Interface Dermatitis

How Specific Are Its Histopathologic Features?

ONE OF THE more challenging aspects of being a dermatopathologist is to try to make specific diagnoses of inflammatory skin diseases. While it is true that, at one time, the tools to do this were inadequate, criteria now exist for the microscopic diagnosis of many inflammatory skin diseases, and most expert dermatopathologists have a sense of how to handle discrepancies between clinical and histopathologic findings. These developments have, hopefully, changed the negative feelings of many clinical dermatologists regarding the utility of biopsy procedures in inflammatory conditions. Because of the work of Herman Pinkus,[1] who ordered inflammatory skin diseases by reaction patterns (eg, lichenoid, eczematous, and psoriasiform dermatitis), Wallace Clark, who outlined patterns of inflammatory cells in cutaneous infiltrates, and Bernard Ackerman, who developed Clark's outline into a method of diagnosis in his *Histologic Diagnosis of Inflammatory Skin Diseases*,[2] present-day dermatopathologists can specifically diagnose many inflammatory skin diseases. Even within the last decade, diagnostic criteria for even common diseases have been further refined, and we have gained an appreciation of how the microscopic appearances of diseases evolve over time.

It has also become apparent that there are many inflammatory skin diseases that simply cannot be told apart histopathologically; for instance, allergic contact, dyshidrotic and nummular dermatitis, the id reaction, and some cases of pityriasis rosea can be indistinguishable.[3] Lists of such "look alikes" often provide an insight into the similar pathophysiologies of disease processes. Acrodermatitis enteropathica, neonatal citrullinemia, necrolytic migratory erythema, and pellagra all have psoriasiform epidermal hyperplasia, with ballooning of keratinocytes in the upper half of the spinous layer and parakeratosis, and are, in part, due to amino acid deficiencies.

This correspondence between pattern and pathophysiology is tweaked by the finding of Bauer et al,[4] published in the July issue of the ARCHIVES, that the eruption of autologous graft-vs-host disease can be histopathologically indistinguishable from the eruption of lymphocyte recovery. Autologous graft-vs-host disease has long been puzzling in that it seems to result from the failure of a patient's reintroduced T cells to recognize their own epithelium as self.[5] The eruption of lymphocyte recovery was first noted in leukemic patients as a macular eruption that occurred as peripheral blood cell counts recovered from chemotherapy administered for leukemia.[6] Both graft-vs-host disease and the eruption of lymphocyte recovery (if they are, indeed, separate conditions) arise when lymphocytes are reintroduced into what should be a familiar milieu, although potentially altered by chemotherapy or radiation, or both.

Refer to July 1993 issue, page 855

When Horn and his colleagues[6] first introduced the concept of eruption of lymphocyte recovery, they proposed that its histopathologic findings were distinguishable from those of graft-vs-host reaction by the absence of "satellite cell necrosis," ie, necrotic keratinocytes with closely apposed lymphocytes. Further experience led these authors to question this finding, and the current study[4] refutes it, as 30% of their specimens of eruptions of lymphocyte recovery showed "satellite cell necrosis." Parenthetically, satellite cell necrosis is not pathognomonic of graft-vs-host disease, but occurs in most interface reactions.[7] Several questions also arise regarding the biology of these diseases. Are autologous graft-vs-host disease and the eruption of lymphocyte recovery transient and persistent forms of the same phenomenon? If so, what is the mechanism that shuts down autoreactivity in the eruption of lymphocyte recovery and can we subvert it to help patients with graft-vs-host disease?

This article also presents an opportunity for dermatopathologists, and clinicians with an interest in how histopathologic diagnoses are made, to take an inventory of the interface dermatitides and the specificity of their microscopic pictures.

Interface reactions are so named because they are cell-mediated immunologic reactions whose targets are basal keratinocytes that reside above the dermoepidermal junction. Interface dermatitides have in common infiltrates (usually composed mostly of lymphocytes) that appear to obscure the junction when sections are observed at scanning

magnification. Closer scrutiny usually shows vacuolar change, necrotic keratinocytes, and spongiosis that diminishes rapidly with ascent into the mid-spinous zone. Immunohistochemical studies of these reactions have shown them to be more alike than different with cytotoxic T cells ascending into the epidermis, especially in late stages, and helper T cells in the papillary dermis in many interface reactions.[8] Immune complex deposition might play a role in some interface dermatitides, and antibody-mediated cellular cytotoxicity could be key in others.

In Ackerman's[2] method of analysis of inflammatory skin disease, the initial step is for the histopathologist to determine which of nine patterns of inflammatory skin disease obtains. If the epidermis is affected, then a determination must be made as to whether there is spongiosis, psoriasiform hyperplasia, an interface reaction, or a combination of these features. In the interface dermatitides, the two possible patterns are superficial perivascular dermatitis, and superficial and deep perivascular dermatitis. Ackerman divides interface dermatitides into vacuolar and lichenoid interface dermatitis depending on the density of the infiltrates—vacuolar having sparse and lichenoid dense infiltrates.[2] The prototypical vacuolar interface dermatitis in this classification is erythema multiforme, and lichen planus is the exemplar of lichenoid interface dermatitis. An advantage of this method is that it enables histopathologists to make an initial classification at first glance, using the same method (determination of the pattern of inflammatory cells) as in any other inflammatory skin disease. A disadvantage is that it places little weight on the differences in epidermal reactions among diverse conditions. Another disadvantage is that it is sometimes difficult to determine whether the deep vascular plexus is involved, which is the first determination in Ackerman's approach. Do two or three lymphocytes around a single venule indicate superficial and deep rather than superficial perivascular dermatitis? Whether or not the deep plexus is involved sometimes depends on what stage of lesion a biopsy is performed and whether or not the plane of section displayed on a slide includes the edge of the lesion, or its center, where the most fully developed changes reside.

Another complementary, but not necessarily superior, approach is to classify interface dermatitis by the nature of its epidermal changes. Reed[9] has noted many aspects of epidermal reactions to interface dermatitis, dividing them into lichenoid reactions and lichenoid lymphocytic vasculitis, a classificiation that is pathophysiologically rather than observationally based, and difficult to use. The schema to follow borrows both on Reed's and Ackerman's insights.

One pattern of epidermal reaction in interface dermatitis has as its prototype erythema multiforme. In that condition, and in toxic epidermal necrolysis, fixed drug eruption, pityriasis lichenoides, phototoxic dermatitis, and subacute radiation dermatitis necrotic keratinocytes form clusters that can ascend into the spinous (and sometimes granular) layers (**Figure 1**). In erythema multiforme, fixed drug eruption and toxic epidermal necrolysis, a rapid injury evidently does not stimulate epidermopoiesis, so that orthokeratosis is generally preserved. In pityriasis lichenoides, phototoxic dermatitis, subacute radiation dermatitis, and, in some cases of acute graft-vs-host disease, immunological injury stimulates epidermopoiesis, resulting in parakeratosis. If the basal layer of the epidermis is affected, it is by hyperplasia, resulting in an increase in the numbers of layers of cells with scant cytoplasm. In all of these conditions, lymphocytes can ascend within the epidermis and are not only found at the interface.

Both epidermal kinetics and microscopic appearances differ in lichen planus and lichen planus–like reactions. Basal keratinocytes acquire polygonal shapes and abundant pink (in hematoxylin-eosin–stained sections) cytoplasm, a change termed "squamatization of the basal layer." The interstices between keratinocytes in the spinous layer become narrower, and the granular layer thickens, especially above acrosyringia (wedge-shaped hypergranulosis) (**Figure 2**). The cornified layer becomes thickened and compact. These epidermal changes are remarkably similar to those seen in the

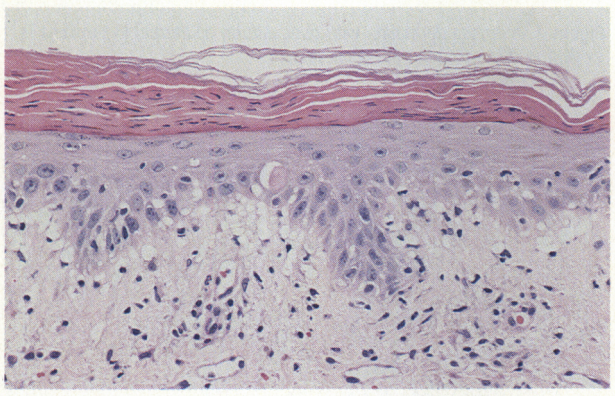

Figure 1. *Interface dermatitis can be classified on the basis of its epidermal changes. An erythema multiforme–like epidermal reaction, in which vacuolar change is evident at the dermoepidermal junction and in which lymphocytes and necrotic keratinocytes can be seen above the junction, is present in this specimen of pityriasis lichenoides et varioliformis acuta.*

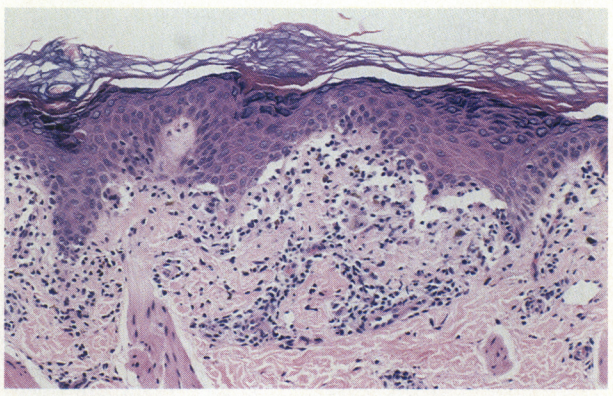

Figure 2. *This case of lichen striatus exemplifies the lichen planus–like epidermal reaction. In the lichen planus–like pattern, there is squamatization of the basal layer, narrowing of the interstices between keratinocytes of the spinous layer, and focal thickening of the glanular layer, ie, the epidermis comes to resemble that seen normally on acral skin.*

early, hyperplastic phase of wound healing. Perhaps as a consequence of an epidermis whose intercellular spaces are more constricted, necrotic keratinocytes do not ascend into the epidermis but drop into the papillary dermis (or are layered with basement membrane material and incorporated into the papillary dermis) to mummify as colloid bodies, and few lymphocytes are present high in the epidermis in most of these conditions. A bandlike infiltrate is not always found with a lichen planus–like epidermal reaction—witness chronic (lichenoid) graft-vs-host disease in which epidermal changes indistinguishable from lichen planus occur, yet only a sparse lymphocytic infiltrate is found.

Some epidermal reactions change as lesions evolve. Acute cutaneous graft-vs-host disease, in its earliest stages, resembles erythema multiforme microscopically, and, indeed, it may be extraordinarily difficult to discriminate between early lesions and erythema multiforme without clinical information. As lesions evolve, squamatization of the basal layer and compact hyperkeratosis or parakeratosis supervene, features that do not occur in erythema multiforme. If graft-vs-host disease persists, the epidermal changes can be indistinguishable from lichen planus.[10] Similarly, it remains to be seen whether the eruption of lymphocyte recovery only resembles acute graft-vs-host disease because its changes are too early to be distinctive. While the eruption of lymphocyte recovery damages basal keratinocytes, squamatization of the basal layer and compact hyperkeratosis or parakeratosis, as are seen in acute graft-vs-host disease, has not yet been observed, perhaps because the process switches off before substantial damage to the epidermis occurs.

An exaggeration of the irregular epidermal hyperplasia of lichen planus occurs when its lesions are persistently rubbed, resulting in hypertrophic lichen planus. Irregular epidermal hyperplasia is also seen in lichenoid drug eruptions due to quinacrine, administered during World War II as an antimalarial, and in the verrucous variant of discoid lupus erythematosus. Interface dermatitis with irregular epidermal hyperplasia typifies only a few diseases, but it is, thus, a third epidermal pattern of interface dermatitis (**Figure 3**).

A fourth group of interface reactions displays psoriasiform epidermal hyperplasia, either with or without spongiosis (**Figure 4**). This constellation of features was first noted by Ackerman,[11] and the conditions that show it are mostly ones in which cytotoxic damage to basal keratinocytes is not primary, such as secondary syphilis, the urticarial stage of bullous pemphigoid, and a neoplastic disease, mycosis fungoides. Of the diseases that are "psoriasiform, lichenoid" or "psoriasiform, spongiotic, and lichenoid" only in lichen striatus does cytotoxic damage to basal keratinocytes appear to be primary.

Epidermal atrophy, accompanied by fibrosis of the papillary dermis, occurs in a fifth group of conditions

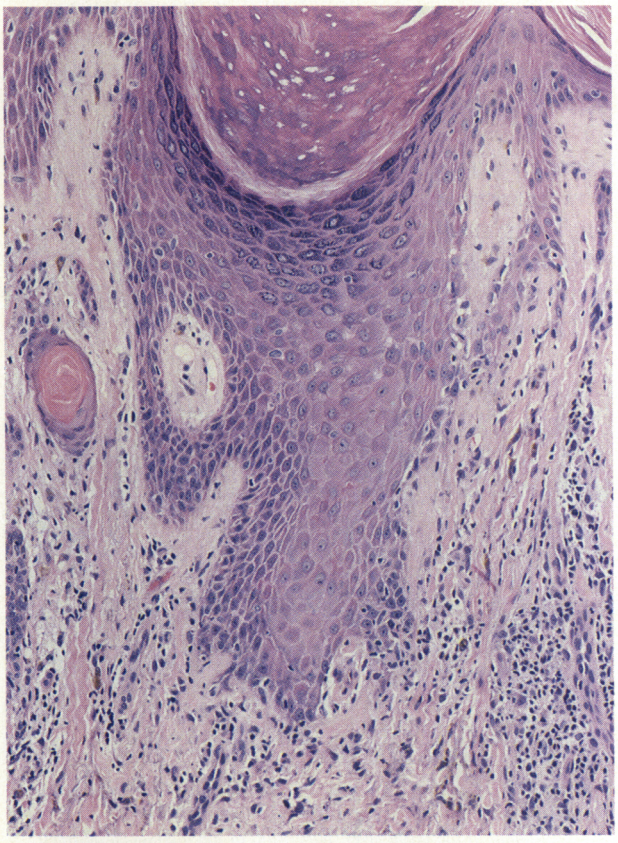

Figure 3. *Interface dermatitis with irregular epidermal hyperplasia is a pattern seen in only a few conditions, of which hypertrophic lichen planus is the most common.*

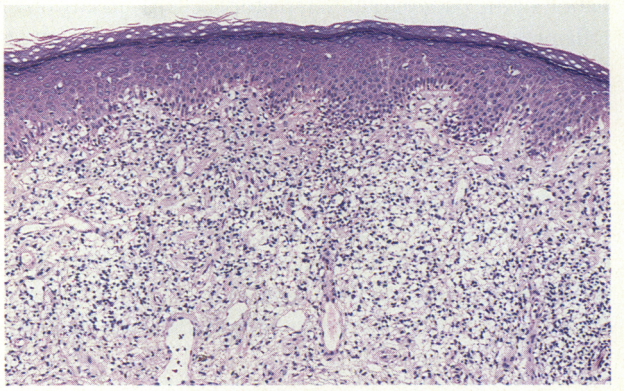

Figure 4. *Interface dermatitis with psoriasiform epidermal hyperplasia is evident in this specimen of lichen aureus.*

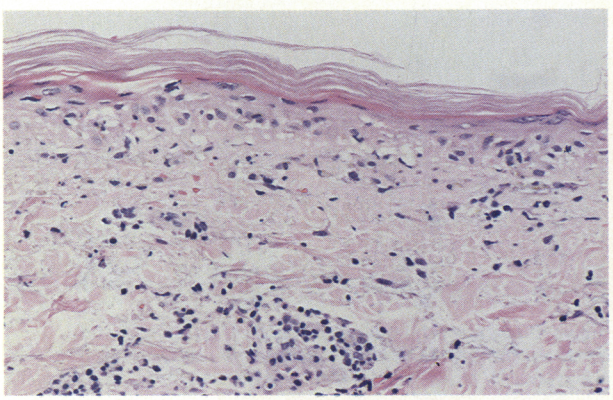

Figure 5. *Interface dermatitis can produce epidermal atrophy, as is the case in this section from a patient with systemic lupus erythematosus.*

Epidermal Patterns in Interface Reactions*

Erythema Multiforme–Like Epidermal Reactions

Erythema multiforme
Toxic epidermal necrolysis (very sparse infiltrates)
Fixed drug eruption (eosinophils, neutrophils, deep melanophages, involvement of the deep plexus)
Pityriasis lichenoides (parakeratosis with neutrophils, lymphocytic vasculitis sometimes, superficial and deep often)
Acute lesions of systemic lupus erythematosus (mucin in the reticular dermis, hyperkeratosis)
Subacute radiation dermatitis (parakeratosis, keratinocytes with atypical nuclei)
Phototoxic dermatitis (band of parakeratosis beneath orthokeratosis)
Acute graft-vs-host reaction, early lesions
Eruption of lymphocyte recovery
Papular lesions of herpes simplex and zoster (superficial and deep, often with papillary dermal edema)
Viral exanthems (sparse infiltrates with few necrotic keratinocytes)
Some morbilliform drug eruptions (sparse infiltrates with few necrotic keratinocytes)

Lichen Planus–Like Epidermal Reactions

Lichen planus
Hyperplastic phase of wound healing (fibrosing granulation tissue)
Acute graft-vs-host reaction, fully developed lesions (squamotization of basal layer, hyperkeratosis)
Lichenoid, chronic, graft-vs-host reaction (sparse lymphocytic infiltrates, sometimes superficial and deep, sclerosis of reticular dermis sometimes)
Lichen planus–like keratosis (contiguous solar lentigo, parakeratosis, spongiosis)
Lichenoid drug reactions (superficial and deep, eosinophils, plasma cells, parakeratosis)
Lichen striatus, usually (granulomatous foci on occasion, infiltrates along eccrine ducts)
Discoid lupus erythematosus (superficial and deep, hyperkeratosis with orificial plugging, thickening of basal lamina, dermal mucin)
Keratosis lichenoides chronica (plasma cells, parakeratosis with neutrophils, telangiectases)

Interface Dermatitis With Irregular Epidermal Hyperplasia, a Variant of the Lichen Planus–Like Reaction

Hypertrophic lichen planus
Late lesions of some lichenoid drug eruptions, eg, those due to quinacrine (plasma cells, eosinophils, keratinocytes with atypical nuclei)
Verrucous lupus erythematosus (see discoid lupus erythematosus)

Interface Reactions With Psoriasiform Hyperplasia, With or Without Spongiosis

Lichen aureus (siderophages, lymphocytes in basal layer without proportionate spongiosis)
Lichen striatus, sometimes (see above)
Mycosis fungoides, a neoplastic disease (lymphocytes within epidermis without proportionate spongiosis, enlarged, hyperchromatic or hyperconvoluted nuclei, deep plexus may be involved)
Bullous pemphigoid, urticarial stage (spongiosis with eosinophils, eosinophils along d-e junction)
Secondary syphilis (superficial and deep usually, plasma cells, macrophages numerous, epidermal pallor, spongiform pustules rarely)
Some drug eruptions
Porokeratosis of Mibelli, reaction to a neoplastic disease (cornoid lamellation)
Pityriasis lichenoides, sometimes (see above)
Acrodermatitis chronica atrophicans, early lesions (plasma cells)
Chronic photoallergic or photoallergic contact dermatitis, sometimes (marked papillary dermal fibrosis, superficial and deep)
Lichen sclerosus et atrophicus, early lesions (plasma cells, homogenization of papillary dermis)

Atrophic Interface Reactions

Atrophic lesions of lichen planus
Poikilodermatomyositis (sparse infiltrates, dermal mucin, few necrotic keratinocytes)
Atrophic lesions of discoid and systemic lupus erythematosus (epidermis thinned to two or three layers of cells, dermal mucin)
Acrodermatitis chronica atrophicans, late lesions (plasma cells, telangiectases)
Poikilodermatous mycosis fungoides (see above)
Poikiloderma congenitale
Actinic porokeratosis (cornoid lamellation)
Regression of malignant melanoma (melanophages in a broad band)
Inflammatory changes induced by superficial basal cell carcinoma (severe solar elastosis, level sections show nests of basaloid cells)

**Clues to diagnoses are listed in parentheses.*

(**Figure 5**). Some of these, such as atrophic lichen planus, are the waning manifestations of diseases in which more distinctive changes are present in earlier lesions, while others, such as poikilodermatomyositis, are atrophying from the outset. Still others are not truly inflammatory skin diseases but rather atrophying reactions to neoplasms, such as poikilodermatous mycosis fungoides and porokeratosis.

Interface dermatitides can, thus, either be ratio-

nally classified by the pattern of inflammatory cells, or by the epidermal reaction to them. The **Table** displays these conditions grouped by epidermal reaction patterns.

Whatever overarching classification histopathologists begin with in analyzing an interface dermatitis, they need to use adjunctive features to arrive at a specific diagnosis. Such features as dermal mucin, follicular plugging, and a thickened basement membrane in lupus erythematosus; eosinophils and neutrophils in the infiltrates of fixed drug eruption; parakeratosis, eosinophils, and plasma cells in lichenoid drug eruptions; and keratinocytes with atypical nuclei in subacute radiation dermatitis and in some patients with acute graft-vs-host disease (depending on their conditioning regimen), when seen in the proper context, allow histopathologists to issue diagnoses more specific than "interface dermatitis." Clues are listed in parentheses next to the diseases they pertain to in the Table. It remains to be seen whether the absence of such clues in the eruption of lymphocyte recovery and in the early lesions of graft-vs-host disease imply their identity, a common pathogenesis, or only the histopathologic similarities of two incompletely developed, but unrelated, conditions.

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REFERENCES

1. Pinkus H. Lichenoid tissue reactions: a speculative review of the clinical spectrum of epidermal basal cell damage with special reference to erythema dyschromicum perstans. *Arch Dermatol.* 1973;107:840-846.
2. Ackerman AB. *Histologic Diagnosis of Inflammatory Skin Diseases: A Method by Pattern Analysis.* Philadelphia, Pa: Lea & Febiger; 1978.
3. Salem OS, Maize J. Clinicopathologic correlation in diagnosis of diseases of the skin. *Am J Dermatopathol.* 1986;8:53-56.
4. Bauer DJ, Hood AF, Horn JD. Histologic comparison of autologous graft-vs-host reaction and cutaneous eruption of lymphocyte recovery. *Arch Dermatol.* 1993;129:855-858.
5. Hood AF, Vogelsang GB, Black LP, Farmer ER, Santos GW. Acute graft-vs-host disease: development following autologous and syngeneic bone marrow transplantation. *Arch Dermatol.* 1987;123:745-750.
6. Horn TD, Redd JV, Karp JE, Beschorner WE, Burke PJ, Hood AF. The cutaneous eruption of lymphocyte recovery. *Arch Dermatol.* 1989;125:1512-1517.
7. LeBoit PE. Transfusion associated graft-vs-host disease. *Hum Pathol.* 1987; 18:414-415.
8. Mauduit G, Fernandez-Busey R, Thivolet J. Sequential enumeration of peripheral blood T cell subsets in lichen planus. *Clin Exp Dermatol.* 1984;9:256-262.
9. Reed RJ. Erythema multiforme: a clinical syndrome and a histologic complex. *Am J Dermatopathol.* 1985;7:143-152.
10. Saurat JH, Glucksman E, Busel A, et al. The lichen planus-like eruption after bone marrow transplantation. *Br J Dermatol.* 1975;92:675-681.
11. Ackerman AB. *Supplement to the Fourth Printing of Histologic Diagnosis of Inflammatory Skin Diseases: A Method by Pattern Analysis.* Philadelphia, Pa: Lea & Febiger; 1988.