Adult Langerhans cell histiocytosis with multi-system bone, skin, lung and liver involvement: A case report

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Received May 15, 2024; Accepted June 18, 2024

DOI: 10.3892/br.2024.1850

Abstract. Langerhans cell histiocytosis (LCH) is a rare neoplastic disorder marked by the uncontrolled proliferation and accumulation of immature myeloid dendritic cells, which originate from the bone marrow. Although LCH can involve various organs, including bone, lymph nodes and skin, multi-system bone, liver and lung involvement with LCH is rare in adults. A case of a 49-year-old man diagnosed with multi-system, aggressive LCH involving bone, skin, lung and liver is presented in the present study. The initial radio-clinic presentation of the patient was initially suggestive of a bone tumor. The current case report aims to draw attention to this rare disease and discuss the diagnostic approach and therapeutic management, which should be noted to help physicians more rapidly identify, diagnose and treat comparable cases.

Introduction

Langerhans cell histiocytosis (LCH) is an uncommon hematological disease with an average incidence of 2-5 cases per million children and 1-2 cases per million adults annually worldwide (1). The precise etiology and pathogenesis of this disorder remain to be understood. Early hypotheses suggested that LCH may be a reactive process, but recent evidence identifying oncogenic BRAF or MAP2K1 mutations in the majority of LCH cases has prompted a reassessment (1,2). This evidence points to LCH as a clonal neoplasm originating from unchecked proliferation and accumulation of immature myeloid dendritic cells in bone marrow (1-3). The clinical presentations of LCH include granulomatous lesions consisting of clonal pathologic histiocytes and are linked to a mortality rate of 10 to 20% (4).

Under the updated revised classification system of histiocytoses, LCH has been split into three categories: Single-system LCH, lung LCH and multi-system LCH with or without risk organ involvement (spleen, liver and bone marrow) (5). The most common form of single-system LCH is bone involvement, which can manifest as uni- or multi-focal (5). In the case of multi-system LCH, the bones are usually the most affected site, followed by the pituitary gland and lung (6). Liver involvement is less frequent, with incidence rates in adults of 16-27% of all LCH cases, while it is more frequent in children with multisystem LHC, with an incidence reported from 19-60% (7).

The current study presents a rare case involving bone, skin, lung and liver involvement in an adult multi-system LCH, with the aim of contributing to reviewing the current literature on this disease and providing guidance for medical practitioners who encounter similar cases in their practice.

Case report

A 49-year-old man presented to the First People's Hospital of Foshan, Foshan, China with a 1-week history of itchy skin over his entire body on October, 2023. At first, food allergies were suspected given that the patient presented with red rashes scattered across his back and face. The vital signs were stable after admission and the findings of physical examination were all normal. CT imaging revealed multiple nodules and spots in the chest and liver, indicating the possibility of infectious lesions (Fig. 1A and B). However, conventional laboratory tests (such as routine blood tests, condensation profile, procalcitonin, protein C, α-fetoprotein and bone marrow examination) did not find any

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Abbreviations: LCH, Langerhans cell histiocytosis; CT, computed tomography; MRI, magnetic resonance imaging

Key words: Langerhans cell histiocytosis, neoplastic disease, BRAF mutation, MAP2K1 mutation

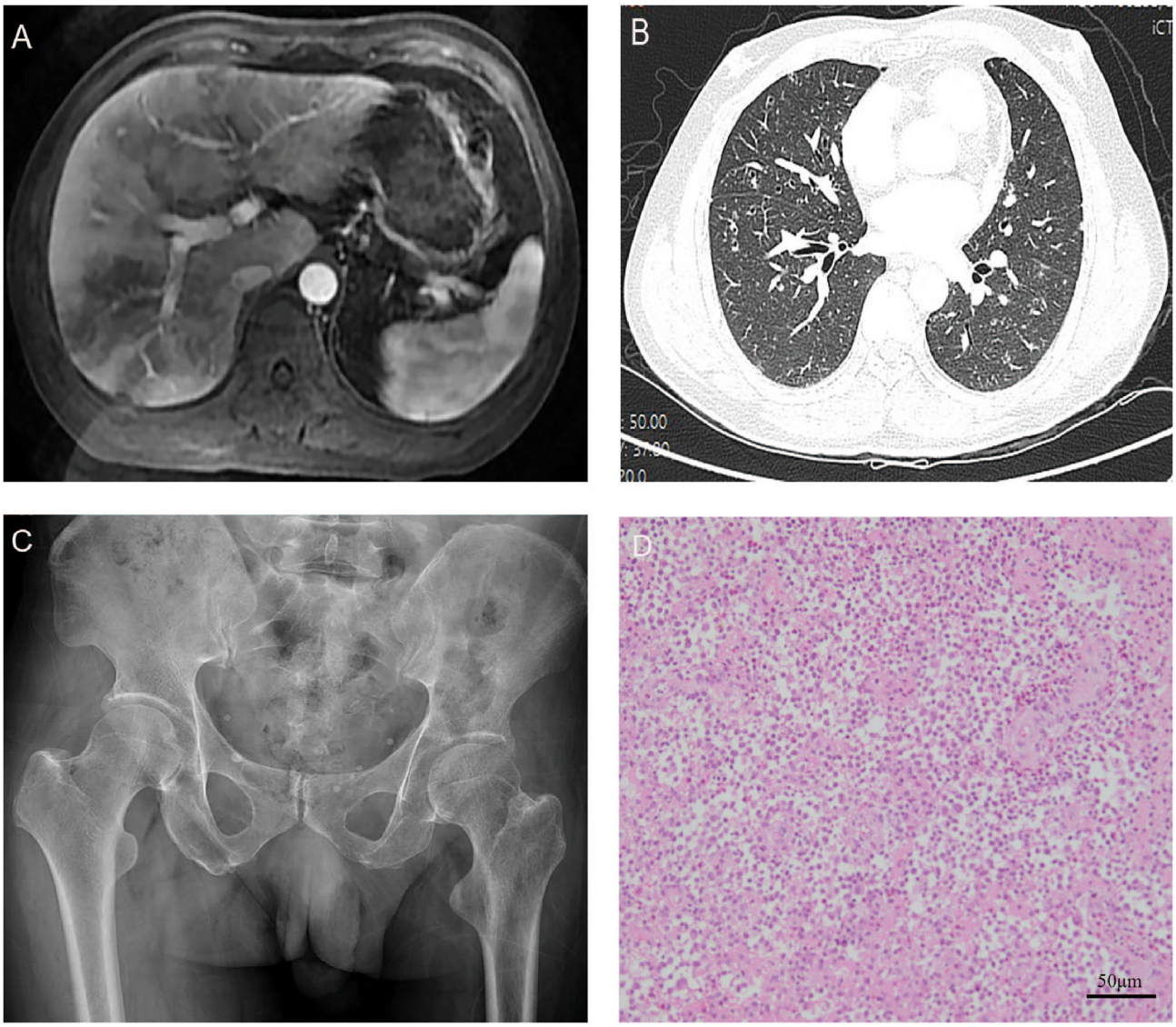

Figure 1. (A) MRI (axial view) scan reveals numerous scattered, flaky abnormal signals in the liver. (B) Axial CT scan (axial view) demonstrates multiple cavitary nodules in the lungs. (C) X-ray revealing a round lesion in the left iliac bone. (D) Pathological examination reveals a substantial infiltration of eosinophils and inflammatory cells in the liver tissue (magnification, x200). CT, computed tomography; MRI, magnetic resonance imaging.

abnormalities. The medical history of the patient revealed that the patient had previously undergone resection of left iliac bone lesions (Fig. 1C and D), and the histopathology examination confirmed that the diagnosis was Langerhans cell histiocytosis (LCH). Immunohistochemistry analysis showed positive staining for S-100 protein, CD163, CD68, CD1a, lysozyme and langerin (CD207) antigen. Therefore, the final diagnosis was determined to be multi-system LCH with bone, skin, lung and liver involvement. The patient was initiated on the front line drug, cytarabine, and after three rounds of treatment, his condition did not improve significantly. At the 2-year follow-up from the initial diagnosis, the patient was still alive at the last follow-up on April, 2024.

Discussion

LCH, a rare inflammatory myeloid neoplasm that affects both children and adults, may present with the accumulation of mononuclear phagocytes in a wide range of tissues and organs, including bone, oral cavity, skin, anogenital regions, liver, lungs, spleen and lymph nodes (8). Children tend to be more affected than adults. The pathogenesis of LCH is not fully understood (9). Whether LCH is reactive inflammation or neoplastic remains a matter of debate. Nowadays, the etiology is generally considered to be a $BRAF^{V600E}$ mutation, while activated MAP2K1 is the most prevalent mutation in non-$BRAF^{V600E}$ mutation cases (3). It is reported that $BRAF^{V600E}$, BRAF deletion and MAP2K1 mutation were detected in 38.8, 25.4 and 19.4% of patients, respectively (6). BRAF deletion has been revealed to be associated with multisystem LHC in adult patients, specifically those with liver involvement (6). Pathologically, LCH is distinguished by the presence of abnormal Langerhans cell-like cells mixed with inflammatory cells (10). The pathogenesis of LCH may be related to cytokine storm in serum and lesions. Ismail *et al* (11) confirmed the finding of higher levels of plasma inflammatory factor IL-17A in patients with LCH compared with controls. The disease may manifest

as a single-system disorder or as a multi-system disorder, and acute-phase protein ITIH4 levels may distinguish multi-system from single-system LCH (10). In the present study, although only one enhancement lesion in the left iliac bone was pathologically confirmed, typical imaging and findings of LCH were observed in the skin, lung and liver. Therefore, the LCH in the current report was considered to be multi-system.

Bone is the most commonly affected organ in patients with LCH, involving single or multiple osseous sites. The head and neck region is particularly susceptible, while iliac bone infringement is relatively uncommon (12). Hashimoto *et al* (9) reported that all pediatric cases involved the bones of the extremities, and all adult cases involved the bones of the trunk. Patients with osseous LCH typically present with symptoms such as swelling or pain. Skin involvement of LCH may mirror a skin-limited disease that may resolve spontaneously or with brief chemotherapy (13). It is reported that 53% of individuals with multi-system LCH developed skin lesions (13), which appear to be a clinical indicator of a potentially multi-system LCH. Lung involvement is not a common manifestation of LCH, and is associated with smoking (14). Pulmonary LCH is typically identified on CT as the presence of multiple nodules and cysts.

In the present case, the predominant radiological finding was that of multiple cystic lesions. Liver involvement is a poor prognostic factor that indicates poor overall survival (OS) and event-free survival (EFS) in adult LCH (6). Furthermore, simultaneous involvement of the lung, skin, liver, and bone is uncommon, making multi-system LCH a high-risk condition. In multi-system LCH with risk organ involvement, survival rates decline to 70%, and roughly one-third of patients witness disease reactivation post-treatment (3). Clinical manifestations are very heterogeneous and the type and number of organs involved will determine the symptoms that occur. Pathologic diagnosis is characterized by infiltration of oval shaped cells with coffee bean-like nuclei that express CD1a, S100 and Langerin (CD207) (3,15). The current frontline treatment for multi-system LCH remains empirically derived chemotherapy, consisting of agents such as vinblastine, prednisone, cytarabine and nucleoside analogues (such as cladribine) (15).

In a recent cohort, it was found that patients receiving cytarabine-based first-line treatment had improved event-free survival and overall survivals compared with patients receiving other treatments (6). However, the symptoms of the patient in the current study did not improve when using cytarabine. Promising targeted agents (such as BRAF and MEK inhibitors) alone or in combination with chemotherapy are also under investigation.

Awada *et al* (16) described a 41-year-old female LCH patient with an activated $BRAF^{V600E}$ mutation who had a remarkable response to dabrafenib (BRAF inhibitor) 150 mg twice daily and trametinib (MEK inhibitor) 2 mg once daily within days. In addition, the patient was PET/CT negative after 2 months and plasma $BRAF^{V600E}$-mutant ctDNA became undetectable during treatment (16). As described by Awada *et al* (16), to the best of our knowledge, this is the first report of successful treatment of $BRAF^{V600E}$ mutant LCH with combined BRAF MEK inhibition, and it also shows that detection of $BRAF^{V600E}$ mutant circulating tumor DNA in plasma is a promising biomarker for this disease. Messinger *et al* reported that the MEK inhibitor trametinib results in a strong response in patients with LCH (17). In that report a neonatal LCH with MAP2K1p.K57_G61del mutation did seem to have a complete response lasting 22 months, and two adolescent male patients with LCH with BRAF p.N486_P490del mutation received trametinib for >1 year with no reactivation in one and partial response in another (including stable lung disease). Experience with patients with LCH suggests that future prospective clinical trials will most likely involve a combination of targeted drugs or targeted drugs combined with chemotherapy to achieve the optimal therapeutic benefits and safety profile of this promising new therapeutic strategy.

LCH is a rare and complex disease that can affect multiple organ systems. It is often under-diagnosed or delayed in diagnosis. The current study presents the case of a patient with LCH affecting multiple organs including the bone, skin, lung and liver. The aim of the present study is to raise awareness of this disease and to help healthcare professionals identify, diagnose and treat similar cases more quickly.

Acknowledgements

Not applicable.

Funding

The present study was supported by the Key Cultivation Project of '14th Five-Year Plan' in Foshan (grant no. FSPY145202) and the Foshan Science and Technology Program Project (grant no. 2220001005255).

Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

QL and HZ wrote the manuscript. QL, XH and JY contributed to initial patient assessment and follow up. QL and HZ obtained and analyzed patient clinical data. QL and FD contributed to conception and have reviewed the manuscript and consistently improved its content. FD and HZ confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Written informed consent was provided by the patient for publication of data and images.

Competing interests

The authors declare that they have no competing interests.

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