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Case Report

Targeted therapy with trametinib in infantile refractory langerhans cell histiocytosis: A case report

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ABSTRACT

Langerhans cell histiocytosis (LCH) is a rare hematologic neoplasm characterized by a clonal proliferation of Langerhans-like cells. LCH affects all ages and in children with a frequency ranging from 4.1 to 8.9/million/year with an increased incidence in children <1 year of age. Infantile LCH refractory to frontline therapy is difficult to treat but targeted therapies in patients with BRAF mutations are promising. We treated an infant of refractory multisystem LCH with risk organ involvement with MAP kinase inhibitor (trametinib) with excellent outcomes.

Keywords: Infantile, Refractory Langerhans cell histiocytosis, Trametinib, Case report, BRAF mutation

INTRODUCTION

Langerhans cell histiocytosis (LCH) is a rare hematologic neoplasm characterized by a clonal proliferation of Langerhans-like cells. LCH affects all ages and in children with a frequency ranging from 4.1 to 8.9/million/year[1] with an increased incidence in children <1 year of age. LCH has a varied clinical presentation, many children are cured with combination chemotherapy, but the risk of relapse remains high despite contemporary treatment protocols.[2] Recently diagnosed gene mutations in histiocytosis have generated options for targeted therapies. A rare but potentially fatal complication of systemic LCH is secondary hemophagocytic lymphohistiocytosis (HLH),[3] which has been seen in 9.3% of cases. Here, we report a case of infantile refractory multisystem LCH with risk organ (RO) involvement which did not respond well to conventional chemotherapies but responded to targeted therapies.

BRIEF HISTORY

A 3-month-old baby born out of non-consanguineous marriage became symptomatic from 2 weeks of age in view of generalized erythematous maculopapular rash [Figures 1 and 2] with crustations which started over the face and then progressed over the trunk and all over the body. Rash resolved partially with topical creams followed by residual hypopigmentation. At the age of 2 months, he had melena. He was evaluated further and was found to have severe anemia and thrombocytopenia requiring blood transfusion support. Ultrasound abdomen showed significant hepatosplenomegaly. Skin biopsy showed features suggestive of LCH. They came to our hospital for further management. On evaluation, he had abdominal distension due to massive hepatosplenomegaly and his complete blood count showed bicytopenia. His

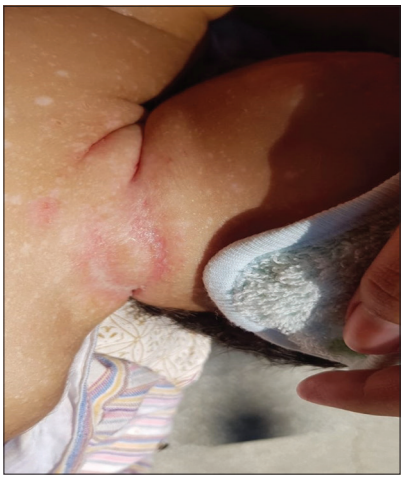

Figure 1: Erythematous rash over flexor aspect of neck.

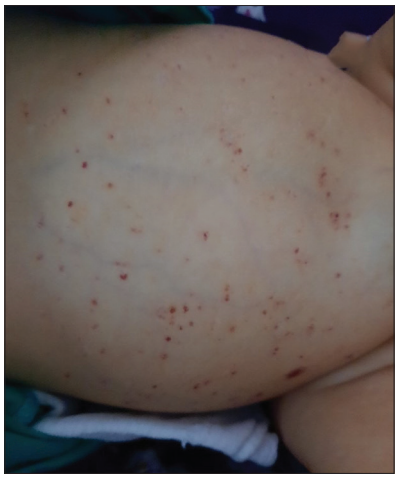

Figure 2: Erythematous skin rash and abdominal distension secondary to massive hepatosplenomegaly.

liver function test showed severe hypoalbuminemia. The coagulation profile was normal. His viral screening for HIV, hepatitis B virus surface antigen, and hepatitis C virus were non-reactive. Bone marrow aspiration and biopsy showed features consistent with a diagnosis of bone marrow infiltration by LCH associated with hemophagocytosis. Other workup for HLH was normal (normal ferritin, triglyceride, and fibrinogen levels). Skin biopsy blocks were reviewed and showed features suggestive of LCH which was confirmed by IHC as tumor cells were diffusely positive for CD1a, focally positive for S100 and LCA while negative for CD3, CD20, and CD56 with Ki-67 of 6–7%. He was started on LCH III protocol with vinblastine and oral prednisolone.

He received weekly vinblastine for 6 weeks. His course was complicated by *Candida parapsilosis* sepsis. Whole body positron emission tomography and computed tomography scan after six doses of weekly vinblastine revealed hepatosplenomegaly with a metabolically active right axillary lymph node, with minimal bilateral pleural effusion and diffusely increased marrow uptake suggestive of partial remission. He was continued on weekly vinblastine and BRAF mutation testing was sent and BRAF exon 15 – Mutant was found positive. His cytopenias were not improving and he was requiring packed red blood cells and platelet transfusions very frequently. In view of his poor response to conventional chemotherapy, the family was counseled in detail about targeted therapy and he was started on tab Trametinib (targeted therapy) 0.25 mg (0.03 mg/kg) along with syp omnacortil forte for 3 consecutive days every week for next 6 weeks. Post 6 weeks of therapy, his skin rash, hepatosplenomegaly, and cytopenias improved completely, and presently, he has completed his 2nd birthday and is symptom-free on targeted therapy treatment.

DISCUSSION

Genomic alterations resulting in activation of the mitogen-activated protein kinase pathway are a key molecular pathogenic feature of the histiocytic neoplasms and in LCH usually involve activating mutations in BRAF and MAP2K.[4,5] While targeted therapy with BRAF V600E-specific inhibitors has demonstrated significant responses in adults and children with LCH,[6] longitudinal experience with targeted therapy in infants with RO-positive LCH remains limited.

Some cases have been reported in which refractory patients responded to BRAFV600E-specific inhibitor dabrafenib (range, 3–5 mg/kg/dose, by mouth, twice daily) and in rare cases used trametinib as an alternative means of BRAF/MEK inhibition to treat refractory cases. A 2-year-old male child with multisystem disease with RO involvement, LCH diagnosed at 2 weeks of age having a low level of MAP2K1 p.K57_G61del was treated with a short corticosteroid pulse and trametinib 0.125 mg (0.030 mg/kg) daily. His lesions rapidly responded and he continued on trametinib monotherapy 0.25 mg daily (0.018 mg/kg/day) with no active disease after 22 months of therapy. Toxicity observed was Grade 1 skin rash and Grade 1 creatine phosphokinase (CPK) elevation.[7] There are few adult cases of LCH treated with trametinib. The dose and length of therapy of trametinib needed to inhibit the mitogen activated protein kinase (MAPK) pathway in LCH are not established. A retrospective study of 21 pediatric LCH patients with MAPK pathway somatic mutation (BRAFp.V600E, n = 20; MAP2K1c.293_310del, n = 1) who received MAPK pathway inhibitors after the failure of at least one prior therapy was recently reported by the North American Consortium for Histiocytosis-LIBRE Study Group A and reported 86% response rate to therapy, and six patients in that group received trametinib either in combination with BRAF inhibitors or alone. The dose of trametinib in that report ranges from 0.0125

to 0.018 mg/kg or is reported as 1 mg or 2 mg daily.[8] Similarly, we also treated our patient with tab trametinib along with pulse steroids and he responded well to it.

CONCLUSION

A significant proportion of histiocytic neoplasms relapse or recur despite the best available therapies so all patients should undergo genomic profiling to identify candidate driver mutations. This facilitates the selection of targeted therapies, sparing the toxicity of more aggressive retrieval chemotherapy regimens. Our case demonstrates that targeted therapy (trametinib) can quickly achieve disease control in infants with BRAF V600E-mutant high-risk LCH.

Ethics statement

Proper informed consent from the mother of the infant (patient in this case) has been documented for the case publication as well as the use of the above photographs.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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