Extra skeletal manifestations of the Histocytosis in pediatrics

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Learning objectives

Objectives

Langerhans' cell histiocytosis (LCH) is not uncommon pathology that implies an abnormal proliferation of these kinds of cells associated with a granular infiltration that affects different structures of the human body, including the lung , liver, spleen , lymph nodes , brain , mucocutaneous, soft-tissue (head and neck), and salivary glands. Our objectives are to :-

- To recognize the pathogenesis of Langerhans cell histiocytosis (LCH).
- To describe the radiologic criteria that are suggestive of LCH in different organs rather than the bones.
- To illustrate the appropriate differential diagnoses for LCH in each of the common extra-osseous sites.

Background

Langerhans cell histiocytosis (LCH) is a rare multi system disease with a wide and heterogeneous clinical spectrum and variable extent of involvement. LCH is a disease of abnormal clonal proliferation of a unique type of cell in the monocyte-macrophage cell line known as the Langerhans cell. It is named after the medical student Paul Langerhans, the first scientist to describe the cell (1868). Paul went on to be a German pathological anatomist. In 1985, the Writing Group of the Histiocyte Society established histiocytosis classification system based on distinct pathologic criteria and on the clinical evolution of disease. Under the definitive name Langerhans cell histiocytosis, the disease was designated as class I of the histiocytic disorders.

LCH encompasses a spectrum of clinical manifestations ranging from a solitary chronic lesion, known as an eosinophilic granuloma, to a fulminant multisystem process called Letterer-Siwe disease. An intermediate form, Hand-Shüller-Christian disease, is composed of the triad of calvarial lesions, diabetes insipidus, and exophthalmos. The pathophysiology of LCH is incompletely understood, with disagreement over whether the mechanism is a reactive or neoplastic one. The occurrence of spontaneous remissions and the absence of karyotypic abnormalities support a reactive progression. however, studies demonstrating monoclonality and response to chemotherapeutic agents lend support to a neoplastic process.

Clinically: LCH is more common in children, with a peak incidence between 1 and 3 years of age. With a slight male predilection.

Essentially any part of the body can be affected; however bone is the primary site of affection.

Findings and procedure details

1. Skeletal manifestations of Langerhans cell histiocytosis

The commonest site of affection In LCH is the **skeleton** and is by far the most common location for single lesion, (**eosinophilic granuloma (EG). In about 60-80% of the cases skeleton affected solely by LCH.**

Clinically: these bony lesions may be asymptomatic and discovered as an incidental radiographic finding. In other patients may present by pain, swelling and tenderness around the lesion. Systemic symptoms may also be present, including general malaise and, on occasion, fever with leukocytosis.

Skull bones are the most common affected bone 49% followed by pelvis: 23% ,femur: 17% ,ribs: 8% (most common in adults) ,humerus: 7% and mandible: 7%

Imaging features:

Plain radiography:- Solitary or multiple punched out lytic lesions with or without sclerotic rim .

In skull: - double contour or beveled edge appearance may be seen. Greater involvement of the inner than the outer table. (Fig.1).

In mandible: - floating tooth may be seen secondary to loss of lamina dura

In Spine: - sever vertebral collapse may result in vertebrae plana which seen often in thoracic spine (Fig.2).

In Long bones: - It mainly involves diaphysis and respect growth plates , it shows endosteal scalloping, cortical thinning and intracortical tunneling.

CT: shows the same bony lesions as the plain radiography did, but it used to assessment of the associated soft tissue masses. (Fig.1).

MRI also may used to assess the associated lesions especially in the cranial lesions

Scintigraphic studies (Bone Scan):- Variable appearance on bone scintigraphy with lesions shows an increased or decreased tracer uptake depending on the histological picture. Nonetheless bone scans are helpful in other asymptomatic lesions. **(Fig.3).**

The main differential diagnosis of multiple bony lytic lesion in a child is the metastases from the neuroblastoma and the hematological malignancies i,e lymphoma and leukemia

2. Pulmonary Langerhans cell histiocytosis

Pulmonary Langerhans' cell histiocytosis (PLCH) is an uncommon but important cause of interstitial lung disease, and it occurs predominantly in adult cigarette smokers. Pulmonary lesions have been found in fewer than 10% of children with a solitary site of involvement in Langerhans cell histiocytosis but in 23%-50% of those with multisystem involvemen. The established diagnostic procedures are lung biopsy and bronchoalveolar lavage with a score of more than 5% CD1a-positive cells.

Clinically, Patients with PLCH commonly present with nonspecific respiratory symptoms, such as cough and exertional dyspnea . About 25% of patients are asymptomatic at the time of presentation or have a mild cough. Spontaneous pneumothorax is the presenting symptom in about 10% to 15% of patients. Variable severity of constitutional symptoms occurs in up to thirty percent of patients. The physical examination, including auscultation of the lungs, is frequently normal, and digital clubbing is unusual. In advanced stages of the disease, decreased breath sounds and prolonged expiration may be appreciated.

Imaging Features

Pulmonary Langerhans cell histiocytosis has variable appearance depending on the stage of disease, ranging from small peribronchiolar nodular opacities to multiple irregularly-shaped cysts. There is a mid and upper zone predilection.

Plain film

The chest radiograph appearance is abnormal in most patients; the earliest change is a diffuse bilateral reticulonudolar pattern with predilection for the mid and upper zones with relative sparing of costophrenic angles. As the disease progresses, the radiographic features gradually metamorphose from a reticulonodular pattern to a honeycomb like pattern corresponding to the summation of air-filled cysts

Lung volumes as assessed by a chest radiograph may be either normal or increased, a feature helpful in distinguishing PLCH from other interstitial lung diseases (with the exception of lymphangioleiomyomatosis) that are usually associated with reduced lung volumes

Uncommon chest radiograph manifestations of PLCH include alveolar infiltrates, hilar or mediastinal adenopathy, prominent pulmonary arteries, pleural effusion, and presentation as a solitary pulmonary nodule without interstitial infiltrates. Occasionally the chest radiograph may be normal.

CT

Thin-section HRCT has proved valuable for the diagnosis and follow-up of PLCH. The predominant findings on HRCT are nodules and cysts . Distribution is the key in differentiating PLCH from other cystic lung disease , PLCH involve predominantly upper lung zones with relative sparing of the lung bases. Relative sparing of lung bases is a useful discriminating feature from pulmonary lymphangioleiomyomatosis, another cystic lung disease that may mimic PLCH radiologically. Cysts are often bizarre shaped, variable in size (although usually less than 20 mm in size), and typically have a thin (1 mm or less) wall. In advanced PLCH, confluent cysts may form, which gives a radiologic appearance that may be difficult to distinguish from emphysema. Serial HRCT studies have shown that the lesions of PLCH evolve in the following sequence: nodules, cavitated nodules, cysts, and eventually confluent cysts. In early disease, combinations of nodules and cysts are commonly seen, whereas in advanced disease cystic change and architectural distortion tend to predominate. nonspecific patterns may be encountered. Ground-glass attenuation, adenopathy, and consolidation also have been reported to occur. **(Fig.4).**

The main differential diagnosis of PLCH is lymphangioleiomyomatosis, cystic bronchiectasis and sarcodosis.

- The HRCT features of **lymphangioleiomyomatosis** include evenly distributed small cysts with thin and well-defined walls and with a predominant location in the lung bases; pulmonary nodules are not seen. In emphysema, too, there is an absence of nodules and cysts.

- **In cystic bronchiectasis**, the cystic lesions exactly follow the course of the bronchial tree and are contiguous with one another.

- The thin-section CT features **of sarcoidosis** include small subpleural cysts, which produce a honeycomblike appearance. These cysts are generally accompanied by irreversible architectural distortion of the lung parenchyma because of fibrosis. The cysts are predominantly apical in location . Sarcoidosis may be further characterized by perilymphatic nodules and mediastinal adenopathy, features that are not seen in pulmonary Langerhans cell histiocytosis **.**

The main complication of the PLCH is spontaneous pneumothorax from the rupture of a peripherally situated lung cyst and Pulmonary hypertension may result from extensive parenchymal destruction.

3. Abdominal Langerhans cell histiocytosis

The liver and spleen are both "risk organs" and involvement denotes a worse prognosis. Hepatobiliary involvement occurs mainly in multisystem LCH. It is seen in 50%-60% of children with multisystem disease but in only 14.4%-18% of those affected by LCH generally.

Langerhans cells directly infiltrate the periportal regions of the liver, showing marked affinity for the bile ducts. Radiologic findings of liver involvement reflect the underlying histopathologic process, which comprises four phases of progression, from an initial proliferative phase to granulomatous, xanthomatous, and, finally, fibrous phases.

Hepatic involvement can include periportal infiltration **(Fig. 5).**, tumor-like or cystic lesions (Fig.6), or overall hepatomegaly (Fig.7) .

periportal inflammation with edema, which appears as bandlike or nodular areas of relative hypoechogenicity at US, hypoattenuation at CT, and moderate to high signal intensity at T2-weighted MR imaging. Associated periportal contrast enhancement may be suggestive of portal triaditis.

Primary or secondary sclerosing cholangitis may produce extra- and intrahepatic biliary irregularities with segmental narrowing and focal areas of slight dilatation, resulting in a beaded appearance of the bile ducts at conventional cholangiography, ERCP, or MRCP

Differential diagnosis include:- Other diffuse infiltrating liver diseases, such as lymphoma, leukemia, or hepatitis . The main differential diagnosis of sclerosing cholangitis in children includes underlying inflammatory bowel disease. Cholangiopathies caused by infectious agents such as cryptosporidium or HIV, ischemia, or mechanical causes, with the development of secondary sclerosing cholangitis, are less common

4. Central nervous system Langerhans cell histiocytosis

Involvement of the central nervous system occurs in 23% - 35% of children with LCH, mostly in those affected by multisystem disease.

MRI is the standard imaging modality for CNS assessment.

Neuropathologic patterns of LCH may be classified into:-

- Soft tissue masses associated with the clavarial and spinal bony lesions.

- Infindibular stalk thickening and enhancement.

- Meningeal thickening and enhancement.

- White matter changes.

- Neurodegenerative changes associated with LCH.

Infindibular stalk thickening and enhancement is the commonest finding denoting CNS affection in LCH cases. MR imaging findings have been correlated with symptoms of diabetes insipidus. The hypothalamus, the pituitary stalk, or both are frequently enlarged and demonstrate gradually increasing homogenous enhancement, with subsequent washout.

The normal pituitary stalk is widest superiorly and tapers inferiorly. It measures 3.5 mm near the median eminence, 2.88mm at its midpoint and 199 mm at its insertion at the pituitary. Enlargement of the pituitary stalk greater than 3.5 mm on MRI is pathologic. The loss of normal tapering is the earliest sign of infiltration. **(Fig.8,9).**

The differential diagnosis includes other infundibular diseases, such as adenohypophysitis, which can be differentiated from LCH by a sharp increase in contrast enhancement and rapid washout after the administration of the intravenous contrast medium. Grandulomatous diseases such as sarcoidosis, Wegener disease and leukemia also must be considered in the differential diagnosis.

The regression of pituitary thickening observed on MR images after treatment should be taken as an indication of the clinical remission of diabetes insipidus, which generally persists.

Meningeal thickening and enhancement is not a common sign of LCH. It is more common with the non langerhans histocytosis i.e.: Ereihdhium chester disease. It may resemble in the extraaxial tumors. At MR imaging, these lesions are characterized by intermediate signal intensity on T1 and T2wi, with moderate or marked uniform intense contrast enhancement after intravenous gadolinium. **(Fig.10).**

Neurodegenerative Langerhans Cell Histiocytosis

Intraaxial neurodegenerative changes are now well known association with LCH. The signal intensity abnormalities in the cerebellum were composed of symmetric hyperintense signal intensity alterations on T2wi and hypointense or hyperintense signals on T1wi involving the gray matter only or extending to the surrounding white matter, eventually resulting in CSF-intense "holes". On T1-weighted images. Pontine lesions have been reported as T2 hyperintense signal intensity abnormalities in the pontine tegmentum or symmetrical T2 hyperintensities in the pontine pyramidal tracts. In the basal ganglia, the abnormalities consisted of hyperinenseiteis on T1-weighted images and variable signal intensities on T2-weighted images. **(Fig.12&13).**Insatiably, inflammation may lead to contrast enhancement of the tiny, sharply demarcated lesions. Eventually, these lesions did not show contrast enhancement or mass effect and inconsistently displayed calcifications.

Results of histopathologic examination of tissue from cerebellar biopsies and autopsies of patients with such MR imaging changes revealed neuron loss and axonal degeneration along with a profound T-cell inflammation. Thus, the described MR imaging signal intensity abnormalities were interpreted as indicative for a neurodegenerative process (ND). MR imaging findings compatible with neurodegenerative disease (radiologic ND-LCH) are frequently detected in patients without suggestive clinical symptoms. Neurologic a symptoms of ND-LCH (clinical ND-LCH) range from subtle deficits abnormalities, gait disturbance and behavioral disturbances to profound ataxia, dysarthria, spastic diparesis or psychiatric disease.

The differential diagnosis includes acute disseminated encephalomyelitis, acute multiphasic disseminated encephalitis, disseminated encephalitis, various metabolic and degenerative disorders, leuckencephalopathy secondary to chemotherapy or radiation therapy and paraneoplastic encephalitis. These entities can be distinguished from Langerhans cell histiocytosis only with reference to the clinical history.

5. Head and Neck involvement.

Craniofacial involvement with osseous lesions in the bones of the orbits and the calvaria has long been recognized as a classic presentation of LCH. LCH affect head and neck region in about 60%082% of patients. The forms of this involvement can be classified into:-

- Bone and soft-tissue lesions. **(Fig. 15).**

- Cervical lymphadenopathy. **(Fig.16).**

Craniofacial osseous destruction has occurred in association with adjacent soft-tissue infiltration in more than 50% of cases. Many sites of soft-tissue involvement in LCH are reported including the orbits (Fig), the paranasal sinuses, the naso and oropharynx, the temporal region with the masticator space and the ear, the larynx and hypopharynx, the thyroid and salivary glands and the adjacent muscles.

Here CT is modality of choice to evaluate the extent of osseous erosion or destruction, and MRI imaging is preserved to assess the intracranial extensions.

LCH typically presents as rapidly progressive facial swelling. Distinguishing an aggressive process such as LCH from a more benign process such as osteomyelities can sometimes be difficult. Both may present with rapidly progressive facial swelling. CT show aggressive, lytic punched out lesion with an associated soft-tissue mass. Mandible, petrous bone and orbit are the most common location of facial LCH involvement.

Images for this section:

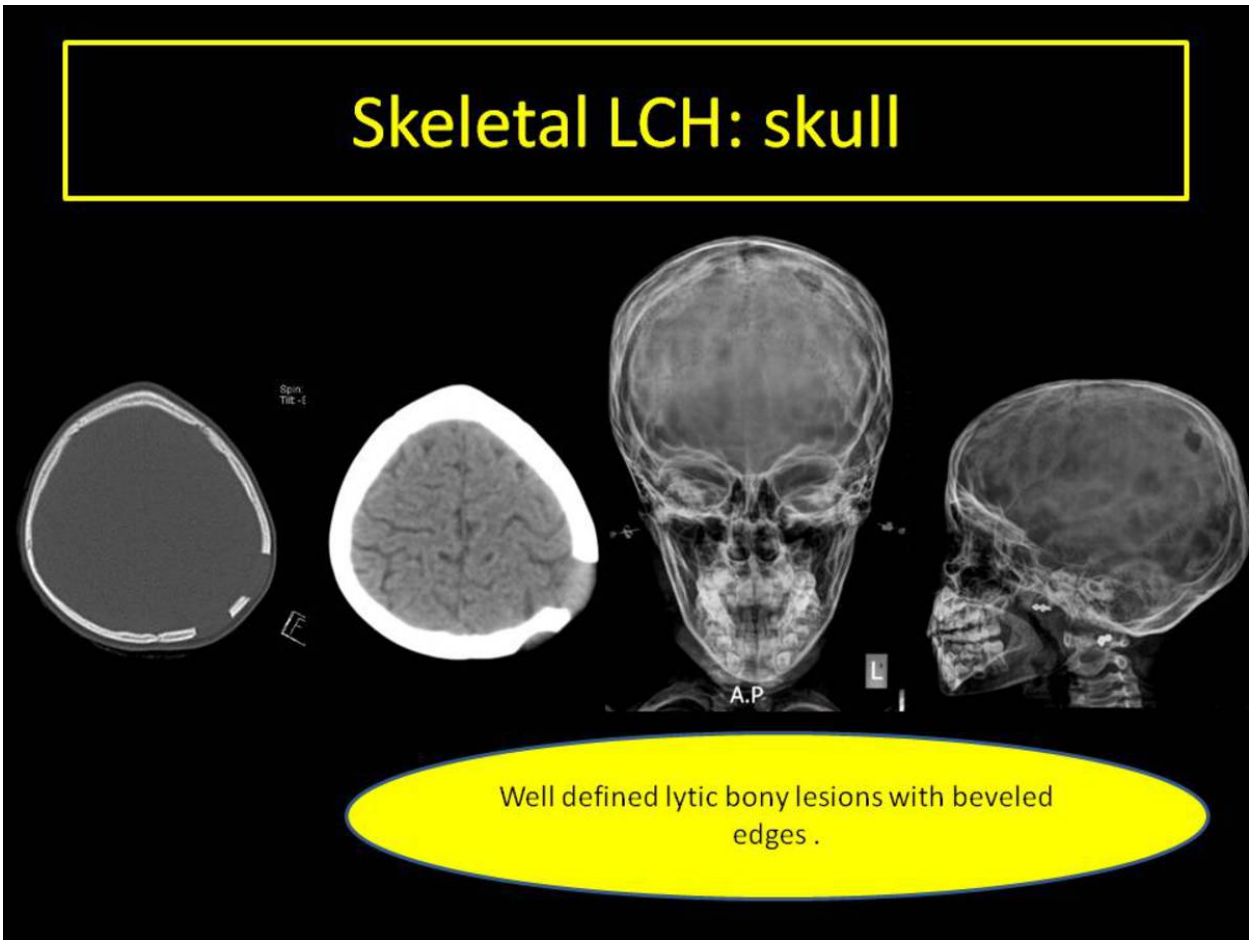

Fig. 1

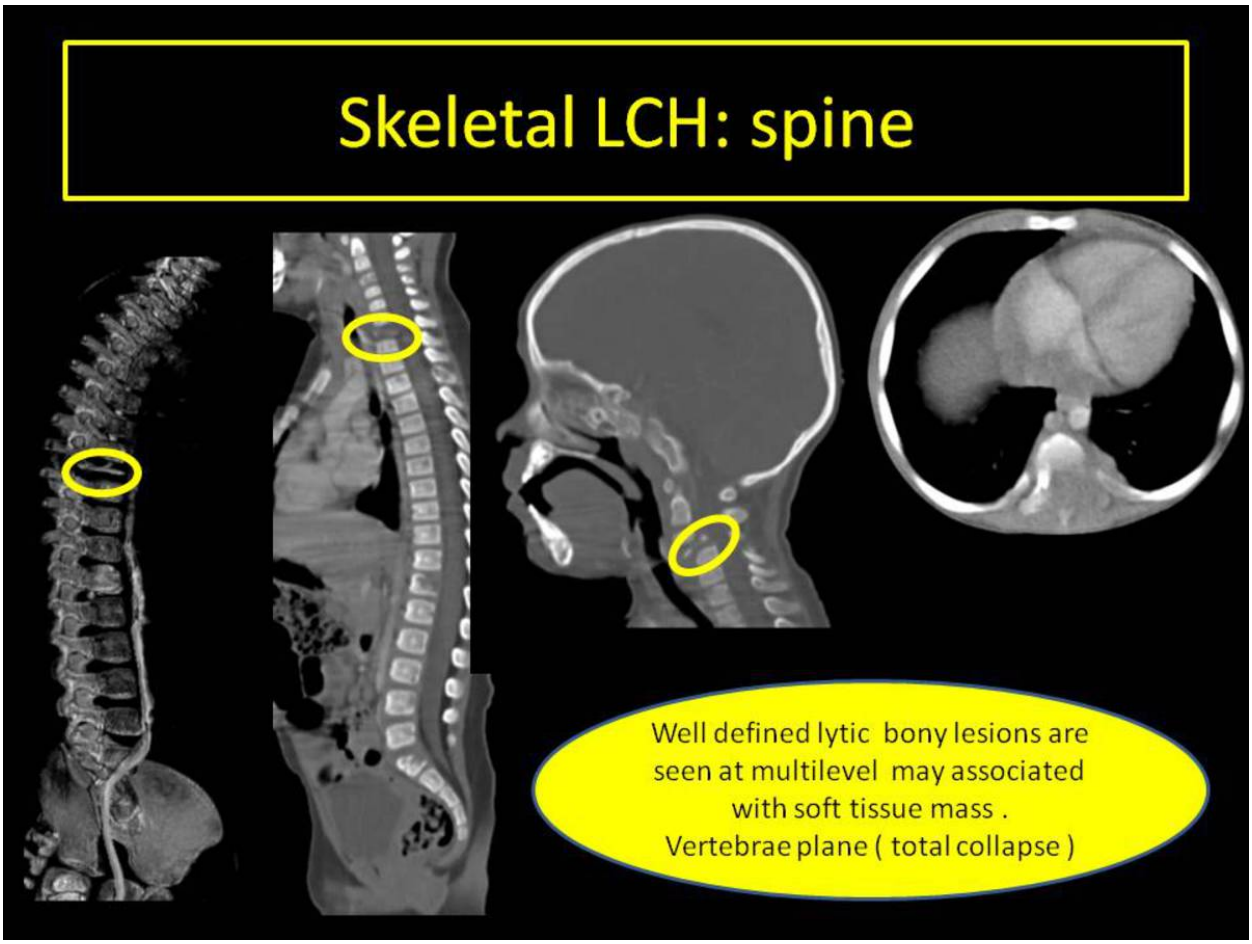
Skeletal LCH: spine
Well defined lytic bony lesions are seen at multilevel may associated with soft tissue mass .
Vertebrae plane (total collapse)

Fig. 2

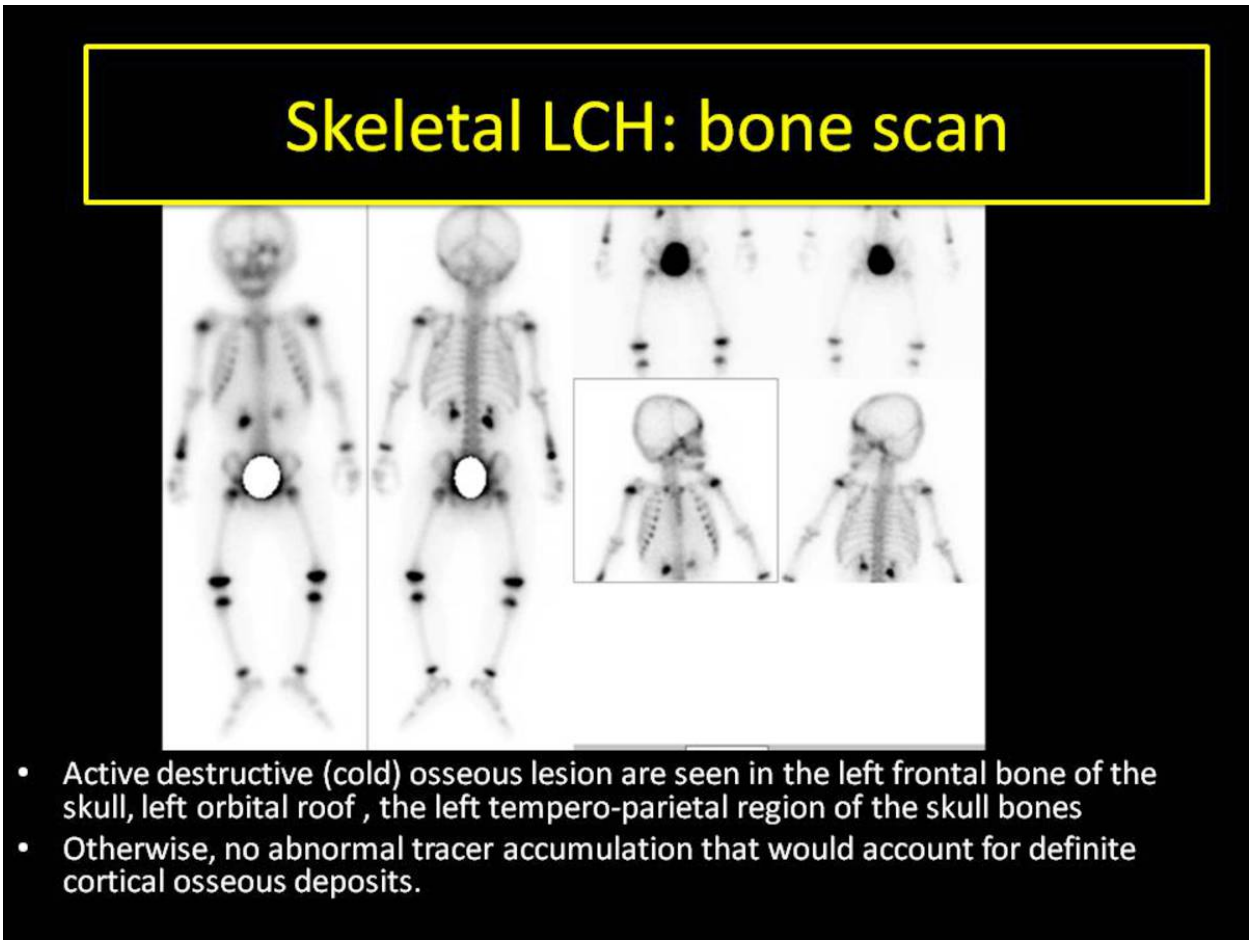
Skeletal LCH: bone scan
• Active destructive (cold) osseous lesion are seen in the left frontal bone of the skull, left orbital roof , the left tempero-parietal region of the skull bones
• Otherwise, no abnormal tracer accumulation that would account for definite cortical osseous deposits.

Fig. 3

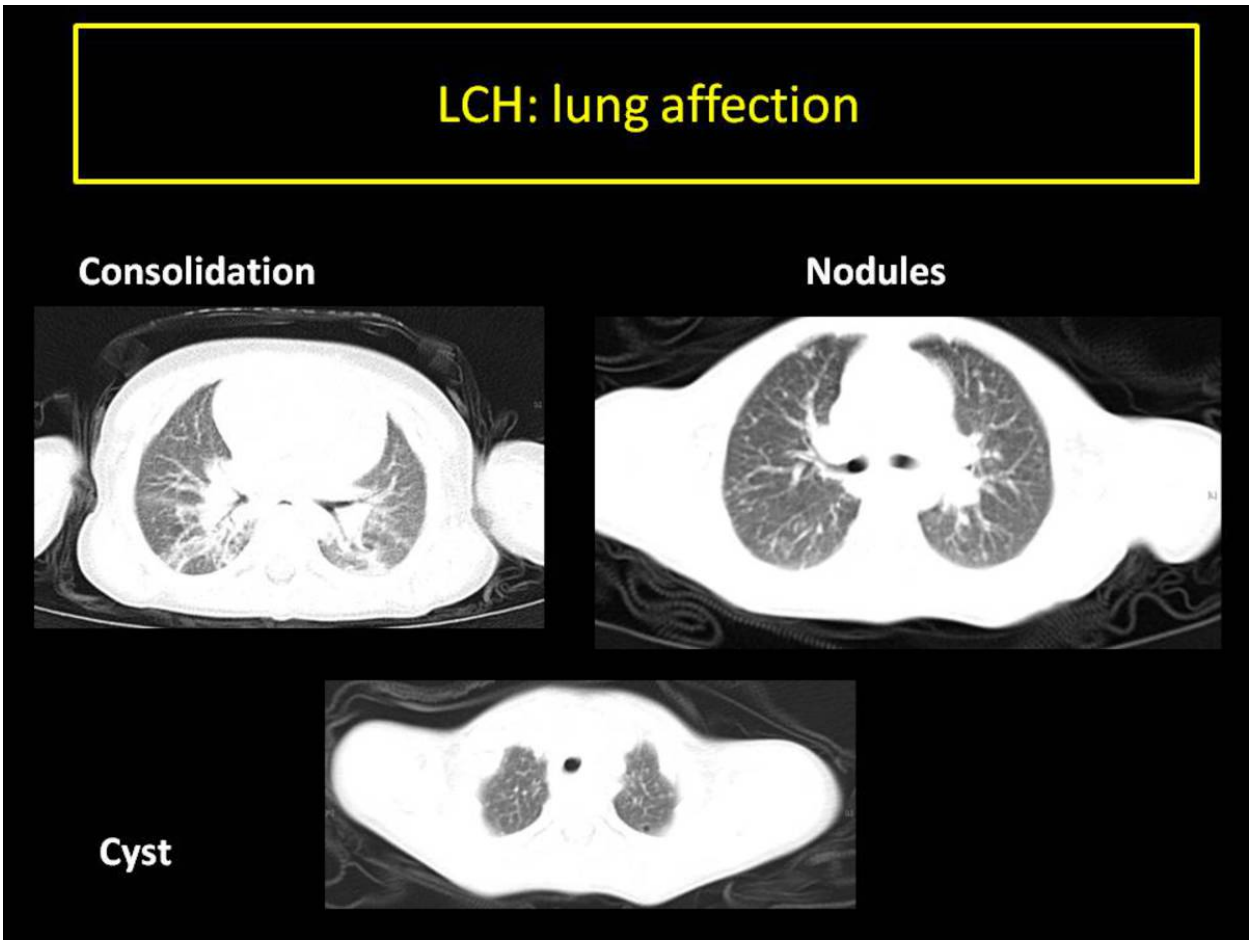

Fig. 4

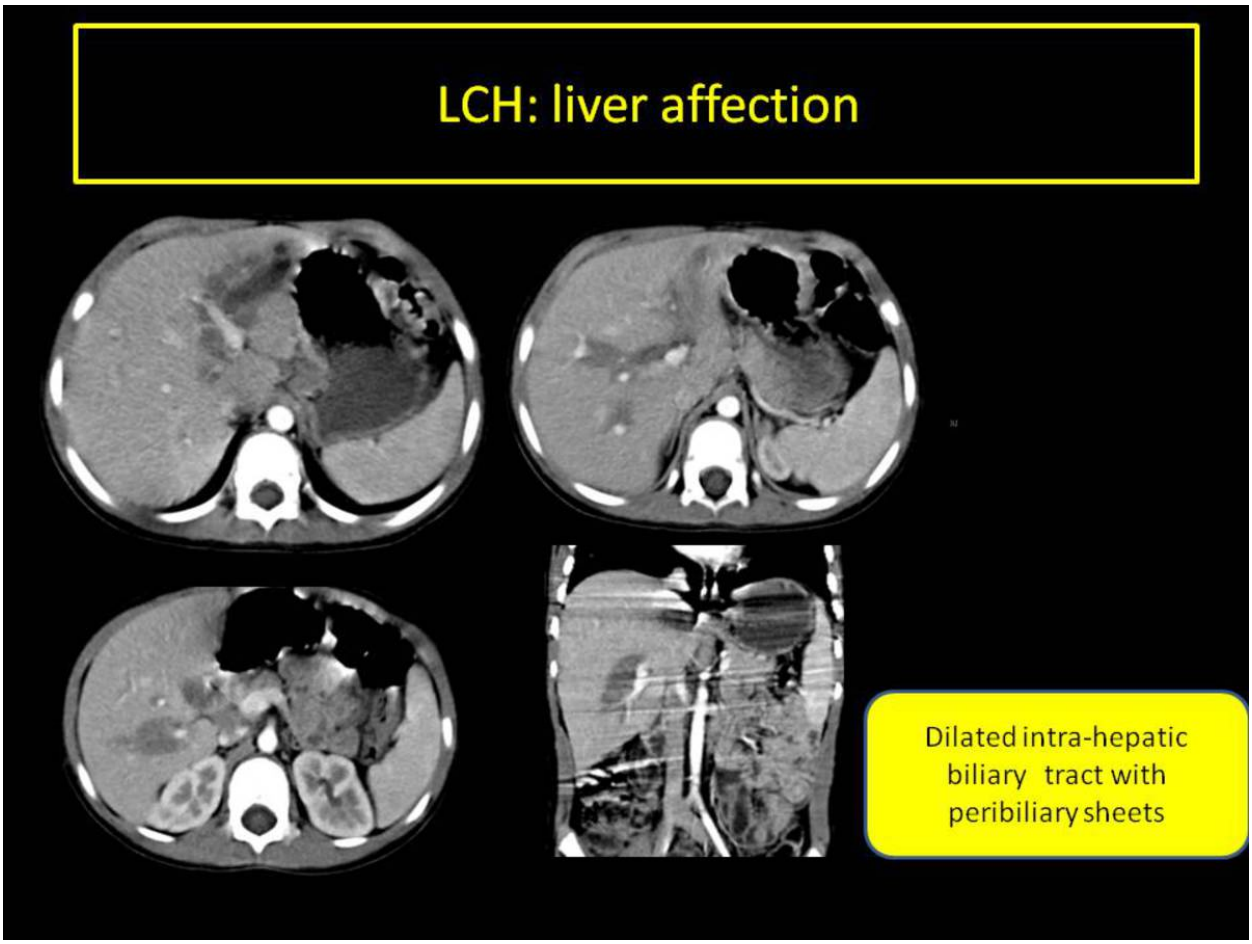
LCH: liver affection
Dilated intra-hepatic biliary tract with peribiliary sheets

Fig. 5

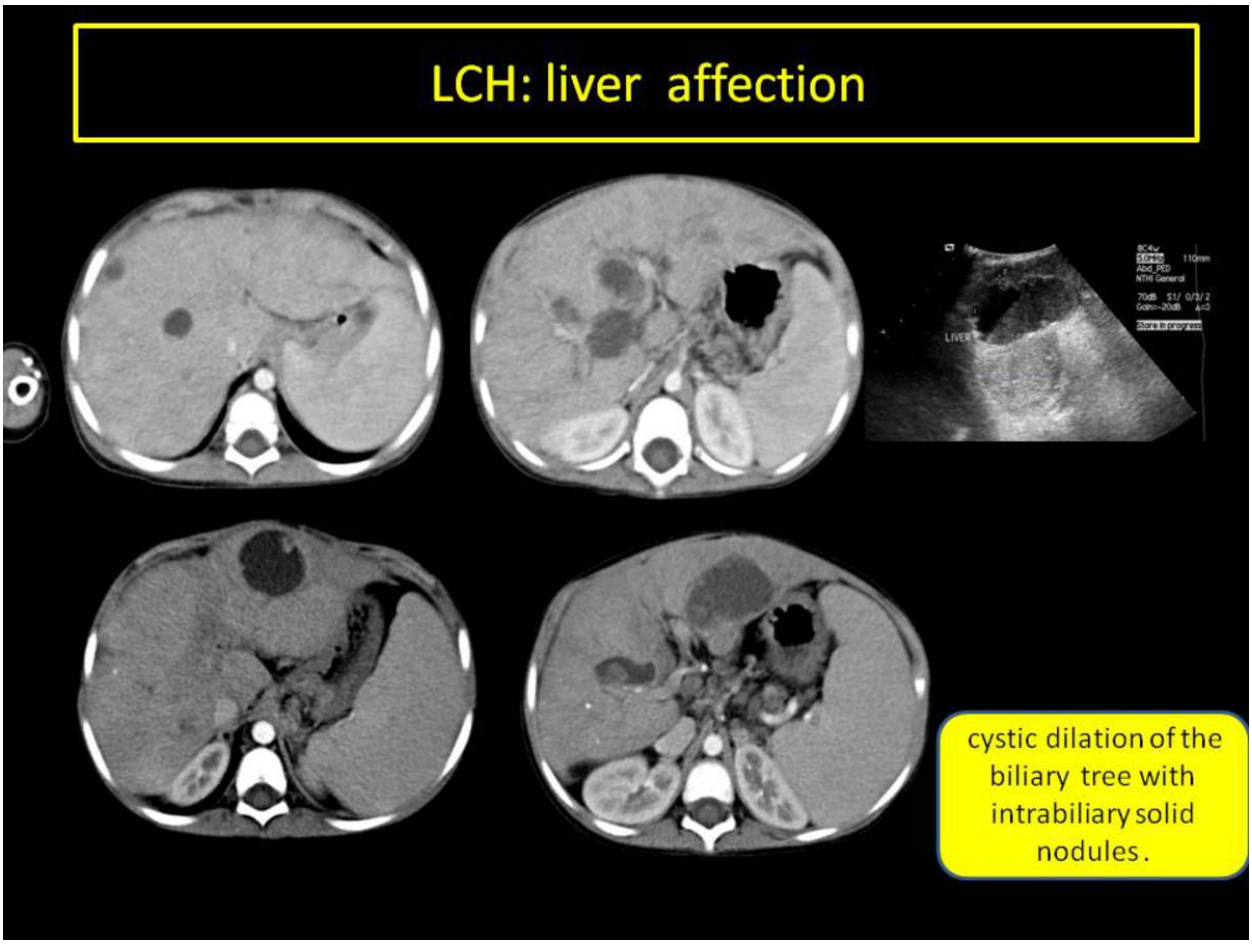
LCH: liver affection
cystic dilation of the biliary tree with intrabiliary solid nodules.

Fig. 6

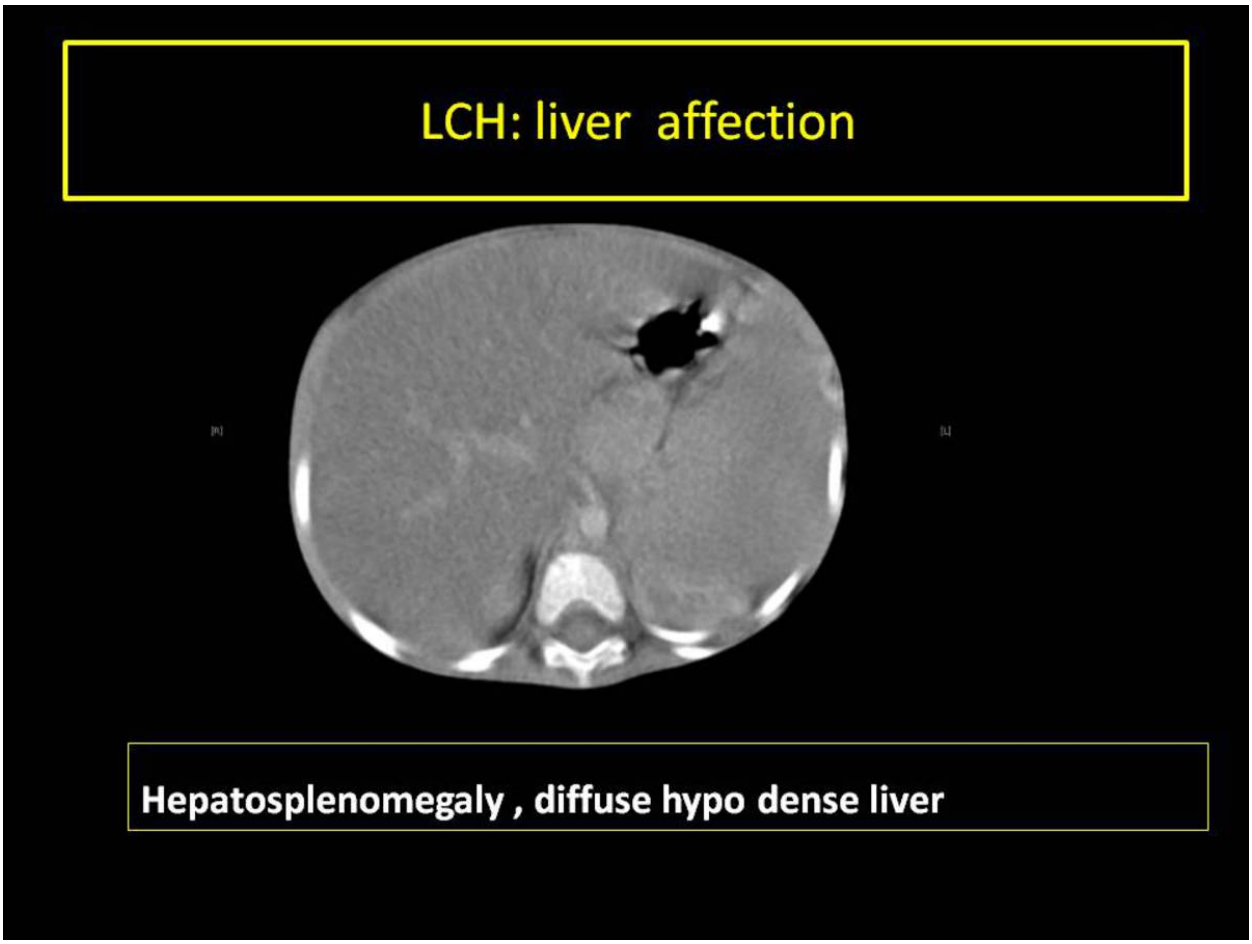
LCH: liver affection
Hepatosplenomegaly , diffuse hypo dense liver

Fig. 7

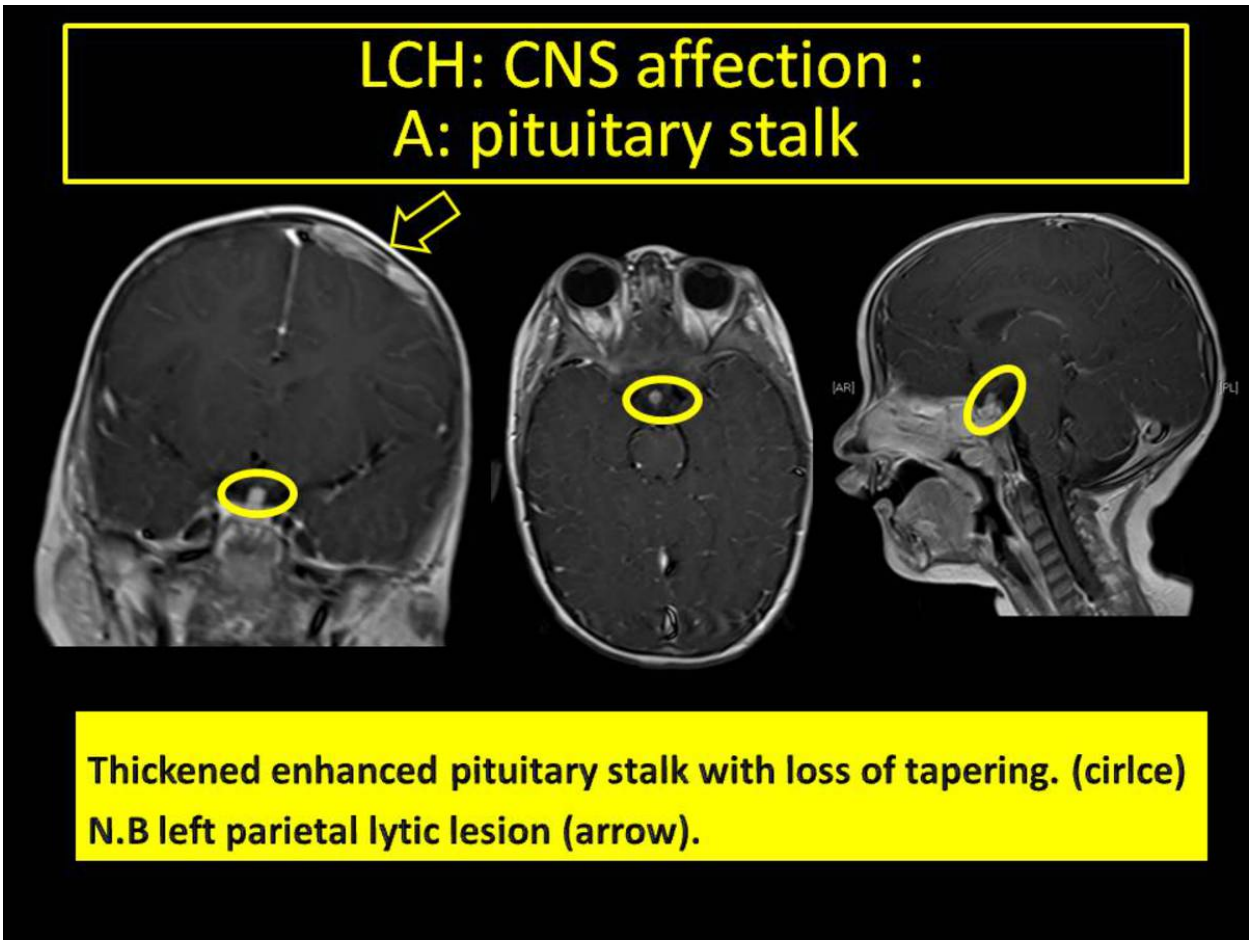
LCH: CNS affection :
A: pituitary stalk
Thickened enhanced pituitary stalk with loss of tapering. (cirlce)
N.B left parietal lytic lesion (arrow).

Fig. 8

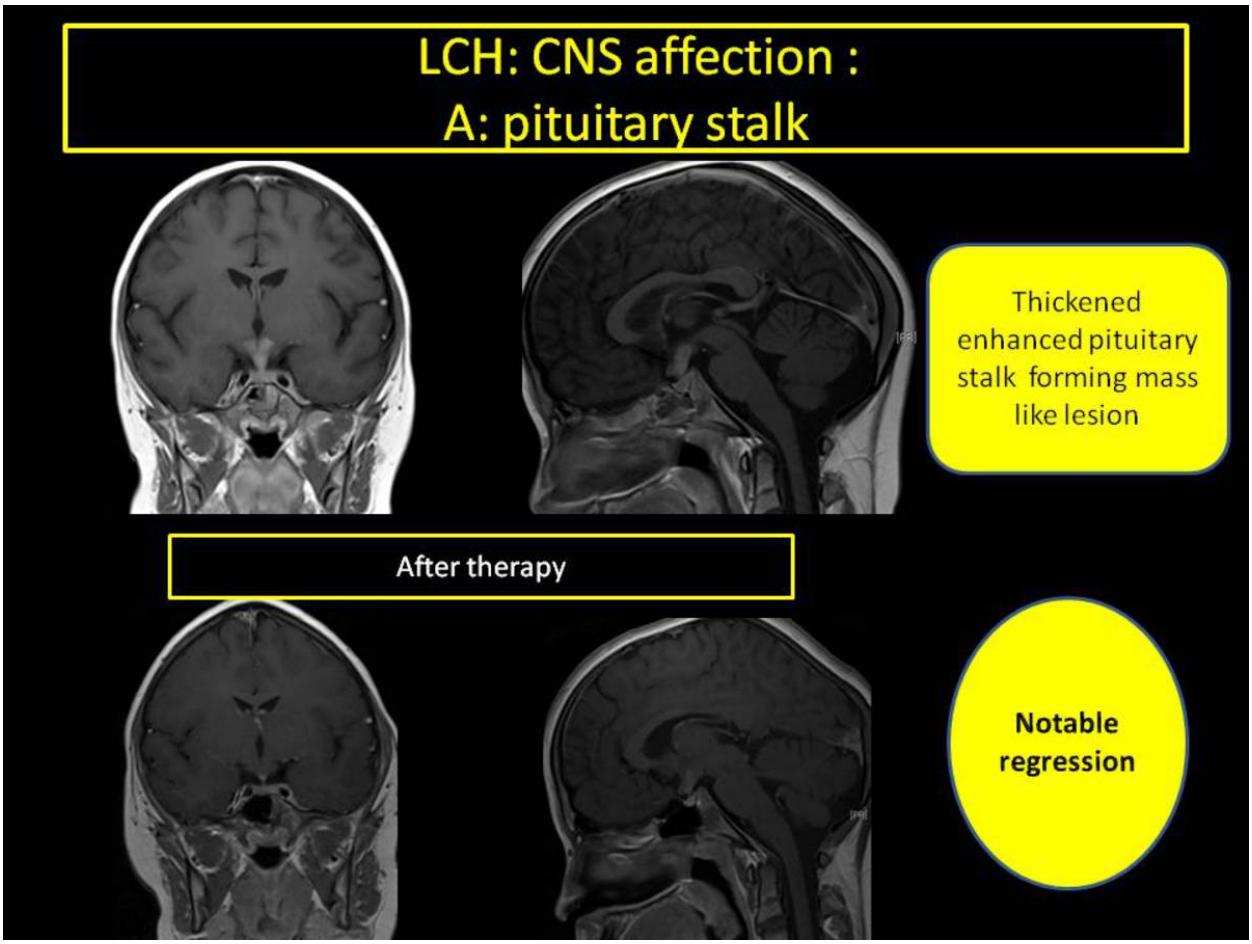
LCH: CNS affection :
A: pituitary stalk
Thickened enhanced pituitary stalk forming mass like lesion
After therapy
Notable regression

Fig. 9

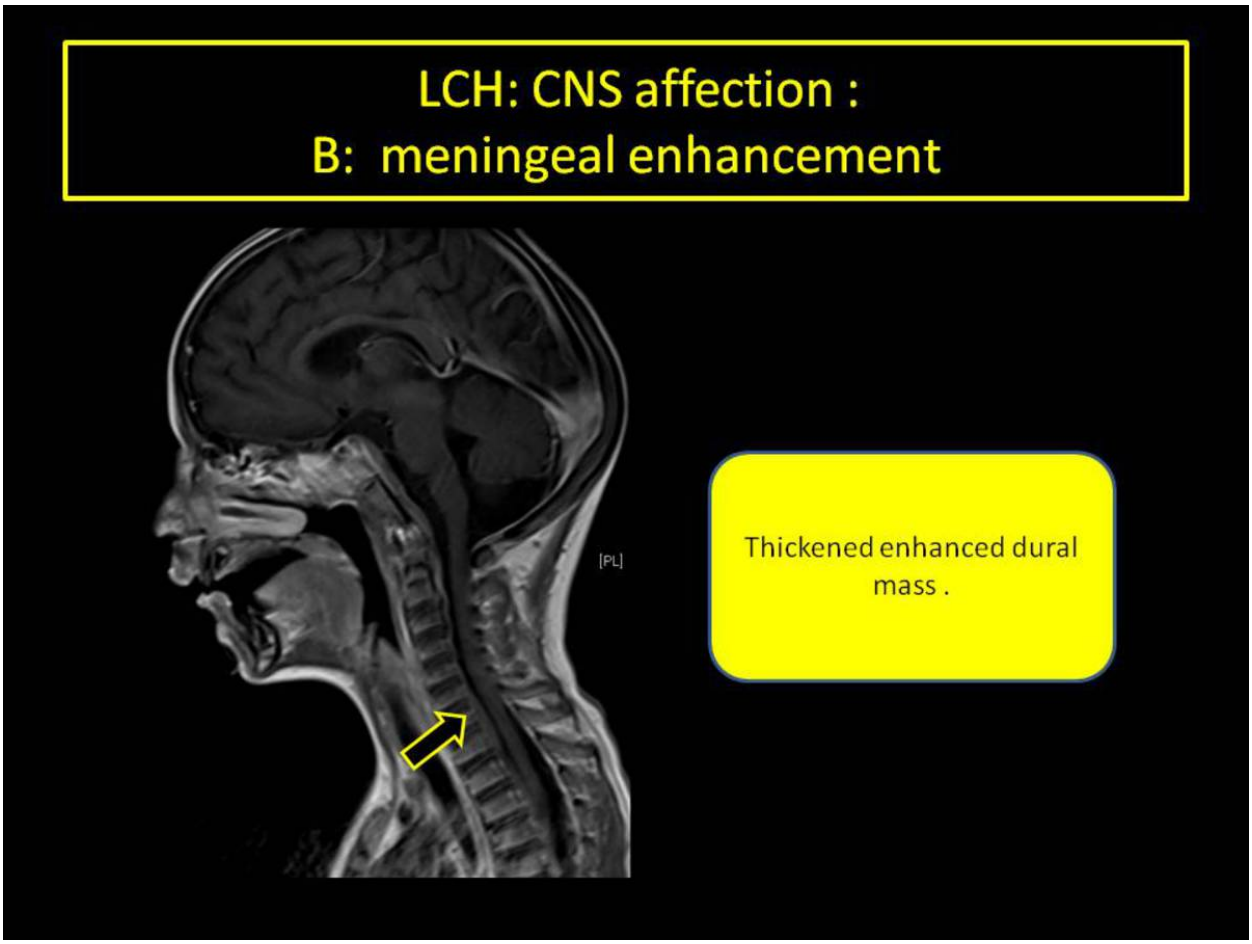
LCH: CNS affection :
B: meningeal enhancement
[PL]
Thickened enhanced dural mass .

Fig. 10

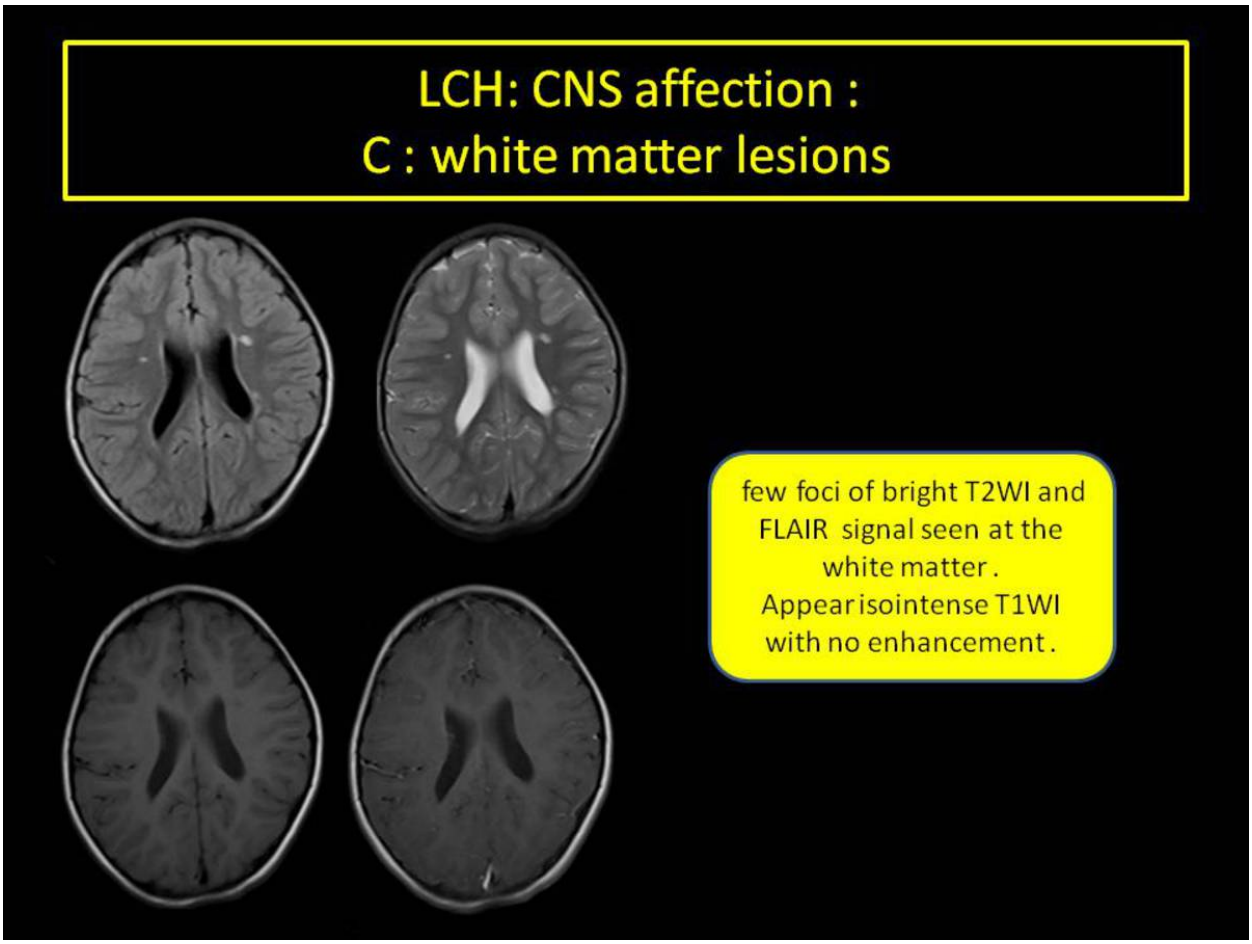
LCH: CNS affection :
C : white matter lesions
few foci of bright T2WI and FLAIR signal seen at the white matter .
Appear isointense T1WI with no enhancement .

Fig. 11

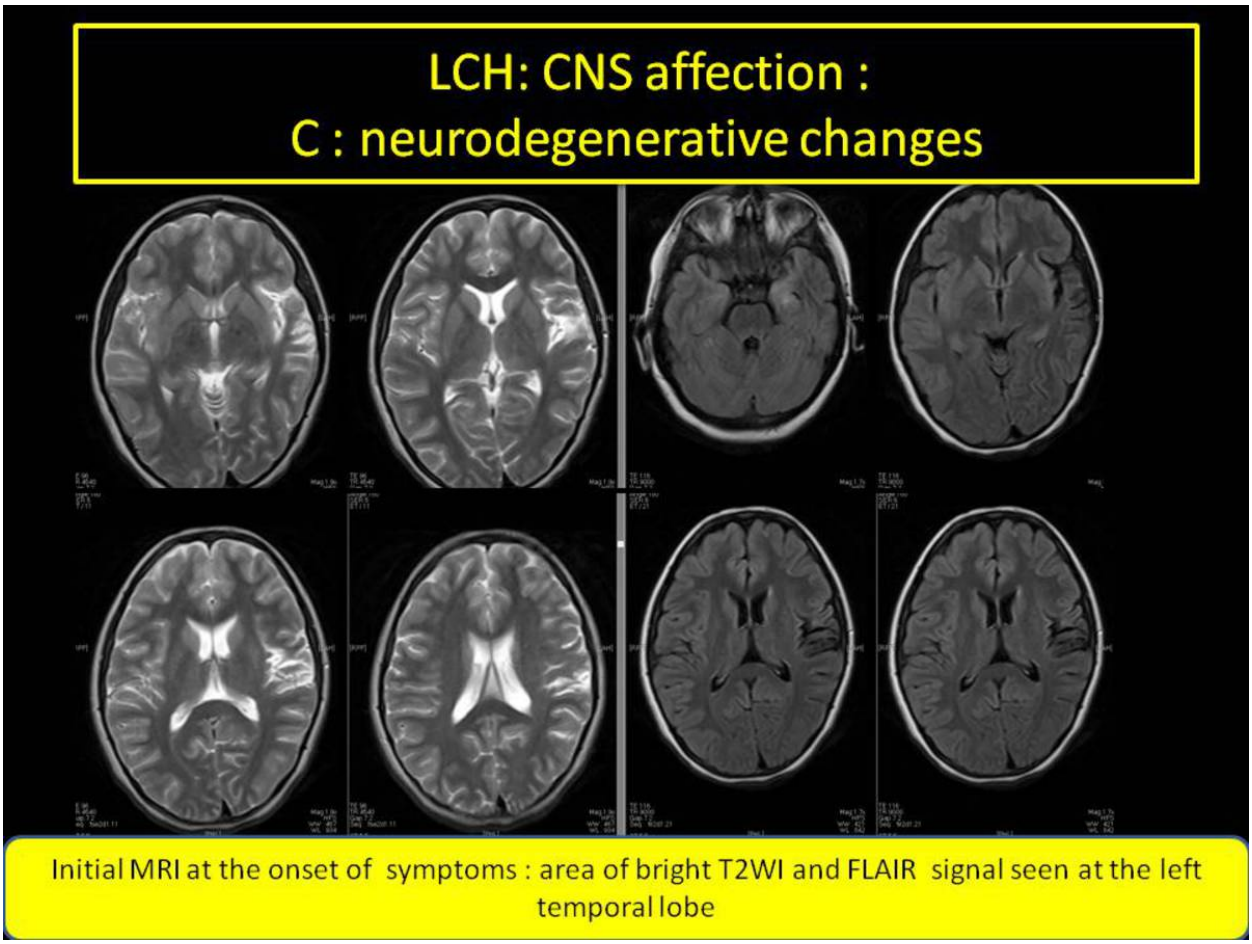
LCH: CNS affection :
C : neurodegenerative changes
Initial MRI at the onset of symptoms : area of bright T2WI and FLAIR signal seen at the left temporal lobe

Fig. 12

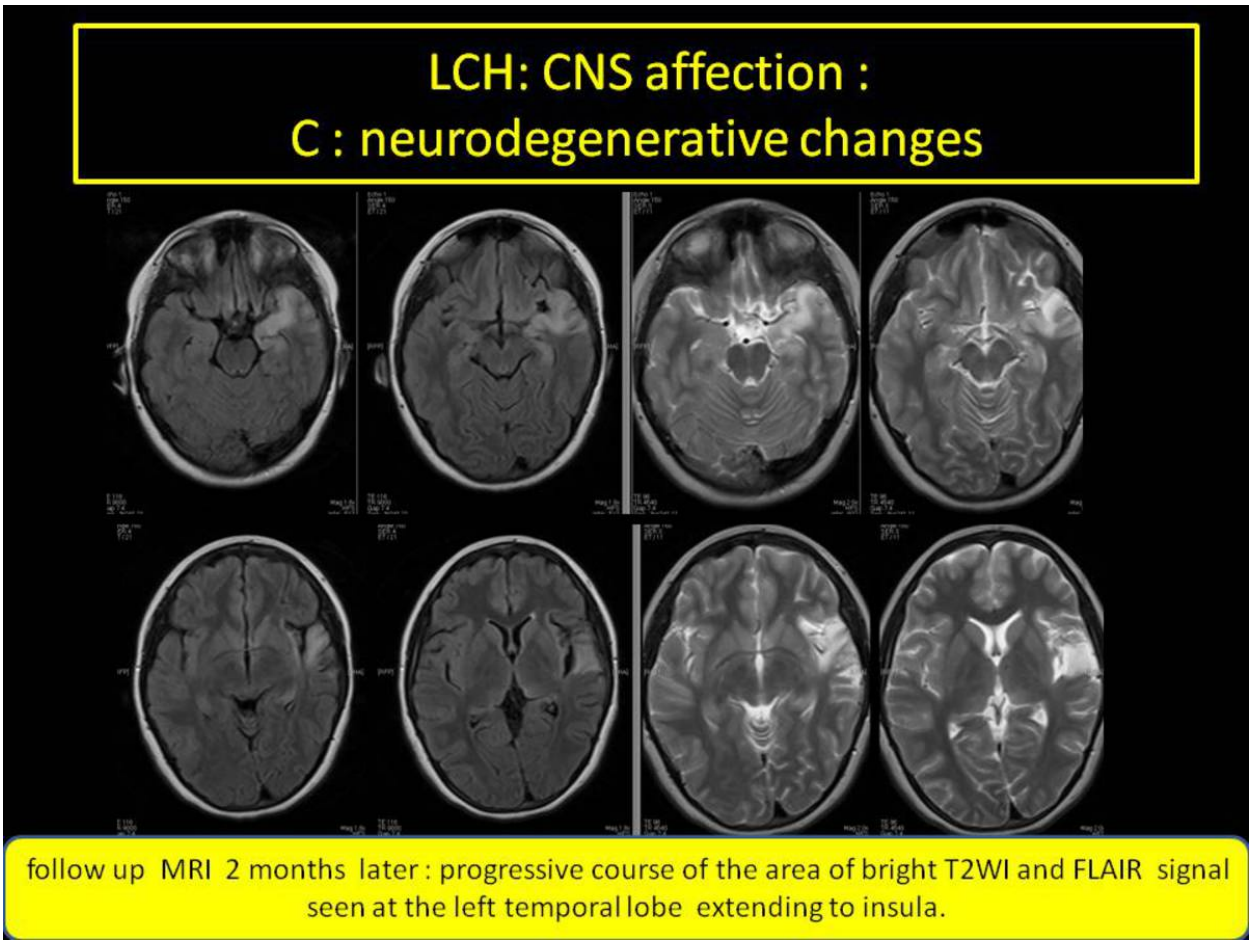
LCH: CNS affection :
C : neurodegenerative changes
follow up MRI 2 months later : progressive course of the area of bright T2WI and FLAIR signal seen at the left temporal lobe extending to insula.

Fig. 13

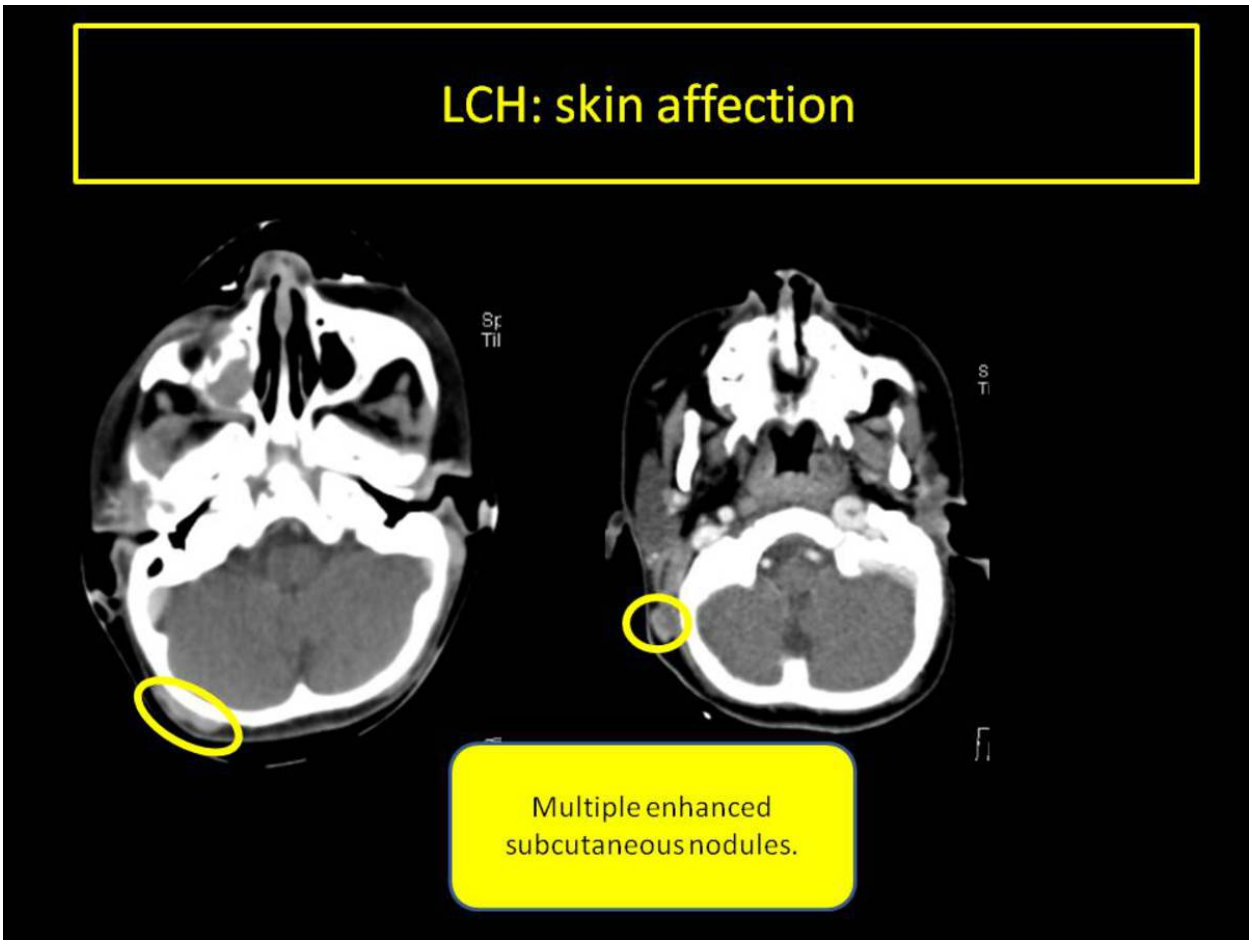
LCH: skin affection
Multiple enhanced subcutaneous nodules.

Fig. 14

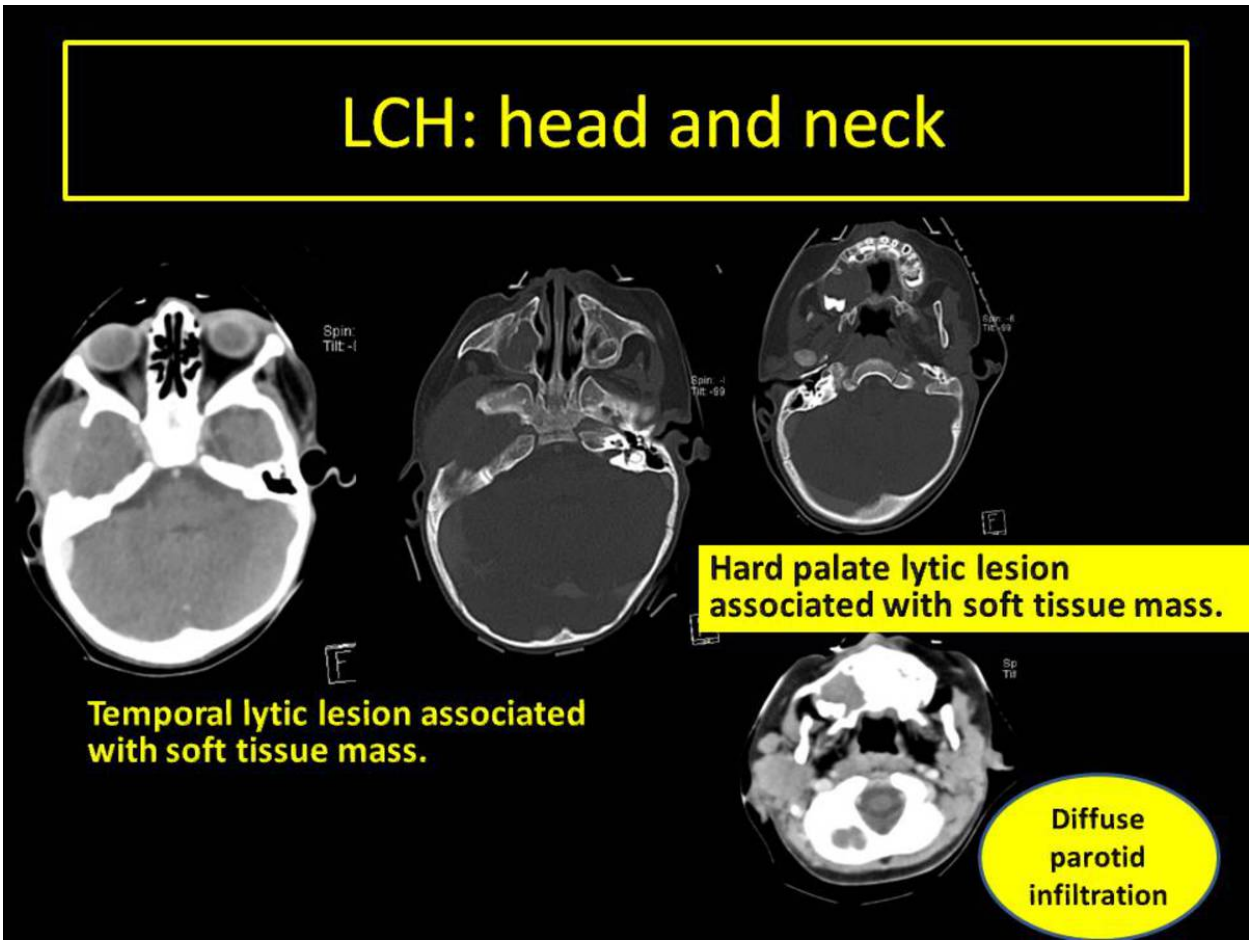
LCH: head and neck
Temporal lytic lesion associated with soft tissue mass.
Hard palate lytic lesion associated with soft tissue mass.
Diffuse parotid infiltration

Fig. 15

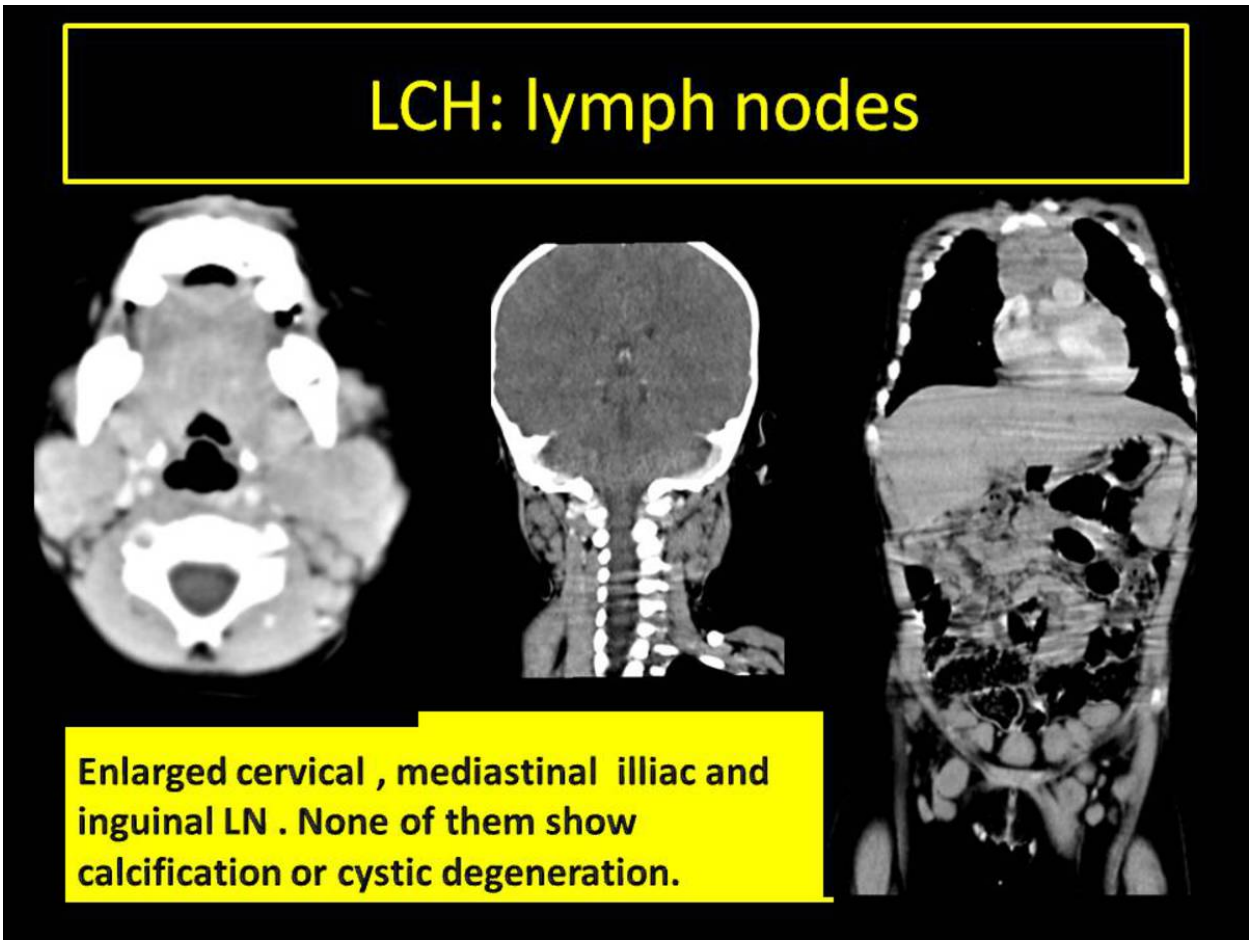
LCH: lymph nodes
Enlarged cervical , mediastinal illiac and inguinal LN . None of them show calcification or cystic degeneration.

Fig. 16

Conclusion

Because of the frequent LCH children radiologist need to be familiar with its presentation in different organs and regions of body outside the commonest site of affection (bones). A high-index suspicion should be raised a biopsy is recommended in the presence of radiological suspicion. Chemotherapy is the preferred therapeutic modality.

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