

Ultrasonographic analysis of Langerhans cell histiocytosis in children: a report of 55 cases

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Abstract

Objective: To explore the value of ultrasonography in the diagnosis and treatment of Langerhans cell histiocytosis (LCH) in children.

Method: The clinical and imaging features of 55 children with pathologically confirmed LCH were retrospectively analyzed.

Results: Thirteen patients had bone LCH and 42 had multisystem LCH. Among the 13 cases of bone LCH, 8 cases involving the skull and 2 involving the scapula were characterized by osteolytic bone destruction, 1 case involving the clavicle and 1 involving the iliac bone showed multiple irregular bone destruction, and 1 case involving the tibia showed local hypoechoic cortical bone. Soft tissue echo filling was present in the local areas of bone destruction. Among the 42 cases of multisystem LCH, 33 involved the bone, 35 showed an enlarged liver, 15 involved the spleen, 2 involved the pancreas, 3 involved the lung, 3 involved the thymus, and 21 affected the lymph nodes in different regions.

Conclusions: Ultrasonography of the flat bones in children with LCH mainly showed punched-out osteolytic bone destruction. Long bone lesions were characterized by fan shell changes in the endosteum of long bones, and some also showed bone destruction. Multisystem LCH can affect almost any organ. Ultrasonography is important for early diagnosis.

Keywords

Langerhans cell histiocytosis, bone, children, ultrasound, imaging, diagnosis

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Introduction

Langerhans cell histiocytosis (LCH) refers to a group of diseases with unexplained proliferation of the mononuclear macrophage system and dendritic cell system.¹ LCH is a rare disease that affects 4 to 8 children per 1 million.^{2,3} Langerhans cells were first recognized by Paul Langerhans in 1868.⁴ The term “LCH” is more frequently used than the older term “histiocytosis X,” which was coined by Lichtenstein to describe three related syndromes: eosinophilic granuloma (unifocal LCH with a solitary or a few lytic bone lesions), Hand–Schüller–Christian disease (multifocal LCH with the classic triad of exophthalmos, diabetes insipidus, and lytic bone lesions), and Letterer–Siwe disease (fulminant and disseminated LCH).^{5,6}

The exact pathogenesis of LCH is unclear. In 2010, Badalian-Very et al.⁷ reported that the pathological CD1a+/CD207+ histiocytes in 57% of patients with LCH had the oncogenic somatic BRAF^{V600E} mutation. BRAF is a central kinase of the RAS–RAF–MEK signal transduction pathway, which is involved in numerous cell functions. The BRAF^{V600E} mutation causes the MAPK pathway to be constitutively active.⁸ This discovery provided a powerful argument for the neoplastic nature of LCH and defined LCH as an inflammatory myeloid neoplasia. Approximately 10% to 25% of patients with LCH have mutations in the MAP2K1 gene.^{8,9} Small in-frame BRAF deletions or insertions localized to exon 12 were reported in 5% to 10% of patients with LCH.^{10,11} Mutations in ARAF, ERBB3, NRAS, and KRAS have also been reported in patients with LCH, but the incidence of such mutations is low (Figure 1).^{5,9,12}

The clinical outcomes of LCH widely vary from natural regression to chronic

progression and even death. As opposed to multisystem involvement in children, single-system disease has a better prognosis and outcome, and it most commonly affects the skeletal system. This study was performed to analyze the ultrasonographic findings of bone and multisystem LCH and to review the related literature to provide an imaging basis for the early diagnosis and treatment of LCH in children.

Methods

Patients

This retrospective study was conducted using the clinical data of patients who were confirmed to have LCH by histopathology in our hospital from January 2015 to October 2021. All patients met the diagnostic criteria for LCH; i.e., immunohistochemical positivity for CD1a and/or langerin, or the presence of tissue cells with Birbeck particles or Langerin positivity under electron microscopy. The patients' data were extracted from the medical records and analyzed retrospectively. The analyzed data included demographics, clinical presentation, imaging findings, and histopathologic findings. All patients' details were de-identified. The reporting of this study conforms to the STROBE guidelines.¹³ This study was approved by the Ethics Committee of Shenzhen Children's Hospital (approval number: 2016[003], ChiCTR-ONh-16009236). All patients or their guardians provided verbal and written informed consent.

Instruments

The ultrasonographic examination was performed with Voluson E8 and Logiq E9 color ultrasound instruments (GE Healthcare, Chicago, IL, USA) using a convex array probe with a frequency of

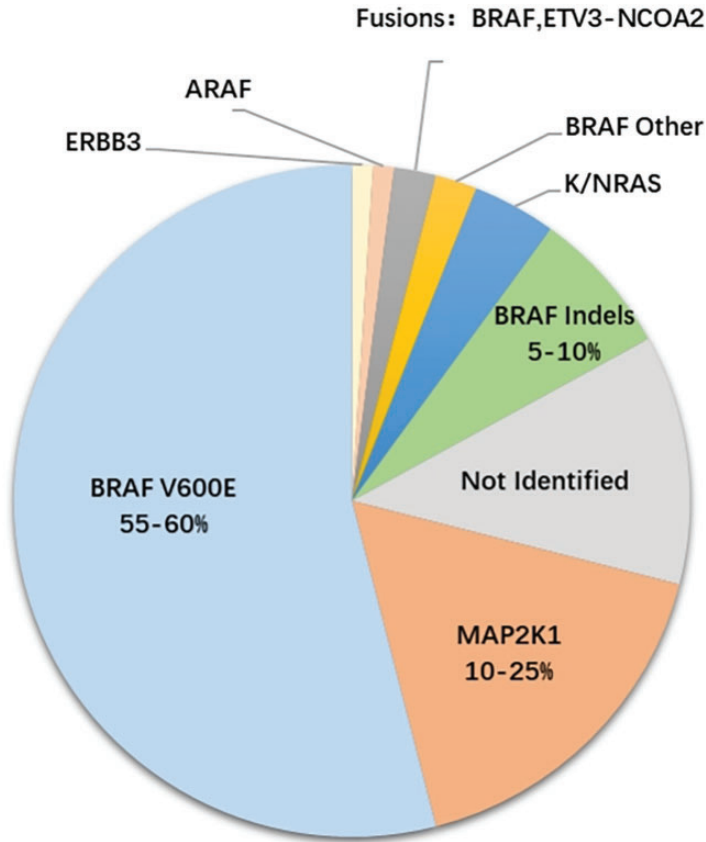


Figure 1. Distribution of somatic gene alterations in childhood Langerhans cell histiocytosis.

2.5 to 5.0 MHz and a linear array probe with a frequency of 6 to 15 MHz. Contrast-enhanced ultrasonography was performed with intravenous injection of SonoVue (Bracco, Milan, Italy) at 0.03 mL/kg, computed tomography (CT) was performed with Optima 64 and Revolution 256-slice spiral CT scanners (GE Healthcare), and magnetic resonance imaging (MRI) was performed with a MAGNETOM Skyra 3.0T magnetic resonance scanner (Siemens Healthineers, Erlangen, Germany).

Data analysis

The classified data were calculated using frequency counts and percentages.

Results

Demographics and clinical presentation

Fifty-five patients (22 male and 33 female patients) were identified by reviewing the medical records. The patients' ages ranged from 2 months to 12.6 years, and their median age was 4.1 years. Among the 13 patients with bone LCH, 8 had craniofacial LCH, 2 had scapular LCH, and 1 each had clavicular, iliac, and tibial LCH. Six patients sought treatment for a local mass and two for facial swelling and pain (including one patient who was misdiagnosed as having mumps), and two patients' lesions were accompanied by claudication and

pain. Two patients had a fever and one had recurrent pain in the scapula. Of the 42 children with multisystem LCH involving more than 2 systems, 12 sought treatment for body surface masses, 5 had a fever, 9 had a rash, 2 had ear discharge, 2 had yellow skin staining, 3 had pallor or skin bleeding, 5 had cough, 1 had abdominal pain, 2 had claudication, and 1 had polydipsia. A total of 54 patients received chemotherapy, and 1 abandoned treatment. Twenty-eight patients responded well to treatment (2 were cured and 26 improved), 22 responded moderately to treatment (5 showed a mixed response and 17 showed stable disease), and 4 responded poorly to treatment (4 patients' condition became severe). During follow-up, two patients died and the remaining patients survived.

Pathological results

Of the 13 patients with bone LCH, 6 underwent tumor resection and 7 underwent tumor puncture biopsy. Automatic immunohistochemistry showed CD1a (+) in 11 patients and langerin (+) in 10. Of the 42 patients with multisystem LCH, 18 underwent mass resection or biopsy, 8 underwent bone marrow aspiration, 3 underwent lymph node biopsy, and 5 underwent skin biopsy. Automatic immunohistochemistry showed CD1a (+) in 36 patients and

langerin (+) in 34. All patients met the diagnostic criteria for LCH; i.e., immunohistochemical positivity for CD1a and/or langerin, or the presence of tissue cells with Birbeck particles or Langerin positivity under electron microscopy.

Ultrasonographic findings versus CT/MRI findings in 13 patients with bone LCH

Local bone destruction was found in all 13 patients with bone LCH, including skull destruction in 8 (parietal bone destruction in 3, frontal bone destruction in 2, occipital bone destruction in 1, and mandible destruction in 2) and scapular destruction in 2. The destroyed bones had clear and irregular edges and exhibited osteolytic bone destruction. Among them, four patients had echo signals of bone fragments inside (Figure 2(a)). Multiple irregular bone destruction was found in one patient with clavicle involvement and one patient with ilium involvement, with echo signals of bone fragments inside. One patient with tibial lesions showed less uniform local cortical bone echo (Figure 3(a)). Contrast-enhanced ultrasonography was performed in one patient with a mandibular lesion and one patient with a tibial lesion, and the results showed equal enhancement at the edge of the bone defect. All the local areas of bone destruction showed soft tissue echo and a hypoechoic mass with

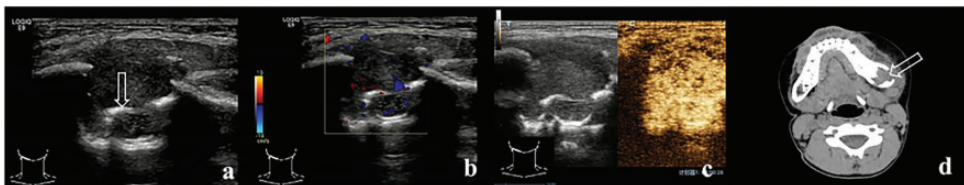


Figure 2. Images of a 5-year-old girl with mandibular Langerhans cell histiocytosis. (a) Hypoechoic mass at the mandible with less uniform internal echo, or the echo of bone fragments (arrow), and stepladder bone destruction. (b) Dotted blood flow signal inside the hypoechoic mass. (c) Rapid appearance of high enhancement and rapid clearance in the mass on contrast-enhanced ultrasonography and (d) Bone destruction in the left mandible on plain computed tomography with high-density soft tissues (arrow) inside; the computed tomography number is 43 HU.

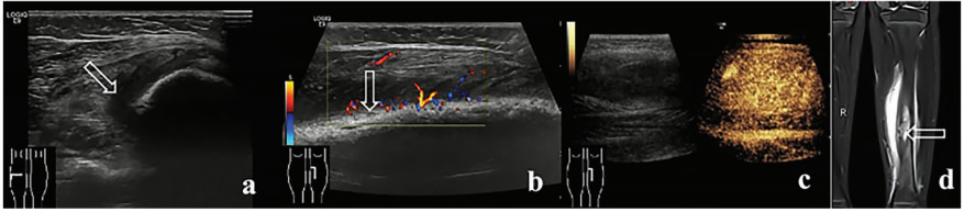


Figure 3. Images of a 4-year-old girl with tibial Langerhans cell histiocytosis. (a) A hypoechoic mass (arrow) was found under the membrane and in the muscular layer of the anterior-medial aspect of the left tibia. The mass surrounded about half of the tibia and showed uneven internal echo. (b) The echo of the tibial cortex was rough and not smooth (arrow), and the hypoechoic mass had rich blood flow signals. (c) Contrast-enhanced ultrasonography revealed rapid appearance of high enhancement and rapid clearance in the hypoechoic mass and (d) Magnetic resonance imaging revealed a fat-suppressed sequence on T2-weighted imaging and high signal intensities in the bone marrow cavity of the middle and upper part of the left tibia (arrow).

a clear boundary and less uniform internal echo. In two of these patients, a liquid dark area was seen inside the mass. Color Doppler flow imaging showed no blood flow signals in three patients, a dotted blood flow signal in four, a strip blood flow signal in three (Figure 2(b)), and a rich blood flow signal in three (Figure 3 (b)). Contrast-enhanced ultrasound was performed in two patients with a mass and showed rapid and high enhancement in the hypoechoic mass and rapid clearance of the contrast medium (Figures 2(c) and 3(c)).

CT examination was performed in 9 of the 13 patients, and 11 lesions were found. Among them, one patient had an occipital bone lesion with a parietal bone lesion, and one patient had a mandible lesion with a temporal bone lesion. The CT findings revealed bone destruction with irregular soft tissue images and uneven density inside. The CT number of the plain scan was about 43 HU (Figure 2(d)). Two patients showed expansive bone destruction. MRI examination was performed in four patients, and three lesions were found. The MRI findings revealed local bone defects. A strip blood flow signal with low or equal signal intensity was seen on T1-weighted imaging, and inhomogeneous slightly high signal intensity was

seen on T2-weighted imaging and FLAIR (Figure 3(d)).

Ultrasonographic findings versus CT/MRI findings in 42 patients with multisystem LCH

Of all 42 patients with multisystem LCH who underwent whole-body ultrasonography, bone lesions were observed in 33 (78.57%), liver enlargement in 35 (83.33%), thickening and echo enhancement in the portal vein area in 20, and unequal echo of the hepatic parenchyma in 4 (with hypoechoic and hyperechoic nodules of different sizes scattered in the liver). Thickening of the bile duct wall and echo enhancement were found in five patients (Figure 4(a)), and this was accompanied by biliary dilatation in two patients. Spleen enlargement at different levels was seen in 15 (35.71%) patients, and this was accompanied by hypoechoic nodules in 2 (Figure 4(b)). Pancreas enlargement was seen in two (4.76%) patients, and this was accompanied by dilation of the main pancreatic duct in one. Lung involvement was seen in two patients, and this was accompanied by atelectasis and pneumonia in one patient and localized nodules under the pulmonary pleura in the other (Figure 4(c)).

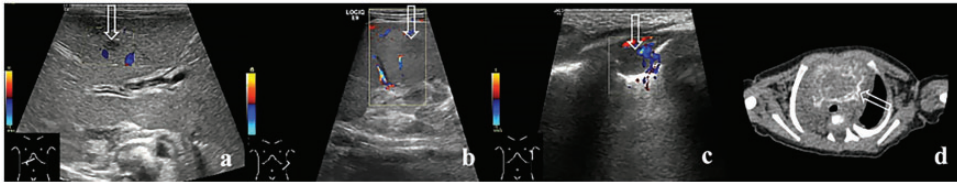


Figure 4. Images of a 1-year-old boy with multisystem Langerhans cell histiocytosis. (a) A hypoechoic mass was present in the left lobe of the liver, with less uniform internal echo (arrow). (b) A hypoechoic mass was present in the spleen (arrow). (c) The surface of the lung showed hypoechoic nodules with abundant blood flow signals (arrow) and (d) A plain computed tomography scan revealed a huge space-occupying mass of soft tissue in the mediastinum with a poorly defined border, eggshell calcification (arrow), and a solid computed tomography number of 49 HU.

Thymus enlargement and abnormal shape were seen in one patient. Lymph node enlargement at different levels was found in the neck, mediastinum, hilar area, retroperitoneum, and groin in 21 (50.00%) patients.

Chest CT/MRI was performed in 42 patients, of whom 6 showed enlargement of the axillary, cervicothoracic, and mediastinal lymph nodes on CT. Thymic lesions were indicated in three (7.14%) patients, among whom enlargement of the thymus with calcification was found on thymic CT scan in two patients (Figure 4(d)) and an abnormally shaped thymus was found on thymic MRI scan in one patient. The CT features of three (7.14%) patients suggested multiple pulmonary air sacs and nodules with cavities. A bone CT scan was performed in 33 patients and showed bone destruction accompanied by a local mass in all 33.

Discussion

LCH results in clonal proliferation of Langerhans cells with dendritic cell features. Single-system LCH has a satisfactory prognosis. However, multisystem LCH is characterized by invasive growth that can rapidly involve multiple organs and systems and even vital organs (such as the blood, liver, and spleen), thus endangering the

patient's life. It has a poor prognosis and a high incidence of recurrence and sequelae.¹⁴⁻¹⁶

Bone lesions are present in about 75% to 80% of patients with LCH, and the presence of a single lesion is most common. LCH can involve any bone, but it mainly affects the axial bones. More than 50% of bone lesions are located in flat bones.¹⁷ In the present study, the flat bone involvement rate of 84.6% among the 13 patients with bone LCH is consistent with previous reports. Bone lesions are often detected as masses. In one case, a mandibular lesion was misdiagnosed as mumps, thereby delaying treatment.¹⁸ Ultrasonography of LCH-affected flat bones mainly shows punched-out osteolytic bone destruction, and the inner and outer plates of the skull become separated, with the outer plate markedly damaged and the inner plate less severely damaged. The bone exhibits uneven osteolytic destruction that is trumpet- or ladder-shaped.^{19,20} Long bone lesions usually affect the femur and rarely involve the hands or feet.²¹ The lesions are characterized by fan shell changes in the endosteum of long bones. Some are accompanied by bone destruction, and some fail to show changes in the medullary cavity because of the effect of ultrasonography on bone penetration. However, MRI shows worm-like and patchy destruction

in the cortical bone and medullary cavity. Few reports to date have focused on contrast-enhanced ultrasonography in patients with LCH. In this study, one patient with mandible involvement and one patient with tibia involvement were examined by contrast-enhanced ultrasonography, which showed high enhancement in the arterial phase and low enhancement in the delayed phase. This was likely related to active proliferation of the tissue mass and stimulation of new microvessel formation by angiogenic factors.²²

Multisystem LCH can involve any organ. Liver involvement accounted for about 50% to 60% of cases in previous reports, and in the present study, liver involvement occurred in 83.33% (35/42) of patients and spleen involvement in 35.71% (15/42). This involvement was characterized by enlargement of the liver and spleen. Active proliferation of tissue cells in the liver can result in the formation of multiple nodules of different sizes and echogenicity in the liver and spleen.²³ Histiocytic proliferation may destroy the bile duct wall and form scar tissue, thus leading to biliary thickening and dilatation.²⁴ Pancreatic involvement in the present study was mainly characterized by enlargement of the pancreas and irregularity in its shape. Some patients showed dilatation of the main pancreatic duct, and some showed scattered cystic anechoic lesions. The rate of lung involvement was 7.14% (3/42). In previous studies, children with LCH rarely showed lung involvement. According to previous research, lung involvement is reportedly due to the rapid proliferation of histiocytes in the bronchial epithelium, resulting in the formation of destructive granular tumors near small airways; these tumors block the airways, and thick-walled cystic lesions of different sizes and shapes subsequently develop.²⁵ The rate of lymph node involvement in the present study was 50.00% (21/42). Lymph node involvement

was characterized by enlarged lymph nodes. Invasion of the thymus was rare, and the thymus showed diffuse enlargement. Some studies have suggested that the possibility of thymus involvement should be considered if the child's skin, bones, or lungs are involved with simultaneous punctate or serpentine calcification of the thymus.^{26,27} In the present study, the rate of thymus involvement was 7.14% (3/42), and calcification of the thymus was present in two of these patients.

Thus, ultrasonography is an important means to understand the involvement of bone, abdominal organs, superficial lymph nodes, or the thymus in LCH. An ultrasonography examination is relatively simple to perform, allowing patients to undergo repeated examinations. The present study was limited by its retrospective design and small sample size. In future studies, we will continue to increase the sample size to improve the accuracy and credibility of our findings.

Conclusion

Ultrasonography of LCH-affected flat bones mainly showed punched-out osteolytic bone destruction, and long bone lesions were characterized by fan shell changes in the endosteum of long bones. Some lesions were accompanied by bone destruction. Multisystem LCH can affect almost any organ. Ultrasonography is an important means to understand the involvement of bone, abdominal organs, superficial lymph nodes, and the thymus. A thin-slice CT scan of the chest can be applied to diagnose early lung disease and evaluate its severity; the clinician may observe multiple small nodules in both lungs and signs of digging out in the early stage or unequal thickness of the cyst wall. Doctors should be familiar with the most appropriate imaging mode for each organ or system to facilitate early diagnosis.

Author contributions

Lei Liu made substantial contributions to the conception and design of this study. Lei Liu and Zhouqin Lin wrote the manuscript. Ruijie Wang and Fusui Xie collected the data. Bei Xia critically reviewed the manuscript and supervised the whole study process. All authors read and approved the final manuscript. All authors agreed to be accountable for all aspects of the work.


Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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