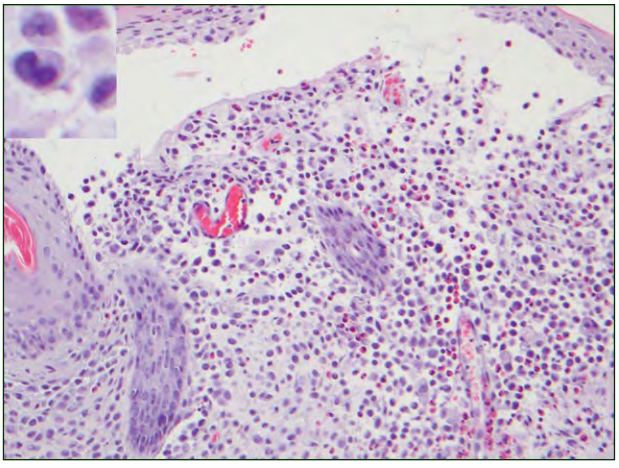
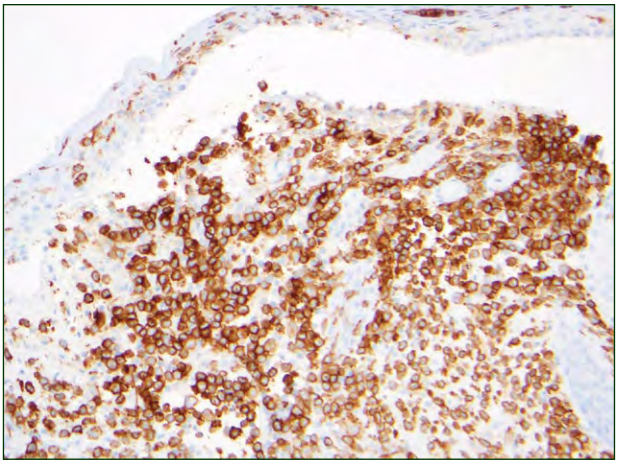


H&E, original magnification ×200 (original magnification ×400 [inset in top left corner]).



CD1a, original magnification ×200.

The best diagnosis is:

a. extramammary Paget disease
b. Langerhans cell histiocytosis
c. melanoma in situ
d. pagetoid Bowen disease
e. patch-stage mycosis fungoides

PLEASE TURN TO PAGE 67 FOR DERMATOPATHOLOGY DIAGNOSIS DISCUSSION

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The authors report no conflict of interest.
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Langerhans Cell Histiocytosis

Langerhans cell histiocytosis (LCH), previously known as histiocytosis X,[1,2] is an abnormal clonal proliferation of Langerhans cells that is histologically characterized by papillary dermal infiltration of uniformly large ovoid cells that are 15 to 25 μm in diameter, with abundant eosinophilic cytoplasm and vesicular reniform (kidney-shaped) nuclei with inconspicuous nucleoli (Figure 1). Epidermotropic Langerhans cells may be prominent, both singular or in clusters.[3]

In LCH, the dermal Langerhans cells often are admixed with variable numbers of eosinophils, lymphocytes, histiocytes, neutrophils, plasma cells, and mast cells.[3,4] Secondary features such as crust, pustule formation, hemorrhage, and/or necrosis may obscure the usual LCH infiltrate, rendering diagnosis difficult on routine hematoxylin and eosin histologic sections. Older nonproliferative lesions of LCH may appear granulomatous, xanthomatous, or fibrotic.[5,6]

Immunohistochemical (IHC) markers for Langerhans cells include CD1a (Figure 2), HLA-DR antigen, S-100, and langerin (also known as CD207).[7-10] The presence of Birbeck granules on electron microscopy is pathognomonic for Langerhans cells. Birbeck granules are tennis racket–shaped or rod-shaped organelles with a zipperlike appearance along the handle. Although diagnostic of Langerhans cells, the availability of reliable IHC stains has superseded electron microscopy in confirming the diagnosis of LCH.

The dense, often bandlike, papillary dermal infiltrate of LCH invites histologic comparison to patch-stage mycosis fungoides (MF)(Figure 3), which is further complicated by epidermotropic Langerhans cells mimicking the Darier-Pautrier microabscesses of MF. However, unlike the large eosinophilic cells of LCH, the infiltrating cells of patch-stage MF are small, round, basophilic lymphocytes with a high nuclear to cytoplasmic ratio. The neoplastic lymphocytes of MF typically have a $CD4^+$ helper T cell immunohistochemical profile and generally are negative for Langerhans cell IHC markers. An atypical lymphoid infiltrate rarely may have few $CD1a^+$ cells.[11]

The atypical melanocytes of melanoma in situ do not share the reniform nuclei of Langerhans cells. Melanoma cells are variably epithelioid or spindled, often with conspicuous eosinophilic nucleoli and finely pigmented cytoplasm (Figure 4). Nesting of melanocytes along the dermoepidermal junction may be another helpful distinguishing feature.[12]

The tumor cells of extramammary Paget (EMP) disease are large with abundant pale cytoplasm, copious mucin, and pleomorphic nuclei with mitotic figures. As in LCH, lesions of EMP exhibit large intraepidermal cells that are either single or in small clusters (Figure 5). In contrast, the greatest concentration of EMP tumor cells is localized to the basal and parabasal epidermis, and EMP cells rarely invade the dermis. Extramammary Paget cells stain positively with carcinoembryonic antigen, CA15-3, KA-93, CD5, CD23, epithelial membrane antigen, and low-molecular-weight keratins. Intracellular mucin may be highlighted with mucicarmine, Alcian blue, colloidal iron, and periodic acid–Schiff stains.

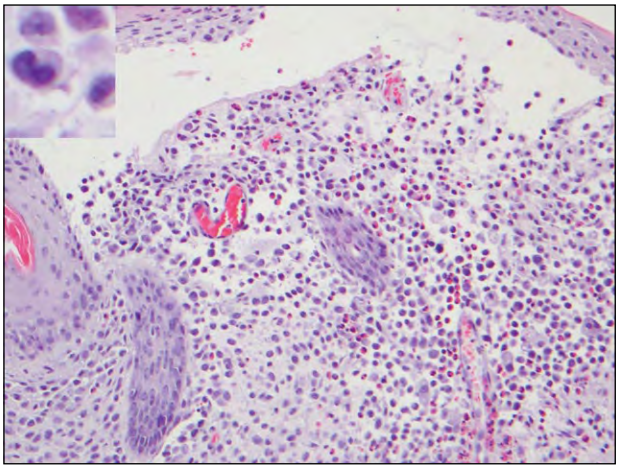

Figure 1. Papillary dermal infiltrate with epidermotropism of large ovoid Langerhans cells causing a subepidermal cleft with several interspersed eosinophils (H&E, original magnification ×200). Characteristic reniform nucleus of a Langerhans cell (H&E, original magnification ×400 [inset in top left corner]).

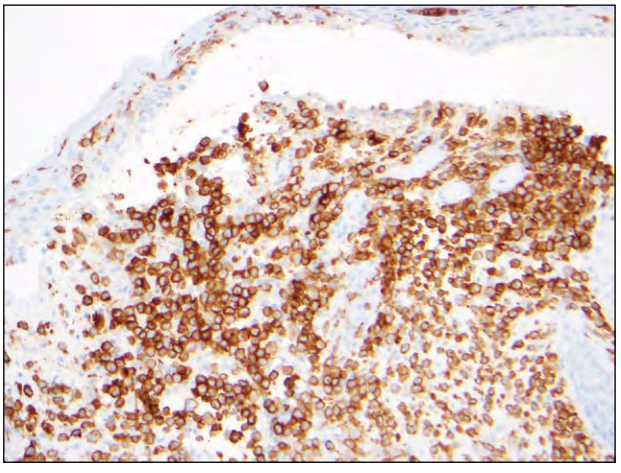

Figure 2. Langerhans cells stain diffusely positive with CD1a (original magnification ×200).

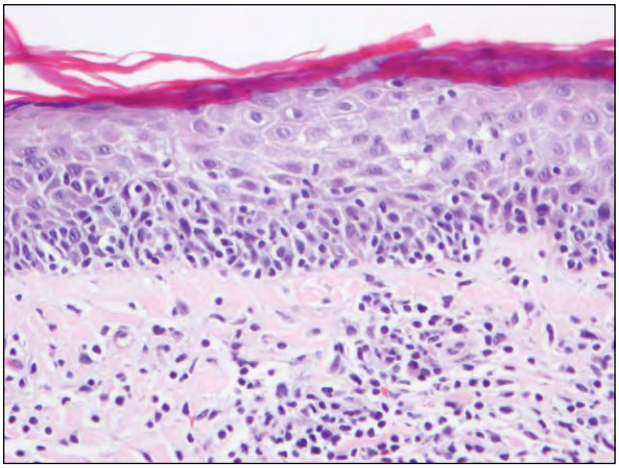

Figure 3. Bandlike infiltrate of atypical lymphocytes with epidermotropic cells, as seen in patch-stage mycosis fungoides (H&E, original magnification ×200).

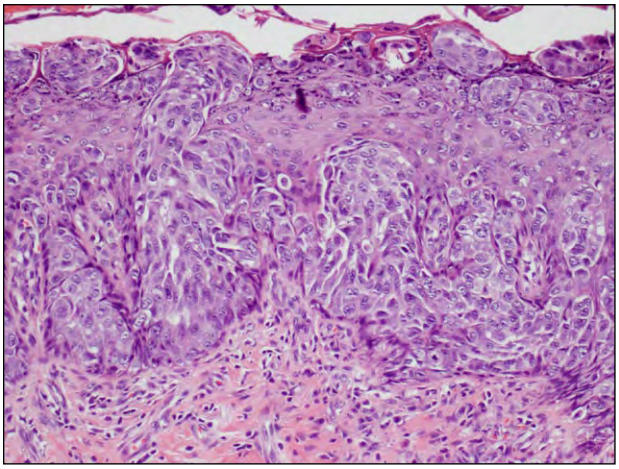

Figure 5. Extramammary Paget disease is characterized by large pleomorphic cells with abundant pale cytoplasm, copious mucin, and crushing of the basal layer (H&E, original magnification ×100).

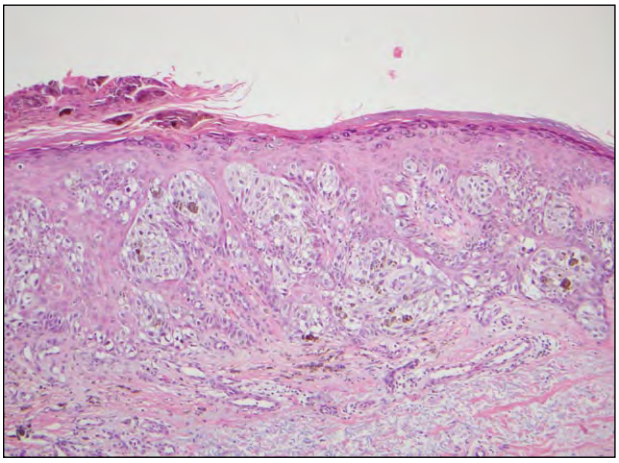

Figure 4. Nested and single atypical pigmented melanocytes throughout all layers of the epidermis and invading into the superficial dermis, as seen in superficial spreading melanoma (H&E, original magnification ×100).

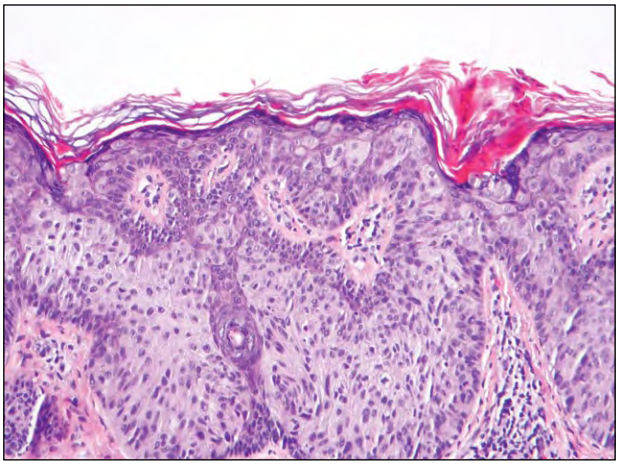

Figure 6. The pagetoid variant of Bowen disease (squamous cell carcinoma in situ) reveals nests of large atypical keratinocytes and intervening thin strands of relatively normal keratinocytes (H&E, original magnification ×100).

Extramammary Paget cells do not stain with Langerhans cell markers.

Bowen disease, a form of cutaneous squamous cell carcinoma in situ, is histologically characterized by full-thickness keratinocyte atypia of the epidermis, mitotic figures, dyskeratosis, and loss of the granular layer with overlying parakeratosis. The pagetoid variant of Bowen disease is distinguished by nests of large atypical keratinocytes with pale cytoplasm and thin intervening strands of relatively normal keratinocytes, giving the appearance of epidermotropism (Figure 6). Invasive carcinoma develops in approximately 8% of untreated cases, which makes dermal invasion of the malignant cells rare.[13] In cases where it is difficult to distinguish pagetoid Bowen disease from the epidermotropism of LCH, IHC staining becomes helpful, as the tumor cells of Bowen disease are negative for CD1a and other Langerhans cell markers.

REFERENCES

1. Lichtenstein L. Histiocytosis X; integration of eosinophilic granuloma of bone. Letterer-Siwe disease and Schüller-Christian disease as related manifestations of a single nosologic entity. *AMA Arch Pathol*. 1953;56:84-102.
2. Newman B, Hu W, Nigro K, et al. Aggressive histiocytic disorders that can involve the skin [published online

ahead of print October 9, 2006]. *J Am Acad Dermatol*. 2007;56:302-316.
3. Harrist TJ, Bhan AK, Murphy GF, et al. Histiocytosis-X: in situ characterization of cutaneous infiltrates with monoclonal antibodies. *Am J Clin Pathol*. 1983;79:294-300.
4. Foucar E, Piette WW, Tse DT, et al. Urticating histiocytosis: a mast cell–rich variant of histiocytosis X. *J Am Acad Dermatol*. 1986;14(5, pt 2):867-873.
5. Altman J, Winkelmann RK. Xanthomatous cutaneous lesions of histiocytosis X. *Arch Dermatol*. 1963;87:164-170.
6. Risdall RJ, Dehner LP, Duray P, et al. Histiocytosis X (Langerhans' cell histiocytosis). prognostic role of histopathology. *Arch Pathol Lab Med*. 1983;107:59-63.
7. Rowden G, Connelly EM, Winkelmann RK. Cutaneous histiocytosis X. the presence of S-100 protein and its use in diagnosis. *Arch Dermatol*. 1983;119:553-559.
8. Rabkin MS, Kjeldsberg CR, Wittwer CT, et al. A comparison study of two methods of peanut agglutinin staining with S100 immunostaining in 29 cases of histiocytosis X (Langerhans' cell histiocytosis). *Arch Pathol Lab Med*. 1990;114:511-515.
9. Emile JF, Wechsler J, Brousse N, et al. Langerhans' cell histiocytosis. definitive diagnosis with the use of monoclonal antibody O10 on routinely paraffin-embedded samples. *Am J Surg Pathol*. 1995;19:636-641.
10. Lau SK, Chu PG, Weiss LM. Immunohistochemical expression of Langerin in Langerhans cell histiocytosis and non-Langerhans cell histiocytic disorders. *Am J Surg Pathol*. 2008;32:615-619.
11. Pigozzi B, Bordignon M, Belloni Fortina A, et al. Expression of the CD1a molecule in B- and T-lymphoproliferative skin conditions. *Oncol Rep*. 2006;15:347-351.
12. Billings TL, Barr R, Dyson S. Langerhans cell histiocytosis mimicking malignant melanoma: a diagnostic pitfall. *Am J Dermatopathol*. 2008;30:497-499.
13. Kao GF. Carcinoma arising in Bowen's disease. *Arch Dermatol*. 1986;122:1124-1126.