Adult Onset of BRAF\textsuperscript{V600E}-Mutated Langerhans Cell Histiocytosis with Cutaneous Involvement Successfully Diagnosed by Immunohistochemical Staining

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Key Words
Adult onset of Langerhans cell histiocytosis · BRAF\textsuperscript{V600E} · Clinical type · Chemotherapy

Abstract
Langerhans cell histiocytosis (LCH) is characterized by the clonal proliferation of Langerhans cells; it is categorized as a single-system disease with single or multifocal lesions, and as a multi-system disease with or without the risk of organ involvement. Although the skin is not categorized as a risk organ, the precise diagnosis of skin lesions is necessary to determine the protocol for the treatment of LCH. In this report, we describe a 28-year-old Japanese man with adult onset of BRAF\textsuperscript{V600E}-mutated LCH with cutaneous involvement successfully diagnosed by immunohistochemical staining. Our report suggests that immunohistochemical staining for the BRAF\textsuperscript{V600E} gene could be a diagnostic tool to determine the clinical type of LCH.

Introduction

Langerhans cell histiocytosis (LCH) is characterized by a clonal proliferation of Langerhans cells that occurs predominantly in children [1]. LCH is categorized as a single-system (SS) disease with single or multifocal lesions, and as a multi-system (MS) disease with or
without involvement of risk organs (hematopoietic system, lung, liver or spleen) [2]. Although the skin is not categorized as a risk organ, the precise diagnosis of skin lesions is necessary to determine the protocol for the treatment of LCH [2]. In this report, we present a case of LCH mimicking prurigo chronica multiplex that carried the p.V600E mutation in the BRAF gene, successfully detected by immunohistochemical staining.

Case Report

A 28-year-old Japanese man visited our outpatient clinic with a 1-year history of pruritic papules on his extremities. He had noticed a slow-growing subcutaneous nodule on his right chest 2 years before, and half a year before this nodule had been diagnosed as adult-onset LCH and irradiated locally. On his initial visit, physical examination revealed multiple crusted papules on the trunk, lower legs and dorsal region of the foot (fig. 1). A biopsy specimen showed atypical large lymphocytes infiltrated mainly in the perivascular region of the upper dermis with involvement of the overlying epidermis (fig. 2a). Immunohistochemical staining revealed that these atypical lymphocytes were positive for CD1a (fig. 2b). Since the infiltrating cells were limited to the perivascular areas and it was difficult to diagnose these eruptions as cutaneous involvement of LCH or dermadromes of LCH, we employed immunohistochemical staining for BRAFV600E mutation. We detected p.V600E-mutated cells in the perivascular region of the upper dermis (fig. 2c, d). From the above findings, we diagnosed this patient as having adult-onset BRAFV600E-mutated LCH with cutaneous involvement. He was treated for LCH with a regimen of the Japan LCH Study Group protocol C (vinblastine, prednisolone, methotrexate, mercaptopurine) as described previously [2]. One month after the administration of this regimen, in parallel with the induction of complete remission of LCH, his pruritic eruption disappeared.

Discussion

LCH can roughly be divided into two categories: a SS disease with single or multifocal lesions, and a MS disease with or without the risk of organ involvement (hematopoietic system, lung, liver or spleen) [2]. In adults, systemic chemotherapy is required for multifocal SS or MS LCH lesions, whereas systemic chemotherapy is not recommended for those with localized SS disease [2]. Since cutaneous involvement of adult LCH is frequent and its manifestation is variable [3], exact histological diagnosis of a skin lesion is necessary to determine the clinical type of LCH. Although LCH is characterized by the proliferation of S100 protein, CD1a and Langerin-positive cells, sometimes it is difficult to differentiate skin lesions of LCH from other inflammatory skin diseases such as prurigo [4]. Therefore, a more sensitive marker for LCH is needed.

Recent reports suggested that the oncogenic BRAFV600E mutation could be one of the markers for cutaneous LCH [5]. Moreover, another report also suggested that BRAFV600E mutation in circulating CD11c+/CD14+ cell fractions can even determine the prognosis of LCH [6]. Notably, Kobayashi and Tojo [7] reported that the BRAFV600E mutation in circulating cell-free DNA could be a biomarker of high-risk adult LCH. These reports suggested that the expression of BRAFV600E could be one of the diagnostic tools for the cutaneous involvement of LCH with various presentations. Although the skin is not categorized as a risk organ, the exact diagnosis of cutaneous involvement of LCH is necessary to determine the protocol for the treatment of LCH. Since immunohistochemical staining and quantitative RT-PCR were
useful for the detection of BRAF\textsuperscript{V600E} mutation \cite{7,8}, in this report we selected immunohistochemical staining with 3,3′-diaminobenzidine tetrahydrochloride and its enhancer. We could not detect p.V600E mutation in the BRAF gene by quantitative RT-PCR because of the lower cell densities in the skin lesion. Our present report suggested that, in such cutaneous lesions, immunohistochemical staining is suitable for the detection of the gene mutation.

**Statement of Ethics**

This patient gave written informed consent.

**Disclosure Statement**

The authors declare no conflict of interest.

**References**

\begin{itemize}
  \item 7 Kobayashi M, Tojo A: The BRAF-V600E mutation in circulating cell-free DNA is a promising biomarker of high-risk adult Langerhans cell histiocytosis. Blood 2014;124:2610–2611.
\end{itemize}
Fig. 1. Multiple crusted papules on the dorsal region of the left foot.

Fig. 2. Atypical large lymphocytes infiltrated mainly in the perivascular region of the upper dermis with involvement of the overlying epidermis (a). Paraffin-embedded tissue samples were deparaffinized and stained with anti-CD1a antibody (b) and anti-BRAF^{V600E} antibody (c, d). The sections were developed with 3,3'-diaminobenzidine tetrahydrochloride (b) or with 3,3'-diaminobenzidine tetrahydrochloride and its enhancer (c, d). Original magnification: ×100 (a, b), ×200 (c), ×400 (d).