Non Langerhans Histiocytic Disorders: radiological pathological correlation.

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Learning objectives

The non-Langerhans Cell Histiocytoses (non-LCH) are a group of disorders defined by the accumulation of histiocytes that do not meet the phenotypic criteria for the diagnosis of Langerhans cell. The non-LCH consists of a long list of diverse disorders which have been difficult to categorize. Our objectives are to:-

- Identify the cell origin of the different types of the histocytic disorders.
- Increase awareness of the imaging findings of this disease affection in different organs.

Background

The histiocytosis is a diverse group of hematologic disorders defined by the pathologic infiltration of normal tissues by cells of the mononuclear phagocyte system. In 1996, the World Health Organization (WHO) Committee on Histiocytic/Reticulum Cell Proliferations proposed a system in which the overall classification of histiocytic proliferations was based on the cell of origin. WHO has proposed a classification for histiocytosis syndromes in children, with 3 main classes:-

- Class I includes Langerhans cell histiocytosis.
- Class II includes histiocytosis of mononuclear phagocytes other than Langerhans cells, familial and reactive hemophagocytic lymphohistiocytosis, sinus histiocytosis with massive lymphadenopathy, Rosai-Dorfman disease, JXG, and reticulohistiocytoma.
- Class III includes malignant histiocytic disorders, acute monocytic leukemia, malignant histiocytosis, and true histiocytic lymphoma.

Clinically the non-LCH can be divided into 3 groups, those that predominantly affect skin, those that affect skin but have a major systemic component, and those that primarily involve extra-cutaneous sites, although skin may be involved.

These disorders includes:-

- **Juvenile Xanthogranuloma (JXG)** which is dermal dendrocyte-derived non-LCH.
- **Sinus histiocytosis with massive lymphadenopathy (Rosai-Dorfman disease)**, which is a rare benign idiopathic proliferative disease that involve phagocytic histiocytes.
- **Erdheim-Chester disease** which is a rare sporadic multisystem non-Langerhans cell histiocytosis of unknown cause
Hemophagocytic lymphohistiocytosis (HLH) is a nonmalignant disorder of immune regulation, with overproduction of cytokines and diminished immune surveillance. 

Histiocytic Sarcomas which is malignant transformation of dendritic cells

Findings and procedure details

**Juvenile xanthogranuloma (JXG)**

JXG is a rare benign proliferative histiocytic disorder experienced during childhood and adolescents. JXG is not a true neoplasm, but rather a reactive proliferation of histiocytes, and belongs to the category of non-Langerhans dendritic cell disorders. However, the etiology and pathogenesis of JXG are still unknown. First described in 1905, and initially thought to be of endothelial derivation (hence the previous designation as nevoxanthoendothelioma). In most cases, an XG appears as a solitary yellow-red cutaneous nodule in the head and the neck region that regresses spontaneously over a course of months to years. An extracutaneous XG is uncommon, and it can occur with or without a cutaneous XG. An extracutaneous XG most commonly occurs in the eye, but findings at other sites such as the central nervous system, lungs, liver, spleen, kidneys, and bone have also been reported. The pathogenesis of XGs is unknown. Although physical and infectious factors have been considered, most investigators postulate that they are caused by a reactive response to an unknown stimulus.

Periorbital xanthogranuloma is a rare entity that may occur in both adults and children. Although the diagnosis may be suspected clinically from the characteristic macroscopic appearance of diffuse, yellow, plaque-like masses in the eyelid, the diagnosis is confirmed histologically. As affected patients present with a spectrum of ocular symptoms and signs, including displacement of the globe and restriction of lid or eye movements. Imaging of the orbit with CT or MRI should generally be included as part of the clinical investigations, to assess the extent of involvement of preseptal and retrobulbar tissues before biopsy of orbital tissue for histopathology.

The radiological features include the presence of a large retrobulbar soft tissue mass which was predominantly extraconal but with extraocular muscle infiltration - a recognized feature-causing proptosis and displacement of the globe. The soft tissue mass had a lower attenuation centre, which is likely to reflect the characteristic histological appearance of large lipid laden histiocytes together with foreign body and Touton giant cells.

**Intracranial involvement is uncommon.** Solitary intracranial lesions are more commonly seen than multiple lesions. However, such an extensive dural and parenchymal involvement as seen in our case is extremely uncommon.
Intracranial lesions may be seen in the cerebral parenchyma, meninges, choroid plexus, or cranial nerves. Clinically, the affected children may be asymptomatic or may present with seizures, ataxia, weakness, or growth retardation. Intracranial involvement in JXG is associated with increased mortality and morbidity. The intracranial lesions have a tendency to grow slowly and must be followed up.

JXG is also reported in the breast where it is misdiagnosed radiologically as a malignant lesion. Also it was reported in the liver and heart yet these are extremely rare.

**Rosai-Dorfman disease**

Sinus histiocytosis with massive lymphadenopathy (Rosai-Dorfman disease) is a rare benign proliferative disorder characterized histologically by lymphatic sinus dilatation due to histiocyte proliferation. The disease was first described by Destombes in 1965 and was recognized as a distinct clinicopathologic entity by Rosai and Dorfman in 1969. It usually affects children and young adults, with a slight male predominance. Rosai-Dorfman disease often has a chronic, relapsing course.

Patients presenting with Rosai-Dorfman disease usually have cervical lymphadenopathy as well as fever and leukocytosis. Rosai and Dorfman list 43% of patients as having at least one site of extranodal involvement. A few present with isolated extranodal disease. These sites include the respiratory tract, skin, nasal cavity, orbit and eyelid, and skeletal system. While rare, intracranial involvement has been reported in several cases. Patients with extra nodal disease have a poorer prognosis than those with nodal disease.

The characteristic histopathologic feature is emperipolesis, in which histiocytes phagocytize lymphocytes, plasma cells, erythrocytes, or polymorphonuclear leukocytes.

The underlying causes of Rosai-Dorfman disease remain unclear. It has been considered a neoplastic, immune, or infectious process in various reports. Several viruses have been associated with the onset of the disease. Epstein-Barr virus and human herpes virus 6 have been detected by in situ hybridization in some patients with Rosai-Dorfman disease.

Rosai-Dorfman disease is a disease with protean imaging manifestations.

**Enlarged cervical lymph nodes** are the most frequently encountered manifestation of the Rosai-Dorfman disease. These lymph nodes usually have no special feature, as it has no intranodal calcification, cystic degeneration or special enhancement pattern. Differential considerations include lymphomas, tuberculosis, metastatic papillary thyroid carcinoma, Kaposi sarcoma, and rare diseases such as Castleman disease, all of which are associated with lymph node enhancement.
**Intracranial Rosai-Dorfman disease** may present by solitary or multiple dural-based enhancing mass lesions and it is most frequently confused with meningioma. Yet these lesions do not have bone destruction or hyperostosis as a feature, which may have helped in distinguishing these lesions from meningiomas, which frequently induce bony changes. The meningeal Rosai-Dorfman disease has the same signal pattern of meningioma to be isointense relative to gray matter on T1 and T2wi with homogeneous contrast enhancement on MR images.

**Head and neck manifestation** may include:

Diffuse infiltration of the lacrimal or salivary glands usually presented by painless masses and appears in CT as enlarged homogenously enhanced masses.

Paranasal sinus involvement is reported and may have aggressive disease with bony destruction. Such aggressive disease is difficult to differentiate from malignant conditions, making the diagnosis of Rosai-Dorfman disease a mainly histologic diagnosis and not a radiologic one. We report a case of Rosai-Dorfman disease with ill defined nasal mass destructing the adjacent bone and a well defined polypoidal upper tracheal soft tissue mass. (Fig. 1).

**Cutaneous lesions** are the most common form of extra-nodal Rosai-Dorfman disease.

However, purely cutaneous Rosai-Dorfman disease is rare because it is usually a manifestation of systemic disease.

**Erdheim-Chester disease**

Erdheim-Chester disease is a rare form of non-Langerhans histiocytosis. It is an endogenous non inherited disorder. Patient age at diagnosis ranges from 7 to 84 years (mean, 53 ± 14 years), and the male-to-female ratio is 1:3. Clinical manifestations range from asymptomatic or minimally symptomatic bone pain or hypopituitarism to severe multisystem involvement.

Clinical manifestations range from a focal asymptomatic process to fatal systemic disease that may involve virtually all organ systems.

In 1930, William Chester and his mentor, a Viennese pathologist named Jakob Erdheim, described two patients with a distinctive lipoidosis different from other histiocytic disorders, particularly Hand-Schüller-Christian and Niemann-Pick diseases. The disease was characterized by proliferation of lipid-containing foamy histiocytes in the skeleton, especially in the long bones, without visceral involvement.
**Bone involvement** is an almost constant finding in Erdheim-Chester disease and is asymptomatic in about 60% of patients and appears classically bilateral symmetric osteosclerosis of the long tubular bones, predominating in the metaphysis and diaphysis of the lower limbs with sparing of the epiphysis. Bone scanning usually shows the classic appearance is an intense uptake in a bilateral and symmetric diaphyses-metaphysial distribution. This appearance has been described as virtually pathognomonic for Erdheim-Chester disease.

**Renal and Perirenal Involvement** is relatively frequent, found in 29% of Erdheim-Chester cases. This involvement is usually asymptomatic and is revealed on CT, which classically shows hypoattenuated homogeneous tissue infiltration with weak contrast enhancement in the renal fossae (Fig. 2). The "hairy kidney" appearance, due to symmetric and bilateral infiltration of both the perirenal and posterior pararenal space, is highly suggestive of the diagnosis. Extension to the renal sinuses and pedicles and also to the proximal ureters and lumbar ureters is possible and may cause upper urinary tract obstruction.

**Vascular involvement** by Erdheim-Chester disease is relatively uncommon. CT typically shows periaortic tissue infiltration, extending from the ascending aorta to the iliac junction and creating the appearance of a "coated aorta".

**Pulmonary involvement** by Erdheim-Chester disease is uncommon. However, once pulmonary involvement develops, the resulting lung disease significantly contributes to morbidity and mortality. Clinically, dyspnea and cough are the most frequent symptoms. The most common findings is an interstitial process characterized by smooth interlobular septal thickening and centrilobular nodular opacities, fissural thickening, and pleural effusions. On CT, pericardial fluid and thickening or extrathoracic soft-tissue masses may be also encountered. Definitive diagnosis requires correlating skeletal findings and lung biopsy findings.

**Central nervous system involvement** may be revealed by diabetes insipidus, cerebellar syndrome, exophthalmos due to retro-orbital masses, and symptoms consistent with extraaxial masses. (Fig.3,4) These manifestations correlate with diverse radiological and pathological findings: involvement the hypothalamic pituitary axis where nodular or micronodular masses of the infundibular stalk may be present, retro-orbital masses, involvement of the dentate area of the cerebellum and meningeal lesions of the dura. Other less common involvements include thickening of the bones of the face and skull, intracranial peri-arterial infiltration, intraluminal involvement of the superior sagittal sinus, involvement of the choroid plexus and masses involving the cerebral hemispheres. The location, size and nature of the lesion at hand determine whether the patient will be completely asymptomatic, suffer from various neurological deficits, severe disability or succumb to his disease.
Hemophagocytic lymphohistiocytosis (HLH)

HLH is included within the histiocytic disorder spectrum. It is a rare disorder that is characterized by proliferation of benign histiocytes. It may either present as a primary disease or occur as a secondary, reactive disease. The primary form (familial or sporadic) result from a defect of the immune system, occurs in young infants, and is fatal if untreated. The secondary form occurs as a reactive process in response to infective agents (such as bacteria, viruses, and parasites) as well as to malignancies and tends to occur in immunocompromised individuals. When it is secondary to a viral infection, it can also be called "virus-associated HPS." This form is usually self limiting but may require treatment with chemotherapy and/or immunosuppressive agents. The diagnostic criteria include fever, splenomegaly, cytopenia that affect more than 2 cell lines, hypertriglyceridemia, hyperferritinemia and/or low fibrinogen level, and hemophagocytosis in the reticuloendothelial system.

Approximately 30% of patients show neurological abnormalities such as seizures, alterations of the level of consciousness, hemiparesis, nuchal rigidity and ataxia. The CSF is normal in approximately 50% of cases. The CSF abnormalities are nonspecific, and they include increased levels of protein and low levels of glucose.

The histopathologic findings of HLH in pediatric patients with involvement of the CNS could be classified on the basis of the stages of the disease as determined microscopically, and the stages are characterized by increasing severity:

- Stage I primarily shows only leptomeningeal infiltrates of lymphocytes and histiocytes/macrophages.
- Stage II shows additional parenchymal involvement with perivascular infiltrations
- Stage III shows signs of cerebral tissue necrosis and demyelination in addition to the massive tissue infiltration that particularly affects the white matter

The reported CT findings are diffuse parenchymal atrophy, low attenuated lesions in the white matter and calcifications. Reduction of the volume leads to dilatation of the ventricular system and/or subdural fluid collections. The calcifications appear as gyriform linear areas that are more prominent in the regions of gray-white matter junctions. Some low attenuated parenchymal lesions show nodular or ring enhancement after contrast enhancement. The reported MR findings include diffuse leptomeningeal and perivascular enhancement, which corresponds to meningeal and perivascular infiltrations of histiocytes and lymphocytes, patchy areas of an increased T2 signal intensity in the white matter of the both cerebral hemispheres, and a diffuse parenchymal volume loss of the cerebrum and cerebellum (Figs 6-8). In some cases, nodular or ring enhancement of the parenchymal lesion appears due to the compromised blood-brain barrier that is associated with active demyelination.
Histiocytic Sarcomas

Histiocytic sarcoma (HS) is a rare high grade hematopoietic neoplasm, it is defined in World Health Organization (WHO) Classification as a malignancy with morphologic and immunophenotypic features that resemble those of mature tissue histiocytes. First described by Mathé et al in 1970, HS is a rare, but aggressive hematopoietic neoplasm. It commonly occurs in lymph nodes, and in extranodal sites including gastrointestinal tract, skin and central nervous system. Clinical presentation of HS depends largely on the organ involved, most commonly the intestine, skin, spleen, lymph nodes and bone marrow. Patients may be asymptomatic or may present with a mass and symptoms related to compression of surrounding organs.

The site of involvement in gastrointestinal tract includes stomach, ileum, colon, rectum and anus. Regardless of site, this tumor has an aggressive behavior and most often presents with a high stage of disease.

Images for this section:
**Fig. 1:** CECT study of neck showing an ill defined solid soft tissue mass lesion seen eroding the nasal septum. Bilateral enlarged cervical lymph nodes with no calcification or cystic degeneration. A well defined polypoidal solid lesion seen at the posterior aspect of the trachea. Pathological diagnosis: ROSI-DORFMAN

**3 year old male patient presented by bony exophthalmus**

**Fig. 2:** CECT shows enlarged amalgamated mediastinal lymph nodes, bilateral enlarged kidneys showing hypodense parenchyma with loss of cortico-medulalry differentiation. Pathological DX. Erdheim-Chester disease
3 year old male patient presented by bony exophthalmus

Fig. 3: CECT of facial region shows diffuse lytic bony lesions of the skull base. Diffuse enlargement of the extra-ocular muscles with uniform hypodesne infiltration are noted. Pathological DX: Erdheim-Chester disease
Fig. 4: MRI of brain of brain shows : Diffuse enlargement of the extra-ocular muscles with uniformly enhanced infiltration are noted. The temporalis muscle also affected. Enhanced thickened tenterium and choroid plexus also noted Pathological DX. Erdheim-Chester disease
Fig. 5: Follow up after 1 month, Progression of the orbital and temporalis muscle and renal affection
**Fig. 6:** CEMRI of brain shows: multiple bilateral intraxial patchy areas of altered signal being hyperintense on T2WI and isointense on T1WI, peripheral hyper intense rim is noted on T1. They show heterogenous dotty enhancement on post contrast series and restricted diffusion in DWI. Final diagnosis is: Hemophagocytic lymphohistiocytosis (HLH)
Follow up 2 weeks later, patient presented with disturbed concious level.

**Fig. 7:** Follow up 2 weeks later, patient presented with disturbed concious level. Marked progression of the lesions with newly developed basal ganglia lesions.
**Fig. 8:** CEMRI shows right cerebellar, bilateral temporal, basal ganglia and deep white matter altered signal being hyper intense on T2WI and isointense on T1WI, peripheral hyper intense rim is noted on T1. They shows heterogonous dotty enhancement on post contrast series. Final diagnosis is: Hemophagocytic lymphohistiocytosis (HLH)
Conclusion

Although uncommon, awareness of the radiological presentation of the non Langerhans histolytic syndromes is utmost important as misdiagnosis of these diseases cause delay or mismanagement of such patients.

Personal information

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References


