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Treatment of congenital Langerhans cell histiocytosis with cobimetinib

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Abstract

We report a case of congenital multisystem Langerhans cell histiocytosis with cutaneous and hematopoietic involvement. After the failure of first-line (vinblastine and prednisolone) and second-line (vincristine and cytarabine) therapies, treatment with cobimetinib, a mitogen-activated protein kinase (MEK) inhibitor, led to the remission of disease and a sustained response after 11 months of ongoing treatment. Protein kinase inhibitors targeting *BRAF* or *MEK* could represent a promising future therapeutic option, also in children with LCH.

KEYWORDS

BRAF V600E mutation, cobimetinib, congenital Langerhans cell histiocytosis, MEK mutation

1 | INTRODUCTION

Langerhans cell histiocytosis (LCH) is a very rare and heterogeneous disorder characterized by an uncontrolled accumulation of CD1a +/CD207+ dendritic cells. The organs involved and the clinical presentations are varied, which can sometimes lead to delayed diagnosis and dictate the treatment, management, and prognosis of the disease.

2 | CASE REPORT

A newborn male infant presented at birth with multiple violaceous papulopustules and a purpuric eruption covering approximately 90% of the skin (Figure 1). Buccal mucosal erosions also appeared after a few days of life. Ocular mucosa and nails were not affected. He had no hepatosplenomegaly and the remainder of the clinical examination was normal.

He was born at term from a 33-year-old mother by cesarean section due to fetal distress. The pregnancy was a result of medically assisted reproduction and was marked by gestational diabetes treated with insulin. Maternal serologies were negative for toxoplasmosis, human immunodeficiency virus (HIV), hepatitis B and C, and syphilis and had been IgG positive for cytomegalovirus (CMV), varicella, and rubella.

Several diagnoses were considered including infectious pustular rashes (herpes, neonatal varicella, congenital syphilis, neonatal candidiasis) and noninfectious pustular rashes, such as Langerhans cell histiocytosis. Screening for infections was negative. Blood tests at birth showed hemoglobin levels (Hb) within the normal range (Hb: 18.3 g/dL, NV: 15–22 g/dL), elevated C-reactive protein (19 mg/L, NV: <5 mg/L), thrombocytopenia (80,000/mm^3, NV: 150000–400,000/uL), and leukopenia (5800/mm^3, NV: 9000–30,000/mm^3—including neutrophils at 3580/mm^3 [NV: 1000–20,000/mm^3], lymphocytes at 1640/mm^3 [NV: 2000–10,500/mm^3] and monocytes at 400/mm^3 [NV 540–1800 mm^3]).

In addition, the patient had cholestasis at birth without biliary dilatation (conjugated hyperbilirubinemia 7.3 mg/dL, NV: 0–0.3 mg/dL). Serum levels of gamma-glutamyl transferase (GGT) increased progressively (418 U/L, NV: <60 U/L), but glutamic oxaloacetic transaminase (SGOT), glutamic pyruvic transaminase (SGPT), and albumin levels remained normal. On day 15 of life, biliary sludging was noted on hepatic ultrasound. The abdominal ultrasound, the cardiac ultrasound, and total body radiography otherwise showed no abnormalities. Treatment with ursodeoxycholic acid was effective in restoring bilirubin to normal levels.

A skin biopsy showed the presence of large histiocytic cells and inflammatory cells infiltrating the dermis. Immunostains for

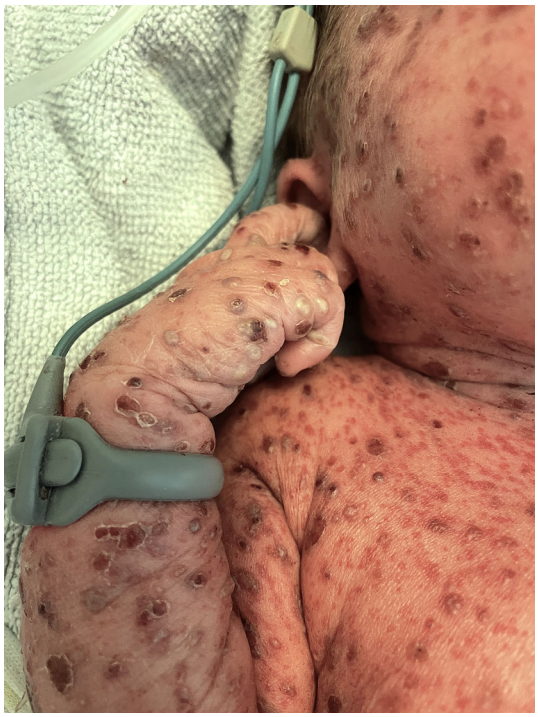

FIGURE 1 Clinical presentation with multiple and diffuse violaceous papulopustules at birth.

CD1a, S100, and CD207 (Langerin) were positive, confirming the diagnosis of LCH. A bone marrow biopsy sample showed no evidence of LCH.

Based on the clinical, histopathological, and blood test data (thrombocytopenia, leukopenia), the patient was diagnosed with high-risk multisystem Langerhans cell histiocytosis (with skin and hematopoietic involvement). The clinical score for disease activity of LCH was calculated at 7 at diagnosis (>25% skin area involved and >2 platelet transfusions, GGT>3-10 N) which represents a high score (≥7).[1] A next-generation sequencing (NGS) panel on the skin biopsy specimen was performed and showed a *MAP2K1* (mitogen-activated protein kinase kinase) mutation (c.173_187del, p.(58_62del)), but no *BRAF* V600E mutation. Treatment with vinblastine (0.2 mg/kg once a week) and prednisolone (1 mg/kg/day) was started with a good initial response but followed by cutaneous and hematological relapse after four courses (4 weeks) of therapy. Subsequently, treatment with vincristine (0.23 mg, 0.05 mg/kg once every 3 weeks) and cytarabine (15 mg, 3.3 mg/kg, first 4 days in a cycle of 3 weeks) for 4 months resulted in only a moderate response followed by cutaneous and hematological disease progression after 4 months. Based on the presence of a *MAP2K1* mutation, a third-line therapy with cobimetinib (0.8 mg/kg on days 1–21 of a 28-day cycle) was initiated when the child was 6 months old. This treatment led to a complete regression of the disease with no relapse to date, after 11 months of ongoing treatment.

Cardiac ultrasound and ophthalmological consultation are planned every 3 months as part of the toxicity assessment of cobimetinib treatment and, to date, have shown no abnormalities.

3 | DISCUSSION

Langerhans cell histiocytosis affects around 5–6 per million children per year, is predominant in males, and can occur at any age, but peak incidence in childhood is between 1 and 4 years old.[2] Congenital presentation of LCH is even rarer, affecting 1–2 per million newborns. Hematopoietic involvement mostly occurs in younger children with multisystemic LCH and constitutes a negative prognostic factor.[3] The absence of LCH cells in bone marrow biopsy samples does not exclude hematopoietic involvement and this diagnosis, like in our case, can be made based on abnormal complete blood counts.[4]

Risk factors for developing LCH have been identified, such as blood transfusion,[5] solvent exposure, family history of thyroid disease, neonatal infections,[6] and in vitro fertilization,[7] as in the reported case.

As the clonal proliferation of CD1a+/CD207+ dendritic cells in LCH results from an activating mutation in the mitogen-activated protein kinase/extracellular signal-regulated kinase pathway (MAPK/ERK pathway also called the Ras–Raf–MEK–ERK pathway), targeted treatment could be considered. *BRAF* (v-raf murine sarcoma viral oncogene homolog B1) and *MAP2K1* mutations, found in certain cancers such as melanoma, activate the MAPK/ERK pathway and provide cells with the ability to escape proliferation regulation processes and to become resistant to apoptosis signals. The MAP-kinase pathway, to which the RAF (Rapidly Accelerated Fibrosarcoma) protein belongs, is involved in the maturation and differentiation of myeloid cells, which may partially explain the importance of the *BRAF* mutation in the origin of LCH. Activation of the RAS–RAF–ERK–MEK pathway is constant in LCH lesions.[8] In a study of 50 cases of LCH performed by Alayed et al, no association was observed between *BRAF* or *MAP2K1* mutation and anatomical site of disease, unifocal or multifocal presentation, nor with clinical outcome.[9] Moreover, no significant differences in presence of high-risk organ damage, age, gender, nor survival were noted when comparing the genotype of *BRAFV600E* or *MAP2K1* mutations.[8] Mutated *BRAF* V600E is present in more than half of LCH cases in children but is less frequent in adults.[10] In unmutated *BRAF* LCH, *MEK* mutations (such as *MEK1*, also known as *MAP2K1*) have also been found in 20%–25% of cases.[8] It has been shown that BRAF and *MAP2K1* mutations in LCH are mutually exclusive.[8,9]

The efficacy of *BRAF* inhibitors, such as dabrafenib or vemurafenib, has been reported in a few cases of recurrent multisystemic LCH carrying the *BRAF*V600E mutation, or when unresponsive to first-line treatment with corticoids, vinblastine, or cytarabine.[11,12]

MEK inhibitors act by blocking the MEK1 and MEK2 proteins in the MAPK pathway. Trametinib, then cobimetinib were the first MEK inhibitors approved by the Food and Drug Administration for the treatment of LCH.[13] It has been observed that the *MAP2K1* mutation is nonresponsive to trametinib in vivo and in vitro, whereas cobimetinib was effective regardless of the genotype. Therefore, determining the genotype could be an important factor to determine a targeted treatment plan.[13,14] Response to treatment with cobimetinib seems consistent and seems to last as long as the treatment is maintained, with no acquired resistance observed to date.[15] Current data show reactivation of disease in 75% of patients after therapy is stopped.[14]

In a study by Diamond et al., some side effects such as decrease in ejection fraction (5 patients out of 18), diarrhea (2 patients out of 18 and thrombocytopenia (one patient out of 18) required a decrease in the administered dose; however, clinical response was maintained.[15] There is little published information regarding the treatment of childhood LCH with MEK inhibitors. Yet, *BRAF* inhibitors may be particularly effective in children with bone marrow and liver LCH refractory to standard therapy.[16] Data on the use of cobimetinib in pediatric LCH are lacking. In a multicenter phase I/II study, the dose of cobimetinib administered to children aged 6 months to 18 years ranged from 0.8 to 1 mg/kg on days 1 to 21 of each 28-day cycle.[17] The optimal duration of treatment in LCH with this drug is unknown at present.

4 | CONCLUSION

We report a rare case of refractory high-risk multisystem congenital Langerhans cell histiocytosis, treated with cobimetinib, a MEK inhibitor, with favorable response and good tolerance. Activation of the MAPK pathway is a key factor in LCH. Therefore, protein kinase inhibitors targeting *BRAF* or *MEK* may represent a promising future therapeutic option for LCH in children. Their use suggests that genotyping of LCH lesions may become central to therapeutic strategies. However, we lack long-term data on the side effects of cobimetinib in children and on the optimal treatment duration. Further studies are warranted to investigate these issues.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflict of interest to declare.

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