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Case Report

Development and Successful Treatment of Spinal Mixed Histiocytosis in an Elderly Woman following Two Relapses of BRAF-mutated Unifocal Skull Langerhans Cell Histiocytosis

Tsuneyoshi Hamada[1], Miyako Kobayashi[1], Ayaka Fukui[2], Naoki Nakajima[2], Naoyuki Anzai[1] and Shinsaku Imashuku[1,3*]

[1]*Department of Hematology, Uji-Tokushukai Medical Center, Uji, Kyoto, Japan;* [2]*Department of Diagnostic Pathology, Uji-Tokushukai Medical Center, Uji, Kyoto, Japan;* [3]*Department of Laboratory Medicine, Uji-Tokushukai Medical Center, Uji, Kyoto, Japan*

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Abstract

Development of mixed histiocytosis (Langerhans cell histiocytosis (LCH))/Erdheim–Chester disease (ECD)) after treatment in patients with an initial skull LCH lesion has not been well recognized. An elderly woman initially developed LCH at the left temporal bone, preceded by polyuria and polydipsia five years earlier; the lesion was surgically removed. Two years thereafter, she experienced her first LCH relapse with a right parietal skull lesion, in which a BRAF V600E mutation was confirmed, and chemotherapy was initiated. After a second LCH relapse involving the left parietal bone, the patient presented with a third relapse at the L2 vertebra. This lesion was pathologically diagnosed as mixed histiocytosis (LCH/ECD), resulting in refractoriness to conventional chemotherapy, and was successfully treated with targeted therapy using BRAF and MEK inhibitors. Spinal mixed histiocytosis (LCH/ECD) may develop following relapses of skull LCH after chemotherapy, for which targeted therapy could be effective.

Introduction

Histiocytic diseases include Langerhans cell histiocytosis (LCH) and non-LCH entities such as Erdheim–Chester disease (ECD). Histiocytic disorders are classified into five groups: among these, LCH and ECD belong to the L-group, cutaneous juvenile xanthogranuloma (JXG) to the C-group, and Rosai–Dorfman disease (RDD) to the R-group, with additional two groups. Extracutaneous or disseminated JXG with identifiable genetic mutations has been proposed to be ECD within the L-group.[1] LCH, the most common form of histiocytosis, is now recognized as an inflammatory myeloid neoplasia.[2]

The majority of LCH and ECD cases harbor somatic oncogenic mutations in the MAPK pathway genes (RAS–RAF–MEK–ERK), most commonly involving BRAF and MAP2K1 mutations.[3,4] In both pediatric and adult LCH, the skull bones are the most frequently affected sites.[5–7] Most parietal bone lesions resolve with limited curettage alone, without the need for prosthetic reconstruction or adjuvant therapy.[4] However, temporal and facial bone LCH carries a substantially higher risk of late relapse; in pediatric LCH, the relapse rate has been reported to be 43.2%. Sakamoto *et al*. further noted that craniofacial bone lesions in children may relapse up to the sixth occurrence, whereas spinal LCH typically relapses only up to the third episode.[5] The most common CNS manifestation, central diabetes insipidus resulting from pituitary stalk involvement in LCH, may precede the eventual diagnosis of LCH by less than one year or by several years.[8,9] The paradigms in the management of LCH in adults are mostly derived from pediatric experiences.[4]

In addition, "mixed histiocytosis," defined as the presence of two or more histiocytic neoplasms in a single patient, either concurrently or asynchronously, has attracted increasing attention.[10,11] Among these, LCH/ECD mixed histiocytosis is particularly notable, as it has been hypothesized to arise from a common progenitor cell.[12] Here, we report an elderly patient who developed BRAF-positive relapsed cranial bone LCH, followed by a subsequent relapse involving the L2 vertebra, in which biopsy confirmed mixed histiocytosis.

Case presentation

In 2024, a 76-year-old woman presented with lumbago, and com-

Keywords: Langerhans cell histiocytosis; Erdheim-Chester disease; Mixed histiocytosis; BRAF gene mutation; Targeted therapy; PET/CT.

***Correspondence to:** Shinsaku Imashuku, Department of Laboratory Medicine, Uji-Tokushukai Medical Center, Uji, Kyoto 611-0041, Japan. ORCID: https://orcid.org/0000-0001-9795-0819. Tel: +81-774-20-1111, Fax: +81-774-20-2336, E-mail: shinim95@mbox.kyoto-inet.or.jp

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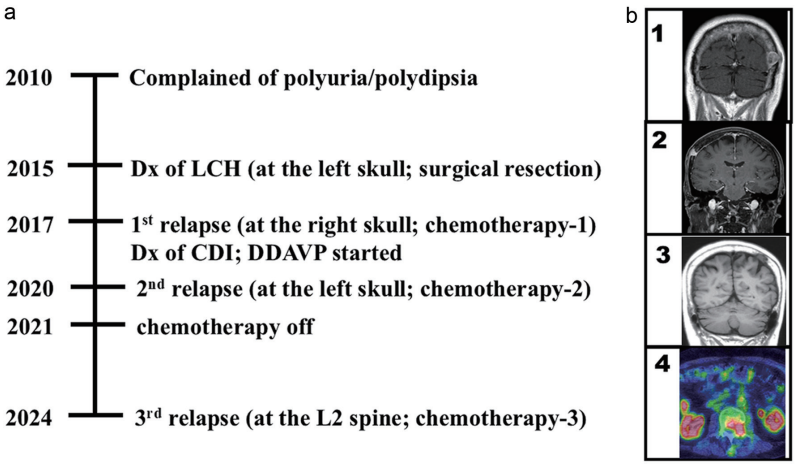

Fig. 1. Clinical course of the patient (a) and images of LCH lesions (b). b1 is a coronal T1-weighted and enhanced MRI showing a left temporal bone mass (initial presentation), b2 is a coronal T1-TFE and enhanced MRI showing a right parietal bone mass (first relapse), b3 is a coronal T1-COR MRI showing a left parietal bone mass (second relapse), and b4 is a PET/CT showing L2 involvement of the vertebral body and left transverse process (third relapse). Chemotherapy-1: Special C regimen; chemotherapy-2: modified Special C regimen; chemotherapy-3: CHOP regimen (see further therapy in the text). CHOP, cyclophosphamide, doxorubicin, vincristine, prednisolone; DDAVP, 1-deamino-8-D-arginine vasopressin; LCH, Langerhans cell histiocytosis; MRI, magnetic resonance imaging; PET/CT, positron emission tomography–computed tomography; T1-COR, T1-weighted coronal; T1-TFE, T1-weighted turbo field echo.

puted tomography revealed a lesion involving the L2 spine, which was diagnosed as the third relapse of BRAF V600E-positive LCH. Her medical history included bronchial asthma and a prior transient ischemic attack; however, these comorbidities did not influence the treatment strategy for LCH.

Regarding LCH, as summarized in Figures 1a and b1-4, the patient had first experienced polyuria and polydipsia in 2010 but attributed these symptoms to aging and did not seek medical attention. In 2015, she was diagnosed with unifocal LCH (pathologically, CD1a+, S100+) of the left temporal skull, which was totally excised without adjuvant therapy. In 2017, LCH relapsed in the right parietal skull, in which the BRAF V600E gene mutation was positive in the biopsied tissue, using the BRAF V600E mutation analysis kit (real-time polymerase chain reaction assay; BRAF RT-50, EntroGen Inc.). At that time, central diabetes insipidus related to LCH was also confirmed from a thickened pituitary stalk on magnetic resonance imaging. She was treated with 10 courses of the Special C regimen [vinblastine 0.1 mg/kg (max. 6 mg), day 1; prednisolone 2.0 mg/kg (max.60 mg), days 1–5; methotrexate 20 mg/m2, day 15; 6-mercaptopurine 1.5 mg/kg, days 1–28] q4 weeks,[13] along with nasal desmopressin (1-deamino-8-D-arginine vasopressin). A second relapse occurred in the left parietal skull and was managed with 10 courses of a modified Special C regimen [methotrexate was replaced with cytosine arabinoside (60 mg/m2), day 15] q4 weeks. After the treatment, complete remission was achieved, and chemotherapy was discontinued.

A third relapse occurred at the L2 spine, nine years after the initial chemotherapy for skull LCH and three years after cessation of therapy. The lesions were visualized on ^{18}F-fluorodeoxyglucose–positron emission tomography/computed tomography (PET/CT) (Fig. 1b4). A biopsy of the left paravertebral soft tissue adjacent to the L2 lesion was performed. Low-power histology revealed mixed areas of proliferating CD1a-positive cells consistent with LCH, alongside areas consisting of predominantly foamy histiocytes with CD1a-negative and CD68-positive staining, including Touton-like multinucleated giant cells, indicative of ECD (Fig. 2a–d). High-power examination confirmed this admixture, showing both CD1a-positive cells (Fig. 2e) and CD68-positive histiocytes, including multinucleated cells (Fig. 2f), within the same lesion.

After receiving two courses of modified CHOP (cyclophosphamide 10 mg/kg, day 1; doxorubicin 35 mg/m2, day 1; vincristine 0.05 mg/kg, day 1; prednisolone 30 mg/day, days 1–5) q4 weeks for the mixed LCH/ECD relapse,[14] PET/CT revealed a poor response, with persistence of the L2 lesion (Fig. 3a) and emergence of new lesions in the left 6th rib (Fig. 3b) and the proximal metaphysis of the left femur (data not shown). In addition, the patient achieved only a partial response after five courses of cladribine (0.09 mg/kg, days 1–5) q4 weeks, prompting a switch to reduced doses of targeted therapy with daily oral dabrafenib (50 mg/day) and trametinib (1 mg/day) due to cladribine-induced myelosuppression. Ultimately, all fluorodeoxyglucose-avid lesions disappeared on PET/CT following targeted therapy. Continuation of dabrafenib/trametinib with an increase in doses is planned to maintain remission, given reports of disease recurrence upon interruption of targeted therapy.[15,16]

Discussion

Although mixed histiocytosis has been well recognized recently,[10,11] it has not been clarified whether it was noted at the initial diagnosis of histiocytosis or developed after treatment for LCH or for non-LCH histiocytosis. This report is novel because we have described that the first skull masses were LCH and the subsequently relapsed spinal L2 lesion was mixed histiocytosis. In addition, despite mixed histiocytosis (LCH/ECD) being noted more frequently in the long bones,[11] it was observed in the spinal bone in this case.

In this case, mixed histiocytosis (LCH/ECD) developed nine years after the initial chemotherapy for skull LCH. At the time of spinal recurrence, pathological examination of the lesion revealed features of both LCH (CD1a+, S100+) and JXG or ECD, which showed foamy CD68-positive histiocytes associated with multinucleated giant Touton cells, as noted in ECD (Fig. 2).[17,18] The pathology of JXG and ECD can mimic each other, making histopathological distinction challenging; however, we diagnosed this case as mixed LCH/ECD based on the criteria,[1] though the patient

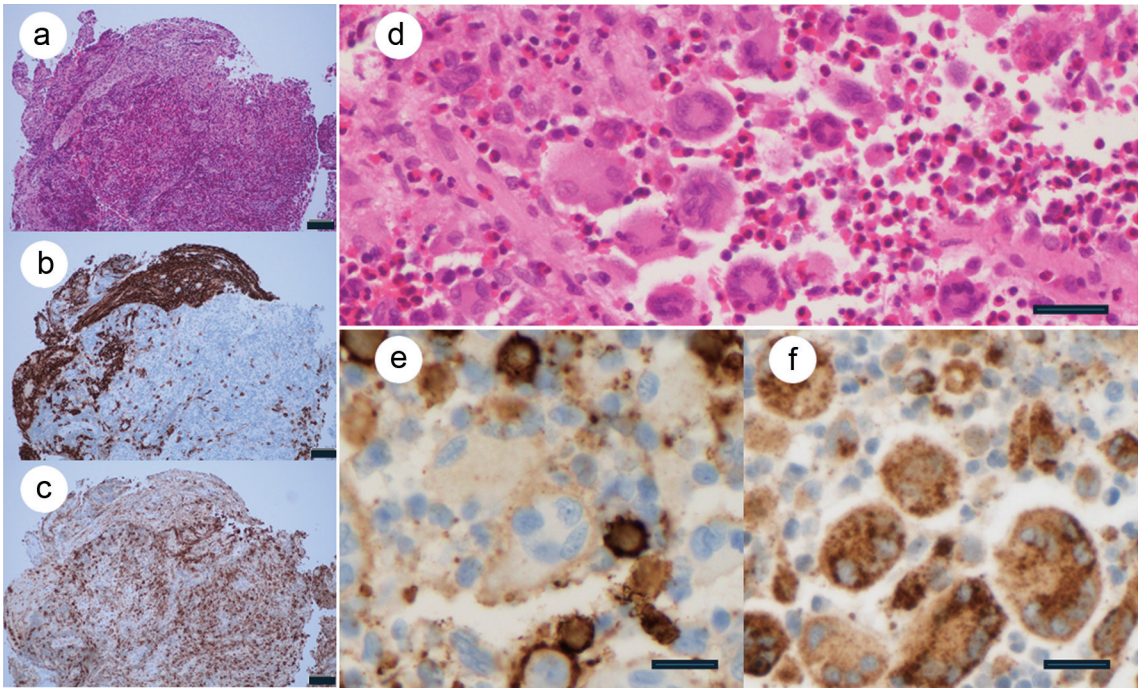

Fig. 2. Histology of mixed histiocytosis (LCH/ECD). Low-power histology showed (a) H&E stain, (b) CD1a stain, and (c) CD68 stain. CD1a-positive area (b) and CD68-positive area (c) were separated (original magnification ×100; scale bar indicates 100 µm). High-power histology showed (d) H&E stain of the ECD area (original magnification ×200; scale bar indicates 50 µm), in which CD1a-positive cells were intermingled (e), while CD68-positive cells with multinucleated giant cells were dominant (f) (original magnification ×400; scale bar indicates 20 µm). ECD, Erdheim–Chester disease; H&E, hematoxylin and eosin; LCH, Langerhans cell histiocytosis.

lacked typical clinical features of ECD, such as long bone pain, retroperitoneal fibrosis, hairy kidneys, and coated aorta. Analysis of reported mixed histiocytosis cases revealed LCH/ECD in 19, LCH/RDD in 1, ECD/RDD in 6, and ECD/RDD/LCH in 1 case, predominantly in adults, with pediatric cases being rare.[10] In the context of LCH and JXG, a pediatric case demonstrating coexistence of both LCH and JXG cell populations within cutaneous JXG lesions has been reported.[19] Additionally, disseminated JXG occurring after treatment for LCH has been described in pediatric cases[20,21]; however, those cases did not exhibit a mixed phenotype within the involved lesions.

In 27 of 69 reported cases of mixed histiocytosis (LCH/ECD), the diagnosis of mixed ECD was delayed, with a median interval of 4 years after the initial LCH diagnosis.[11] These cases often demonstrate poor responsiveness to conventional therapy but show marked sensitivity to targeted treatments.[10] Given the presence of BRAF mutations in LCH/ECD,[22] molecularly targeted agents, such as BRAF and/or MEK inhibitors, could be effective.[23] In the present case, the relapsed spinal lesion exhibiting mixed histiocytosis was refractory to modified CHOP therapy, whereas partial remission was achieved with a cladribine regimen. Complete metabolic remission on PET/CT was subsequently obtained with combined BRAF and MEK inhibition. However, the contribution of cladribine to the therapeutic response cannot be excluded, as the two regimens were administered consecutively and targeted therapy was initiated at low doses, as shown in the Case presentation. Despite the efficacy of targeted therapies, Pegorano *et al*. reported that, after a median follow-up of 71 months, 24 of 69 patients (35%) had died, indicating that outcomes in mixed histiocytosis are poorer than in LCH or ECD alone,[11] suggesting that longer follow-up of our case is needed. Furthermore, important clinical aspects of the transition from LCH to mixed histiocytosis remain unknown. Unresolved questions regarding mixed histiocytosis after LCH treatment include how frequently it might be detected in older patients with careful evaluation, the role of prior chemotherapy for LCH in this transition, and whether early introduction of targeted therapy could reduce its incidence.

This report has several limitations. Although cases of mixed histiocytosis developing after treatment for LCH have rarely been described, this is a single-case report. In addition, BRAF mutation analysis was available only on the first relapsed skull LCH lesion. No comprehensive genetic analyses could be performed on other lesions, such as the further relapsed skull lesion and the spinal mixed lesion. In addition, the follow-up period for the mixed histiocytosis was relatively short.

Conclusions

This case is instructive in several respects. First, when patients initially present with symptoms of polyuria and polydipsia, a thorough search for LCH lesions is warranted. Although these symptoms are characteristic of LCH, the diagnosis may be delayed for several years. In the present case, LCH was diagnosed five years after symptom onset. Second, LCH lesions involving the skull are known to have a relatively high relapse rate. Therefore, even when skull lesions achieve remission, the possibility of subsequent recurrence in other skeletal sites cannot be excluded. Third, when LCH recurs at any site, mixed histiocytosis should be considered in the differential diagnosis. Based on these findings, we recommend routine PET/CT for systemic disease screening, along with

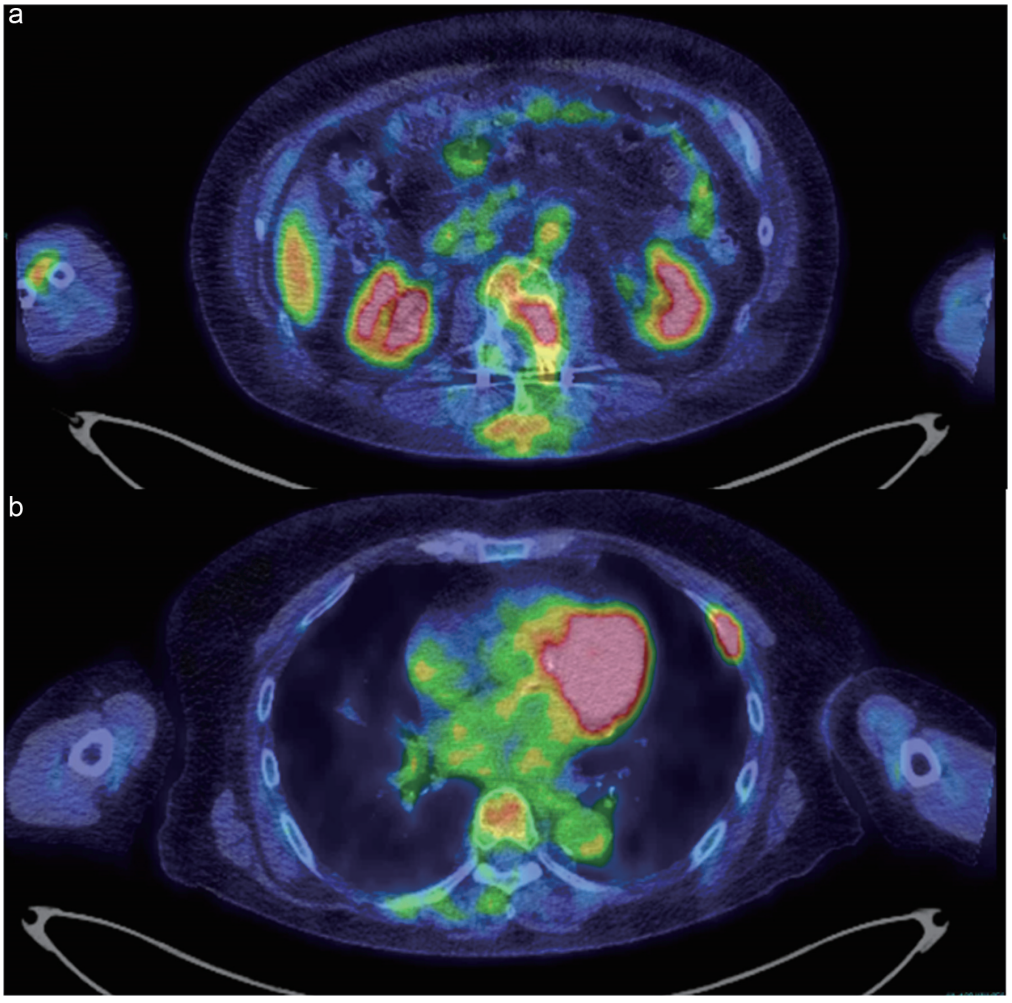

Fig. 3. PET/CT images of the refractory histiocytic lesions after chemotherapy with the CHOP regimen. FDG-avid signals persisted at the L2 vertebral body and the left vertebral arch (SUVmax = 5.4) (a). In addition, newly developed signals at the left rib (SUVmax = 18.6) (b) and at the proximal metaphysis of the left femur (SUVmax = 3.8) (data not shown) were noted. CHOP, cyclophosphamide, doxorubicin, vincristine, prednisolone; CT, computed tomography; FDG, fluorodeoxyglucose; PET, positron emission tomography; SUVmax, standardized uptake value (maximum).

thorough pathological examination and genetic testing, including BRAF mutation analysis of all lesions during the management of patients with LCH.

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Conflict of interest

The authors declare no conflicts of interest.

Author contributions

Manuscript drafting (TH, MK, SI), patient management (TH, MK, NA, SI), and pathological diagnosis (AF, NN). All authors have made significant contributions to this study and have approved the final manuscript.

Ethical statement

The study was conducted in accordance with the ethical standards of our affiliated institution and the principles of the Declaration of Helsinki (as revised 2024). Written informed consent was obtained from the patient for publication of this case and the accompanying images.

References

[1] Emile JF, Abla O, Fraitag S, Horne A, Haroche J, Donadieu J, *et al*. Revised classification of histiocytoses and neoplasms of the macrophage-dendritic cell lineages. Blood 2016;127(22):2672–2681. doi:10.1182/blood-2016-01-690636, PMID:26966089.

[2] Allen CE, Merad M, McClain KL. Langerhans-Cell Histiocytosis. N Engl J Med 2018;379(9):856–868. doi:10.1056/NEJMra1607548,

PMID:30157397.
[3] Durham BH. Molecular characterization of the histiocytoses: Neoplasia of dendritic cells and macrophages. Semin Cell Dev Biol 2019;86:62–76. doi:10.1016/j.semcdb.2018.03.002, PMID:29526544.
[4] Goyal G, Tazi A, Go RS, Rech KL, Picarsic JL, Vassallo R, *et al*. International expert consensus recommendations for the diagnosis and treatment of Langerhans cell histiocytosis in adults. Blood 2022;139(17):2601–2621. doi:10.1182/blood.2021014343, PMID:35271698.
[5] Sakamoto K, Morimoto A, Shioda Y, Imamura T, Imashuku S, Japan LCH Study Group (JLSG). Relapses of multisystem/multifocal bone Langerhans cell histiocytosis in paediatric patients: Data analysis from the JLSG-96/02 study. Br J Haematol 2023;200(6):769–775. doi:10.1111/bjh.18583, PMID:36511451.
[6] Lang M, Cai HC, Lin H, Chang L, Dai JW, Chen J, *et al*. Clinical features, genomic profiling, and outcomes of adult patients with unifocal Langerhans cell histiocytosis. Orphanet J Rare Dis 2023;18(1):372. doi:10.1186/s13023-023-02989-8, PMID:38037140.
[7] Sato A, Kobayashi M, Yusa N, Ogawa M, Shimizu E, Kawamata T, *et al*. Clinical and prognostic features of Langerhans cell histiocytosis in adults. Cancer Sci 2023;114(9):3687–3697. doi:10.1111/cas.15879, PMID:37364599.
[8] Shioda Y, Adachi S, Imashuku S, Kudo K, Imamura T, Morimoto A. Analysis of 43 cases of Langerhans cell histiocytosis (LCH)-induced central diabetes insipidus registered in the JLSG-96 and JLSG-02 studies in Japan. Int J Hematol 2011;94(6):545–551. doi:10.1007/s12185-011-0965-x, PMID:22139588.
[9] Catalina PF, Rodr'iguez Garc'ia M, de la Torre C, P'aramo C, Garc'ia-Mayor RV. Diabetes insipidus for five years preceding the diagnosis of hypothalamic Langerhans cell histiocytosis. J Endocrinol Invest 1995;18(8):663–666. doi:10.1007/BF03349786, PMID:8655927.
[10] Friedman JS, Durham BH, Reiner AS, Yabe M, Petrova-Drus K, Dogan A, *et al*. Mixed histiocytic neoplasms: A multicentre series revealing diverse somatic mutations and responses to targeted therapy. Br J Haematol 2024;205(1):127–137. doi:10.1111/bjh.19462, PMID:38613141.
[11] Pegoraro F, Papo M, Cohen-Aubart F, Peyronel F, Lugli G, Trambusti I, *et al*. Long-term outcome and prognosis of mixed histiocytosis (Erdheim-Chester disease and Langerhans Cell Histiocytosis). EClinicalMedicine 2024;73:102658. doi:10.1016/j.eclinm.2024.102658, PMID:38841707.
[12] Badalian-Very G. A common progenitor cell in LCH and ECD. Blood 2014;124(7):991–992. doi:10.1182/blood-2014-06-581736, PMID: 25124781.
[13] Morimoto A, Shimazaki C, Takahashi S, Yoshikawa K, Nishimura R, Wakita H, *et al*. Therapeutic outcome of multifocal Langerhans cell histiocytosis in adults treated with the Special C regimen formulated by the Japan LCH Study Group. Int J Hematol 2013;97(1):103–108. doi:10.1007/s12185-012-1245-0, PMID:23243004.
[14] Morimoto A, Ikushima S, Kinugawa N, Ishii E, Kohdera U, Sako M, *et al*. Improved outcome in the treatment of pediatric multifocal Langerhans cell histiocytosis: Results from the Japan Langerhans Cell Histiocytosis Study Group-96 protocol study. Cancer 2006;107(3):613–619. doi:10.1002/cncr.21985, PMID:16804933.
[15] Abla O. Management of ECD: the era of targeted therapies. Blood 2020;135(22):1919–1920. doi:10.1182/blood.2020005803, PMID: 32463888.
[16] Reiner AS, Durham BH, Yabe M, Petrova-Drus K, Francis JH, Rampal RK, *et al*. Outcomes after interruption of targeted therapy in patients with histiocytic neoplasms. Br J Haematol 2023;203(3):389–394. doi:10.1111/bjh.18964, PMID:37400251.
[17] Guo S, Yan Q, Rohr J, Wang Y, Fan L, Wang Z. Erdheim-Chester disease involving the breast—a rare but important differential diagnosis. Hum Pathol 2015;46(1):159–164. doi:10.1016/j.humpath.2014.10.005, PMID:25454479.
[18] Ding H, Li Y, Ruan C, Gao Y, Wang H, Zhang X, *et al*. Chinese Erdheim-Chester disease: clinical-pathology-PET/CT updates. Endocrinol Diabetes Metab Case Rep 2015;2015:150055. doi:10.1530/EDM-15-0055, PMID:26527559.
[19] Martín JM, Jordá E, Martín-Gorgojo A, Beteta G, Monteagudo C. Histiocytosis with mixed cell populations. J Cutan Pathol 2016;43(5):456–460. doi:10.1111/cup.12687, PMID:26968131.
[20] Lee TK, Jung TY, Baek HJ, Kim SK, Lee KH, Yun SJ. Disseminated juvenile xanthogranuloma occurring after treatment of Langerhans cell histiocytosis: a case report. Childs Nerv Syst 2018;34(4):765–770. doi:10.1007/s00381-017-3675-8, PMID:29209883.
[21] Sako M, Ishii T, Okada K, Mochizuki T, Hara J, Kudo K, *et al*. Successful unrelated cord blood transplantation for extensive meningeal juvenile xanthogranuloma developing after treatment of Langerhans cell histiocytosis in a child (in Japanese). Rinsho Ketsueki 2020;61(5):468–473. doi:10.11406/rinketsu.61.468, PMID:32507810.
[22] Hervier B, Haroche J, Arnaud L, Charlotte F, Donadieu J, Néel A, *et al*. Association of both Langerhans cell histiocytosis and Erdheim-Chester disease linked to the BRAFV600E mutation. Blood 2014;124(7):1119–1126. doi:10.1182/blood-2013-12-543793, PMID: 24894769.
[23] Roeser A, Jouenne F, Vercellino L, Calvani J, Goldwirt L, Lorillon G, *et al*. Dramatic Response After Switching MEK Inhibitors in a Patient With Refractory Mixed Histiocytosis. J Hematol 2022;11(5):185–189. doi:10.14740/jh1030, PMID:36406830.