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A Childhood Langerhans Cell Histiocytosis With a Novel *BRAF*$^{N486\_T491delinsK}$ Mutation: Good Response to Conventional Chemotherapy

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Abstract: Langerhans cell histiocytosis (LCH) is characterized genetically by diverse gene mutations of the mitogen-activated protein kinase signaling cascade. *BRAF*$^{N486\_T491delinsK}$ mutation is a rare mutation that involves the β2-αC ring domain, causing activation of the mitogen-activated protein kinase pathway, and is predicted to be resistant to the chemotherapy and *BRAF*^{V600E} inhibitor in adult LCH cases. Here, we report a childhood LCH case with this novel *BRAF* mutation and had a good response to conventional chemotherapy. This case report suggests that children with *BRAF*$^{N486\_T491delinsK}$ mutation might differ from adult counterparts in terms of clinical behavior, and conventional chemotherapy might still be an effective therapy.

Key Words: Langerhans cell histiocytosis, *BRAF*$^{N486\_T491delinsK}$ mutation, chemotherapy, childhood

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Langerhans cell histiocytosis (LCH) is the most common histiocytic disorder in children and is characterized pathologically by langerin-positive (CD207+) dendritic cell proliferation and inflammatory cell infiltration, and molecularly by recurrent activating mutations of the mitogen-activated protein kinase (MAPK) signaling pathways.[1] *BRAF*$^{N486\_T491delinsK}$ mutation is a rare mutation and has rarely been reported in children. A single adult LCH case with this novel mutation was resistant to the chemotherapy or *BRAF*^{V600E} inhibitor.[2] We report an unusual case of childhood LCH with confirmed *BRAF*$^{N486\_T491delinsK}$ mutation and the patient showed good response to the prednisone and vincristine.

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CASE REPORT

A 6-year-old boy presented to our outpatient department with irritating pain in the right iliac region for more than 3 months. He denied trauma, fever, rash, or other obvious symptoms. On physical examination, there was no redness or swelling in the pain area, but the patient had a claudication. Routine blood analyses, and liver and kidney function were normal. Multifocal bone destructions, including right ilium, thoracic vertebrae, and left humerus, were documented by chest-abdominal and pelvic computed tomography (CT) scanning (Fig. 1A). Moreover, chest and abdominal CT scanning found no lesions in lung, liver, or spleen. Single photon emission CT of whole bone image found obviously increased metabolism of pelvis, right femur, lumbar and thoracic vertebrae. A biopsy from the right iliac crest revealed granulomatous lesions, which expressed CD1a and Langerin, but negative *BRAF*^{V600E} mutation (Fig. 2A–F). Altogether, the diagnosis of single-system LCH with multifocal bone lesions was established.

The patient was started on 6 weeks of induction chemotherapy with prednisone (40 mg/m^2/d orally, days 1 to 28, afterward weekly reduction) and vincristine (2 mg/m^2/d, iv, bolus, days 1, 8, 15, 22, 29, 36) according to the LCH-III protocol. Due to the unavailability of vinblastine in China, vincristine was utilized as a substitute. Further genetic analysis of biopsied histologic material revealed *BRAF*$^{N486\_T491delinsK}$ mutation (Fig. 2G). The patient's right iliac region pain completely disappeared after 3 weeks of induction chemotherapy, and the disease was stable on chest CT evaluation after 6 weeks of induction chemotherapy (Fig. 1B). Therefore, the patient had repeated 6-week induction chemotherapy, and he achieved partial disease resolution after 12 weeks of induction on single photon emission CT imaging. LCH-III–based chemotherapy was continued, and the patient remained disease-free for more than 3 years since completion of chemotherapy (Fig. 1C).

DISCUSSION

LCH is characterized genetically by diverse gene mutations of the MAPK signaling cascade, with up to 50% of cases harboring the *BRAF*V600E mutation, other activating mutations in *BRAF* gene, and mutations in *MAP2K1, ARAF, ERBB3, NRAS,* and *KRAS* gene.[3,4] Though pathologic extracellular signal-regulated kinase activation occurs in almost all LCH cells, somatic mutations in MAPK pathway genes have just been identified in ~75% of LCH cases, and the mechanism of the extracellular signal-regulated kinase activation of remaining pediatric patients with LCH remains undefined.[5] Here, our patient is a childhood LCH case with the *BRAF*$^{N486\_T491delinsK}$

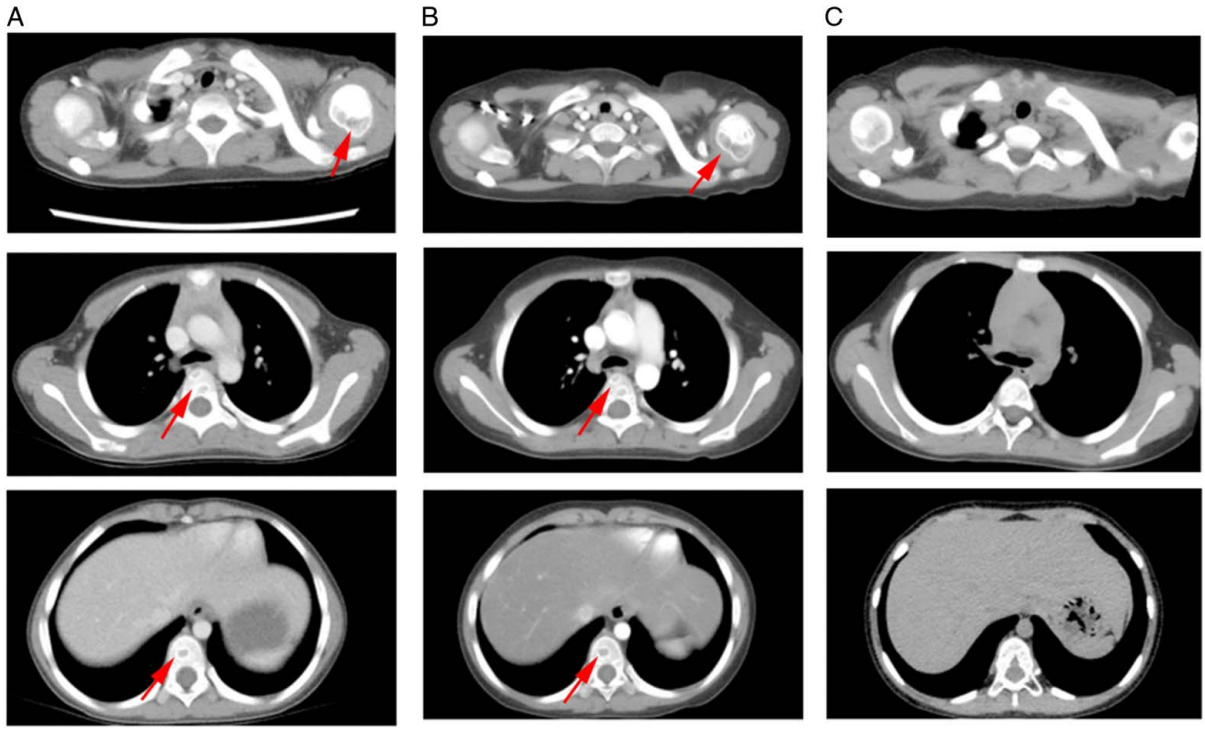

FIGURE 1. Radiology of bones. A, Initial radiologic examination of the bones, as demonstrated by enhanced computed tomography (CT) scans of the chest and abdomen, revealed multifocal bone destruction in the thoracic vertebrae and left humerus. B, After 6 weeks of induction chemotherapy, there was no observed improvement or progression in the bone destruction. C, Upon completion of the chemotherapy regimen, subsequent chest and abdominal CT scans indicated the resolution of multifocal bone destruction in the thoracic vertebrae and left humerus.

mutation, and identification of this novel mutation adds new information to the MAPK pathway mutations.

Overall outcomes have been improved in LCH clinical trials over the past decades in children.[6–8] In the LCH-III trial, children with multisystem LCH treated with frontline vinblastine and prednisone improved the 5-year survival to 84%, but reactivation rate still remains high (27%).[6] Risk organ (liver, spleen, and hematopoietic system) involvement and poor response to induction therapy are the known independent risk factors for poor prognosis.[6] Molecular risk stratification is still not clear, even though some studies suggested that patients with $BRAF^{V600E}$ mutation more commonly displayed resistance to frontline treatment and showed a higher reactivation rate.[9] As to refractory LCH in children, salvage treatment with cladribine and cytarabine improved cure rates, but resulted in prolonged hospitalization and high rates of treatment-related death.[10] Also, some case reports suggest the potential benefit of $BRAF^{V600E}$ inhibitor in children with refractory LCH.[11,12] $BRAF^{N486\_T491delinsK}$ mutation is a rare mutation that involves the β2-αC ring

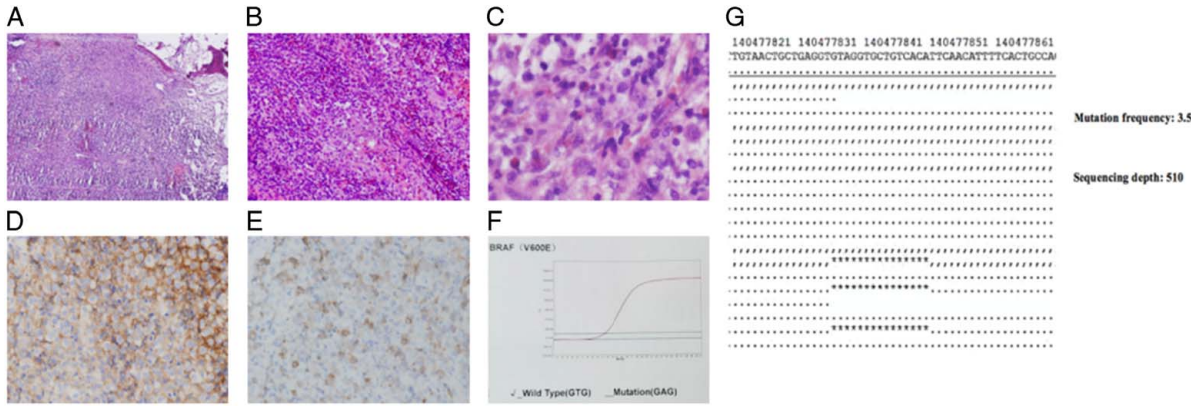

FIGURE 2. Pathologic and genetic testing of the right iliac crest. The biopsy of the right iliac crest demonstrated the presence of mononucleated cells, eosinophils, and multinucleated giant cells, as evidenced by hematoxylin and eosin staining at magnifications of ×40 (A), ×100 (B), and ×400 (C). Immunohistochemical analysis revealed positivity for CD1a (D) and Langerin (E). Genetic analysis indicated the absence of the $BRAF^{V600E}$ mutation (F) and identified the presence of the mutation in the patient (G).

domain causing constitutive activation of the MAPK pathway and is predicted to be resistant to the classic $BRAF^{V600E}$ inhibitor vemurafenib.[2] A single LCH case with the $BRAF^{N486\_T491delinsK}$ mutation was enrolled in a cohort of 18 refractory or resistant adult histiocytic neoplasms treated with cobimetinib, a mitogen-activated extracellular signal-regulated kinase 1 and 2 inhibitor downstream of *BRAF*. Complete response was achieved 10 months after the initiation of MEK inhibition, strongly indicating that the efficacy of MEK inhibitors for this particular category of LCH lacking $BRAF^{V600E}$ mutation, and was validated by in vitro cell line studies. This adult pilot phase 2 clinical trial clearly suggested that adult LCH harboring $BRAF^{N486\_T491delinsK}$ mutation tends to be chemoresistant and should be selectively treated with MEK targeting therapy.[2]

Nevertheless, our index LCH patient was treated according to the LCH-III protocol, and achieved disease resolution after 12 weeks of induction with prednisone and vincristine. Comprehensive mutation analysis disclosed a novel *BRAF* mutation during the course of induction. However, considering the elevated 5-year reactivation rate, it was recommended that further follow-up was conducted even if the patient had been disease-free for over 3 years. Similarly, Tang et al[13] reported a case of a pediatric patient with LCH harboring the $BRAF^{N486\_T491delinsK}$ mutation, who presented with a unifocal bone lesion involving the rib and exhibited no recurrence for more than 1 year after chemotherapy. These case reports suggest that children with $BRAF^{N486\_T491delinsK}$ mutation might differ from adult counterparts in terms of clinical behavior, and conventional chemotherapy might still be an effective therapy, though further studies are needed.

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