Cutaneous Hypertrophic Lupus Erythematosus
A Challenging Histopathologic Diagnosis in the Absence of Clinical Information

David P. Arps, MD; Rajiv M. Patel, MD

Hypertrophic lupus erythematosus (HLE) is a rare variant of chronic cutaneous lupus characterized histologically by irregular epidermal hyperplasia associated with features of classic chronic cutaneous lupus, including interface changes. Lesions frequently demonstrate reactive squamous atypia of the basal layer and may show histopathologic overlap with other more common cutaneous atypical squamousproliferative lesions. Typical histologic features of cutaneous lupus, such as follicular plugging, angiocentric lymphocytic inflammation, and dermal mucin, are very helpful clues to the diagnosis of hypertrophic lupus erythematosus. Recently, immunohistochemistry for CD123 used to detect increased plasmacytoid dendritic cells (Figure 1). Based on these features, a diagnosis of hypertrophic lupus erythematosus (HLE) was rendered.

PATHOLOGIC FINDINGS
The term “interface dermatitis” can be applied to a heterogenous group of dermatitides in which the dermal-epidermal junction is obscured by an infiltrate, typically lymphocytic, with evidence of epidermal basal cell damage. Injury induces cytoplasmic vacuolization and edema of the basal layer, with separation from the underlying lamina densa resulting in a ragged-appearing dermal-epidermal junction. Interface dermatitis also produces reactive keratinocytes, which may appear cytologically atypical. Apoptotic keratinocytes with condensed eosinophilic cytoplasm, with or without pyknotic nuclei, are also appreciated. The extent of vacuolar change and keratinocyte death is variable and depends on the etiology of the interface dermatitis. Lupus erythematosus is the prototypic interface dermatitis associated with a perivascular and perifollicular lymphocytic infiltrate, increased dermal mucin, and follicular plugging (Figure 2).

Lupus erythematosus can be subdivided into 3 major clinical variants: chronic discoid (DLE), which is limited to the skin; a subacute form in which skin lesions accompany mild systemic symptoms; and the systemic (acute) form. Hypertrophic lupus erythematosus is regarded as a rare variant of DLE, representing 2% of all lesions of chronic cutaneous lupus. Hypertrophic lupus erythematosus was described by Bechet in 1942 as “lupus erythematosus hypertrophicus et profundus,” with the latter descriptor emphasizing the depth of the infiltrate.1 However, this is not to be confused with lupus profundus, as there is no panniculitic component present in HLE. Hypertrophic lupus erythematosus most often presents in association with classic lesions of DLE, although rarely patients may present with HLE in the absence of other cutaneous manifestations of LE.2 Patients are predominantly middle-aged and female, and they present with erythematous verruciform plaques (Figure 3, A) on sun-damaged skin of the face, arms, and, less commonly, the chest. Lesional plaques may develop indurated borders with occasional atrophic or cribiform centers. A subset of patients with HLE develop hyperkeratotic papules with central keratinous plugging clinically and histologically reminiscent of keratoacanthomas (KAs; Figure 3, B). These KA-like HLE proliferations have been described as developing at the site of previous typical cutaneous LE lesions. These KA-like
Figure 1. Hypertrophic lupus erythematosus. Punch biopsy demonstrated interface changes and a perivascular and periadnexal infiltrate involving the superficial and deep dermis (A) in association with irregular papillomatous epidermal hyperplasia (B). Follicular plugging (C) and keratinocyte apoptosis (D) were also present. The infiltrate was predominantly lymphohistiocytic (E) and present in a background of increased dermal mucin (F). Medium power showing an increased number of plasmacytoid dendrocytes (G), which were CD123 positive by immunohistochemistry (H) (hematoxylin-eosin, original magnifications ×20 [A], ×40 [B], ×100 [C and D], ×600 [E], and ×200 [F and G]; CD123, original magnification ×200 [H]).
proliferations respond to retinoids and steroids, offering supportive evidence that they are HLE-related rather than neoplastic proliferations.\(^3,4\) In some patients, hyperkeratotic lesions may evolve into cribriform scars. Cutaneous manifestations may be chronic and progressive, but systemic LE is not present in most cases.\(^5,6\) A short course of topical or intralesional steroids may be recommended for lesions with significant histologic overlap with squamous neoplasia. Lesions associated with HLE should show evidence of resolution, whereas squamous neoplasia should persist, a finding that should prompt additional biopsies to rule out squamous cell carcinoma.

Figure 2. Discoid (chronic cutaneous) lupus. Lupus is the prototypic inflammatory dermatosis associated with a perivascular and periadnexal infiltrate occurring both superficially and deep, increased dermal mucin, follicular plugging (A), and interface changes (B) (hematoxylin-eosin, original magnifications ×20 [A] and ×600 [B]).

Figure 3. Clinical presentations of hypertrophic lupus erythematosus. Typical erythematous verrucous plaque on sun-damaged skin of the lower arm (A). Photo in panel A is courtesy of Harrold Carter, University of Michigan Department of Dermatology. Less common keratoacanthoma-like papules (B). Photo in panel B is courtesy of Julia Dahl, MD, Mosaic Pathology Partners of Memphis, Tennessee.

Figure 4. Inflamed keratoacanthoma. Note overlapping histologic features with hypertrophic lupus erythematosus, including prominent epidermal hyperplasia (A), interface-like change, and keratinocytic apoptosis (B) (hematoxylin-eosin, original magnifications ×20 [A] and ×600 [B]).
Correlation with clinical findings and history is essential to avoid misdiagnosing HLE as squamous neoplasia or other lichenoid interface dermatitides with pseudoepitheliomatous hyperplasia.

Histopathology

Two types of HLE lesions have been described.7–10 Most cases are defined by a dense, bandlike infiltrate, most similar to hypertrophic lichen planus, in association with irregular pseudoepitheliomatous hyperplasia and vacuolar interface changes. Varying numbers of apoptotic keratinocytes may be appreciated. Mild reactive squamous atypia, particularly of basal keratinocytes, is quite common. Hyperkeratosis with follicular plugging and an associated perivascular and periadnexal lymphocytic inflammation in a background of variable amounts of dermal mucin and basement membrane thickening represent useful clues to the diagnosis of HLE when present. Plasma cells may be prominent. Elastotic material is often present between epidermal cells in the tips of elongated rete, and there may be transepidermal elimination of this material. The second, less common type of lesion is distinctly KA-like, consisting of a crateriform keratinous center with an exuberant squamous epithelial proliferation. Both types may be mistaken for squamous neoplasia or other lichenoid interface dermatitides with epidermal hyperplasia, particularly in superficial biopsies interpreted in the absence of adequate clinical information.

Differential Diagnosis

The histopathologic differential of HLE includes lesions that display pseudoepitheliomatous hyperplasia in association with varying amounts of squamous atypia and necrotic keratinocytes. Paramount among these are atypical squamous proliferative lesions with lichenoid inflammation, such as benign lichenoid keratosis, lichenoid actinic keratosis, and squamous cell carcinoma. Primary interface dermatitides in this group include hypertrophic lichen planus (HLP) and lichenoid drug eruptions (LDEs). Other entities with exuberant pseudoepitheliomatous hyperplasia not typically considered interface processes may rarely enter the differential, including deep fungal infections, the halogenodermas (bromoderma, iododerma), and some perforating disorders. It cannot be overemphasized that rigorous clinicopathologic correlation is the key to avoiding misdiagnosis of HLE as squamous neoplasia or another hypertrophic lichenoid dermatitis.

Distinguishing HLE from squamous neoplasia is the most important, and potentially the most challenging, task. When detailed clinical data, such as location (face, arms, or chest), history of typical DLE, positive serologies, or direct immunofluorescence studies, are provided, the presence of only mild keratinocytic atypia in association with corroborative histologic findings (vacuolar change, follicular plugging, dermal mucin, superficial and deep infiltrate) enable the pathologist to make a definitive diagnosis of HLE. This distinction is made much more challenging when the pathologist is faced with a superficial biopsy of an inflamed atypical squamous proliferative lesion in the absence of clinical information. In this circumstance, the coexistence of a mildly atypical hyperplastic epidermis in association with inflammation and interface changes may only allow a descriptive diagnosis and a comment indicating that both squamous neoplasia and an interface dermatitis, such as lupus, are diagnostic possibilities. This histologic overlap is highlighted in an excisional biopsy of a KA demonstrating epidermal hyperplasia, interface-like changes, and focal apoptotic keratinocytes (Figure 4). Direct immunofluorescence may be a useful adjunct to the diagnosis of HLE in this instance, it typically shows deposition of immunoglobulin (Ig) G and IgM along the basement membrane zone with a frequency similar to that of typical DLE (50%–90%), with complement present less often. However, interpretation must be tempered by the fact that direct immunofluorescence may be falsely positive when applied to sun-damaged skin. Intraepidermal elastin seen in HLE has also been observed in both inflamed squamous cell carcinoma and KAs.11 A final confounder is that squamous cell carcinoma is an uncommon late complication of HLE. Interestingly, a recent study suggests that CD123-positive plasmacytoid dendritic cells are abundant at the dermoeidermal junction in HLE, but they are present only as single or rare scattered clusters in squamous cell carcinoma and actinic keratoses.11 Earlier studies have shown that these cells may play an important role in the initiation of immune responses and can be found in increased numbers in several inflammatory disorders.13–15 Immunohistochemical staining for CD123 in our case of HLE demonstrated a large number of strongly immunoreactive cells in the superficial dermis (Figure 1, H).

Hypertrophic lupus erythematosus may closely mimic HLP, but the clinical features are quite different. Hypertrophic lupus erythematosus usually arises on the face and arms and less often on the chest, whereas HLP occurs on the lower extremities. Several histologic features are also helpful in resolving the differential (Figure 5). Basal cell damage in HLP is often limited to the tips of the elongated rete ridges. Hypertrophic lichen planus also tends to have more hypergranulosis than HLE. Furthermore, HLP lacks the follicular plugging, intraepidermal elastic fibers, angiocentric lymphocytic inflammation, and dermal mucin that may be seen in HLE.

Lichenoid drug eruptions with prominent epidermal hyperplasia may resemble HLE, but LDEs lack other histopathologic features of HLE, such as dermal mucin, follicular plugging, and basement membrane thickening. The infiltrate of LDE is often less dense and less bandlike compared with HLE. Although LDE may contain eosinophils in the infiltrate and parakeratosis, eosinophils have also been reported within a subset of HLE lesions (Figure 6).8,11

Other disorders with prominent epidermal hyperplasia and inflammation not considered primary interface dermatitides may rarely enter the differential of HLE. The halogenodermas are a group of dermatoses caused by chronic application or ingestion of halogens. There is striking epidermal hyperplasia, but clinical history and the presence of intraepidermal microabscesses containing neutrophils and eosinophils, and the lack of prominent interface changes allow its distinction from HLE. Deep fungal infections may also demonstrate pseudoepitheliomatous hyperplasia (Figure 7, A). Interface changes are typically lacking, and special stains for fungi (Gomori-Grocott methenamine silver stain, periodic acid–Schiff) and tissue cultures will demonstrate organisms. Finally, perforating disorders with transepidermal elimination of elastin (elastosis perforans serpiginosa, perforating folliculitis, perforating pseudoxanthoma elasticum) may resemble HLE, but these lesions contain neutrophils and histiocytes with fewer lymphocytes and typically do not demonstrate vacuolar interface changes (Figure 7, B). Special stains for elastin...
Figure 5. Hypertrophic lichen planus (HLP). Punch biopsy of HLP showing a superficial rather than deep infiltrate. Note lack of typical features of hypertrophic lupus erythematosus (HLE), such as follicular plugging, angiocentric inflammation, and dermal mucin (A). Hypertrophic lichen planus demonstrates wedge-shaped hypergranulosis and shows less basal cell damage than HLE (B) (hematoxylin-eosin, original magnifications ×20 [A] and ×400 [B]).

Figure 6. Lichenoid drug eruption (LDE). Hyperplastic LDE may resemble hypertrophic lupus erythematosus (HLE), but the infiltrate is superficial and there is a lack of dermal mucin, follicular plugging, and basement membrane thickening (A). Although eosinophils may be seen in HLE, many more are typically present in LDE (B) (hematoxylin-eosin, original magnifications ×20 [A] and ×600 [B]).

Figure 7. Other disorders with prominent epidermal hyperplasia that may rarely mimic hypertrophic lupus erythematosus (HLE) include deep fungal infections that are typically special stain and/or culture positive (A) and perforating disorders. The latter contain neutrophils and histiocytes, unlike HLE, and have more altered elastic tissue (B) (hematoxylin-eosin, original magnification ×400).
Verhoeff, Movat) show greater amounts of altered elastic tissue in the perforating disorders than is seen in HLE.

**Prognosis and Treatment**

Discoid lupus erythematosus, including HLE, is a chronic, relapsing condition that may result in significant scarring. First-line therapies include antimalarials, and topical and intralesional steroids, together with sun protection. Hypertrophic lupus erythematosus is often refractory to treatment. Recently some success has been seen with regimens using thalidomide and pulsed dye laser therapy.

**Summary**

A high index of suspicion and careful clinicopathologic correlation are the keys to making the diagnosis of HLE, because concurrent, classic lesions of DLE are common. One may consider HLE when confronted with a superficial biopsy from the face, arms, or chest that resembles a lichenoid actinic keratosis. In the absence of clinical information, it would be appropriate to issue a comment stating that an interface process such as lupus cannot be ruled out given the presence of a lichenoid tissue reaction pattern. When present, typical histologic features of lupus, such as follicular plugging, angiocentric lymphocytic inflammation, and dermal mucin, are very helpful clues to the diagnosis of HLE. These changes are not seen in the other lesions in the differential. Recognition of HLE is essential to avoid the overdiagnosis of squamous neoplasia; however, the fact that squamous cell carcinoma is a rare complication of longstanding lesions of HLE should be appreciated.

**References**