Different imaging faces of Langerhans cell histiocytosis

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Learning objectives

The aims of our study are:

- to review and describe the current and particular aspects of Langerhans cell histiocytosis (LCH);
- to present our experience and illustrate elementary imaging features that are suggestive for Langerhans cell histiocytosis, focusing on the bone lesions;
- to describe and illustrate some cases of differential diagnosis of this pathology.

Background

WHAT IS LCH?

LCH is a rare multi-systemic group of idiopathic disorders, characterized by the uncontrolled proliferation in different tissues of immunophenotypically and functionally immature histiocytes cells similar to Langerhans cells of the epidermis, including normal inflammatory cells (T cells, eosinophiles, macrophages).

The pathogenesis of LCH is still unclear, despite numerous studies supporting equally the reactive and the neoplastic hypothesis.

Formerly known as “histiocytosis X”, the term Langerhans cell histiocytosis is now used, because the histiogenesis basis has been clarified[1].

LCH may involve:

- single organ (single-system LCH, which may be unifocal or multifocal);
- multiple organs (multisystem LCH).

Clinical presentation may vary from an asymptomatic lesion to a life threatening manifestation and depends on the site of the involvement and the phase of the disease [2,12].

ETIOLOGY

The etiology of LCH remains unknown, although factors such as a viral infection (ex: EBS, CMV, HHV-6), genetic disorders or different malignancies (ex: medulloblastoma,
glioma, retinoblastoma) have been implicated in the pathogenesis, these thesis have not been confirmed [3,9].

Each single factor may influence the immune system and predispose somehow to LCH, but there is no evidence for one factor to play a crucial role [11].

**INCIDENCE and SEX RATIO**

The annual incidence of LCH has been estimated to be two to ten cases per 1 million children aged 15 year or younger, with a male-to-female ratio of 2:1[3].

**RISK FACTORS**

Although risk factors such as: solvent exposure in parents, family history of cancer or thyroid disease, perinatal infections have been identified for LCH, they have not yet been demonstrated [3].

**AGE**

It affects patients from the neonatal period to adulthood, although it appears more common in children aged 0-15 years [5]. The age at onset varies according to the variant of LCH, as follows [3]:

- Letterer-Siwe disease occurs predominantly in children younger than 2 years
- Hand-Schüller-Christian syndrome, has a peak of onset in children aged 2-10 years
- Localized eosinophilic granuloma occurs mostly frequently in children aged 5-15 years
- Pulmonary LCH is more common during the third and fourth decades of life.

**TYPES of LCH**

Conform to the working group of the Histiocyte Society, LCH includes three clinical major variants, which depends on the extent of dissemination:

- Eosinophilic granuloma (unifocal with solitary bone lesion);
- Letterer-Siwe disease (fulminant, multisystemic involvement);
- Hand-Schüller-Christian disease (multifocal and usually associates the triad of diabetes insipidus, proptosis and lytic bone lesions).

A congenital, self-healing form called Hashimoto-Pritzker disease has also been added at this group.
PROGNOSIS

Prognosis is closely linked to the extent of disease at presentation and to the response to initial treatment.

Depending of the risk of mortality, specific organs are considered:

- high-risk (such as liver, spleen and bone marrow) or
- low-risk (such as skin, bone, lung, lymph nodes, gastrointestinal tract, pituitary gland, central nervous system) when involved at disease diagnose [4].

Age at diagnosis: Studies show the overall survival is poorer in neonates with risk-organ involvement compared with infants and children with the same extent of disease [4].

Response to treatment: Response to therapy in early weeks has been shown to be a more important prognostic factor than age [4].

Organ involvement: Involvement of cranio-facial bones is associated with an increased risk of diabetes insipidus and neurologic problems [4].

DIAGNOSE and TREATMENT

To confirm the diagnosis a biopsy is needed, usually from the most accessible lesion (a lytic bone lesion, skin and lymph nodes are the most frequent sites for biopsy).

Diagnose confirmed by:

- the morphologic identification of the abnormal Langerhans cells (identification of Birbeck granules at electron microscopy);
- positive staining with antibodies to CD1a or/and CD207 [5].

The treatment depends on extend and severity of LCH and may include:

- local therapy (such as low dose radiation therapy, surgical excision);
- systemic therapy (such as chemotherapy, corticosteroid therapy, even stem cell transplant) [2,6].

RADIO - IMAGING METHODS

Imaging in LCH patient is based principally on radiography [2].
Radiography is the "gold standard" in the diagnostic and staging procedure. [2]

Once a patient is with a biopsy-proven LCH, a radiologic and imagistic protocol should be performed.

First of all a chest X-ray and a complete skeletal survey must be performed for diagnosis and analysis of the disease extent [2].

Computer tomography (CT) and magnetic resonance imaging (MRI) evaluation may be necessary to evaluate the degree of the bone erosion, soft tissue infiltration or SNC involvement; these methods can also be used for a bone biopsy or a surgical planning [2].

Newer diagnostic imaging techniques, such as somatostatin analog Scintigraphy or PET-CT - positron emission tomography- computer tomography with fludeoxyglucose F 18 (18F-FDG) and whole body MRI provide informations related to the disease activity, the response to therapy or can detect the extra skeletal extent, but do not replace the standard tests [2].

GENERALLY RADIO-IMAGING FEATURES

Radiological appearance of bone lesions [7]:

- unifocal or multifocal osteolytic lesions, round or oval shaped having a well or poorly defined border, associated with a periosteal reaction in buttressed pattern;

- sclerotic margins may appear during the healing process, but is usually limited;

CT appearance: used for better demonstration of cortical erosion and tissue involvement

MRI appearance: Extensive signal intensity changes within bone marrow on MRI are a helpful sign for the diagnosis. Includes these signal characteristics [7]:

- typically low signal on T1 wi

- isointense to hyperintense on T2 wi

- hyperintense on Stir wi

- often shows contrast enhancement on T1+Gd

OSSEOUS FEATURES (Fig. 1 on page 9)

The lesions may be asymptomatic and incidental discovered at a plain radiography or may associate symptoms like pain, tenderness or swelling [7].
**Long bones:**

LCH mainly involves the diaphysis, the lesion respects the grown plates [12].

*Appearance:* well defined medullary area of osteolysis, which may associate periosteal reaction or endosteal scalloping, responsible for the "budding appearance" on CT or MRI, as well as an extensive oedema in the bone marrow and in the adjacent soft tissue [2].

**Flat bones and pelvis:**

Rib lesions are lytic, usually associated with pathological fracture. An extrapleural mass may result from soft-tissue extension [2].

In pelvis LCH frequently involves the iliac wings and the supra-acetabular area.

*CT scan and MRI* of the pelvis are useful tools:

- CT scan can provide reliable data concerning soft tissue tumoral involvement and large osseous lesions, but less sensitive for small spongious lesions

- MRI is more sensitive concerning soft tissue tumoral extension being mandatory for spongious primitive or secondary tumoral lesion [2].

**Calvarium and skull base:**

Calvarium is more often affected than the skull base, with a more frequently interest in parietal and frontal region.

From the skull base, the temporal bone is the most commonly affected part and usually associates a soft-tissue mass witch may involve the mastoid or, in rare cases, the auditory ossicles.

**Mandible and maxilla:**

Panoramic radiographs may show severe alveolar bone destruction, which produces the appearance of "floating teeth" [15].

**Spine:**

LCH has a predilection for the thoracic spine.

In most cases, it involves the vertebral bodies and may result in anterior wedging or in complete collapse with a characteristic "vertebra plana” appearance [15].
Asymmetrical vertebral body collapse may be encountered.

Spinal cord compression is extremely rare [16].

**Orbit:**

LCH has been reported to involve more often the superior or supero-lateral orbit region and manifests with: ptosis, proptosis, eritema and enlarging palpebral fissure.

CT and MRI provide more informations than ultrasound regarding the extent of disease and the juxta-neural or intracranial extension.

**EXTRA-OSSEOUS FEATURES**

Extra-osseous LCH may be more difficult to identify and depending on the sites of involvement and the organ or organs that affect, it can demonstrate a more aggressive behavior than the osseous type.

**Pulmonary:**

Lung involvement is has been seen in about 25% of children with multi-systemic LCH.

Less than a half patients with lung involvement on imaging present respiratory symptoms or signs, that is why a chest X-ray should be performed at all newly diagnosed LCH patients.

The main diagnose procedure for patients with radiographically demonstrated pulmonary involvement, is biopsy of the lung preceded by broncho-alveolar lavage (BAL) to exclude opportunistic infections [8].

CT scan of the lung required for patients with abnormal chest X-rays or pulmonary infiltrates or a cyst lesion. Spontaneous pneumothorax can complicate cyst rupture [18].

**Lymph nodes and thymus:**

The cervical nodes are most frequently involved and may be associate with lymphedema. Mediastinal involvement is rare (<5%) and usually presents with dyspnea, superior vena cava syndrome, cough and tachypnea [3].

Thymic involvement is common in multisystem disease and coexist with pulmonary involvement.
CT: thymic enlargement, intra-thymic calcifications, cysts or septal enhancement suggest a thymic involvement [16].

**Abdominal organs:**

Hepatic LCH patients present hepatomegaly or hepato-splenomegaly with solid or cystic-like lesions and elevated liver levels [17].

The liver biopsy is the only definitive way to determine whether active LCH or hepatic fibrosis is present [4].

US, CT, MR imaging: hepatomegaly, splenomegaly; periportal inflammation, fatty changes, concentric periductal fibrosis [16].

**Gastrointestinal:**

This type of LCH is exceedingly rare.

Findings at conventional barium studies are nonspecific, resembling features seen in exudative enteropathies or inflammatory bowel diseases.

CT and MR imaging depict few specific features: circumferential bowel wall thickening with pathologic mucosal contrast enhancement; edematous infiltration of the mesenteric fat; free fluid [16].

**Head and neck:**

The involvement of this anatomically region is common and because of the proximity of the various anatomic structures in the head and neck, lesions often are complex, involving multiple structures simultaneously [16].

CT is performed to evaluate the extent of osseous erosion or destruction and MR imaging is used to evaluate the adjacent soft tissues invasion.

**Central nervous system (CNS):**

The incidence of CNS involvement is higher if the facial bones or anterior or middle cranial fossa are affected. The most common clinical CNS manifestation of LCH is diabetes insipidus secondary to infiltration of the posterior pituitary gland, which results in decreased secretion of antidiuretic hormone. For pituitary involvement, the MRI-T1W and contrast-enhanced MRI images will evaluate the abnormal thickening, enhancement or absence of the posterior bright spot [17].
Images for this section:

Fig. 1: Bone lesions distribution in LCH.
Findings and procedure details

In this exhibit we will describe and illustrate imaging findings of LCH encountered in our clinic:

# 24 children were diagnosed with biopsy proved LCH in our Institute, between 2004 and 2014.

# there were 14 males and 10 female, aged 3 to 11 years at presentation (means M:F ratio of 1.4:1).

# 20 patients underwent to radiography or imaging procedure in our department, from which:

• all patients underwent standard roentgen examinations and US
• 7 underwent CT examinations;
• 6 patients performed RMI acquisitions.

# the bones were the most common affected anatomical regions, encountered in about 50% of cases (10 of 20 patients), with a predilection for the axial skeleton, especially for the flat bones, the most common locations were:

• Skull - 7 patients;
• Pelvis - 2 patients;
• Femur - 2 patients;
• Ribs - 1 patient.

# unifocal bone lesions were more frequently than multifocal involvement (only 2 patients with multifocal involvement)

# there were 4 patients with pulmonary manifestation and 2 with intra-abdominal involvement

Radiological features encountered in our clinic:

Calvarium and skull base:

Skull X-ray:

• solitary or multiple (Fig. 2 on page 14) osteolytic lesions;
• typically round, with regular, well-defined nonsclerotic margins (Fig. 3 on page 14);
many lesions can enlarge, coalesce and create an "geographic skull" appearance (Fig. 4 on page 15) with slightly lobulated or irregular borders, but still well defined.

**CT:**
- a characteristic beveled-edge appearance because of their unequal involvement of the inner and outer tables (Fig. 5 on page 16);
- may contain a fragment of residual bone inside the lytic lesion, called "button".

**MRI:**
- tumor-like lesion inhomogeneous iso-intense at T1-weighted imaging, heterogeneously hyper-intense at T2-weighted imaging, with intense enhancement after gadolinium injection (Fig. 6 on page 16).

**Orbit:**

**CT:**
- soft-tissue lesion that replaces/destroys osseous structures, with soft tissue intra-orbital or zygomatic involvement (Fig. 7 on page 17);
- may show moderate to marked enhancement after iodine contrast administration.

**MRI:**
- tissular mass with heterogeneous signal on T1W1, hyper/hypo-intense on T2W1, with enhancement on T1 weighted after contrast injection (Fig. 8 on page 17);
- showing the extra-osseous and meningeal extension.

**Femoral bone:**

**Radiological appearance:**
- sharply defined medullary area of osteolysis (Fig. 9 on page 18 a);
- lesions may disappear without or with little deformity after treatment (Fig. 9 on page 18 b).

Some secondary complications, such as aseptic necrosis/ avascular necrosis may occur after chemotherapy treatment (Fig. 10 on page 19).

**Ribs:**
Radiological appearance:

- osteolytic lesions with pathological fracture associated in our case (Fig. 11 on page 20).

Pelvis:

Radiological appearance:

- well defined area of osteolysis with sharply non sclerotic limits.

CT:

- provides reliable data concerning soft tissue tumoral involvement and large osseous lesions, especially with cortical bone destruction (Fig. 12 on page 21).

MRI:

- multicentric lesions with tumoral characters - hyper intense on fat sat T2 weighted, hypointense on T1 weighted images and post-contrast enhancement (Fig. 13 on page 22).

Pulmonary involvement:

Chest X-ray:

- diffuse, bilateral, symmetrical reticulo-micronodular opacities and interstitial infiltrate in the mid zone and base of the lungs, sparing the costo-phrenic angles (Fig. 14 on page 23);
- or interstitial diffuse pattern with "honeycomb" appearance (Fig. 15 on page 24).

Liver, spleen determination:

Ultrasound:

- homogeneous hepato-splenomegaly and small epigastric adenopathies (Fig. 16 on page 25 a,b).

CT with and without contrast enhancement:

- homogeneous hepato-splenomegaly with no portal hypertension sign and associated multiple adenopathies (Fig. 16 on page 25 c).

Mediastin and neck lymph nodes involvement:
CT:

- latero-cervical enlarged lymph nodes (Fig. 17 on page 26 a);
- mediastinal multiple adenopathies (located in anterior and middle mediastinum) and/or thymic involvement (Fig. 17 on page 26 b).

Differential diagnosis:

Include [7,13]:

- osteomyelitis (Fig. 18 on page 26): focal lytic lesion, with periosteal reaction/thickening, which may include formation of a Codman's triangle in aggressive forms, without cortical destruction, with eventual formation of a sequestrum in chronic cases.
- metastatic neuroblastoma (Fig. 19 on page 28): bone metastasis are usually ill-defined, with periosteal reaction and metaphyseal lucency; sclerotic margins are uncommon.
- leukemia (Fig. 20 on page 28): bone areas with reduce mineralization
- Ewing's sarcoma (Fig. 21 on page 29): primary bone tumor with aggressive bone appearance, that may include: laminated ("onion skin") periosteal reaction, Codman triangles or spiculated ("sunburst") periosteal reaction and important extension into adjacent soft tissues.
- simple bone cyst: sharply delimited radiolucent lesion, with no periosteal reaction.
- primary bone tumors: medullary and cortical bone destruction, with wide zone of transition, aggressive periosteal reaction, soft tissue mass with variable calcification.

Best Keys to describe the LCH lesions:

a. Bone involvement(s):
   - uni or multifocal lesions (complete skeletal survey);
   - typically osteolytic well defined lesions;
   - nonsclerotic margins.

b. Local extension- orbit /skull bones/pituitary region:
- periorbital extension;
- meningeal involvement;
- posterior pituitary tumors.

c. Extraosseous dissemination (non-specific):
- lymph nodes;
- hepato-splenomegaly.

**Images for this section:**

![Skull X-ray](image)

**Fig. 2:** Langerhans cell histiocytosis: bone lesions. Skull X-ray (a. frontal view; b. lateral view): typically multiple frontal, parietal and occipital osteolytic lesions
Fig. 3: Langerhans cell histiocytosis: bone lesion. Skull X-ray (lateral view): unique parietal osteolytic lesion with typically round, nonsclerotic margins
**Fig. 4:** Langerhans cell histiocytosis: bone lesion. Skull X-ray (lateral/front view): right parietal osteolytic lesion with slightly irregular and well defined border.

**Fig. 5:** Langerhans cell histiocytosis of calvarium. a. Axial CT scan (bone window); b. Axial NECT scan: osteolytic lesion of the right parietal bone, with the destruction of the inner table and thinning of the outer table.
Fig. 6: Langerhans cell histiocytosis of calvarium- MRI evaluation a. Axial T1 SE Fat Sat before/ b. after Gd injection: moderate peripheral contrast enhancement into small tissular lesion located into the the right frontal bone c. Axial STIR MR image: moderate hyperintense and inhomogeneous lesion in the right frontal bone (central cystic-like appearance)

Fig. 7: Langerhans cell histiocytosis of the orbit - CT aspect. NECT of the head using a soft tissue window (a) and a bone window (b)- homogeneous, soft tissue mass involving the left external orbital wall (white arrows) with bone destruction and osteolytic lesion in the left sphenoid bone(black arrow)
**Fig. 8:** Langerhans cell histiocytosis of the orbit - MRI aspect. a. Axial T2 weighted RM image: ovalar tumoral mass of the external wall of the left orbit involving the greater wing of sphenoid bone and the frontal process of zygomatic bone b. Axial T1WI with Gd: heterogeneous enhancement of the mass that protrude into the orbit and extend into the adjacent soft tissues -temporal muscle; linear enhancement of the left temporal meningeal structures c/d. Coronal T1WI Fat Sat before and after Gd iv.inj.: tumoral lesion with heterogeneous enhancement; extraosseous soft tissue extension of the left zygomatic lodge (c-white arrow); meningeal extension - thickening of the left basal frontal meninges with contrast enhancement (d-white arrow).
Fig. 9: Follow-up of bone lesions. Pelvis and femoral bones X-ray show changes of the osteolytic lesions after treatment. a. Sharply irregular geographic appearance lytic lesion of the both iliac wings and bilateral femoral diaphysis. b. After 9 months treatment evolution: iliac and left femoral lesions disappeared and right femoral lesion is nearly cured (small osteosclerotic islet).
**Fig. 10:** Vascular necrosis of the knee. MRI images: coronal/axial STIR-FS (a/b); T1Wi before and after contrast injection (c/d) Multiple confluent lesions of the metaphysis (distal femoral and proximal tibial) with irregular and lobulated margins, heterogeneous signal hyper-peripheral and hypo-central with characteristic "double line" sign; peripheral contrast enhancement, typical for necrotic vascular lesion after corticotherapy.
**Fig. 11:** Histiocytosis involving the left ribs. Left chest X-ray: multiple well defined osteolytic lesions of the ribs with osteolysis (arrows)
Fig. 12: Langerhans cell histiocytosis of left iliac wing - CT aspect. a, b. Axial enhanced CT in venous phase: slightly enhanced soft tissue mass involving the left ilio-psoas muscle (white arrow) and the left iliac wing. c, d. Axial CT (bone window): multifocal isolated and confluent osteolytic lesions of the left iliac wing (white arrows)
Fig. 13: Langerhans cell histiocyteosis of right iliac wing - MRI aspect. Plurifocal lesions involving right iliac wing: hyper intense on STIR (a.b. axial STIR), discreetly hyperintense on T1 FS with moderate enhancement after contrast injection (e,f: coro T1 FS before and after Gd injection) associated with extra-osseous invasion into adjacent soft tissue; similar lesion affecting right hemisacrum with sacral foraminal invasion (c: coronal oblique T2WI); micro adenopathies located in the right pararectosigmoidian and obturator spaces.
Fig. 14: Lung involvement by histiocytosis. Chest X-ray (frontal view): interstitial pattern with micronodular predominance
Fig. 15: Lung involvement by histiocytosis. Chest X-ray (frontal view): interstitial pattern with reticular predominance (honeycomb) and small infiltrates
**Fig. 16:** Liver and spleen involvement by histiocytosis. a,b Axial and sagittal ultrasound: homogeneous hepato-splenomegaly (liver: arrow hed, spleen: wide arrow), periceliac lymphnode (circle). c. Contrast enhanced CT-portal phase: homogeneous hepato-splenomegaly without portal hypertension sign; celio-mesenteric adenopathies.

**Fig. 17:** Mediastin and neck involvement. a. CECT-late arterial phase: supraclavicular left adenopathies (white star) b. CECT-late arterial phase: multiple large adenopathies involving anterior and middle mediastinum (white star), with thimic invasion (white arrow)
**Fig. 18:** Chronic osteomyelitis. Shoulder X-ray AP view: two lytic lesions, with osteosclerotic margins and widened of proximal humerus metaphysis, without periosteaal reaction

![Images of chronic osteomyelitis](image)

**Fig. 19:** Bone metastasis of neuroblastoma. a. Knee X-ray (frontal view): osteolytic lesion of the proximal tibia metaphysis with slightly sclerotic margins and pathological fracture. b./c. Lumbar spine MRI images (sagittal T1 SE and T1 SE FS after Gd injection): multiple lumbar and sacral tumoral lesions; sacral mass with presacrat and epidural extension; all lesions are hypointense on T1WI with a hypoenhancing pattern after Gd iv. injection
Fig. 20: Leukemia. Ankle X-ray frontal view: osteolytic lesions in leukemia with radiolucent metaphyseal bands
Fig. 21: Ewing's sarcoma. Mixed osteolytic and sclerotic lesion with characteristic "sun burst" periosteal reaction involving the left ischium (a. left pelvis X-ray in frontal view; b. / c. axial NECT using a soft tissue and a bone window)
Conclusion

- The children with LCH diagnosed in our Institute have had skeletal locations in the majority of cases, matching with the published statistics studies.
- We have encountered multiple locations, from cranial to pelvis and limbs involvement, with different local invasion that makes from LCH a highly aggressive systemic disorder with a wide spectrum of radiologic appearances.
- Imaging has an important role in diagnosis, staging and follow up of LCH, and recognition of its radiological features is mandatory in various differential diagnostic of lytic bony lesions in children.

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