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Thalidomide for the treatment of hydroa vacciniforme-like lymphoma: Report of four pediatric cases from Peru

To the Editor: Hydroa vacciniforme-like lymphoma (HVLL) is a rare cutaneous T-cell lymphoma recently recognized in the 2008 WHO classification of lymphomas [1]. HVLL is an Epstein–Barr virus-associated lymphoma affecting mostly children in Latin America and Asia [2,3]. HVLL, similar to hydroa vacciniforme is characterized by edema, vesicles, necrotic areas, and vacciniforme-like scars in the face and dorsum of the hands. However, unlike HV, HVLL lesions are not induced or exacerbated by exposure to sunlight. The clinical course is variable, and patients may have recurrent skin lesions in exposed and nonexposed areas for 10–15 years [3–6]. HVLL-associated lesions may progress to ulceration and scarring followed by systemic involvement with fever, weight loss, lymphadenopathy, and hepatosplenomegaly. Currently, there is no standard treatment for HVLL. We present here the clinical course of four Peruvian children with HVLL treated with oral thalidomide as frontline therapy. Selected characteristics and representative pathology are shown in Figure 1.

Our first case is a 14-year-old boy who, at age 10, developed itchy skin lesions on face, trunk, and limbs, which temporarily responded to antibiotics and steroids. Two years later, the relapses became more frequent. On physical exam, several urticarial, papulovesicular lesions evolving into varioliform scars were seen on face, neck, trunk, and limbs (Fig. 1; Supporting Information). Skin biopsy revealed acanthotic epidermis with mild spongiosis and scant exocytosis. Superficial dermis had moderate perivascular lymphocytic infiltrate with large atypical cells on a background of eosinophils and neutrophils. The infiltrate did not involve the subcutaneous tissue. The patient started on thalidomide 100 mg orally daily for 8 weeks showing progressive disease. Subsequently, he was treated with interferon with minor response, and oral low-dose methotrexate with progression. The patient was started on high-dose methotrexate and L-asparaginase. He achieved complete response (CR), and is currently receiving weekly oral methotrexate without evidence of disease for 8 months. Our second case is a 13-year-old girl. At age 10, the patient developed nonitchy vesicular rash in chin and face. She was started on oral steroids for 6 months without response. On examination, several facial urticarial, papulovesicular lesions evolving into varioliform scars were seen with bilateral palpebral edema (Fig. 2; Supporting Information). Skin biopsy showed dermal perivascular lymphocytic infiltration. The patient was started on thalidomide 100 mg orally daily, which she continued for 8 weeks. Within 2 weeks, there was 75% reduction in the size of her lesions. However, she developed acute urticaria, which prompted stopping thalidomide. Eight months later, she developed hepatosplenomegaly, lower limb edema, and fever. She started chemotherapy with dexamethasone, methotrexate, ifosfamide, L-asparaginase, and etoposide (SMILE) achieving CR. The patient died 6 months later due to sepsis. Our third case is a 12-year-old girl. The patient had a 4-month course of bilateral malar swelling, reportedly due to trauma. Ten days prior to her presentation, she experienced worsening malar and palpebral swelling associated with fever and scarring lesions on the left side of her face (Fig. 3; Supporting Information). Skin biopsy of her face showed an atypical lymphoid infiltrate of intermediate to large cells with dense chromatin and small nucleoli involving subcutaneous tissue and deep dermis. The patient was started on thalidomide 100 mg orally daily experiencing a CR within 6 weeks without toxicity, after which treatment was stopped. At the moment, she maintains CR for 18 months. Our fourth case is a 15-year-old girl. Six years prior to presentation, she reported slow-growing facial blisters that improved with short courses of corticosteroids. Three weeks prior to presentation to our service, she developed new lesions on her arms and legs, which turned into scars (Fig. 4; Supporting Information). She was started on daily oral thalidomide 100 mg with stable disease in the first weeks. Soon after, however, she showed progression and increased somnolence. Thalidomide was stopped. She then started oral hydroxychloroquine 400 mg daily and methotrexate 10 mg weekly with 80% improvement of her lesions. The patient has no evidence of disease on treatment for 11 months.

Currently, there is no standard therapy for patients with HVLL. Several studies have shown moderate success with current regimens. In the report by Rodriguez-Pinilla et al. [7], 14 HVLL patients were treated with chemotherapy and radiotherapy. Ten HVLL patients had response (five CR and five partial responses). However, patients experienced recurrence at median time of 4.5 months. Only four patients are currently alive with persistent disease. Barrionuevo et al. treated eight of 16 patients (50%) with chemotherapy or radiotherapy, four of which died of disease and three are alive with disease [2]. The 2-year overall survival was 36%. Overall, these reports show that intensive regimens might not be optimal options in pediatric HVLL. However, in a case series of seven Chinese children with HVLL, three patients were treated with interferon alpha leading to improvement of edema and fever. Two other patients were treated with chemotherapy, but the condition worsened. One of the patients received interferon after chemotherapy and was alive after 2 years of follow-up [8]. In the large series reported by Quintanilla-Martinez et al. and reports from China, patients who received conservative treatment appeared to have similar survival than treated patients, although this could have been biased by patient selection. In this report, two of our patients had clinical response to thalidomide therapy albeit only one lasting response. Thalidomide is a drug with immunomodulatory and antiangiogenic properties, approved by Food & Drug Administration for the treatment of multiple myeloma and erythema nodosum leprosum. We believe that the anti-inflammatory and antiproliferative effect of thalidomide may be useful in these cases. The side effects of thalidomide were mild, probably milder than those of chemotherapy and radiation therapy. It is, therefore, important to consider the use of thalidomide for the frontline treatment of HVLL or in situations in which chemotherapy has failed. We must acknowledge, however, the limitations of this report such as the small sample size and its retrospective nature. Additional studies are needed to improve therapies in this hard-to-treat lymphoma.

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	LAD	HSM	BMI	LDH	CD3	CD4	CD8	CD20	CD30	CD56	EBER	TCR
Case 1	No	No	No	404	+	-	+	-	-	-	60%	αβ
Case 2	No	No	No	632	+	-	+	-	-	-	50%	αβ
Case 3	Yes	No	No	685	+	-	+	-	-	-	50%	ND
Case 4	No	Yes	No	513	+	-	+	-	-	-	ND	ND

LAD: lymphadenopathy; HSM: hepatosplenomegaly; BMI: bone marrow involvement; LDH: lactate dehydrogenase; EBER: EBV-encoded RNA; TCR: T-cell receptor gene rearrangement; ND: not done

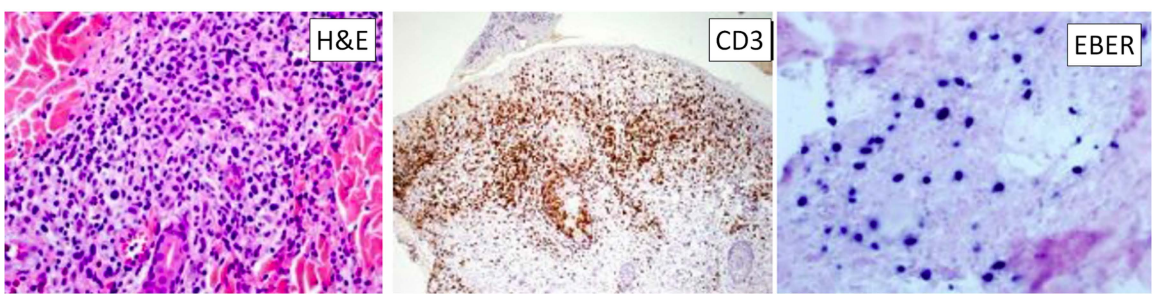

Figure 1. Selected clinicopathological characteristics of four cases with HVLL and representative pathological profile showing atypical lymphocytic infiltrate in dermis and positive expression of CD3 and EBER. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

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Additional Supporting Information may be found in the online version of this article.
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