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Pathology

LANGERHANS CELL HISTIOCYTOSIS: MORPHOLOGY AND IMMUNOHISTOCHEMISTRY STILL REMAIN THE IMPORTANT KEYS FOR DIAGNOSIS

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ABSTRACT Langerhans cell histiocytosis (LCH) is a rare clonal proliferation disorder of cells with phenotype of activated Langerhans cells. It encompasses a spectrum of diseases characterized by the proliferation and infiltration of organs by pathological Langerhans cells.It may have a variable clinical course with remissions and relapses. It occurs mostly in children and young adults and involves one or more body systems such as bone, hypothalmus, posterior pitutary gland, lymph nodes, liver or various soft tissues. It is twice as frequent in males as compared to females, and can occur in all the ages. We conducted a retrospective study, in which all the diagnosed cases of LCH, from November 2016 to October 2017 were selected. Clinical details, Hematoxylin and eosin (H & E) stained and immunohistochemistry (IHC) slides were retrieved from the records.

KEYWORDS : Langerhans cell histiocytosis, Hematoxylin and eosin (H & E) and Immunohistochemistry (IHC)

Introduction

Langerhans cell histiocytosis is a spectrum of clonal proliferation of special type of immature dendritic cell known as Langerhans cell. It is a rare disease and the incidence ranges from 0.5 to 2 per lakh population in children and 0.1 per lakh population in adults. [1] It was previously known as Histiocytosis X. It is named as LCH as it resembles the normal dendritic cells found in epidermis and it was first noted by Langerhans. Males are more frequently affected as compared to females, with male to female ratio being 2:1. It mainly involves children and young adults, but can occur in any age group even in elderly persons. The manifestations of this disease is very diverse, it may range from self-limiting reactive process to a disseminated and aggressive disease. LCH may involve single system or may present as multisystem disease with unifocal or multifocal involvement. Unifocal disease is usually present in older children or adults whereas young children often suffer from multifocal disease. In adult patients with single organ disease, pulmonary LCH is most common followed by osseous LCH and cutaneous LCH. Unifocal disease has excellent prognosis, whereas acute disseminated form of disease has worst prognosis. [2] The etiology and pathogenesis of LCH is not yet clear whether it is a clonal disorder, cytokine mediated cellular proliferation of Langerhans cells or a reactive process following viral infection. [3] The reactive nature of LCH is supported by spontaneous remission, extensive elaboration of cytokines (i.e cytokine storm) and good survival rate of patients without any organ dysfunction. Human herpes virus 6(HHV-6) contributes to the initiation and further progress of pre-existing lesions. The neoplastic nature of the disease is marked by clonal proliferation and its association with BRAF gene. [4] Familial clustering has also been reported for LCH with high degree of incidence among monozygotic twins.

The most common site involved is bone followed by skin, reticuloendothelial system (RES), bone marrow, hypothalamus, posterior pituitary gland and liver. Lymph node involvement occurs as the component of systemic disease or it may even occur as the exclusive manifestation of the disease. It may resolve spontaneously or it may progress especially in multifocal and multisystem involvement and can even compromise the functioning of vital organs and can even prove fatal. [5]The mortality of the disease ranges from 10-20%. [6] There have been few Indian studies about the pathological aspects of LCH. We present our study to discuss the clinicopathological spectrum of Langerhans cell histiocytosis with an emphasis on characteristic histopathological and immunohistochemical features along with review of literature.

Methods: A retrospective study was carried in which all the diagnosed cases of LCH from November 2016 to October 2017 were selected. We identified 10 cases of LCH using the data obtained from the medical records. The type of data collected included clinical details, radiological findings and laboratory investigations. The H&E (hematoxylin and eosin) and IHC (immunohistochemistry) stained slides were retrieved and reviewed. The diagnosis of LCH was made on the basis of histopathological findings and it was further supported by IHC stains which included CD1a, S100 and CD68 in all the reported cases.

Results

Study population:

In our study a total of ten cases were studied out of which seven were males and three were females, (M: F= 2:1). Age of the patients ranged from 1-32 years and the median age was 3 years.

Clinical and radiological details:

Majority of the cases presented with skeletal system involvement (n = 7) followed by lymph node (n=2) and a single case of thyroid involvement was seen in adult male presenting with isolated thyroid swelling. Clinical details were available for nine cases (n=9) and out of these the majority of the patients were 1 to 5 years of age and all of these had single system involvement. The commonest bone involved was skull followed by vertebrae. All the cases with skeletal involvement had lytic lesions on X-ray.

Histopathology:

Biopsy of these patients demonstrates aggregates of Langerhans cells admixed with lymphocytes, eosinophils along with few plasma cells and neutrophils. Langerhans cells are identified as large cells with oval nucleus and a linear groove (coffee bean appearance), delicately clumped chromatin with inconspicuous nucleoli and moderate to abundant pale cytoplasm. (Figure 1,2). Few binucleated and multinucleated cells were also seen. Mitotic figures were present.

Immunohistochemistry:

Immunohistochemistry was performed in all cases (n=10). All the cases were strongly positive for CD1a, S100 and variable positive for CD68 (Figure 3,4,5)

Discussion

Histiocytosis refer to the group of diseases which are characterized by infiltration and accumulation of variable numbers of monocytes, macrophages, and dendritic cells in the affected tissues .Langerhans cells are the antigen processing cells which are derived from bone marrow. The pathological proliferation of Langerhans cells is known as LCH.

LCH represents a type of histiocytosis and it is a rare proliferative disease with unknown etiology.In 1953,after observing the cytoplasmic bodies, known as X bodies, within the histiocytes of the patients suffering from Eosinophilic granuloma, Hand-Schüller-

Christian disease as well as Abt-Letterer-Siwe disease; Lichtenstein grouped these diseases under a common term known as "Histiocytosis X".[7] In 1973, Nezelof discovered that these histiocytes were nothing but the langerhans cells and hence it was renamed as "Langerhans cell Histiocytosis".[8] In 1987, Working Group of Histiocyte Society published first classification of histiocytosis. According to this it was classified into 3 major classes; Langerhans cell histiocytosis was placed in class I, class II included non-langerhans cell histiocytosis and class III consisted of malignant histiocytic disorders".[9] In the recent studies LCH is divided into the following clinical categories according to the extent and localization of the disease; Single system LCH (SS-LCH) and Multi system LCH (MS-LCH). This new classification of the disease into the single or multi system is important as it helps in determining the mode of treatment, prognosis and survival of patients.[10,11] SS-LCH involves one organ or one system, however it may be unifocal or multifocal. MS-LCH is a disease which involved two or more organs or systems with or without the involvement of 'Risk organs'. The risk organs include lung, liver, spleen and bone marrow. Risk organs and their involvement were defined according to modified Lahey criteria.[12](Table 1)

Besides the normal symptoms such as fever, weight loss and fatigue, the clinical features of LCH depend on the severity of the condition and the site or organ of involvement. Clinical course of LCH is highly variable and it may range from a self-healing solitary lesion to a life threatening disease. Extensive forms of LCH may affect multiple organs. The most common organ involved is bone followed by skin. Rarely other organs like lung, liver, spleen, lymph node, soft tissue and bone marrow may be involved. In our study majority of the cases (7 out of 10) presented with skeletal lesion and the most common bone was involved was skull followed by vertebrae. Similarly in the studies conducted by M.Arico et al, Howarth et al and Campos MK et al majority of the cases were from bone i.e 38.8%, 60 % and 69.7% respectively.[13,14,15] In our study males were affected more as compared to females and the predominant age group were children from 1 to 5 years of age, this is in concordance with the literature and other studies by Campos et al, Douglas et al and Christopher et al.[15,4]

The definitive diagnosis of LCH depends on the histopathological findings which includes the presence of characteristics large langerhans cells with folded/ coffee bean shaped nucleus, moderate amount of cytoplasm, delicate chromatin and small inconspicuous nucleoli. These cells are admixed with inflammatory infiltrate consisting of mono or multinucleated histiocytes, eosinophils and neutrophils. LCH of bone consists of variable number of non-neoplastic osteoclasts. Pathologic Langerhans cells are characterized by the presence of antigenic surface markers which react with specific monoclonal antibodies. These cells show strong positivity for CD 68, S100, HLA-DR, CD1a surface antigen, D mannosidase, Peanut agglutinin, surface ATPase. Similarly in our study also the diagnosis of LCH was based on the histopathological findings which were further supported by immunohistochemical stains. All the cases in the present study showed strong positivity for CD1a, S100 and variable positivity for CD68. In typical cases the diagnosis is confirmed by electron microscopy. It shows that pathological Langerhans's cell share many features with histiocytes. They have irregular cell membrane and abundant cytoplasm. They lack interdigitating cell processes or cell junctions. In few of the cases lysosomes are present in the cytoplasm of the cell. The presence of Birbeck's granules is pathognomic of LCH. These are racquet-shaped structures 200 to 400 nm long and 33 nm wide. They have a zipper-like appearance, with a central striated line and a double outer sheath. Birbeck granules are usually found withinthe cytoplasm of the cell but can also be identified within the nucleus. According to some of the studies the role of immunohistochemistry and electron microscopy is controversial in diagnosis of LCH. Many authors believe that definitive diagnosis of LCH can be made by examination of hematoxylin and eosin stained slides in correlation with radiological and clinical data.[16,17] In our study also the diagnosis was made on the basis of H&E slides, which was supported by IHC stains. Electron microscopy was not done in the cases included in our study.

According to the Histiocyte Society International protocol LCH III trail patients are grouped into 3 different groups depending upon the system as well as risk organ involvement.[18] Group I included multisystem risk organ involvement, Group II includes multisystem without risk organ involvement and group III includes single system multifocal disease or localized disease with special site involvement (like orbit, temporal bone or mastoid) with intracranial soft tissue extension. Based on these categories, the patients in the present study were categorized under group III.

The treatment of LCH depends on the age of the patient, site of involvement, size of the lesion. Treatment is usually done only in case of symptomatic patients whereas asymptomatic patients are kept under observation as some of the lesions resolve spontaneously. According to Histiocyte Society International protocol LCH III trail chemotherapeutic agents for multisystem involvement include Vinblastin, Prednisone, 6-Mercaptopurine and Methotrexate. Late complications and recurrence is common in LCH, so lifelong follow up is necessary in these cases. Complications may even occur in patients with single organ involvement. Few of the common complications include: Diabetes insipidus, Hypothalamic-pituitary dysfunction, cerebellar dysfunction, cognitive dysfunction, hearing loss. Patients who receive therapy for LCH are at increased risk of developing Pneumocystis Jiroveci infection Better outcome of the disease is observed in older patients, patients with single system disease and worse outcome is observed in multisystem disease, organ dysfunction, isolated pulmonary disease and in younger patients. The prognosis of the disease is unpredictable, although the universally accepted prognostic factors include age <2 years and involvement of organs like lung, liver, spleen and bone marrow. Disease involving temporal bone has good long term prognosis. The average 10-year survival in case of single organ disease is approximately 100% and for multiorgan disease it is as around 77%.[19] However, the treatment and prognosis mainly depend on the extent (staging) of the disease (Table 2) rather than the microscopic features or the pattern of DNA ploidy.[12,14,20]

Conclusion:

Establishing a diagnosis of LHC is quite challenging from the perspective of a pathologist as well as clinician due to its variable manifestation ranging from a spontaneously regressing solitary lesion of bone to a multisystem, life threatening disorder. The definitive diagnosis is based on histological examination and needs to be confirmed by immunohistochemistry. The relative rarity of LCH has meant that optimal therapy is still unknown because no prospective controlled study has been performed. The treatment and outcome data have been based largely on small case series and single case reports. So LCH should be included in differential diagnosis of localized and disseminated disease of bone, skin, mucosa, lungs, endocrine as well as CNS, regardless of the age of the patients.

Table 1: Lahey's criteria of Risk organs involvement

Parameter	Features
Hematopoietic	Anemia and/or leukopenia and/or thrombocytopenia
Liver	Enlargement > 3 cm below the costal margin, dysfunction, or both
Spleen	Enlargement > 2 cm below the costal margin
Lung	Typical changes via high-resolution computed tomography, histopathological diagnosis, or both

Table 2: Pathologic staging of Langerhans cell histiocytosis (Histiocyte Society)

Stage	Features
A	Bone only or bone with involvement of first level lymph nodes in drainage field (osteolymphatic disease) and/or contiguous soft tissue involvement.
	A1 Monostotic
	A2 Monostotic with osteolymphatic disease
	A3 Monostotic with contiguous soft tissue involvement
	A4 Polyostotic
	A5 Polyostotic with osteolymphatic disease
B	Skin and/or other squamous mucous membranes only or with involvement of related superficial lymph nodes
	B1 Nodular disease; neonatal period without nodal disease
	B2 Nodular disease; neonatal period with nodal disease
	B3 Multiple nodules or diffuse maculopapular disease without nodal disease
	B4 Multiple nodules or diffuse maculopapular disease with nodal disease
C	Soft tissue and viscera only excluding above and multisystem disease. Specify tissue involved, e.g., lung, lymph node, brain
D.	Multisystem disease with any combination of the above. Specify each organ/tissue involved, e.g., skin, bone marrow, bone

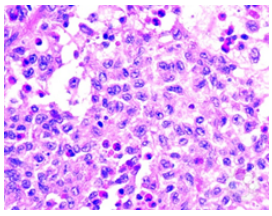

Figure 1: H&E (400 x): Langerhans cells admixed with eosinophils and plasma cells

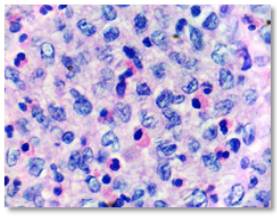

Figure 2: H&E (1000 x): Large cells with oval nucleus and linear groove (coffee bean shaped), delicate chromatin and moderate amount of cytoplasm. Few plasma cells and eosinophils are also seen.

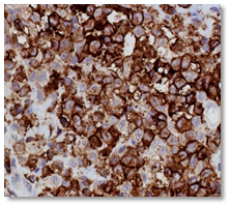

Figure 3: CD1a strong positivity

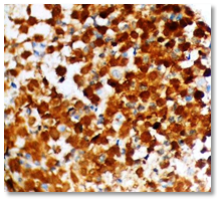

Figure 4: S100 strong positivity

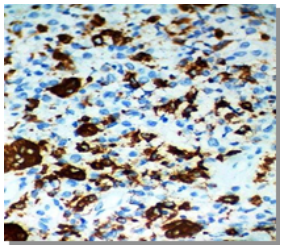

Figure 5: CD 68 variable positivity

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