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Case Report

Multifocal Langerhans cell histiocytosis in a child ☆

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ABSTRACT

Langerhans Cell Histiocytosis (LCH) is a rare disorder sometimes called the disorder of the “monocyte-macrophage system”. This condition is characterized by the proliferation of abnormal Langerhans cells within different tissues. Skin rash is the typical early feature, but bony involvement is the second most common presentation. The most common complications are musculoskeletal disabilities, hearing problems, skin scarring, neuropsychiatric defects and most importantly, progression to secondary malignancies like leukemia. Early recognition and treatment can reduce morbidity and mortality. Herein, we report a case of a 10-year-old male presenting with a tender, palpable mass in the lower limb. On initial imaging, a lesion involving the diaphysis of the fibula was observed, raising concerns of Ewing sarcoma. Biopsy was planned along with whole-body MRI, revealing multifocal single system Langerhans cell histiocytosis. Given the rarity of fibular involvement in LCH, distinguishing between LCH and common malignancies within this age-group can be challenging. Through this case report, we hope to emphasize the importance of considering LCH in the

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differential diagnosis to ensure a timely diagnosis, fitting treatment and improvement in prognosis of the condition.

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Introduction

A histiocyte is an immune cell normally found almost everywhere in the body particularly in the bone marrow, skin, lungs, and liver. Histiocytic means "tissue cell". The most common disorder affecting this system is Langerhans Cell Histiocytosis (LCH) also called Histiocytosis X. The annual incidence of the disease is 4.6 cases and/or million in children under 15 years of age and adults, it is 1-2 cases and/or million [1]. LCH is a granulomatous lesion that can cause an inflammatory infiltrate which affects virtually all organ systems, but commonly it affects bone, skin, and lungs [1]. The pathogenesis involves the uncontrolled or neoplastic proliferation of Langerhans cells in the tissue. There are two types of hypotheses related to how it can happen and these are excessive immune stimulation or intrinsic immune deregulation [2].

There are three types of Langerhans cell histiocytosis namely, Letterer-Siwe disease, eosinophilic granuloma, and Hand-Schüller-Christian disease. The Letterer-Siwe type is malignant and commonly presents with skin rash and cystic skeletal defect along with or without multiorgan involvement. The eosinophilic granuloma type is benign usually presents with pathologic fracture in adolescents. The Hand-Schüller-Christian type is also a malignant variant and classically presents with lytic bone lesion children along with exophthalmos and diabetes insipidus [2]. Recently, these classifications have been changed. They classified it into two, single system involved (unifocal or multifocal) disease or multisystem system involved disease [2]. Varieties of pharmaceuticals agents are used in the treatment either local or systemic and that involves vinblastine and prednisolone. The main challenge in single system LCH diagnosing, is thinking LCH beyond the boundaries of a primary bone malignancy. Because primary bone malignancy is much more common in the pediatric age group and it accounts for 5% of childhood malignancies, particularly Ewing sarcoma [3].

Ewing sarcoma is the most common primary bone tumor among children and adolescents (age <15 years) [3]. This is a very aggressive and highly metastatic tumor. It usually arises from the diaphysis of long bones (like femur, tibia, fibula) and also from pelvic and other flat bones. The peak incidence is between 10-15 years of age. Usually presents with local symptoms of pain and swelling which usually worsens at night. Sometimes it can present as pathologic fracture. Presence of the systemic symptoms, like fever, weight loss, often indicates metastatic disease. Around 20% of the patients have metastasis during the first presentation [4]. Imaging is the investigation of choice. Plain X-ray usually shows "moth-eaten" lesions, "Onion skin" periosteal reaction. The treatment plan includes surgery radiotherapy and chemotherapy depending on localized or metastatic disease [4] (Figs. 1-3).

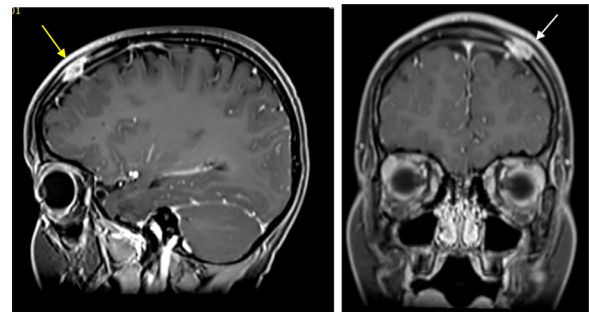


Fig. 1 – Head MRI T1 weighted image with contrast injection (A, sagittal) and (B, coronal).

Case presentation

A previously healthy, 10-year-old male patient, presented to the Orthopedics and Traumatology Department with complaints of pain in his right lower limb. He was otherwise asymptomatic. On closer inspection, a tender, palpable mass was present in the right lower limb. Motor and sensory functions, as well as tendon reflexes were all normal. The rest of the musculoskeletal examination and overall objective clinical examination were unremarkable. Aside from food allergies, the patient's personal and family medical history were not significant for any pathologies or substance abuse.

Most of the routine laboratory examinations were within normal limits. Complete blood count (CBC) was normal, apart from a low Red blood cell distribution width (RDW-SD) count – 34.1 fl (normal range 35.0 – 44.0 fl). A comprehensive metabolic panel (CMP) revealed elevated levels of fasting glucose – 121 mg/dl (60-100 mg/dl) and low levels of Alanine transaminase (ALT) – 14 IU/L (normal range 16 – 49 IU/L). The rest of the CMP including the renal function tests, electrolytes and C-Reactive Protein (CRP) were all normal. Coagulation profile was normal, as well. Urinalysis showed no anomalies.

A chest radiograph showed a normal cardiothoracic ratio, normal cardiophrenic and costophrenic recesses with no signs of blunting or parenchymal consolidation. No pathological findings were detected in the skeletal structures within the imaging area.

Subsequently, a Whole Body MRI (WB-MRI both with and without IV contrast) was ordered. It revealed an intramedullary lesion in the mid diaphyseal level of the right fibula, sized 1.8 × 2.5 cm, with the presence of a central defect. Periosteal reaction that showed enhancement after IV contrast administration, was evident in the adjoining soft tissues. Potentially benign reactive lymph nodes were noted in the right inguinal region. Additionally, two lesions, 1 × 2 cm



Fig. 2 – Whole body MRI and Diffusion – Weighted Imaging.

and 8×10 mm in size and hyperintense in STIR-T2, were present in the antero-lateral aspect of one of the right ribs adjacent to the liver. Furthermore, a prominent, 12×18 mm lesion that was enhanced after IV contrast administration, was evident in the left frontal bone. It was associated with infiltration and destruction of the calvaria and surrounding soft tissues. No pathological findings were present in the cerebral parenchyma and intracranial structures. Paranasal sinuses were normal and well pneumatized.

On account of the patient's age and clinical presentation a diagnosis of Ewing's sarcoma was initially suspected. The lack of localized inflammation signs, fever and inflammatory markers within normal limits, rendered the diagnosis of multifocal osteomyelitis highly unlikely. However, the Whole Body MRI (WB-MRI) findings were suggestive of Langerhans' cell histiocytosis (Histiocytosis X), specifically the periosteal reaction and extensive soft tissue edema surrounding the lytic

bone lesions, were more in line with a diagnosis of LCH, rather than Ewing's sarcoma. Langerhans' cell histiocytosis was ultimately confirmed by the histopathological examination of the lesions.

A lesion that is prominently enhanced after iv contrast administration is noted in left frontal bone. (A, sagittal) (yellow arrow), (B, coronal) (white arrow). It is causing external and interna tabula destruction, meningeal infiltration and it has a soft tissue spread.

Intramedullary infiltrations that are hyperintense in STIR-T2(A) (red arrows) and DWI (E) (white arrow) and ADC (F) (green arrow) are noted in thoracic ribs on the right. Note infiltration in the right fibula (B, C) and in the skull (C) (blue arrow).

Contrast enhancement increase is noted after administration.

Intramedullary infiltration is noted on the mid diaphyseal level of right fibula. A defect is noted in its central as a sec-

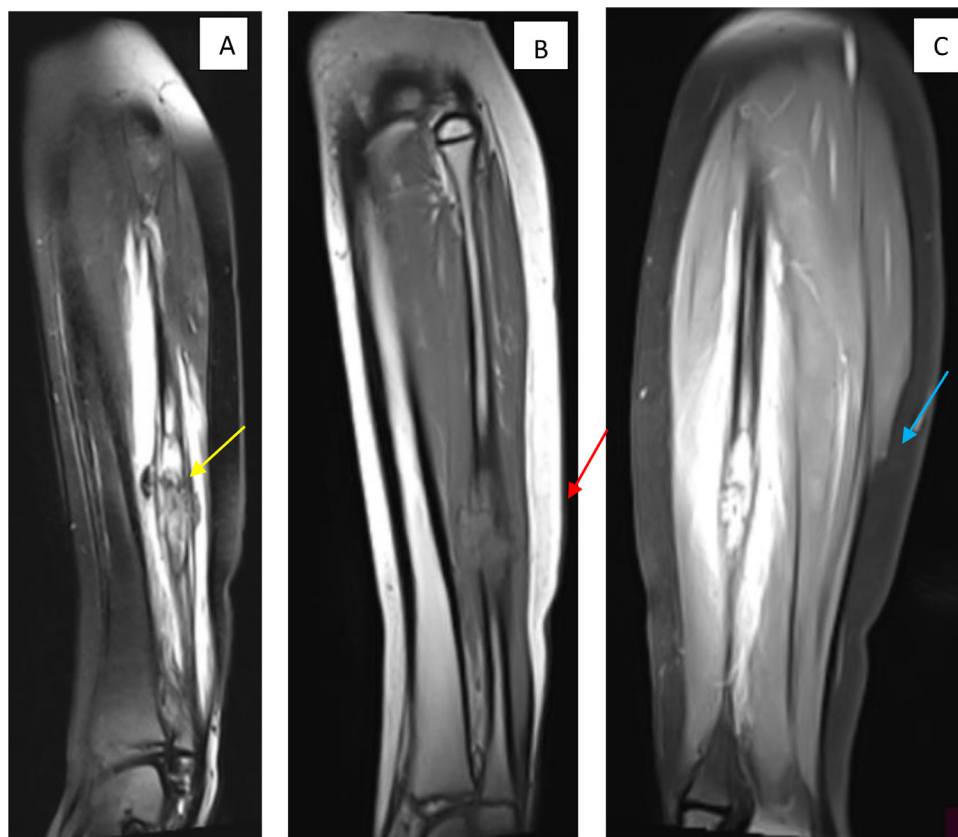


Fig. 3 – STIR (A), T1WI (B) and contrast enhanced T1 WI fat sat.

ondary to operation and is unenhanced after contrast administration. (A) (yellow arrow) Periosteal reaction mild ill-defined contrast enhancement increase is noted in adjacent soft tissue. (B - red arrow, C - blue arrow).

Discussion

Langerhans' cell histiocytosis (Histiocytosis X) is a rare disease involving Langerhans cells' clonal proliferation. These defective cells (histiocytes) are derived from bone marrow and can migrate from the skin to lymph nodes. Paul Langerhans [5] as a medical student first described Langerhans cells in 1868. Clinically, its manifestations may range from isolated bone lesions to multisystem disease. Since the incidence of LCH is low, especially in the skeletal system when present locally, an awareness of this entity is crucial in reaching an early diagnosis. The exact etiology of LCH is still unknown. However, multiple factors have been suggested, such as genetic, malignancies, and viral infection [6,7]. The two-principal reported pathological pathways are (1) neoplastic; genetic anomalies occur in the BRAF gene and (2) the reactive pathway; immunological dysfunctions can cause such a disease [6,8]. There is a clinical division that divides the LCH into two groups: (1) single-system LCH (unifocal or multifocal), which may involve bone, skin, lymph nodes, lung, and central nervous system, or rare organs such as the thymus and thyroid (2) multisystem LCH, in which two or more organs or systems mentioned are involved

also named as Letterer-Siwe syndrome [9]. The reported incidence of LCH is significantly more in children, and nearly 80% of the cases appear under the age of 15 years [10].

Flat bones (skull, pelvis, ribs, and mandible) are the most involved bones by LCH, followed by the spine (mainly thoracic and lumbar), and body involvement is more than posterior elements [11]. Lesions of short tubular bones of hand and feet are only seldom reported [12]. The lesions of LCH mainly present with localized pain and not with the swelling. Plain radiographs or magnetic resonance imaging (MRI) are the primary diagnostic tools, but biopsy is essential for definitive diagnosis. Computed tomography (CT) scan and MRI can be used to assess the degree of cortical bone destruction, and CT scans can also guide for taking the bone biopsy from the right site [9,13]. Newer imaging techniques may aid in diagnosing and managing LCH. These include positron emission tomography-CT (PET-CT) and whole-body MRI. These modalities may help in the better assessment of the severity and extent of the disease. Like our patient has lesions in the intramedullary region of the mid diaphyseal level of the right fibula, anterolateral aspect of one rib adjacent to the liver, and left frontal bone in whole-body MRI. The PET-CT would also help in providing helpful information related to disease activity and response to therapy [14]. However, it is not universally available and is an expensive investigation, and hence, it is not widely used at present.

Due to this disease's rarity, especially in the fibula, ribs, bones of the skull, i.e., frontal bone, other mimicking lesions of other diseases must be kept in mind and excluded. These

lesions include benign bone tumors (like a simple bone cyst, aneurysmal bone cysts, osteoidosteoma, giant cell tumor, and LCH), malignant bone tumors (like Ewing's sarcoma, leukemia, and lymphoma).

Treatment is often warranted for only symptomatic lesions. Asymptomatic patients only need observation as they are known to resolve spontaneously. Treatment modalities may range from (1) surgical procedures, like curettage or excision, (2) irradiation, (3) intralesional steroid injection and (4) chemotherapy. The management option should be selected based on the pattern of involvement: single or multisystem involvement and the size, site of the patient's lesion, and age [15]. Curettage is best for easily assessable unifocal small-sized lesions, as was done in our case. If the lesion is easily assessable and has a large size, then the treatment of choice is excised, combined with bone grafting [11,16]. Surgical treatment alone has a higher recurrence rate; individual-specific lesions like the large-sized, multifocal lesions or multisystem disease. In these situations, the surgery is better combined with low-dose irradiation and chemotherapy [17]. First, radiotherapy is indicated when the disease is symptomatic with significant pain, multifocal bone lesions, potential to fracture, and surgery may cause functional and health problems. Complications of low-dose radiation therapy include disturbance in bone growth in children and secondary malignancies [16] and hence, this modality should be used with caution. In the form of a combination of vinblastine and prednisolone, chemotherapy is effective in multisystem LCH in children. Intralesional injection of 100–150 mg crystalline methylprednisolone has been reported to be effective in the symptomatic bone lesion and may cause a reduction in symptoms and cure. Recently, denosumab (RANKL inhibitor) which at present is commonly being used in giant cell tumors (GCT), has also been tried in skeletal LCH [2,18]. However, no published literature is yet available to show its usefulness for this condition.

Conclusion

Langerhans' cell histiocytosis is a rare, non-malignant disorder characterized by proliferation and accumulation of clonal dendritic cells. Given the paucity of illness, and unusual growing within the fibula, ribs, and frontal bone, LCH can easily be misdiagnosed with malignant bone tumors commonly seen within this age group i.e-leukemia, or Ewing's sarcoma. Although the etiology of disease is unknown, recent studies have discovered mutations within the BRAF and MAP2K1 genes in patients suffering from LCH. Our purpose is to improve our knowledge of the disease, and given the low incidence of LCH, it is crucial that physicians develop a better understanding of it, so that early diagnosis and management can be accomplished promptly.

Patients consent

Patients consent have been obtained.

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