Tender Nodular Lesions in the Axilla and Vulva

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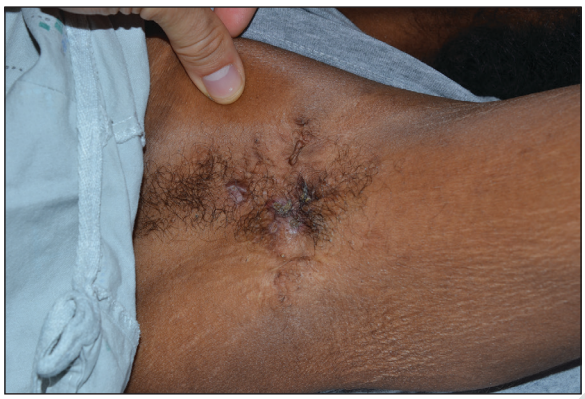

A 28-year-old woman presented with tender burning lesions of the left axillary and vaginal skin that had worsened over the last year. Her medical history was notable for hidradenitis suppurativa, which had been present since adolescence, as well as pulmonary Langerhans cell histiocytosis diagnosed 7 years prior to the current presentation after a spontaneous pneumothorax that eventually led to a pulmonary transplantation 3 years prior. The patient's Langerhans cell histiocytosis was believed to have resolved without treatment after smoking cessation. Physical examination revealed nodular inflammation and scarring with deep undermining along the left axilla as well as swelling of the mons pubis with erosive skin lesions in the surrounding vaginal area. Bilateral cervical, axillary, inguinal, supraclavicular, and femoral lymph node chains were negative for adenopathy. A shave biopsy was performed on the axillary nodule.

WHAT'S YOUR **DIAGNOSIS?**

a. *Actinomyces* infection
b. cutaneous Langerhans cell histiocytosis
c. dermatofibrosarcoma protuberans
d. lymphomatoid papulosis
e. recurrence of hidradenitis suppurativa

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The authors report no conflict of interest.
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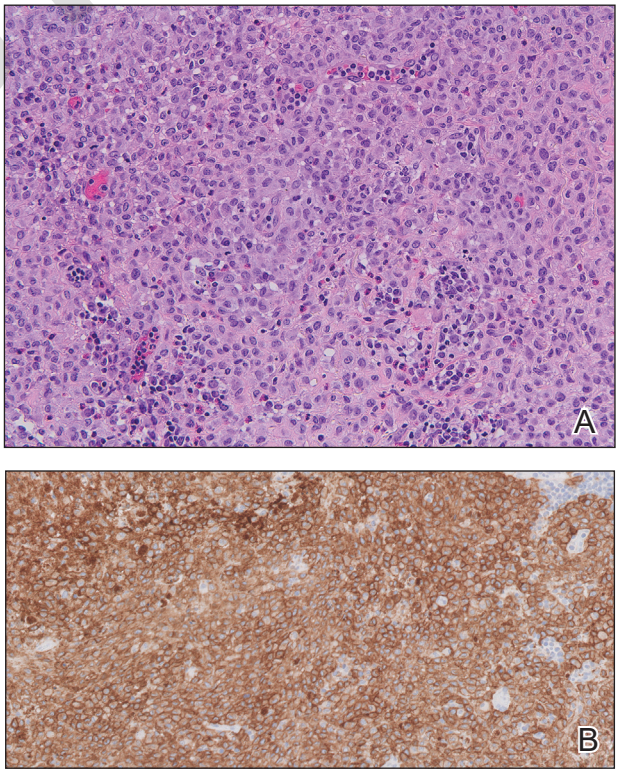
THE **DIAGNOSIS:**
Cutaneous Langerhans Cell Histiocytosis

Histopathologic findings of the left axillary lesion included a diffuse infiltrate of irregular hematolymphoid cells with reniform nuclei that strongly and diffusely stained positively with CD1a and S-100 but were negative for CD138 and CD163 (Figure). Numerous eosinophils also were present. The surrounding lymphocytic infiltrate stained positively with CD45. Polymerase chain reaction of the vaginal lesion was negative for herpes simplex virus types 1 and 2. Biopsy of the vaginal lesion revealed a mildly acanthotic epidermis and an aggregation of epithelioid cells with reniform nuclei in the papillary dermis. Positron emission tomography revealed widely disseminated disease. Sequencing of the mitogen-activated protein kinase/extracellular signal-regulated kinase pathway showed amplified expression of these genes but found no mutations. These results led to a diagnosis of cutaneous Langerhans cell histiocytosis (LCH) with a background of hidradenitis suppurativa (HS). Our patient has since initiated therapy with trametinib leading to disease improvement without known recurrence.

Langerhans cell histiocytosis is a rare disease of clonal dendritic cells (Langerhans cells) that can present in any organ.[1] Most LCH diagnoses are made in pediatric patients, most often presenting in the bones, with other presentations in the skin, hypophysis, liver, lymph nodes, lungs, and spleen occurring less commonly.[2] Proto-oncogene *BRAF V600E* mutations are a common determinant of LCH, with half of cases linked with this mutation that leads to enhanced activation of the mitogen-activated protein kinase pathway, though other mutations have been reported.[3,4] These genetic alterations suggest LCH is neoplastic in nature; however, this is controversial, as spontaneous regression among pulmonary LCH has been observed, pointing to a reactive inflammatory process.[5] Cutaneous LCH can present as a distinct papular or nodular lesion or multiple lesions with possible ulceration, but it is rare that LCH first presents on the skin.[2,6] There is a substantial association of cutaneous LCH with the development of systemically disseminated LCH as well as other blood tumors, such as myelomonocytic leukemia, histiocytic sarcoma, and multiple lymphomas; this association is thought to be due to the common origin of LCH and other blood diseases in the bone marrow.[6]

Histopathology of LCH shows a diffuse papillary dermal infiltrate of clonal proliferation of reniform or cleaved histiocytes.[5] Epidermal ulceration and epidermotropism also are common. Neoplastic cells are found admixed with variable levels of eosinophils, lymphocytes, plasma cells, and neutrophils, though eosinophils typically are elevated. Immunohistochemistry characteristically shows the expression of CD1a, S-100, and/or CD207, and the absence of CD163 expression.

Treatment of LCH is primarily dependent on disease dissemination status, with splenic and hepatic involvement, genetic panel results, and central nervous system risk considered in the treatment plan.[5] Langerhans cell histiocytosis localized to the skin may require follow-up and monitoring, as spontaneous regression of cutaneous LCH is common. However, topical steroids or psoralen and long-wave UV radiation are potential treatments. Physicians who diagnose unifocal cutaneous LCH should have high clinical suspicion of disseminated LCH, and laboratory and radiographic evaluation may be necessary to rule out systemic disease, as more than 40% of patients with cutaneous LCH have systemic disease upon full evaluation.[7] With systemic involvement, systemic chemotherapy may reduce morbidity and mortality, but clinical response should be monitored after 6 weeks of treatment, as results are variably effective. Vinblastine is the most common chemotherapy regimen, with an 84% survival



Cutaneous Langerhans cell histiocytosis. A, Histopathology revealed a diffuse dermal infiltrate of mononuclear cells with cleaved nuclei as well as scattered lymphocytes and eosinophils (H&E, original magnification ×200). B, Lesional cells strongly and diffusely expressed CD1a (original magnification ×200).

rate and 51.5% event-free survival rate after 8 years.[8] Targeted therapy for common genetic mutations also is possible, as vemurafenib has been used to treat patients with the *BRAF V600E* mutation.

Due to the variable clinical presentation of cutaneous LCH, the lesions can mimic other common skin diseases such as eczema or seborrheic dermatitis.[7] However, there are limited data on LCH presenting in infiltrative skin disease. Langerhans cell histiocytosis that was misdiagnosed as HS has been reported,[9-11] but LCH presenting alongside long-standing HS is rare. Although LCH often mimics infiltrative skin diseases, its simultaneous presentation with a previously confirmed diagnosis of HS was notable in our patient.

In our patient, the differential diagnosis included HS, *Actinomyces* infection, lymphomatoid papulosis, and dermatofibrosarcoma protuberans. Cutaneous findings in HS include chronic acneform nodules with follicular plugging, ruptured ducts leading to epithelized sinuses, inflammation, and abscesses in the axillae or inguinal and perineal areas.[11] Histopathology reveals follicular occlusion and hyperkeratinization, which cause destruction of the pilosebaceous glands. Hidradenitis suppurativa features on immunohistochemistry often are conflicting, but there consistently is co-localization of keratinocyte hyperplasia with CD3-, CD4-, CD8-, and CD68-positive staining of cells that produce tumor necrosis factor α, IL-12, IL-23, and IL-32, with CD1a staining variable.[12] An infection with *Actinomyces*, a slow-progressing anaerobic or microaerophilic bacteria, may present in the skin with chronic suppurative inflammation on the neck, trunk, and abdomen. The classic presentation is subcutaneous nodules with localized infiltration of abscesses, fistulas, and draining sinuses.[13] Morphologically, *Actinomyces* causes chronic granulomatous infection with 0.1- to 1-mm sulfur granules, which are seen as basophilic masses with eosinophilic terminal clubs on hematoxylin and eosin staining.[14] Histopathology reveals gram-positive filamentous *Actinomyces* bacteria that branch at the edge of the granules. Lymphomatoid papulosis, a nonaggressive T-cell lymphoma, presents as papulonodular and sometimes necrotic disseminated lesions that spontaneously can regress or can cause a higher risk for the development of more aggressive lymphomas.[15] Histopathology shows consistently dense, dermal, lymphocytic infiltration. Immunohistochemistry is characterized by lymphocytes expressing CD30 of varying degrees: type A with many CD30 staining cells, type B presenting similar to mycosis fungoides with little CD30 staining, and type C with lymphocytic CD30-staining plaques. Dermatofibrosarcoma protuberans is a low-grade soft-tissue malignant tumor with extensive local infiltration characterized by asymptomatic plaques on the trunk and proximal extremities that are indurated and adhered to the skin.[16] Histopathology shows extensive invasion into the adjacent tissue far from the original focus of the tumor.

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