International Journal of Women's Dermatology 7 (2021) 838–840

Contents lists available at ScienceDirect

International Journal of Women's Dermatology

Case Letter

Improvement of primary vulvar Langerhans cell histiocytosis with lenalidomide

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ARTICLE INFO

Article history:
Received 18 June 2021
Revised 17 September 2021
Accepted 21 September 2021

Keywords:
Langerhans cell histiocytosis
vulvar diseases
lenalidomide
thalidomide

What is known about this subject in regard to women and their families?

- Vulvar Langerhans cell histiocytosis (LCH) is a rare disease that affects children more than adults.
- The rarity of vulvar LCH often delays diagnosis and requires multispecialty care.
- Vulvar LCH lacks a standardized treatment regimen.

What is new from this article as messages for women and their families?

- Vulvar LCH causes painful recurrent genital ulcers that affect quality of life.
- Women with vulvar LCH may have extracutaneous involvement.
- Lenalidomide may be a viable treatment option for women with vulvar LCH.

Dear Editors,

A 68-year-old woman presented to dermatology in August 2016 with a decades-long history of worsening recurrent, small, painful vulvar ulcers (Fig. 1A). The initial differential diagnosis was herpes simplex virus versus recurrent genital aphthae. The patient later developed rare crusted papules in the axilla (Fig. 1B), lower abdomen, and external auditory canals. Two initial vulvar biopsies showed nonspecific inflammatory changes. Topical and oral antibiotics, topical and oral corticosteroids, and antivirals were not helpful. A third vulvar biopsy in November 2017 demonstrated a dense Langerhans cell infiltrate (Fig. 2A), and immunohistochemical staining revealed CD1a (Fig. 2B) and S100 positivity consistent with a diagnosis of primary vulvar Langerhans cell histiocytosis (LCH).

The patient was screened for systemic involvement with bone scintigraphy, chest radiography, thyroid-stimulating hormone, liver function tests, erythrocyte sedimentation rate, lactate dehydrogenase, and ferritin, all of which were unremarkable. One year later, magnetic resonance imaging incidentally revealed scattered intrahepatic biliary dilatation, consistent with primary sclerosing cholangitis. Six months after this, the patient began to demonstrate elevated alanine transaminase levels that fluctuated between normal and just under three times the upper limit of normal. A gastroenterology evaluation suggested that this was possibly due to hepatic involvement of LCH, which can rarely show a sclerosing cholangitis-like pattern (Fu et al., 2021), but that the hepatic involvement was not severe enough to warrant systemic therapy from a hepatic standpoint.

The patient was referred to hematology–oncology, and palliative radiation therapy was recommended given her ongoing vulvar pain and interference with daily activities. She completed a total of 30 Gy in 14 fractions daily to her left and right ear canals and vulva in November 2019. Within 1 month after radiation therapy, the patient returned to dermatology with multiple ulcers in the vulva, and biopsy confirmed a recurrence of LCH. She initiated thalidomide 100 mg daily with rapid improvement of her vulvar and cutaneous LCH, although she experienced side effects of fatigue and muscle cramping. Thalidomide was decreased to 50 mg daily, but 1 month later she developed a distal thrombus in her left peroneal vein. Thalidomide was temporarily discontinued and then

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https://doi.org/10.1016/j.ijwd.2021.09.010

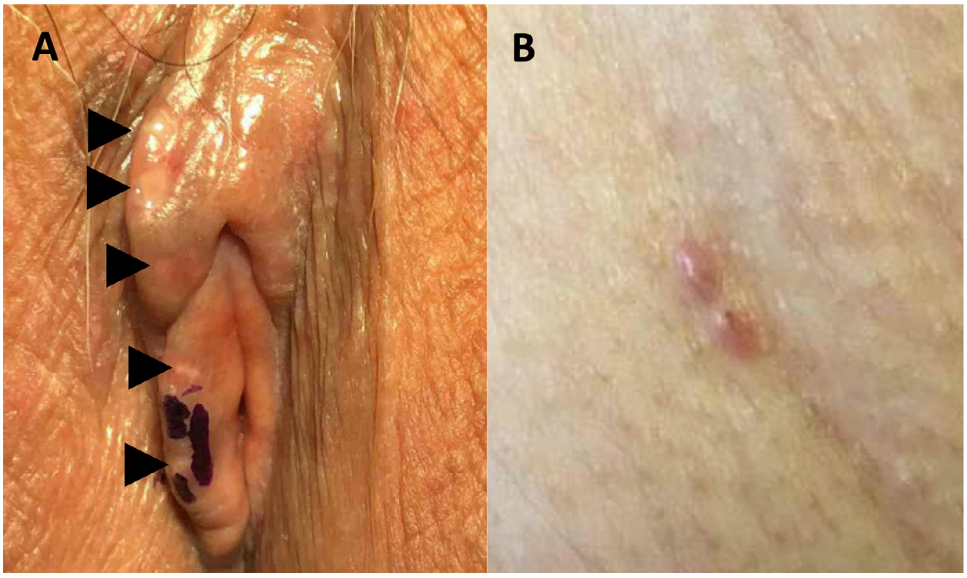

Fig. 1. Clinical presentation of Langerhans cell histiocytosis. (A) Vulva with five 2 to 5 mm, shiny, white-yellow, ulcerated papules on the right labum minus and clitoral hood (arrow heads). Black ink surrounds the biopsy site shown in Figure 2. (B) Axilla with two 3 mm, shiny, pink-yellow papules that demonstrate a Langerhans cell infiltrate on biopsy.

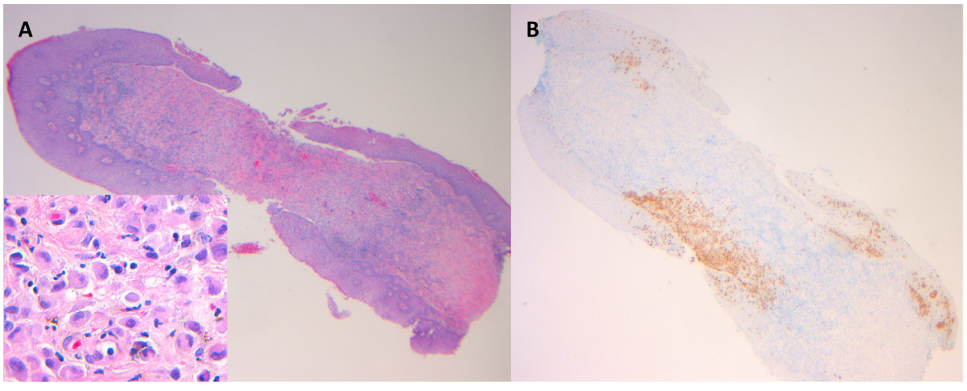

Fig. 2. Histopathology from vulvar biopsy. (A) Hematoxylin and eosin–stained section demonstrating epidermal acanthosis with a central erosion, under which there is a proliferation of epithelioid cells with round-to-oval nuclei, many of which are reniform with eosinophilic-to-amphophilic cytoplasm (magnified in inset) with an associated mixed inflammatory cell infiltrate. (B) Immunohistochemical staining demonstrating CD1a positivity of the cellular infiltrate.

restarted by her oncologist at 50 mg in combination with apixaban for venous thromboembolism prophylaxis. She continued to experience fatigue, nausea, and muscle pain. The patient then switched to lenalidomide 10 mg daily with excellent control of her LCH and no noticeable side effects. Treatment was decreased to lenalidomide 5 mg daily, and the patient remained in remission for at least 1 year. Her liver function tests continued to remain stably elevated throughout her course of treatment and did not appear to worsen or improve with therapy.

Adult-onset primary vulvar LCH is a very rare disease, with <40 cases reported in the literature. LCH of the female genital tract has been described with four patterns of involvement: pure genital LCH, genital LCH with subsequent multiorgan involvement, oral or cutaneous LCH with subsequent genital and multiorgan involvement, and diabetes insipidus with organ involvement. Our patient falls primarily into the first category, although interestingly she had additional involvement of the external auditory canals and rare intertriginous papules, as well as possible hepatic LCH. Hepatic LCH in adults is thought to be rare and carries a poor prognosis, although some reviews suggest that it is underrecognized; thus, milder cases may have a better outcome, as in this case (Fu et al., 2021).

Vulvar LCH treatment is not standardized, but prior case reports have demonstrated response to radiotherapy, chemotherapy, wide local excision, radical vulvar excision, corticosteroids, low-dose methotrexate, acitretin, tacrolimus, and thalidomide alone or in combination. Only one prior case of lenalidomide for treatment of vulvar LCH has been reported (El-Safadi et al., 2012). A randomized controlled trial of lenalidomide versus thalidomide for treatment of multiple myeloma showed that lenalidomide had less discontinuation due to adverse effects than thalidomide (Lonial et al., 2020), consistent with the experience of our patient. Her thrombotic event is noteworthy because, especially when combined with dexamethasone, both lenalidomide and thalidomide increase the risk of venous thrombosis (Weber et al., 2003). Nevertheless, lenalidomide may be a viable treatment for vulvar LCH.

Conflicts of interest

None.

Funding

None.

Study approval: The author(s) confirm that any aspect of the work covered in this manuscript that has involved human patients has been conducted with the ethical approval of all relevant bodies.

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