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LETTER TO THE EDITOR

Langerhans cell histiocytosis associated with classical Hodgkin lymphoma contains *BRAF* V600E mutation

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Dear Editor,

Clinical History

A 13-year-old boy presented with generalized lymphadenopathy, fatigue and weight loss for five months. An excisional biopsy of enlarged left supraclavicular lymph node showed extensive nodal architectural effacement by a nodular proliferation containing scattered large atypical mononucleated, binucleated, and multinucleated cells with prominent eosinophilic nucleoli in the background of eosinophils, small lymphocytes, and plasma cells. The large atypical cells were positive for PAX-5 (weak), CD30 and CD15 (partial), and negative for CD3, CD20, CD45RB, and ALK-1 by immunohistochemical stains (Fig. 1a–c). In addition, there were multiple distinct sheets of large cells with nuclear grooves and abundant eosinophilic cytoplasm, which were positive for CD43, CD1a, S-100, and langerin, confirming them to be Langerhans cells (Fig. 1d–f). To investigate if there is *BRAF* V600E, c.1799T>A mutation, we performed the next-generation sequencing (NGS). Briefly, DNA was extracted from the microdissected Langerhans cells, and the NGS analysis was independently performed two times with the Ion Torrent PGM as described in the manufacturer's protocol (Fusion Method, Life Technologies, https://tools.thermofisher.com/content/sfs/manuals/4468326_IonAmpliconLibraryPrep_FusionMethod_UG.pdf). The *BRAF* mutation p.V600E, c.1799T>A was detected in 2% in both runs and the reads on target have been in the first run 35053 reads and in the second run 31496 reads (Fig. 1g). There were no *MAP2K1* hotspot mutations. Since the DNA extraction could not be repeated due to exhaustion of material, we employed allele-specific PCR followed by melting curve analysis and direct Sanger sequencing as previously described [1]. *BRAF* V600E (c.1799T>A) mutation was confirmed by melting curve analysis of the amplification products (Fig. 1h) and Sanger sequencing (Fig. 1i). A diagnosis of nodular sclerosis classical Hodgkin lymphoma (CHL) with foci of Langerhans cell histiocytosis (LCH) was rendered. The patient was treated as stage IIIA CHL with chemotherapy and focal radiation therapy. He remained disease free five years from his last treatment.

It has been controversial if LCH associated with lymphoma represents a true neoplasm, highlighted by a recent finding that there were no *BRAF* or *MAP2K1* mutations in LCH [2–5]. Our case may represent the first demonstration of *BRAF* V600E mutation in a typical case of LCH associated with lymphoma, supporting that at least some of the LCHs associated with lymphoma are true neoplasm. The twice-confirmed low allele frequency for the *BRAF* V600E mutation despite microdissection could point to an early clonal event in the background of an initially reactive Langerhans cell proliferation.

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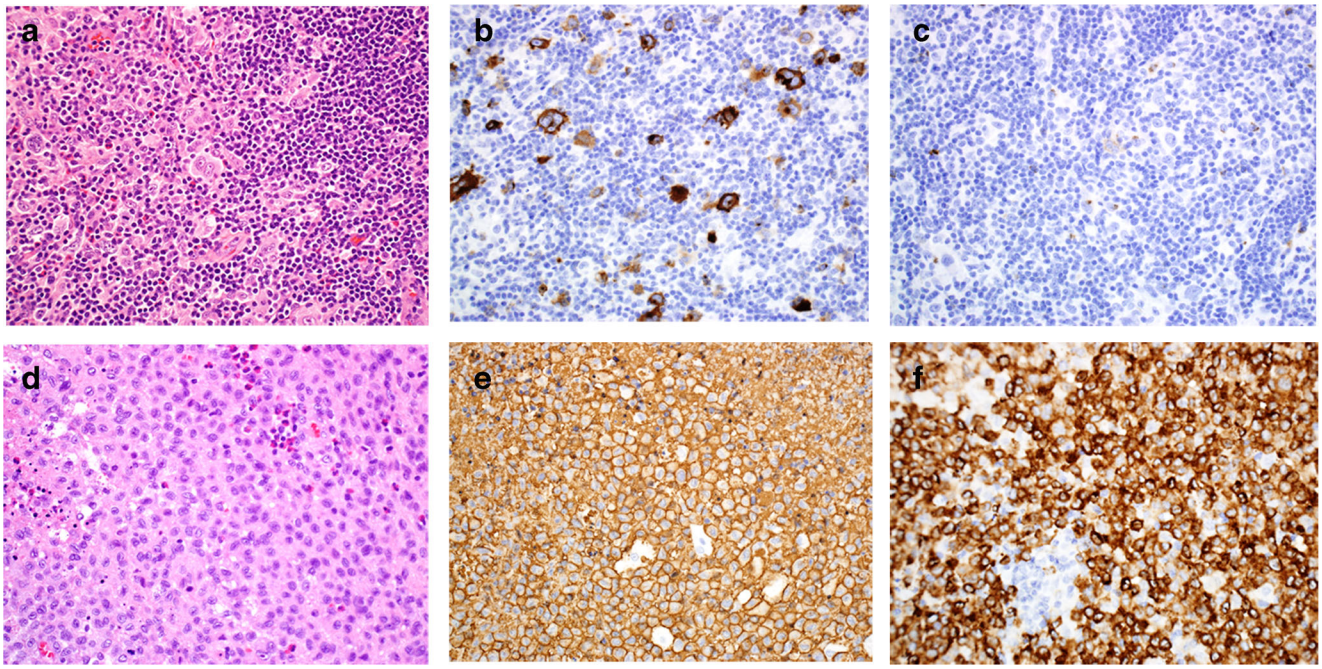

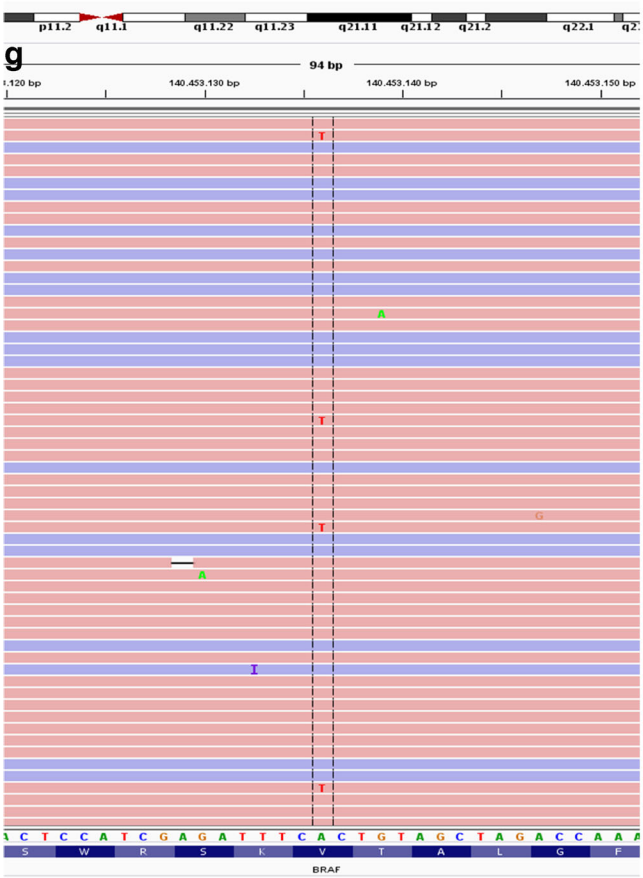

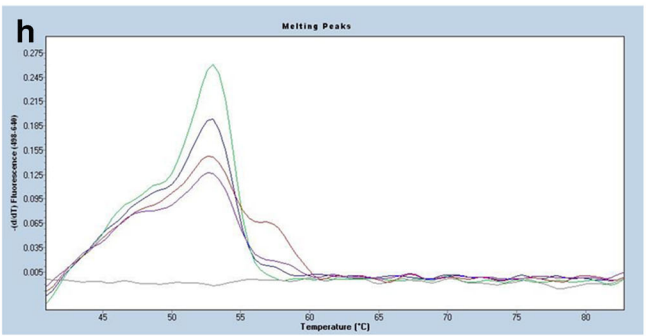

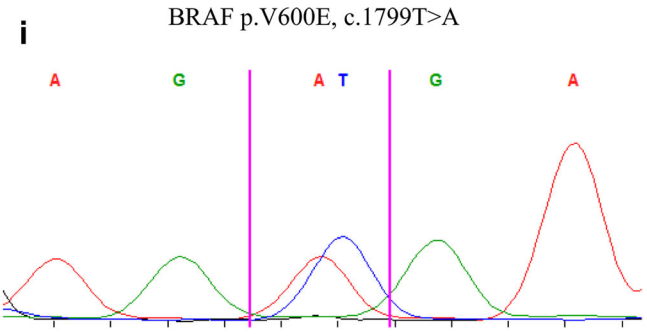

Fig. 1 **a** Classical Hodgkin lymphoma, hematoxylin and eosin, × 40. **b** CD30, immunohistochemistry, × 40. **c** CD15, immunohistochemistry, × 40. **d** Langerhans cell histiocytosis, hematoxylin and eosin, × 40. **e** CD1a, immunohistochemistry, × 40. **f** Langerin, immunohistochemistry, × 40. **g** Integrative Genomics Viewer screenshot showing the BRAF mutation p. V600E, c.1799T>A. Melting curve analysis. **h** The reactions were performed with locked nucleic acid (LNA, 0.05 μM blue and 0.1 μM purple). A control wild-type sample (green), a V600E mutation positive control (red) and a negative control (gray) are also included for comparison

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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