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REVIEW ARTICLE

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Langerhans cell histiocytosis in adults: Advances in pathophysiology and treatment

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Langerhans cell histiocytosis (LCH) is a rare systemic disorder characterized by the accumulation of CD1a+/Langerin+ LCH cells and wide-ranging organ involvement. Langerhans cell histiocytosis was formerly referred to as histiocytosis X, until it was renamed in 1987. Langerhans cell histiocytosis β was named for its morphological similarity to skin Langerhans cells. Studies have shown that LCH cells originate from myeloid dendritic cells rather than skin Langerhans cells. There has been significant debate regarding whether LCH should be defined as an immune disorder or a neoplasm. A breakthrough in understanding the pathogenesis of LCH occurred in 2010 when a gain-of-function mutation in *BRAF* (V600E) was identified in more than half of LCH patient samples. Studies have since reported that 100% of LCH cases show ERK phosphorylation, indicating that LCH is likely to be a clonally expanding myeloid neoplasm. Langerhans cell histiocytosis is now defined as an inflammatory myeloid neoplasm in the revised 2016 Histiocyte Society classification. Randomized trials and novel approaches have led to improved outcomes for pediatric patients, but no well-defined treatments for adult patients have been developed to date. Although LCH is not fatal in all cases, delayed diagnosis or treatment can result in serious impairment of organ function and decreased quality of life. This study summarizes recent advances in the pathophysiology and treatment of adult LCH, to raise awareness of this "orphan disease".

KEYWORDS
adult, histiocytosis, Langerhans cell, mitogen-activated protein kinase, proto-oncogene protein BRAF

1 | OVERVIEW OF LANGERHANS CELL HISTIOCYTOSIS

The Langerhans cell was first described by Paul Langerhans Jr. in 1868.[1] The first definitive case of Langerhans cell histiocytosis (LCH) was reported in 1893 by Alfred Hand.[2] The patient was a 3-year-old boy with polyuria, exophthalmos, and hepatosplenomegaly; similar cases were reported by Henry Christian and Arthur Schuller.[3,4] The disease was named Hand-Schuller-Christian disease. Based on similar histopathological patterns, Hand-Schuller-Christian disease, Letterer-Siwe disease, and eosinophilic granuloma were unified as histiocytosis X in 1953 and renamed LCH in 1985.[5] Histopathologically, LCH is generally defined by CD1a+/Langerin+ Langerhans-like cells. The specific origin of LCH cells has yet to be identified. The incidence of LCH is reported to be 3-5/million; the majority of patients are children younger than 3 years and the incidence in adults is approximately 1-2/million.[6] Incidence appears to be higher in Caucasians in northern European countries, and lower in Asia and Africa.[7]

The clinical manifestation of LCH varies from a single-organ disease that could spontaneously go into remission, to a systemic

and aggressive disease that can lead to death. Any organ can be involved, individually or in combination, but bone and skin have a higher frequency of involvement. Diabetes insipidus (DI) is the most common initial sign of central nervous system (CNS) involvement in LCH. Isolated pulmonary LCH (PLCH), which is the most common manifestation in adult patients, is considered a specific type of LCH. Although PLCH cells have similar histopathologic characteristics, the majority of cell proliferation is polyclonal.[8] Pulmonary LCH is strongly related to smoking; more than 90% of patients are smokers and quitting smoking could lead to remission without treatment.[9,10]

Because LCH varies in its clinical presentation, particularly among adult patients, nonhematological medical professionals are likely to be involved in clinical settings, which could result in improper treatment procedures, including surgical excision and irradiation. It should be noted that LCH is categorized as a myeloid neoplasm, and requires accurate diagnosis and appropriate treatment as necessary.[7,11]

2 | ALTERATIONS OF THE MAPK PATHWAY IN LCH

The identification of an oncogenic *BRAF* -V600E mutation in more than half of all LCH cases represented a major advance in our understanding of the pathogenesis of LCH.[12] The BRAF protein is a member of the serine/threonine kinase RAF family, and is a key component of the MAPK (RAS-RAF-MEK-ERK) signaling pathway that leads to the activation of transcription factors essential for cell growth and proliferation. The V600E (c.1799T>A transversion in exon 15) is the most common mutation in *BRAF*, and is one of the major drivers of human malignancies that lead to downstream constitutive activation of MEK and ERK. The frequency of *BRAF*-V600E in LCH ranges from 25% to 65%.[12-16] Studies have reported that *BRAF*-V600E is more commonly observed in multisystem LCH patients than in patients with isolated disease.[17] It is associated with an increased risk of relapse.[13]

BRAF-V600E mutations have been detected in circulating cell-free DNA extracted from peripheral blood plasma in LCH patients using allele-specific real-time PCR or digital droplet PCR.[18,19] This noninvasive diagnostic procedure, a so-called "liquid biopsy", is a powerful tool for early detection of various cancers. It can be used to analyze cell-free DNA, circulating tumor cells, and tumor-derived extracellular vesicles. Langerhans cell histiocytosis can involve organs and tissues not readily accessible for biopsy, thereby delaying diagnosis. Liquid biopsy can mitigate this difficulty, and is also expected to be a potential biomarker in high-risk LCH.

The introduction of next-generation sequencing analyses, such as whole exome/genome sequencing and targeted sequencing, has revealed several *BRAF* mutations in addition to V600E, including V600D, 600DLAT in-flame insertion, germ line T599A mutation, deletions in the β3-αC loop of the kinase domain (485_490LNVTAP>F, NVTAP486del, and 486_491NVTAPT>K), and a splicing mutation at the end of exon 12 (R506_K507insLLR) (Figure 1).[20-22] The kinase activity of these mutations has not been fully evaluated, but they might function similarly to *BRAF*-V600E, resulting in constitutive activation of BRAF. Additionally, *BRAF*-G466R, a missense mutation in the kinase domain of BRAF, has been described in LCH, although its function is also unknown.[23] In non-LCH histiocytosis, a *BRAF*-F595L mutation was identified in histiocytic sarcoma,[24] and an in-flame deletion-insertion (*BRAF*-T599_V600delinsRE) was identified in Erdheim-Chester disease (ECD).[25] Erdheim-Chester disease and LCH have different morphological and immunohistochemical characteristics; ECD cells have a foamy cytoplasm and lack CD1a staining. The relationship between ECD and LCH is not fully understood, and ECD and LCH occasionally overlap.[26] RNA sequencing has uncovered recurrent *BRAF* fusions, such as *PACSIN2-BRAF* and *FAM73A-BRAF*.[27,28] These two mutations are both in-flame fusions involving a wide range of exons, and lead to constitutive activation of *BRAF*.

The second most commonly mutated gene in LCH is *MAP2K1*, which is also a member of the MAPK pathway. The dual-specificity kinase MAP2K1, also known as MEK1, is located downstream of BRAF and contributes to the activation of ERK1 and ERK2. *MAP2K1* mutation is reported to occur in ~50% of LCH patients with wild-type *BRAF*.[29,30] Studies have indicated that *BRAF* and *MAP2K1* in LCH are mutually exclusive.[30,31]

Nelson et al[32] identified an activating *ARAF* mutation in the kinase domain (F351L) and an in-flame deletion (Q347_A348del). Chakraborty et al[30] identified an *ARAF* mutation (T70M) that co-occurred with *BRAF*-V600E in a patient with ECD/LCH overlap. Non-LCH histiocytosis shows higher frequencies of *ARAF*

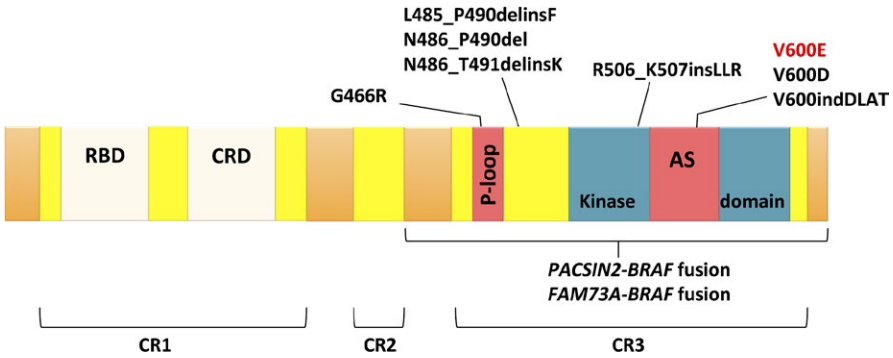

FIGURE 1 Schematic representation of *BRAF* structure and the location of reported mutations in Langerhans cell histiocytosis (LCH). AS, activation segment; CR, conserved region; CRD, cystine-rich domain; RBD, RAS binding domain

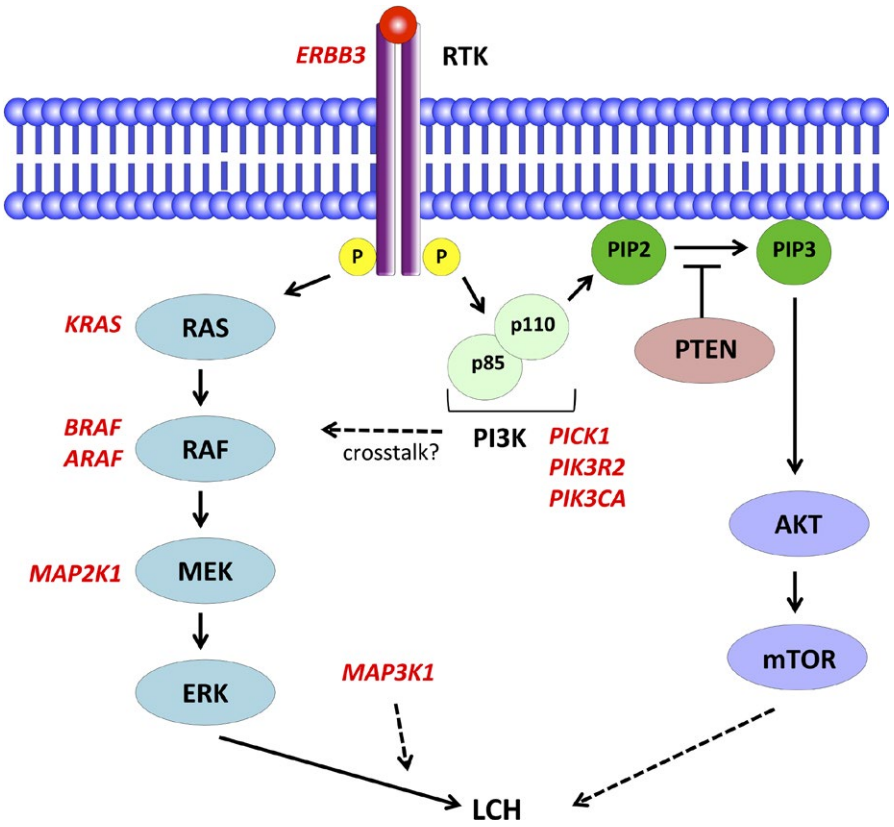

FIGURE 2 Diagram of the MAPK and PI3K pathways. The reported mutations in Langerhans cell histiocytosis (LCH) are indicated in red. The dotted arrow represents an effect that has not been fully evaluated. PIP1, phosphatidylinositol 3-phosphate; PIP3, phosphatidylinositol-3,4,5-triphosphate; PTEN, phosphatase and tensin homolog deleted on chromosome 10; RTK receptor tyrosine kinase

mutations.[33] Two somatic frameshift mutations in *MAP3K1* (T799 fs and L1481 fs) have been reported.[31] Mutations in tyrosine kinase receptor *ERBB3* (P921Q) have also been reported in ECD/LCH patients.[30] Approximately half of ECD patients harbor *BRAF*-V600E as well as LCH, and ~30% carry *MAP2K1* mutations. Whereas 10%-20% of ECD are positive for *NRAS* or *KRAS* mutations, only one activating *KRAS* mutation in non-PLCH has been reported to date.[23] The effects of these recently identified mutations on ERK activation are still unclear. Mutations in MAPK pathway genes have been confirmed in nearly 80% of LCH patients. Additional MAPK mutations could be discovered because the ERK pathway is activated in 100% of LCH patients (Figure 2).[12,30]

3 | OTHER POSSIBLE DRIVERS OF LCH

In addition to those noted above, a number of other mutations have been reported in LCH, although their role in its pathogenesis is unclear. One of the few possible drivers outside of MAPK is the PI3K (PI3K-AKT-mTOR) pathway. The PI3K pathway is an intracellular signaling pathway that regulates the cell cycle; activation of this pathway is a key driver of carcinogenesis. To date, three PI3K pathway alterations have been reported: *PICK1*, *PIK3R2*, and *PIK3CA* (Figure 2).[33,34] Of these, *PIK3CA* (E542K) is the only known activating somatic mutation, leading to constitutive activation of the PI3K pathway. Activating *PIK3CA* mutation is reported in 10%-20% of ECD cases, whereas only a single case was reported in LCH.

4 | THE CELL OF ORIGIN

As indicated by its name, LCH was believed to arise from skin Langerhans cells due to similarities in expression markers (CD1a+/CD207+) and histopathological findings with characteristic Birbeck granules. Results from gene expression analyses indicated that LCH cells were more similar to dendritic cell precursors derived from bone marrow, and did not originate from skin Langerhans cells.[35] Berres et al[13] confirmed *BRAF*-V600E mutation in circulating CD11c+/CD14+ fractions, and in bone marrow CD34+ hematopoietic progenitor cells in high-risk LCH patients. This finding indicated that LCH occurs as the result of a MAPK mutation of a hematopoietic progenitor cell line. Forced expression of *BRAF*-V600E in CD11c+ dendritic progenitor cells caused LCH-like lesions in mice. *BRAF*-V600E has been shown to be present in hematopoietic stem cells and myeloid progenitors in the bone marrow of high-risk LCH patients. Additionally, CD1c+ dendritic cells have been shown to acquire high CD1a and CD207 expression with granulocyte-macrophage colony-stimulating factor and transforming growth factor-beta alone in vitro.[36] In contrast,

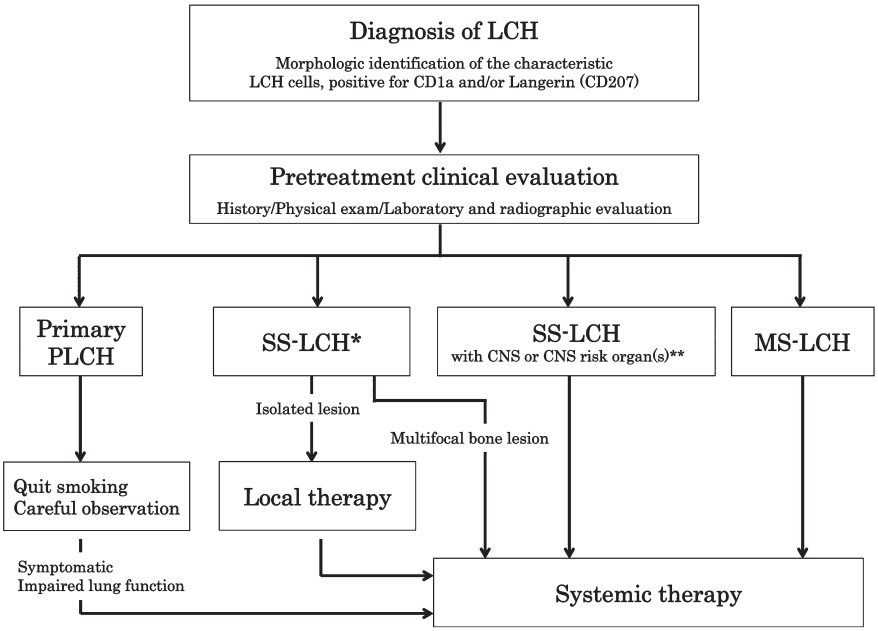

FIGURE 3 Treatment algorithm for adult Langerhans cell histiocytosis (LCH). Diagnosis of LCH is based on histological and immunophenotypic examination. The primary indicators are characteristic LCH cells and positivity for CD1a and/or Langerin (CD207) cells. Confirmation of cytoplasmic Birbeck granules by electron microscopy is no longer necessary. Complete patient history, including smoking history, must be determined, and specific physical examinations should be carried out, including neurological evaluation of central nervous system (CNS) and peripheral nerves. *In certain situations, such as involvement in vertebra or tissues near sensory organs, systemic therapy is recommended. **Involvement in craniofacial bones, eyes, ears, and oral cavity. MS, multisystem; PLCH, pulmonary LCH; SS, single system

classical CD14+ monocytes required additional notch ligation. A recent study revealed the self-renewing capacity of CD34+ cells, which drives the development of histiocytosis in xenograft transplantation assays in vivo.[37] Constitutive activation of the MAPK pathway due to *BRAF* mutation plays a critical role in LCH. A previous study identified *BRAF*-V600E in CD34+ cells in patients with hairy cell leukemia.[38] Another study showed that *BRAF*-V600E expression in murine hematopoietic stem/progenitor cells can cause hairy cell leukemia-like disease.[39] It remains unclear why the same mutation occurring in hematopoietic cells leads to distinctly different conditions, suggesting that mechanisms other than *BRAF* might be involved.

5 | TREATMENT OPTIONS FOR ADULT LCH

There are no standard therapies for adult LCH, and no prospective trials have been undertaken on this population. Treatment of LCH varies due to its heterogeneous presentation; treatment recommendations are based on organ involvement and the extent of the disease (Figure 3). Langerhans cell histiocytosis is categorized as single-system LCH (SS-LCH) with multifocal or unifocal involvement, or as multisystem LCH (MS-LCH) with multiple organ involvement with or without risk organ involvement. Organs at risk include the hematopoietic system (bone marrow), spleen, and liver.

6 | TREATMENTS FOR PRIMARY PLCH

As mentioned, primary PLCH in adults has a strong relation with smoking and nearly all the patients are smokers. Therefore, smoking cessation should be the top priority in the treatment of primary adult PLCH. In non-smokers or patients with progressive disease despite smoking cessation, systemic therapy of glucocorticoids or cladribine (2-CdA) could be an option.[10,40,41] It is important that radiation therapy is not useful in isolated PLCH. In patients with very aggressive PLCH with irreversible lung damage or severe pulmonary hypertension, lung transplantation might be considered.[42]

7 | TREATMENTS FOR SS-LCH

Local therapies are recommended for SS-LCH with isolated skin or bone involvement. Surgical excision of the lesion should be undertaken in very limited cases of SS-LCH with a solitary skin lesion. In skin-only cases, weekly oral methotrexate (MTX) with or without 6-mercaptopurine (or its prodrug azathioprine) is recommended.[43,44] Light therapies in skin-only patients have been reported to be effective.[45,46] In contrast to pediatric patients, radiotherapy could be an option for SS-LCH with bone lesions, with acceptable side-effects.[47-49] Recent reports have indicated that hydroxyurea with or without MTX or bisphosphonates might be effective in SS-LCH with multifocal bone lesions.[50-53] However, in patients with multifocal bone involvement, systemic therapy equivalent to MS-LCH is often undertaken as initial treatment.

TABLE 1 Reported case series of systemic therapies for adult Langerhans cell histiocytosis (LCH)

Reference	No. of pts	Disease type	Median age, y (range)	Treatment	Overall response	Median follow-up (y)
Saven and Burian[58]	12	3 SS, 4 MS	44 (19-72)	2-CdA	75%	3.6
McClain et al[57]	7	7 MS	Not given	VBL, PSL followed by VBL, PSL, 6-MP	43%	0.5
Cantu et al[55]	58	58 SS with bone lesions	32 (18-72)	VBL, PSL for 19 pts (1st 15, 2nd 4) 2-CdA for 22 pts (1st 9, 2nd 9, 3rd 4) HDAC for 24 pts (1st 12, 2nd 5, 3rd 7)	VBL, PSL 16%[a] 2-CdA 31%[a] AraC 79%[a]	8.5
Morimoto et al[56]	14	4 SS, 10 MS	43 (20-70)	VBL, PSL, MTX, 6-MP	72%	2.8
Derenzini et al[59]	11	6 SS, 5 MS	27 (18-62)	CPA, ADR, MTX, VCR, BLEO, PSL (MACOP-B)	100%	6.7
Duan et al[60]	45	4 SS, 41 MS	31 (18-69)	CPA, VDS, ETP, PSL (CEVP) for 31 pts VDS, PSL (VP) for 13 pts	CEVP 70% VP 64%	6.2
Tazi et al[54]	35	7 SS, 28 MS	33 (28-42)	VBL, PSL	72%	7.6

[a]Patients who relapsed within 1 year were excluded.
2-CdA, cladribine; 6-MP, 6-mercaptopurine; ADR, adriamycin; AraC, cytarabine; BLEO, bleomycin; CEVP, cyclophosphamide, epirubicin, etoposide, and cis-platinum; CPA, cyclophosphamide; ETP, etoposide; HDAC, high-dose cytarabine; MACOP-B, methotrexate, doxorubicin, cyclophosphamide, vincristine, prednisone, and bleomycin; MS, multisystem LCH; MTX, methotrexate; PSL, prednisolone; Pts, patients; SS, single system LCH; VBL, vinblastine; VCR, vincristine; VDS, vindesine; VP, vindesine and prednisone.

8 | TREATMENTS FOR MS-LCH

Systemic therapy is strongly recommended for MS-LCH or SS-LCH with multifocal bone lesions. No standard treatments have been identified but a combination of vinblastine and prednisolone therapy could serve as the standard option, as in pediatric LCH (Table 1). Adult patients who undergo vinblastine + prednisolone treatment tend to show higher toxicity than children, resulting in a poor overall response.[54-57] Cytarabine or 2-CdA might be preferred as first-line treatments.[55,58] For patients with CNS lesions, or primary or relapsed/refractory cases, 2-CdA and cytarabine are preferred because of their blood-brain barrier penetration. Retrospective analyses of short-course chemotherapy with MTX, doxorubicin, cyclophosphamide, vincristine, prednisone, and bleomycin in aggressive adult LCH have shown its efficacy. This intensive treatment should be reserved for very severe cases.[59] Allogeneic hematopoietic stem cell transplantation has been successful in some aggressive cases.[61,62]

9 | TREATMENTS FOR HYPOTHALAMIC-PITUITARY MASS LESION

As mentioned, LCH can involve CNS and the most common manifestation is DI due to the hypothalamic-pituitary mass lesion. Mass lesions in hypothalamus and/or pituitary glands are often treated with vinblastine/prednisone or 2-CdA.[63,64] Regardless of the treatment, most reported cases have shown that symptoms of DI or hormone dysfunction could not be reversed and requires constitutive hormone replacement therapy.

10 | TARGETED THERAPIES

Imatinib, a tyrosine kinase inhibitor targeting the receptors expressed in LCH, has been reported to be effective in refractory MS-LCH cases.[65,66] Unfavorable outcomes have also been reported and few experts now recommend imatinib.[67] Vemurafenib, a *BRAF* inhibitor, has shown efficacy in several cases with *BRAF*-V600E mutation. Vemurafenib is the first selective *BRAF* inhibitor approved by the US FDA for malignant melanomas, and was approved for ECD with *BRAF*-V600E in 2017. Despite the efficacy of vemurafenib, severe adverse events, including the development of squamous cell carcinoma, have been reported and the majority of patients experienced early relapse after discontinuation of the therapy.[68] Diamond et al[69] recently reported 2-year efficacy and safety data for vemurafenib in patients with ECD and LCH enrolled in the VE-BASKET study, an open-label, non-randomized, histology-independent evaluation of patients with nonmelanoma cancers harboring the *BRAF*-V600E mutation. A total of 22 ECD and 4 LCH patients were treated with vemurafenib. The 2-year progression-free survival rate was 86% and the overall survival rate was 96%. No patient showed disease progression at the point of best response, and LCH patients showed higher efficacy than ECD patients. However, all patients had at least one adverse event that led to dose reduction and/or discontinuation of the therapy, including an instance of *KRAS*-mutant papillary thyroid cancer that was considered treatment-related. The optimal duration and dosage of vemurafenib require further investigation. A retrospective case series of refractory/relapsed ECD and LCH using dabrafenib, another *BRAF* inhibitor, indicated that it was efficacious and

safe.[70] A total of 11 adult ECD patients (including 4 overlapping with LCH) carrying *BRAF*-V600E were treated with a single dose of dabrafenib: 6 patients were pretreated with vemurafenib and treatment was discontinued due to toxicity; 1 experienced grade 3 toxicity (fever); and all achieved an at-least partial metabolic response. Papapanagiotou et al[71] reported successful treatment of MS-LCH with *MEK1* (E102_I103delEI) mutation using trametinib, a *MEK1/2* inhibitor. However, a cutaneous lesion reappeared after cessation of the treatment, which required retreatment.

11 | CONCLUSION AND PERSPECTIVES

Since the discovery of the *BRAF*-V600E mutation in LCH, advances in next-generation sequencing technology have revealed several driver mutations and resolved the molecular pathophysiology of LCH. These results directly informed the application of targeted therapies, such as *BRAF* or *MEK* inhibitors. It is assumed that additional drivers in the MAPK pathway remain unidentified, and the role of structural alterations and gene fusion has yet to be elucidated. Although the expansion of treatment options has gradually improved outcomes, treatment of LCH remains challenging, particularly in adults. Clinical trials of combined and targeted therapies are ongoing, and the results are awaited with interest.

CONFLICT OF INTEREST

None.

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