

55-year-old man with ulcers in inguinal fold and intergluteal cleft found to have systemic Langerhans cell histiocytosis



Euphemia W. Mu, MD,^a Nigar Anjuman Khurram, MD,^b Zhiheng Pei, MD, PhD,^{c,d} Hao Feng, MD,^a Nicholas Cassai, MS HTL(ASCP),^d Shane A. Meehan, MD,^{a,c} and Jo-Ann Latkowski, MD^{a,d}
New York, New York

Key words: Birbeck granules; *BRAF* V600 mutations; Langerhans cell histiocytosis; ulcers.

INTRODUCTION

This article describes the case of a patient with cutaneous ulcers who was found to have systemic Langerhans cell histiocytosis (LCH). This article includes the clinical, histology, and electron microscopy images, in addition to a description of the presentation, workup, and management of this rare disease in this patients, with a review of the literature.

CASE

A 55-year-old man presented to the Veterans Affairs New York Harbor Hospital for evaluation of ulcers in his left inguinal and intergluteal folds that had been progressing over several months (Fig 1). During a screening colonoscopy for workup of worsening anemia 1 month prior, a polyp was excised and pathology revealed an unusual histiocytic infiltration seen on pathology. Positron emission tomography–computed tomography revealed hypermetabolic cutaneous foci involving the left inguinal and perianal regions corresponding to sites of cutaneous ulceration. The patient described the ulcers as asymptomatic and gradually enlarging in size. He did not have drainage or pain from the affected areas. He also had no sexual activity, nausea, vomiting, abdominal pain, blood in stool, fevers, weight loss, or other constitutional symptoms.

Examination of the patient's left inguinal fold and intergluteal cleft revealed well-demarcated ulcers

Abbreviation used:

LCH: Langerhans cell histiocytosis

with rolled cobblestoned borders and fibrinous granulation tissue at the ulcer base. The lesions were nontender on palpation without an associated odor, erythema, or vesicles. There was shotty inguinal lymphadenopathy. On the soft oral palate, exophytic verrucous plaques were noted.

A complete blood count with differential analysis, basic metabolic panel, and rapid plasma reagin were unremarkable. On histopathologic examination, both skin and colon biopsies showed a dense proliferation of histiocytes and lymphocytes. Immunostaining was positive for S100, CD1a, and CD4 and weakly positive for CD45 and CD68 (Fig 2). CD20 and CD3 were negative. Electron microscopy of the skin biopsy showed Birbeck granules within the cytoplasm of a Langerhans cell (Fig 3). The skin lesion was negative for *BRAF* V600 mutations, including V600E, V600K, V600D, V600R, V600A, V600G, and V600M. A bone marrow biopsy was negative for CD1a and S100.

DISCUSSION

The diagnosis was the systemic LCH in an adult patient. LCH represents a spectrum of diseases characterized by clonal proliferations of Langerhans cells.¹

From the Ronald O. Perelman Department of Dermatology, New York University School of Medicine^a; Department of Pathology, SUNY Downstate Medical Center, New York^b; and Department of Pathology, New York University School of Medicine^c; and Department of Veterans Affairs New York Harbor Healthcare System.^d

Funding sources: Supported in part by the National Cancer Institute, National Institute of Allergy and Infectious Diseases, and National Institute of Dental and Craniofacial Research of the National Institutes of Health under award numbers U01CA182370, R01CA159036, R01AI110372, and R21DE025352. The content is solely the responsibility of the authors and does not necessarily represent the official views of

the National Institutes of Health, the US Department of Veterans Affairs, or the United States Government.

Conflicts of interest: None declared.

Correspondence to: Euphemia W. Mu, MD, 240 East 38th St, 11th floor, New York, NY, 10016. E-mail: euphemia.mu@nyumc.org. JAAD Case Reports 2018;4:837-40.

2352-5126

Published by Elsevier on behalf of the American Academy of Dermatology, Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

<https://doi.org/10.1016/j.jidcr.2018.05.016>

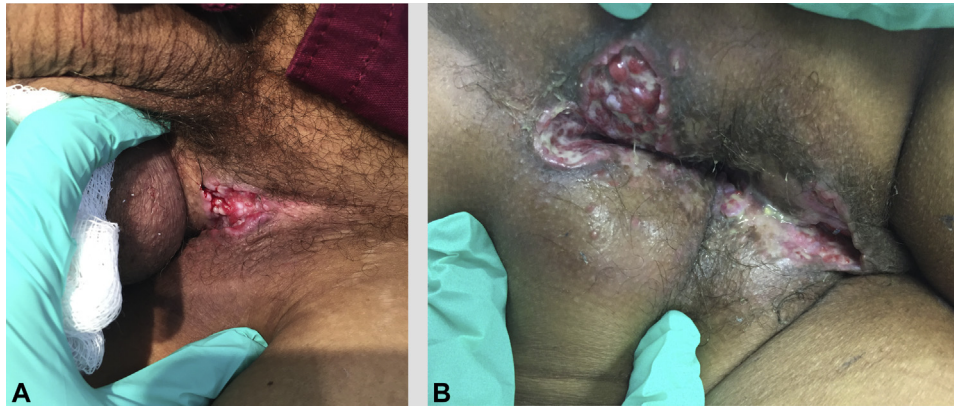


Fig 1. **A** and **B**, Well-demarcated inguinal and intergluteal ulcers found during physical examination were nontender on palpation.

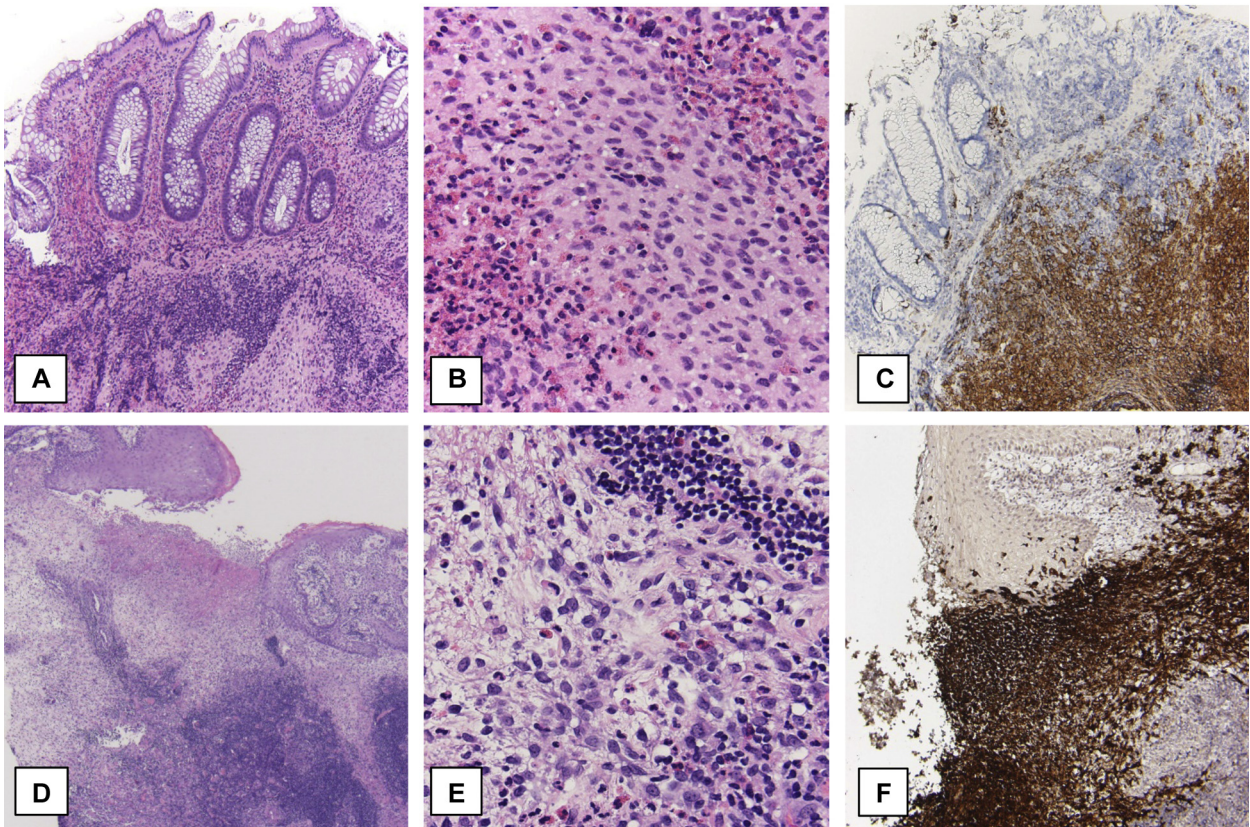


Fig 2. Colon and skin histopathology of patient with Langerhans cell histiocytosis. **A**, Polypoid colonic lesion shows a dense proliferation of histiocytes in the submucosa with eosinophilic abscesses in addition to neutrophilic and lymphocytic infiltrates. **B**, Oval histiocytes approximately 15 μm characterized by folded, indented or lobulated nuclei with fine chromatin, inconspicuous nucleoli, and thin nuclear membranes. The cytoplasm is moderately abundant and slightly eosinophilic. **C**, Langerhans cell histiocytosis involvement at colon. **D**, Skin biopsy reveals similar infiltrate to that of the colon specimen. **E**, Histiocytes with large, pale, folded or lobulated (often reniform), vesicular nuclei and abundant, slightly eosinophilic or amphophilic cytoplasm. **F**, Histiocytic infiltrate. (**A**, **B**, **D**, and **E**; Hematoxylin-eosin stain; **C** and **F**; CD1a stain; original magnification: **A**, **C**, **D**, and **F**, X2; **B** and **E**, X20.)

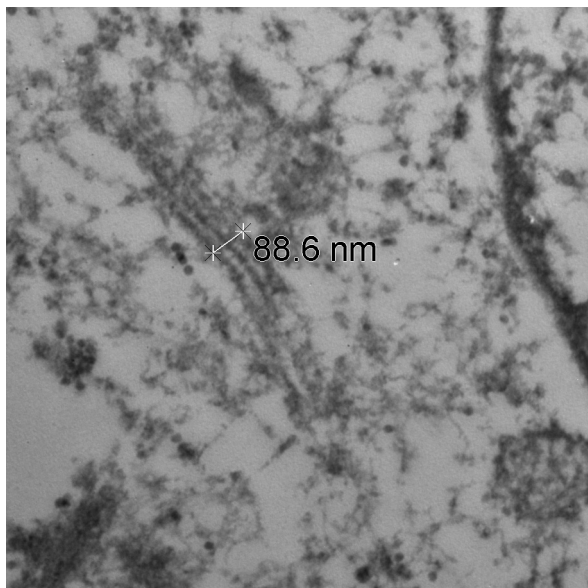


Fig 3. Electron microscopy image of cytoplasm of Langerhans cell shows characteristic Birbeck granules.

The current clinical classification of LCH is based on the extent of involvement of disease, ranging from single system to progressive multisystem LCH.² LCH is most commonly diagnosed in pediatric patients 1-3 years of age.³ A large case series reported 66%-90% of patients presenting before 18 years of age.⁴⁻⁶ LCH has an estimated annual incidence of 5 cases per 1 million children and 1-2 cases per 1 million adults. In children, LCH is more common in boys, with an approximate ratio of 2:1; in adults, there is a slight female predominance.⁵

When systemically involved, LCH tends to affect the skeletal, cutaneous, lymphoreticular, pulmonary, and pituitary gland systems. Involvement of reproductive organs, the central nervous system, the gastrointestinal tract has also been described.¹ LCH with gastrointestinal manifestations is exceedingly rare, with only 4 reported cases in the current literature. One report describes a 49-year-old Japanese woman with sessile protuberances on her stomach wall on endoscopy and biopsy revealing characteristic features of LCH.⁷ Three other patients have been described as having gastrointestinal involvement, and each were treated successfully with surgical resection.⁵

The pathogenesis of LCH has yet to be elucidated; however, immune dysregulation has been implicated.⁸ The detection of clonal populations of histiocytes in different forms of LCH suggests a neoplastic etiology due to mutations of bone marrow precursor cells.⁹ A majority (57%) of LCH specimens were found to contain the *BRAF* V600E mutation, further supporting a neoplastic origin and raising the

possibility of using BRAF inhibitors for future LCH therapy.¹⁰ However, the skin lesion in our patient was negative for the *BRAF* V600 mutations V600E, V600K, V600D, V600R, V600A, V600G, and V600M.

The pathology of LCH can be as variable as the clinical presentation. Classically, LCH involves a proliferation of Langerhans cells in the papillary dermis with reniform (kidney-shaped) nuclei. Often, Langerhans cells can infiltrate the epidermis with interface changes. Dermal Langerhans cells are typically admixed with mast cells, neutrophils, lymphocytes, plasma cells, and eosinophils. LCH lesions were positive for CD1a, Langerin (CD207), and S100 on immunostaining, and lacked classic macrophage/monocyte markers, such as CD68 or HAM6. Electron microscopy revealed Birbeck granules, which are racquet-shaped cytoplasmic structures found in Langerhans cells (Fig 3). Presently, electron microscopy is rarely performed, given the ease of testing via CD1a and Langerin immunostaining.¹¹

The differential diagnosis for inguinal and intergluteal ulcers includes inflammatory conditions such as pyoderma gangrenosum, cutaneous Crohn disease, Behcet disease, and vasculitis; infectious etiologies such as bacterial (*Streptococcus*, *Treponema*, *Haemophilus*, *Klebsiella*), viral (herpes simplex virus), fungal, and parasitic; neoplastic disorders including basal cell carcinoma, squamous cell carcinoma, metastases, and extramammary Paget disease; reactions to medications such as hydroxyurea, methotrexate, interferon, and anticoagulants; and exogenous causes such as traumatic or factitial etiologies.

All patients diagnosed with LCH are recommended to have a hematologic, pulmonary, hepatosplenic, renal, and skeletal systemic evaluation to determine the extent of disease involvement. Central nervous system and bone marrow evaluation might be indicated. Treatment of LCH depends on the number and severity of the organ systems involved. For skin disease, topical corticosteroids, topical antimicrobials, phototherapy, and topical nitrogen mustard have been reported in small case series. More extensive cutaneous disease has been treated with thalidomide with reported efficacy. More extensive disease involving multiple organ systems requires systemic therapy. Treatments include vinblastine, etoposide, multidrug chemotherapy, etanercept, cyclosporine, imatinib, radiation, prednisone, and cyclophosphamide alone or in combination. For severe disease, hematopoietic stem cell, liver, or lung transplantation might be required.¹

We report an unusual case of LCH occurring in a male adult with gastrointestinal involvement. In follow-up, the patient was started on systemic therapy with hydroxyurea and gradually increased

from 500 mg daily to 1500 mg daily. He reports the lesion on his hard palate has improved with less tenderness when eating. Cutaneous lesions have been stable, with minimal improvement with intralesional steroid injections.

REFERENCES

1. Baumgartner I, von Hochstetter A, Baumert B, Luetolf U, Follath F. Langerhans'-cell histiocytosis in adults. *Med Pediatr Oncol*. 1997;28:9-14.
2. Osband ME. Histiocytosis X. Langerhans' cell histiocytosis. *Hematol Oncol Clin North Am*. 1987;1:737-751.
3. Chu T, D'Angio GJ, Favara BE, Ladisch S, Nesbit M, Pritchard J. Histiocytosis syndromes in children. *Lancet*. 1987;2:41-42.
4. Enriquez P, Dahlin DC, Hayles AB, Henderson ED. Histiocytosis X: a clinical study. *Mayo Clin Proc*. 1967;42:88-99.
5. Malpas JS. Langerhans cell histiocytosis in adults. *Hematol Oncol Clin North Am*. 1998;12:259-268.
6. Greenberger JS, Crocker AC, Vawter G, Jaffe N, Cassady JR. Results of treatment of 127 patients with systemic histiocytosis. *Medicine (Baltimore)*. 1981;60:311-338.
7. Iwafuchi M, Watanabe H, Shiratsuka M. Primary benign histiocytosis X of the stomach. A report of a case showing spontaneous remission after 5 1/2 years. *Am J Surg Pathol*. 1990;14:489-496.
8. Leikin SL. Immunobiology of histiocytosis-X. *Hematol Oncol Clin North Am*. 1987;1:49-61.
9. Willman CL, Busque L, Griffith BB, et al. Langerhans'-cell histiocytosis (histiocytosis X)—a clonal proliferative disease. *N Engl J Med*. 1994;331:154-160.
10. Badalian-Very G, Vergilio JA, Degar BA, et al. Recurrent *BRAF* mutations in Langerhans cell histiocytosis. *Blood*. 2010;116:1919-1923.
11. Pileri SA, Grogan TM, Harris NL, et al. Tumours of histiocytes and accessory dendritic cells: an immunohistochemical approach to classification from the International Lymphoma Study Group based on 61 cases. *Histopathology*. 2002;41:1-29.