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Refractory multisystem Langerhans cell histiocytosis in an infant: use of vemurafenib as a therapeutic option

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ABSTRACT

Langerhans cell histiocytosis (LCH) is a rare disease that predominantly affects children, characterized by the abnormal clonal proliferation of Langerhans cells with a broad clinical spectrum and prognosis.

Refractory LCH to standard treatment usually presents multisystem and risk organs involvement, and mainly affects children under 2 years of age. In these cases, more than half present the *BRAF*-V600E mutation; detection of this mutation is essential for targeted treatment, such as vemurafenib, a *BRAF* inhibitor.

We present the case of a 6-month-old patient diagnosed with multisystemic LCH without involvement of risk organs, who responded poorly to first- and second-line therapy. A molecular biology study was performed, which reported a *BRAF*-V600E mutation. Treatment with vemurafenib was indicated, and a good clinical response was obtained after 2 weeks.

Keywords: *Langerhans cell histiocytosis; vemurafenib.*

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INTRODUCTION

LCH is a rare disease that predominantly affects children. It is characterized by the clonal proliferation of Langerhans cells in different organs and systems; it has a heterogeneous clinical expression with variable prognosis. Diagnosis is a significant challenge, and classification is essential to initiate appropriate treatment.

It has been confirmed that more than half of patients with refractory LCH, with a high rate of reactivation and permanent complications, have the *BRAF*-V600E mutation. This knowledge of the molecular pathophysiology involved in LCH opens a new therapeutic door. *BRAF* inhibitors, such as vemurafenib, are promising for children with high-risk, refractory multisystem disease or persistent relapses.

CLINICAL CASE

A 6-month-old patient, born preterm (36 weeks) with adequate weight for gestational age and a history of recurrent suppurative otitis, was referred for dermatosis that had been present for 2 weeks with no improvement after antibiotic treatment. On physical examination, he was in fair general condition, afebrile, with abdominal distention and multiple lymphadenopathies, the largest of which was in the right axilla. Dermatological examination revealed polymorphic lesions: erythematous-brown papulovesicles with crusts, some purpuric, widely distributed with a predominance on the head, trunk, abdomen, and diaper area (*Figure 1A*).

He was admitted for further investigation: laboratory tests revealed iron deficiency anemia, ultrasound showed multiple lymphadenopathies, right femur X-ray showed an osteolytic image, and bone marrow puncture and aspiration were negative.

A skin biopsy showed dense infiltrate in the papillary and reticular dermis, with diffuse histiocytic proliferation of eosinophilic cytoplasm and irregular, elongated nuclei. Immunohistochemistry was positive for CD1a, langerin/CD207, S100, and CD68, consistent with LCH.

Due to skin, lymph node, and bone involvement, a diagnosis of multisystem LCH without involvement of risk organs was established.

Treatment was initiated with a first-line protocol (cytarabine/meprednisone) with partial response. It was replaced by second-line therapy (cladribine, cytarabine, and meprednisone) without the expected clinical response. A new skin biopsy was required for molecular biology testing, which confirmed *BRAF*-V600E-positive oncogene, so targeted therapy with vemurafenib at 15 mg/kg/day (60 mg every 12 hours) orally was initiated. Clinical improvement was evident at 2 weeks.

He has now been undergoing treatment for 18 months and continues to progress well with no complications (*Figure 1B*).

DISCUSSION

LCH is a rare disease characterized by the abnormal clonal proliferation of Langerhans cells that are positive for CD1a and S100 immunophenotype. It predominantly affects children, most commonly between the ages of 1 and 4, with an incidence of 1 child per 200 000 inhabitants.

The spectrum of clinical manifestations is very heterogeneous, and the main manifestations of skin involvement are macules, erythematous-purpuric-crusty papules, and seborrheic eczema.

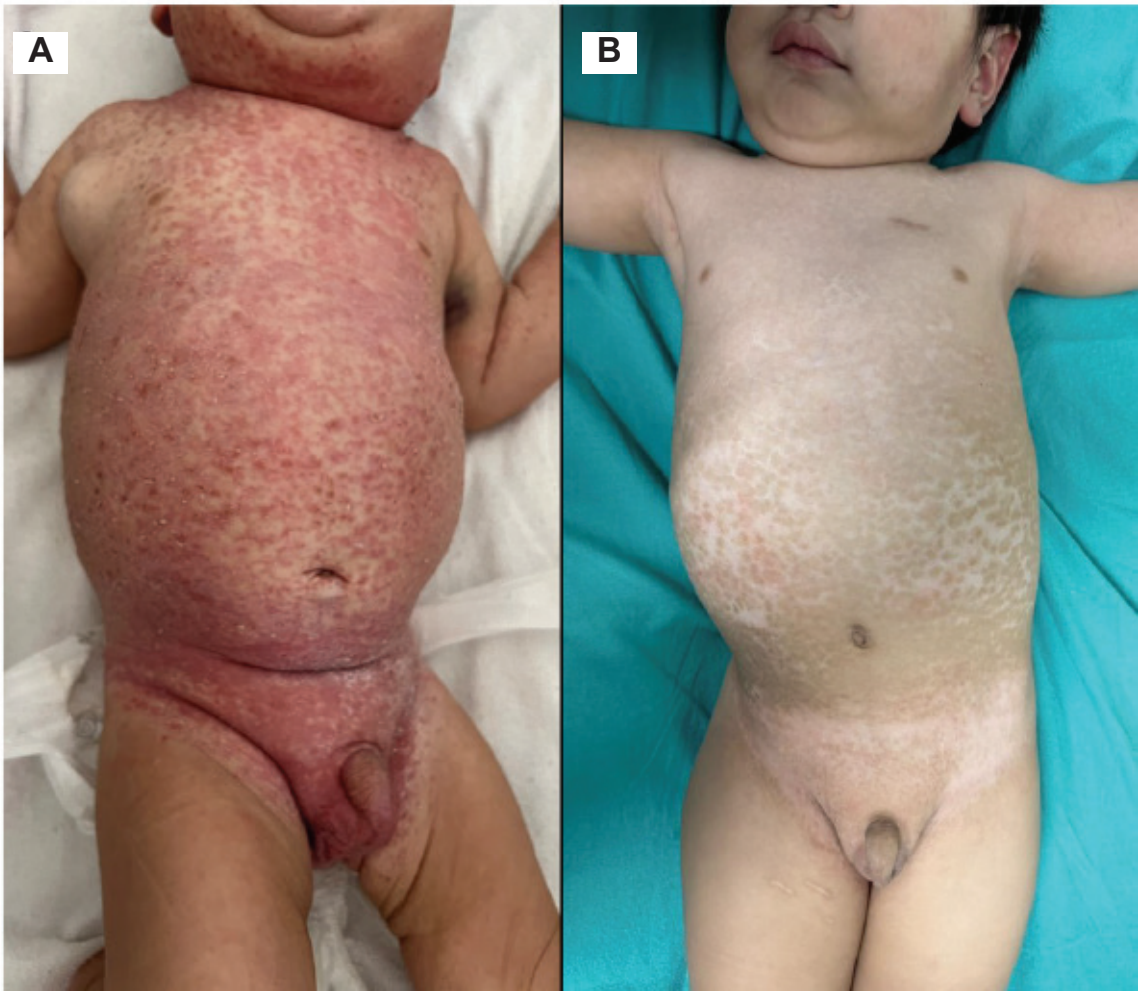
The diagnosis is established based on clinical, histopathological, and immunohistochemical findings. It is essential to know the extent of the disease, which can be mono- or multisystemic, with or without involvement of risk organs (bone marrow, spleen, and liver).

Treatment depends on the degree of involvement of the different organs. When there is multisystem or risk organs involvement, treatment is more aggressive. The first line of therapy continues to be a combination of vinblastine/prednisone or cytarabine/prednisone, and the second line includes cytarabine, cladribine, and corticosteroids.

In general, patients with refractory LCH are usually under 2 years of age and often have the *BRAF*-V600E mutation (54%), which is consistent with our patient. This mutation associated with LCH was first discovered by Badalian-Very G et al. in 2010.[1]

The *BRAF* gene encodes the synthesis of the BRAF protein, which is essential in the RAS/MAPK signaling pathway that regulates cell proliferation, differentiation, migration, and apoptosis. Mutations in this gene cause the abnormal BRAF protein to perpetuate signaling unregulated, leading to uncontrolled growth and differentiation of Langerhans cells. This means that this mutation is associated with more severe clinical symptoms, greater resistance to treatment, and a higher risk of death and relapse.[2]

Figure 1. Pre- and post-treatment skin lesions with vemurafenib



Vemurafenib (a selective BRAF V600 kinase inhibitor) has emerged as a therapeutic option for children with multisystem LCH or LCH with organ involvement that is refractory to conventional treatments. Several studies support the use of vemurafenib in the pediatric population with refractory LCH with the *BRAF*-V600E mutation.

An observational study conducted in Europe in 2019 evaluated the use of vemurafenib in 54 children with LCH with the *BRAF*-V600E mutation; 44 of them had risk organ involvement, and 10 did not. After 8 weeks of treatment, there were 38 complete responses and 16 partial responses, using a mean dose of 21 mg/kg/day, which was adjusted according to patient tolerance. Discontinuation of treatment in 30 patients caused relapses in 24, and it was found that the *BRAF*-V600E allele burden in blood decreased at the start of therapy but was never eradicated.[3]

Another retrospective study conducted in Russia in 2021 with 15 pediatric patients with LCH with the *BRAF*-V600E mutation who received vemurafenib showed a good clinical response with minimal toxicity in both refractory and relapsed patients, with an average initial dose of 40 mg/kg/day and a mean maintenance dose of 13-15 mg/kg/day, with no relapses with dose reduction. However, when treatment was discontinued, three out of four patients relapsed, as the *BRAF* inhibitor managed to block cell differentiation and mutation but did not eradicate the mutant clone in the blood and bone marrow. To eliminate the mutant clone and suspend vemurafenib without relapse, it was combined with chemotherapy regimens, but these objectives were not achieved.[4] The effectiveness and safety of vemurafenib in combination with standard treatment as first-line therapy remain to be evaluated.[5]

Along these lines, some studies suggest that monitoring changes in the *BRAF*-V600E mutation burden could be an indicator for evaluating treatment response.[6]

Regarding adverse effects, a retrospective multicenter observational study conducted in France in 2020 with 57 patients treated with vemurafenib for refractory LCH with *BRAF*-V600E mutation showed the most common adverse effects to be dermatological: photosensitivity, keratosis pilaris, skin rash, xerosis, and neutrophilic panniculitis, most of which were mild with low impact on treatment. No secondary tumors were observed, and the importance of regular dermatological follow-up for better control of adverse effects was emphasized. In other studies, isolated cases of hair loss and QT prolongation were also reported.[7]

In all reported cases, vemurafenib was administered orally, crushing the medication for better tolerance in the pediatric population.

What is conclusive in various studies, as in the case of our patient, is the good clinical response in a short period, with minimal adverse effects and toxicity, provided by vemurafenib in the pediatric population. The dose is individualized according to each patient's tolerance and response. Several questions remain unanswered, including the degree of long-term toxicity, the ideal treatment duration, and whether it will be possible to eradicate the mutant clone.

Targeted therapy, such as *BRAF* inhibitors, is a promising therapeutic option; vemurafenib is an effective and safe option in infants and children. However, a standard dose has not yet been established, as it has been adjusted according to each patient's response. The onset, duration of treatment, and long-term toxicity are still unknown; further studies are needed to obtain certainty in this regard.

Our patient validates the use of vemurafenib as targeted therapy in cases of multisystemic LCH refractory to first- and second-line treatment, demonstrating its efficacy and safety with the results obtained. ■

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