and colleagues<sup>58</sup> to include PL within the classification of “T-cell dyscrasias.”

## Hypereosinophilic Syndrome

Hypereosinophilic syndrome (HES) is a somewhat peculiar entity and is reported to have associations with lymphoma and leukemia (as reviewed by Weller and Buble<sup>68</sup>). However, the most damaging sequelae most often arise from blood and end-organ damage—heart, lung, central nervous system, and skin—all secondary to marked eosinophilia and subsequent release of eosinophilic granules (as reviewed by Gleich and Leiferman<sup>69</sup>).

Myeloproliferative and lymphocytic variants of HES have been described. In addition to end-organ damage caused by peripheral eosinophilia, myeloproliferative and lymphocytic variants both share the possibility of developing myelogenous (myeloid leukemia, “chronic myelogenous leukemia-like disease,” or eosinophilic sarcoma) or lymphoid malignancy (peripheral T-cell lymphoma), respectively.<sup>70</sup>


Skin may be affected in up to 50% of HES cases and typically manifests as urticarial or erythematous papules, nodules, or plaques. Histologically, lesions show a superficial or deep mixed inflammatory infiltrate, as well as a prominent population of eosinophils without vasculitis (as reviewed by

Weller and Buble<sup>68</sup>). Of note, clonal populations of constituent T lymphocytes (either CD4 or CD8 predominant) and a reduction in expression of CD2, CD5, and CD7 have been documented in cases of HES, with a subset of these patients ultimately diagnosed with T-cell lymphoma.<sup>71</sup> One submitted workshop case showed similar histopathologic features, with small and large atypical lymphocytes . Although flow cytometry, fluorescent in situ hybridization, and cytogenetic analyses were all negative, a positive T-cell gene rearrangement study revealed evidence of T-cell clonality. This case was submitted and confirmed by the expert panel as the lymphocytic variant of HES.

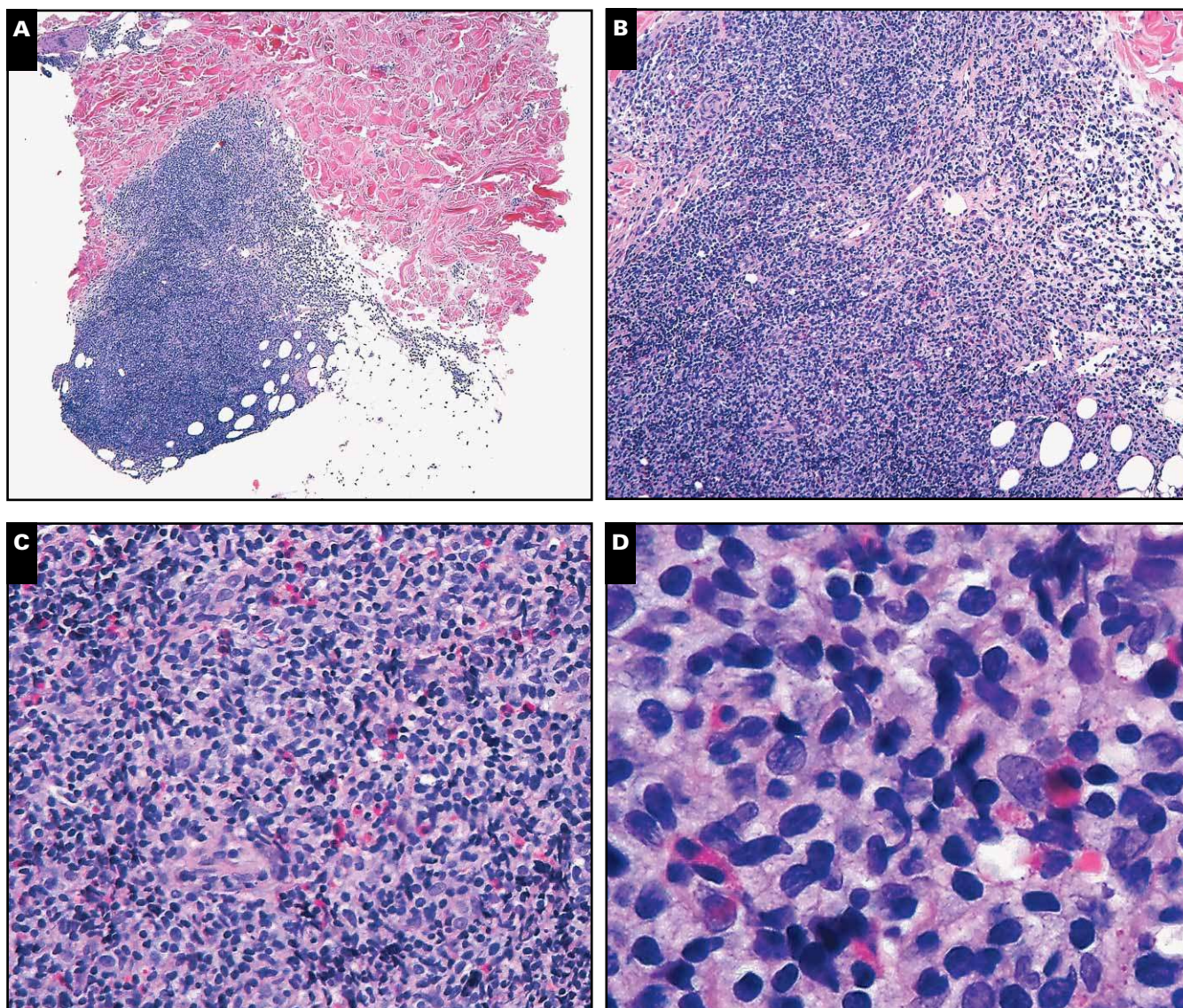
## Kikuchi-Fujimoto Disease

Kikuchi-Fujimoto disease (KFD; aka histiocytic necrotizing lymphadenitis) is a benign, self-limited, fairly acute disease of unknown etiology that most commonly affects women of Asian descent. Patients typically present with cervical lymphadenopathy, local tenderness, fever, and sweats, and cutaneous involvement has been described (as reviewed by Bosch et al<sup>72</sup>). Although considered idiopathic, several causes have been suggested, including neoplasia and infection (HIV, human herpesvirus 8, cytomegalovirus, *Giardia*, and hepatitis C, among others).<sup>73,74</sup> Awareness of this rare disease is important because of its propensity to mimic malignant lymphoma clinically.

Characteristic histopathologic features of KFD include effacement of normal lymph node architecture, large areas of paracortical necrosis, and associated karyorrhectic debris. A range of cell types is seen, including small and large lymphocytes, histiocytes, and plasmacytoid dendritic cells. Immunoblasts are also identified, which may appear atypical. Neutrophils are not seen and plasma cells are typically scarce (as reviewed by Bosch et al<sup>72</sup>). Cutaneous lesions may show changes of interface dermatitis (erythema multiforme or lupus-like) or more nonspecific inflammatory changes with underlying perivascular lymphocyte-predominant inflammation.<sup>75,76</sup> Similar to what is observed within an affected lymph node, abundant karyorrhectic debris may also be identified.<sup>77</sup> Immunohistochemical analysis typically shows a majority of CD3/CD8+ T lymphocytes.<sup>78</sup> Associated histiocytes express CD68, myeloperoxidase (MPO), and CD123.<sup>79</sup> Plasmacytoid dendritic cells express CD123, CD4, and CD68 but are generally negative for MPO.<sup>80,81</sup>

Submitted cases nicely demonstrated the typical cutaneous changes of KFD consistent with lymphocyte-predominant interface dermatitis (mimicking the changes of lupus) with associated enlarged and atypical-appearing lymphocytes . Immunohistochemical staining of skin revealed a T-cell-predominant infiltrate with numerous





**Image 5** Histologic sections of the lymphocytic variant of the hypereosinophilic syndrome reveal superficial and deep dermal lymphocytic infiltrates, often extending into underlying subcutaneous fibroadipose tissues (**A** and **B**, H&E). Close examination of the inflammatory infiltrate reveals large and small lymphocytes with a prominent subpopulation of associated eosinophils (**C** and **D**, H&E). (Case 297, courtesy of Marsha C. Kinney, MD.)

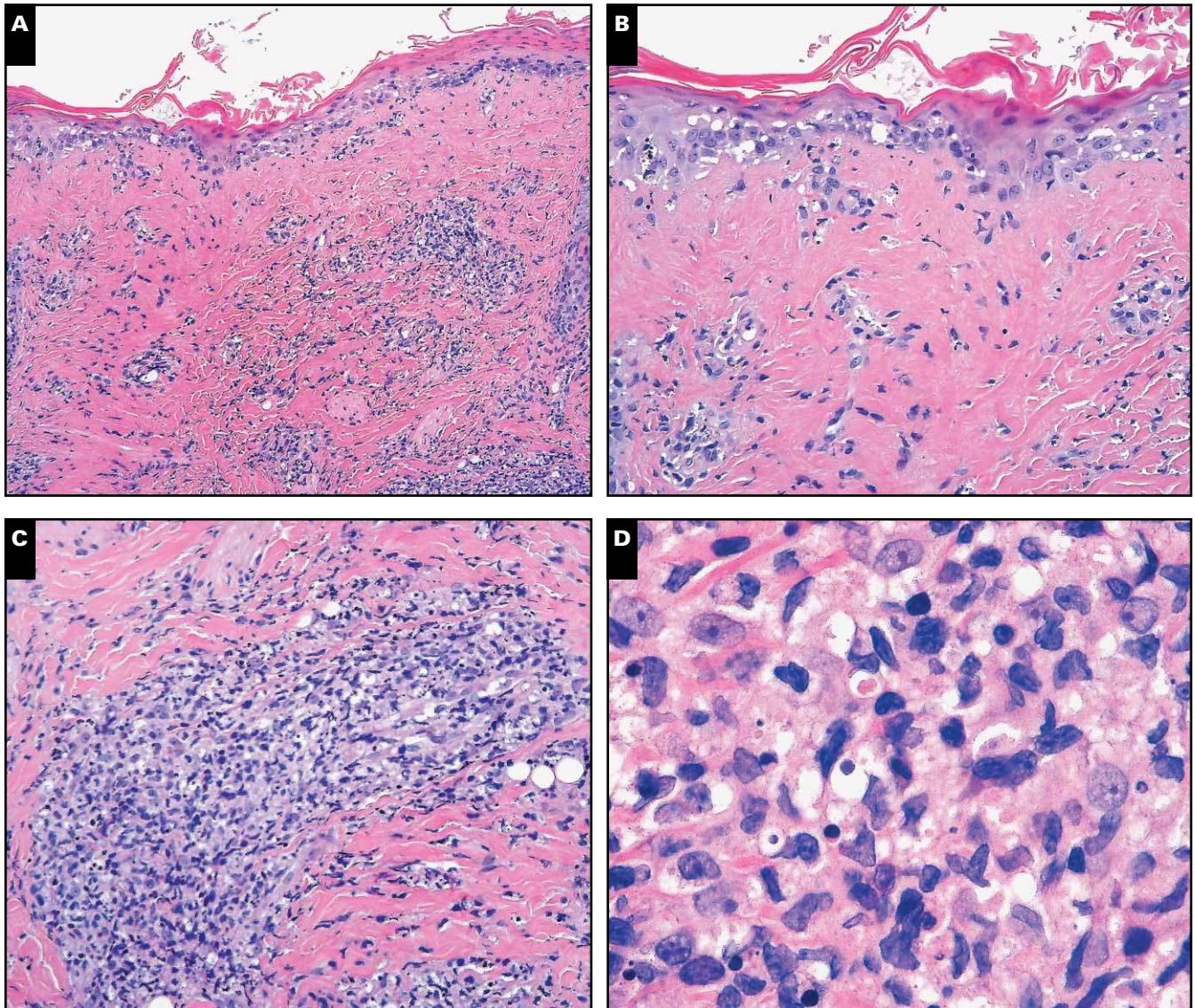
CD68+ histiocytes. Subsequent lymph node biopsy specimens showed changes most consistent with KFD, including a CD8-predominant T-cell infiltrate with numerous CD68+ histiocytes. The expert panel concurred with changes associated with KFD.

### Traumatic Ulcerative Granuloma With Stromal Eosinophils

Traumatic ulcerative granuloma with stromal eosinophils (TUGSE) is a rare benign condition of the oral mucosa that may mimic CD30+ lymphoproliferative disease.

Histologically, TUGSE lesions exhibit a mixed inflammatory infiltrate that may extend deeply into underlying tissues, including numerous eosinophils, associated histiocytes, and plasma cells, as well as a variable population of enlarged lymphoid cells. A key immunohistochemical finding is often positive staining for CD30 within enlarged lymphoid cells, which typically raises concerns for the possibility of anaplastic large-cell lymphoma.<sup>82</sup> In fact, subsequent molecular studies often demonstrate a clonal proliferation, which may further confound the diagnosis or lead to an erroneous “confirmation” of malignancy.<sup>82,83</sup> Submitted cases ultimately labeled consistent with TUGSE by the expert panel shared similar clinical





**Image 6** Cutaneous biopsies of Kikuchi-Fujimoto disease typically show changes of interface dermatitis (erythema multiforme or lupus-like), with basal vacuolar degeneration, apoptotic keratinocytes, and exocytosis of lymphocytes into thinned epidermis (**A** and **B**, H&E). Similar to lymph node findings, histiocytes with abundant karyorrhectic debris may be seen within the dermal lymphocyte-predominant inflammation (**C** and **D**, H&E). (Case 243, courtesy of Stefan Dojcinov, MD, FRCPath, and Katherine Syred, MD, FRCPath.)

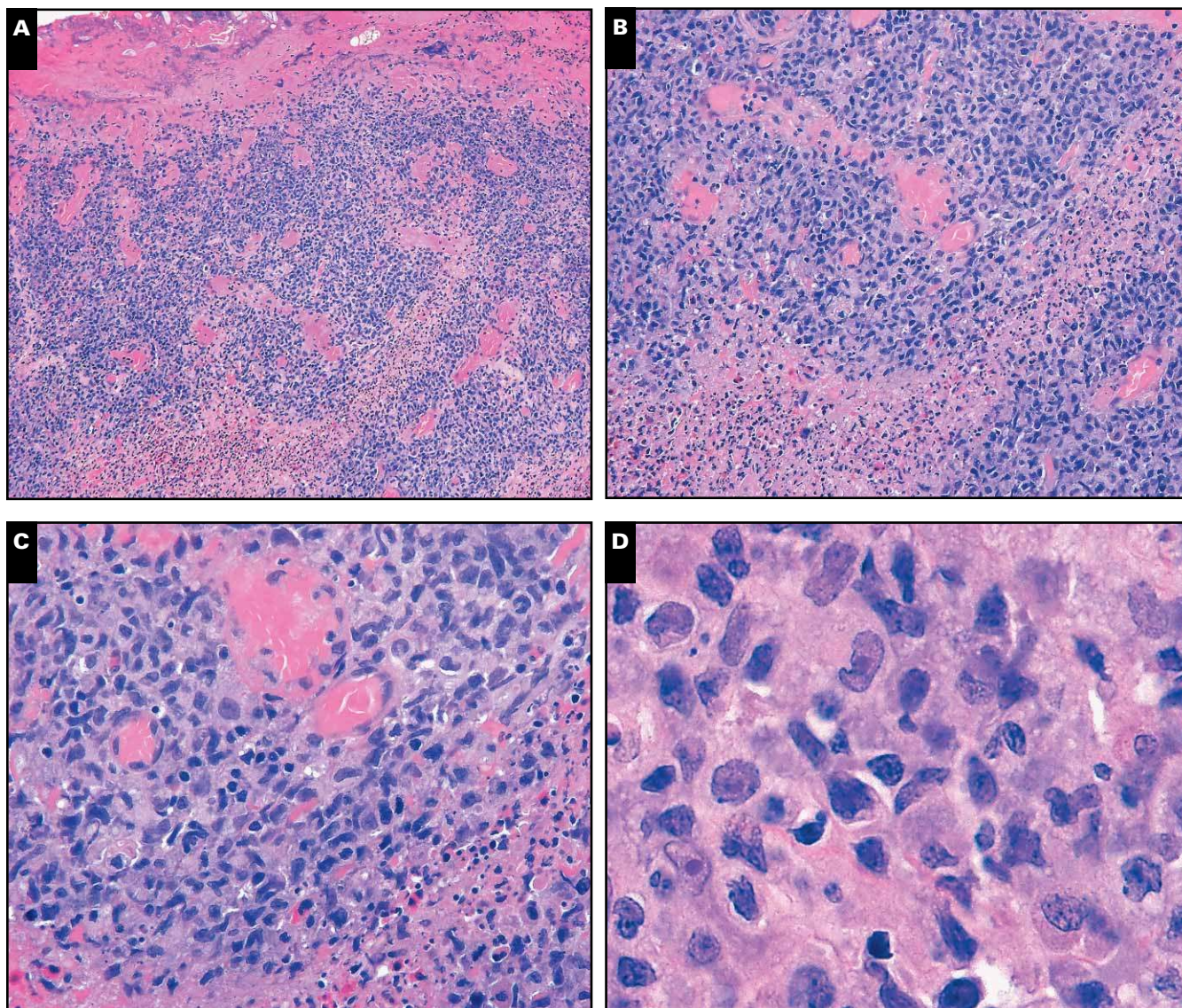
and histopathologic features, including quickly growing oral mucosal lesions with a population of enlarged lymphoid cells in a background of mixed inflammation, including histiocytes, plasma cells, and numerous eosinophils **Image 7**. Of note, 1 submitted case showed a clonal T-cell gene rearrangement by polymerase chain reaction (PCR).

### Pigmented Purpuric Dermatitis

Finally, pigmented purpuric dermatosis (PPD) is considered by the authors as worthwhile because of the increasing evidence linking this group of disorders to cutaneous

lymphoma. There are a number of known and proposed causes for the various forms of PPD. Various systemic diseases, including rheumatoid arthritis, liver disease, lupus erythematosus, lymphoid malignancy, and hyperlipidemia, have all been associated with PPD. Drugs, including nonsteroidal anti-inflammatory drugs, lipid-lowering medications, and interferon, are known common causes of PPD (as reviewed by Sardana et al<sup>84</sup>). In addition, several drug classes, including calcium channel blockers, ACE inhibitors, lipid-lowering agents,  $\beta$ -blockers, antihistamines, and antidepressants, may produce a histologically atypical pigmented purpura with T-cell clonality.<sup>85</sup>





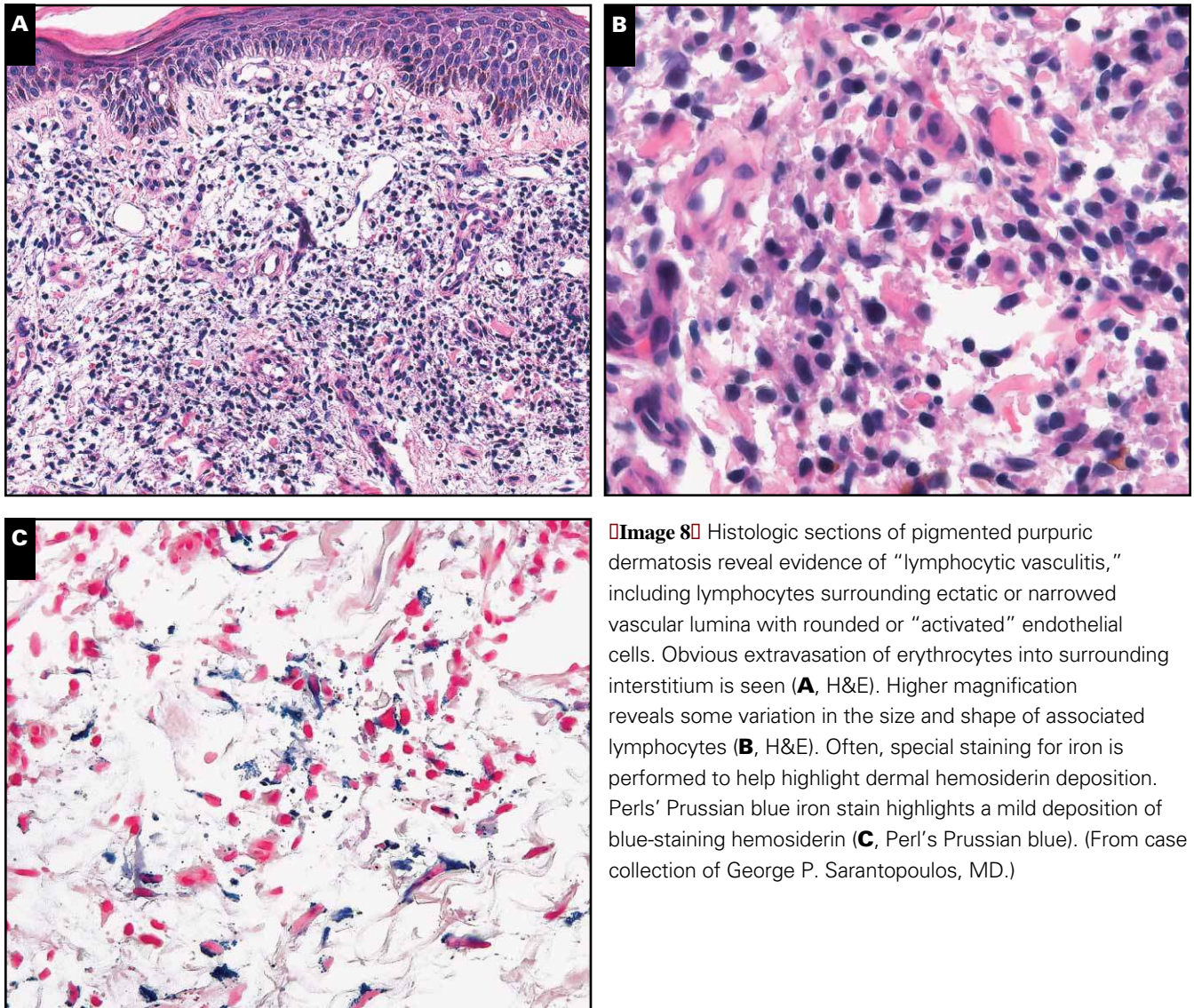
**Image 7** Histologic sections of traumatic ulcerative granuloma with stromal eosinophils often show somewhat nonspecific findings, which include ulceration and ulcer bed overlying a superficial and deep dermal mixed inflammatory infiltrate including eosinophils, plasma cells, and histiocytes (**A-C**, H&E). High magnification of histiocytes highlights often-observed nuclear irregularity (**D**, H&E). A variable population of enlarged (typically CD30+) lymphocytes (not shown) is also observed (H&E). (Case 303, courtesy of Patty M. Jansen, MD, PhD, and Rein Willemze, MD.)

Despite the many described clinical variants, all forms of PPD share similar histopathologic changes. Perivascular lymphocytic inflammation, extravasated erythrocytes, and characteristic (but variable) hemosiderin pigment are identified, either lying free or within associated macrophages or dendritic-appearing histiocytes. Variant-specific changes, including obvious neutrophils within the inflammatory infiltrate and obvious associated spongiosis (itching purpura), an overall predominant lichenoid pattern within the superficial dermal inflammatory infiltrate (Gougerot and Blum), or a thin grenz zone separating uninvolved epidermis from dermal

inflammation (lichen aureus), may help to distinguish borderline cases or those with limited clinical history histopathologically (as reviewed by Sardana et al<sup>84</sup>) **Image 8**.

Obvious overlap exists between cutaneous T-cell lymphoma and the changes observed within PPD. MF, in fact, may even present clinically with purpuric lesions.<sup>86-88</sup> The histopathologic findings observed within PPD may mimic more classical features of MF, including epidermotropism, pseudo-Pautrier abscesses, and “lining up” of lymphocytes along the dermal-epidermal junction, as well as obvious irregularity of nuclear membrane contours of associated lymphocytes.<sup>86,88,89</sup>





**Image 8** Histologic sections of pigmented purpuric dermatosis reveal evidence of “lymphocytic vasculitis,” including lymphocytes surrounding ectatic or narrowed vascular lumina with rounded or “activated” endothelial cells. Obvious extravasation of erythrocytes into surrounding interstitium is seen (**A**, H&E). Higher magnification reveals some variation in the size and shape of associated lymphocytes (**B**, H&E). Often, special staining for iron is performed to help highlight dermal hemosiderin deposition. Perls’ Prussian blue iron stain highlights a mild deposition of blue-staining hemosiderin (**C**, Perl’s Prussian blue). (From case collection of George P. Sarantopoulos, MD.)

In such borderline cases, immunohistochemical studies may offer additional helpful information. A CD8-predominant lymphocytic infiltrate, although positive in a subset (approximately 20%) of early MF cases, is commonly considered an indicator of benignity.<sup>88</sup> However, immunostaining may be of only limited use, as cases of PPD may share a profile similar to that of MF, including a CD4-predominant population of constituent lymphocytes.<sup>84,88</sup> Diminution of staining for CD7, a common finding in cases of MF, may also be seen in cases of PPD; however, this finding was less marked when compared with those cases demonstrating other supportive features of MF, such as monoclonality.<sup>88</sup>

As expected, PPD may also exhibit monoclonality of constituent lymphocytes.<sup>86</sup> A study by Crowson et al<sup>85</sup> demonstrated a drug-related cause for cases of “atypical pigmented purpura,” some of which demonstrated clonality. Similarly, in a study of 23 cases of lichen aureus, although

one half demonstrated a monoclonal gene restriction, no cases progressed to lymphoma in 5 years.<sup>90</sup>

A follow-up study by Magro et al<sup>88</sup> showed that 21 of 43 patients with PPD had clonally restricted molecular profiles via PCR analysis. Eight of these patients progressed to cutaneous T-cell lymphoma, each of whom was known to have taken a drug previously implicated as a trigger for PPD or drug-induced reversible T-cell dyscrasia. Although not a reliable marker of malignancy, the finding of clonality within lymphocytes, in conjunction with associated atypia of constituent lymphocytes—including “cerebriform” nuclear contours—was more commonly identified within cases of MF by Magro et al. Similarly, cases exhibiting clonality were CD4 predominant (vs CD8) and showed marked loss (often >90%) of CD7 in comparison to cases of polyclonal PPD.

A growing number of experts believe that PPD truly represents a form of T-cell dyscrasia that falls within the



spectrum of cutaneous T-cell lymphoma.<sup>85,86,88,91</sup> Therefore, extreme caution is advised when examining a purpuric eruption, particularly those in which no known cause is suspected clinically or when the clinical presentation is atypical and concerning.

## Summary

Caution must be taken when faced with an atypical lymphocytic infiltrate in a cutaneous biopsy specimen. Drug reactions are fairly commonplace—perhaps even underreported—and ingestion of drugs and chemicals may cause a wide range of both benign and atypical skin disorders. Numerous pathologic entities show many overlapping features with lymphoma, and familiarity with these entities is vital. When in doubt, good communication with clinical colleagues, including a comprehensive past medical history, description of the clinical presentation, and a thorough review of the patient's current and past drug regimen, is invaluable. Overreliance on pathologic studies, in contrast, may offer somewhat misleading clues and, therefore, all ancillary information should be interpreted within the overall clinical context of each case. In particular, observed clonality within lesional lymphocytes should not be considered as unequivocal evidence of malignancy. In fact, use of positive serial gene studies at separate anatomic sites has been used as additional evidence of malignancy with a fairly high sensitivity in 1 study.<sup>92</sup> This, too, suggests that negative gene studies separated anatomically and temporally would likely offer additional evidence of a reactive lymphoid process. With that said, it remains important that all diagnostic information be evaluated and used within the overall individual clinical context. When in doubt, the dermatopathologist or hematopathologist is well advised to show a measure of restraint. Often, close clinical follow-up with rebiopsy will reveal natural involution of lesions and resolution of clinical symptoms/signs.

From the <sup>1</sup>Department of Pathology and Laboratory Medicine, UCLA Medical Center, Los Angeles, CA; <sup>2</sup>Department of Pathology, University of Texas at San Antonio; <sup>3</sup>Department of Pathology, University of Pittsburgh Medical Center, Pittsburgh, PA; and <sup>4</sup>Department of Dermatology, Leiden University Medical Center, Leiden, the Netherlands.

Address reprint requests to Dr Sarantopoulos, AS-255C, UCLA Medical Center, CHS, 10833 LeConte Ave, Los Angeles, CA 90095; [gsarantopoulos@mednet.ucla.edu](mailto:gsarantopoulos@mednet.ucla.edu).

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