

Cutaneous Langerhans cell histiocytosis with gastrointestinal involvement treated with dabrafenib



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INTRODUCTION

Langerhans cell histiocytosis (LCH) is a rare disorder characterized by an abnormal clonal proliferation of histiocytes, with adult-onset LCH accounting for an estimated 30% of cases.¹ The clinical spectrum of LCH varies widely, from asymptomatic single-organ involvement to severe and potentially fatal multisystem disease. Although cutaneous lesions are frequently encountered, gastrointestinal involvement in LCH is exceedingly rare, especially in the adult population.

Effective treatment for LCH is poorly characterized because of rarity and heterogeneity of the disease. Twenty percent to 60% of LCH cases harbor the *BRAF* V600E proto-oncogene mutation, and reports show favorable response to *BRAF* inhibitors in this population.²⁻⁴ Dabrafenib is a targeted therapy that selectively inhibits the extracellular signal-related kinase pathway in patients with *BRAF* V600E mutated malignancies.⁵ Here we describe a case of adult primary cutaneous LCH with late-onset gastrointestinal involvement responsive to dabrafenib.

CASE REPORT

A 68-year-old white woman with no significant medical history presented with a painful intertriginous rash of 5 years' duration. The eruption involved her axillae, inframammary (Fig 1, A and B) and inguinal folds, perineum, and gluteal cleft. She denied associated systemic symptoms. She did not respond to previous therapy with oral antibiotics,

Abbreviation used:

LCH: Langerhans cell histiocytosis

topical antifungals, topical steroids, and barrier creams.

Punch biopsy from the inframammary fold found atypical mononuclear cells with eccentric reniform nuclei infiltrating an eroded epidermis with scattered eosinophils (Fig 2) and positive CD1a staining (Fig 3), consistent with LCH. Computed tomography of the abdomen and pelvis found lymphadenopathy in the left upper quadrant. Upper endoscopy with duodenal biopsy showed no evidence of LCH. Results of bone marrow biopsy with flow cytometry were normal.

Treatment with systemic methotrexate was initially effective but poorly tolerated. Further workup with microdissection and Sanger sequencing found *BRAF* V600E (c.1799T>A, p.Val600Glu) mutation, and treatment with dabrafenib, 75 mg daily, was initiated with clearance of cutaneous involvement. Dabrafenib was later stopped because of debilitating arthralgias despite intra-articular steroid injections, and her cutaneous involvement worsened within 1 month of discontinuation. The patient was referred to the radiation oncology department for palliative cutaneous radiation and underwent treatment with favorable outcome.

Shortly thereafter, the patient had new abdominal pain, nausea, vomiting, and anasarca, prompting

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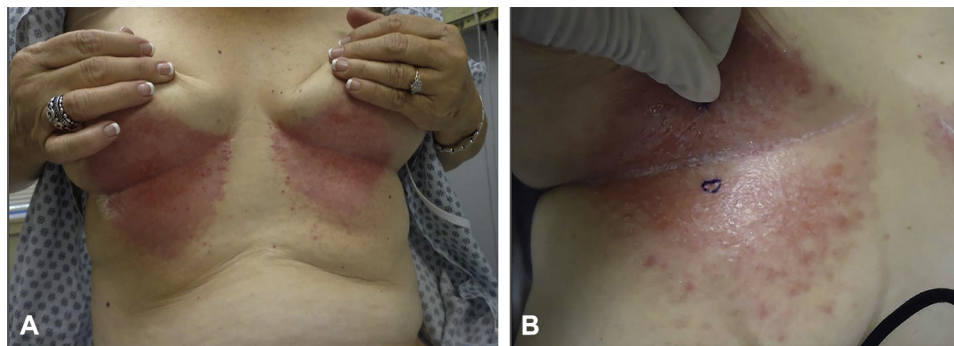


Fig 1. **A** and **B**, Cutaneous Langerhans cell histiocytosis. Macerated erythematous plaques on the inframammary folds.

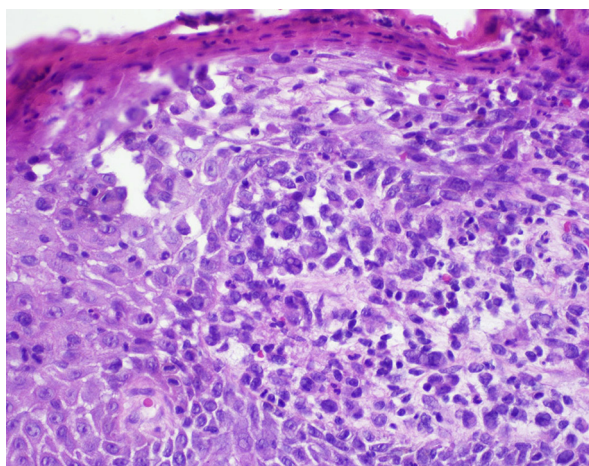


Fig 2. Atypical mononuclear cells with eccentric reniform nuclei infiltrating an eroded epidermis with eosinophils in the background. (Hematoxylin-eosin stain; original magnification: $\times 200$.)

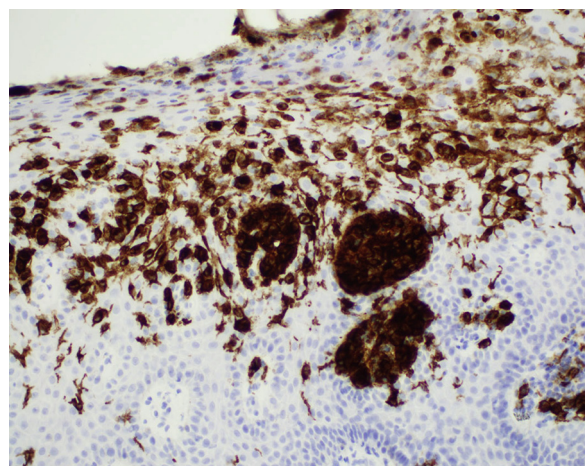


Fig 3. Langerhans cells infiltrating the upper reticular dermis, papillary dermis, and epithelium. (CD1a stain; original magnification: $\times 20$.)

further workup. Biopsies from the gastrointestinal tract found extensive lamina propria histiocytic cells with immunostaining positive for CD1a. Her side effects recurred with her second round of treatment on dabrafenib, including arthralgias and fluid retention. Dabrafenib was thus titrated down to 75 mg by mouth 3 times per week, and there is current discussion of initiating an oral MEK inhibitor, trametinib.

DISCUSSION

Adult-onset LCH is uncommon, accounting for only an estimated 30% of cases. Gastrointestinal involvement by LCH is rare, with most reported cases occurring in children with systemic disease and associated with poor prognosis and high morbidity. Gastrointestinal LCH in adults is often isolated and asymptomatic and can present as polyps on colonoscopy. There are also reports of gastrointestinal LCH mimicking inflammatory bowel disease in

adults.⁶ Although usually isolated, gastrointestinal involvement by LCH in adults can also occur in the setting of systemic disease.^{7,8}

Treatment for adult-onset LCH is not well defined. Recent recognition that 20% to 60% of LCH cases harbor activating *BRAF* V600E proto-oncogene mutations has raised the possibility of targeted *BRAF* inhibition.² Individual case reports and small case series have found favorable responses to *BRAF* inhibitors dabrafenib and vemurafenib in both children and adults with systemic and refractory cutaneous LCH.^{3,4} Gastrointestinal LCH is also poorly understood, and treatment generally consists of systemic steroids or chemotherapy.⁶ In our case, the patient's cutaneous involvement improved dramatically with dabrafenib but recurred within 1 month of cessation. Her gastrointestinal LCH, which was not present on upper endoscopy at the time of initial diagnosis, surfaced after discontinuation of dabrafenib. Her cutaneous and gastrointestinal disease is now well controlled after re-initiation of dabrafenib. Of note,

our patient did experience hyperkeratotic lesions and arthralgias after initiation of dabrafenib, both of which are common adverse effects associated with this medication and may be reduced by dual therapy with dabrafenib and the oral MEK inhibitor, trametinib.⁹

Our case illustrates *BRAF* inhibitors as a promising treatment modality for cutaneous and gastrointestinal LCH in adult patients. Larger studies with longer follow-up periods are needed to establish safety and efficacy in patients with LCH. Compelling treatment considerations include combination therapy with a *BRAF* inhibitor plus another inhibitor of this pathway, such as a selective MAPK kinase (MEK) inhibitor, trametinib, which has provided improved progression-free survival in melanoma patients with *BRAF* V600E mutations.¹⁰ A more detailed understanding of this pathway in LCH could facilitate more effective targeted therapies.

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