

# Disseminated Langerhans cell histiocytosis in a 51-year-old man with cutaneous involvement and multiple endocrinopathies



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## INTRODUCTION

Langerhans cell histiocytosis (LCH) is a rare disorder arising from the abnormal proliferation and subsequent deposition of CD1a<sup>+</sup> myeloid dendritic cells in various organs. Clinical features are heterogeneous and primarily depend on specific organ systems involved, ranging from skin rash and osteolytic skull lesions to treatment-refractory multiorgan failure in severe cases. Although LCH predominantly affects the pediatric population, an increasing number of adult-onset cases are being reported.<sup>1,2</sup> We describe the case of a 51-year-old man with disseminated (multisystem) LCH stemming from an in-frame, oncogenic *BRAF* mutation.

## CASE REPORT

A 51-year-old man presented with a 3-year history of a severe, pruritic scalp rash extending into the ear canals. Associated symptoms included intermittent otalgia, decreased hearing, otorrhea, diplopia, and ataxia. New lesions had also appeared within the last 4 months involving the axillae, abdominal pannicular fold, and groin. The intertriginous lesions were neither painful nor pruritic but had recently opened with purulent drainage. Clinical diagnoses from prior providers included seborrheic dermatitis, psoriasis, folliculitis, and hidradenitis. Symptoms were refractory to treatment with topical steroids, antifungals, and oral antibiotics. On further questioning, the patient also reported weight loss, early satiety, polydipsia, polyuria, night sweats, constipation, and worsening erectile dysfunction.

### Abbreviations used:

ECD: Erdheim-Chester disease  
 LCH: Langerhans cell histiocytosis

Physical examination found erythematous, crusted papules and plaques with ulcerations in the axillae (Fig 1, A), abdominal pannicular fold (Fig 1, B), groin, gluteal cleft, external ear canals, anterior neck, and occipital scalp. A punch biopsy specimen from the external ear canal was obtained.

Histopathology findings showed a dense dermal infiltrate of monomorphic cells with ample eosinophilic cytoplasm and reniform nuclei with longitudinal grooves showing exocytosis into the epidermis and admixed eosinophils (Fig 2). Lesional cells were positive for S100, CD4, CD1a, and CD207 (Fig 3). Based on microscopic findings and clinical presentation, Langerhans cell histiocytosis was diagnosed.

Further workup for systemic involvement followed diagnosis. Head and neck computed tomography scan found expansile and heterogeneously enhancing masses within the pons, medulla, cerebral peduncles, hypothalamus, and external ear canals. Brain magnetic resonance imaging suggested pituitary infundibulum involvement; bloodwork substantiated development of central diabetes insipidus, secondary hypothyroidism, and secondary hypogonadism. Full-body positron emission tomography/computed tomography detected pulmonary and peritoneal nodules—additional areas of metastasis. No lytic lesions or bone metastases were found.

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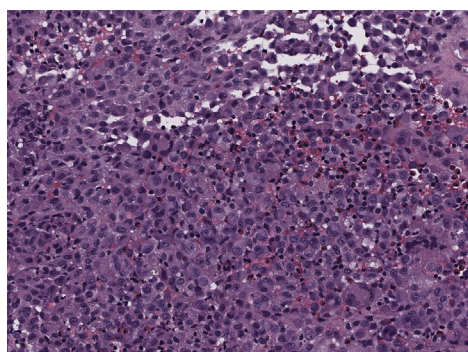
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**Fig 1.** LCH presenting as erythematous, crusted papules and plaques with ulcerations in the left axilla (**A**) and under the abdominal pannicular fold (**B**).



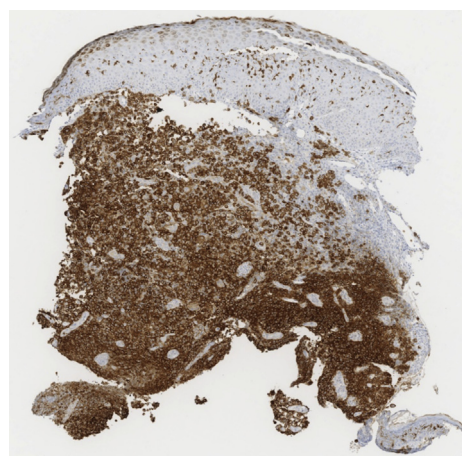
**Fig 2.** Histopathology of LCH. Punch biopsy shows abundant eosinophilic cytoplasm, reniform nuclei, and admixed eosinophils with exocytosis into the epidermis. (Hematoxylin-eosin stain; original magnification:  $\times 250$ .)

Next-generation sequencing identified a rare oncogenic *BRAF* mutation affecting the alpha-C helical region of the *BRAF* kinase domain, resulting in homodimerization and constitutive activation of downstream signaling.

The patient subsequently started monthly cladribine cycles, levothyroxine, testosterone gel, desmopressin, and topical clobetasol, responding rapidly to treatment. His scalp rash began to clear within 3 days of chemotherapy with pruritus resolving completely. One week after completion of his second chemotherapy cycle, he presented to the emergency department with shortness of breath; he was found to have hypotension, tachycardia, and hypoxia on evaluation. He died 1 day later of complications related to a massive saddle pulmonary embolism.

## DISCUSSION

LCH is a rare myeloid neoplasia arising from the accumulation of myeloid dendritic cells (histiocytes)



**Fig 3.** CD1a immunohistochemistry shows positive staining of lesional cells. (CD1a immunohistochemistry stain; original magnification:  $\times 50$ .)

within 1 or multiple organs. Incidence has been estimated at 4 to 4.6 per million children and 1 to 2 per million adults.<sup>3</sup> The major diagnostic element is biopsy demonstrating tissue infiltration by histiocytes with features of the Langerhans cell—reniform coffee-bean nucleus and eosinophilic cytoplasm, with cytoplasmic Birbeck granules viewable under electron microscopy. Positive staining with CD1a, S100, and langerin (CD207) is further diagnostic for the disease.<sup>4</sup>

LCH has been recently reclassified to 1 of 5 groups of histiocytic disorders, now designated to the “L” (Langerhans) group, along with indeterminate cell histiocytosis, Erdheim-Chester disease (ECD) and mixed LCH/ECD. CD207 staining differentiates LCH from indeterminate cell histiocytosis, with absent CD207 expression found in the latter disorder.<sup>5</sup> Approximately 20% of patients with isolated LCH

may go on to have mixed LCH/ECD; clinicians should assess for both diseases at the time of diagnosis, as treatment regimens differ.<sup>6</sup> In this case, LCH was distinguished from ECD and mixed ECD/LCH based on histologic and immunohistochemical findings. Unlike ECD, LCH histiocytes stain positively for CD1a and only minimally for CD68.

The *BRAF*<sup>V600E</sup> mutation is implicated in LCH and is significantly associated with cutaneous involvement and treatment-refractory disease.<sup>4</sup> This patient's underlying mutation was distinct from the commonly identified *BRAF*<sup>V600E</sup> mutations, rendering it insensitive to V600E-specific inhibitors such as vemurafenib. The mutation instead appears sensitive to MEK inhibitors (trametinib) or pan-RAF/RAF dimer inhibitors (LY3009120) based on clinical models and prior case reports.<sup>7,8</sup>

Clinical presentation of LCH is diverse and largely dependent on site and extent of organ system involvement, most commonly including the skeletal system, integumentary system, spleen, and pituitary gland. Cutaneous manifestations may be the earliest recognizable presentation of disease, although isolated skin disease is rare and usually represents LCH dissemination.<sup>4</sup> Importantly, adult patients with LCH first presenting in the skin are at increased risk of a secondary hematologic malignancy—including leukemia, lymphoma, and myelodysplastic syndromes—even years after remission of cutaneous lesions.<sup>3</sup> These patients therefore require close monitoring for detection of later disease sequelae. In addition to cutaneous involvement, this patient also had central diabetes insipidus, secondary hypogonadism, and secondary hypothyroidism caused by pituitary gland metastasis. Although central diabetes insipidus is a recognized complication of LCH, related endocrinopathies are not well defined, particularly in adult patients with the disease.<sup>9</sup>

Management of LCH requires an extensive workup for both underlying disease and organ-specific manifestations. For disseminated LCH, standard chemotherapy is a 12-month course of vinblastine and prednisolone.<sup>4</sup> Cladribine appears to be an effective, albeit less commonly used, treatment for multisystem LCH.<sup>10</sup> Despite initial improvement in clinical symptoms after chemotherapy, this patient ultimately died of

complications from a massive saddle pulmonary embolism. Whether this complication arose from direct pulmonary involvement by LCH or the hypercoagulable state associated with his malignancy remains unclear.

This case highlights a rare, primarily pediatric diagnosis affecting an adult patient with severe, multisystem involvement. With a broad spectrum of clinical presentations, LCH requires a high suspicion for disease; dermatologists should consider LCH in an adult with refractory crusted rash in the appropriate context. Prompt recognition may allow for early intervention and improved prognosis.

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