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Original Research Paper

Orthopaedics

RARE HISTIOCYTIC DISORDERS OF BONE WITH UNUSUAL CLINICAL PRESENTATION

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ABSTRACT The histiocytosis are a diverse groups of disordered characterised by accumulation and proliferation of cells derived from the monophagocytic system called histiocytes, which are immune cells found in various tissues throughout the body with diverse function like housekeeping – via phagocytosis, activating immune system via antigen presentation to 'T' cells and promoting peripheral tolerance via proliferation of regulatory T cells. The bone and bone marrow are preferential sites for both reactive and neoplastic histiocytic proliferation. In tis study we present 3 rare histiocytic disorders affecting the bone with unusual clinical presentation with emphasis on treatment protocols. Upto our knowledge, Rosai Dorfman's disease affecting the soft tissue of back has not been reported and Erdheim Chester presenting with asymmetric bone lesions and Langhan's cell histiocytes affecting the scapula is extremely rare.

KEYWORDS :

INTRODUCTION:

The histiocytosis are a diverse group of disorders characterised by the accumulation and proliferation of cells derived from monophagocyte system called histiocytes, which are immune cells found in various tissue. The bone and the bone marrow are preferential sites for both reactive and neoplastic histiocytic proliferations. Non neoplastic histiocytes accumulating in the bone marrow are associated with increased cellular turn over (eg – in myeloproliferative orders), systemic infections, storage disorders and T cell proliferations in haemophagocytic lymphohistiocytosis (HLH). Neoplastic proliferations include Langerhan's cell histiocytosis, Erdheim Chester Disease and extranodal Rosai Dorfman's disease apart from other disorders specified by WHO.

First classification of the histiocytosis, established by the Working Group of the Histiocytic Society (HS) in 1987, classified them as (1) Langerhan's cell related (2) Non Langerhan's cell related & (3) Malignant. (1) The original classification was updated in 1997 by a joint effort of the Histiocytic Society and the WHO Committee in Histiocytic / Reticulum cell proliferation to "disorders of varied biological behavior and malignant" further classified as dendritic cell related macrophage related as monocyte related. (2) [Table 1.1]

Table 1.1

1997 Contemporary classification of histiocytic disorders: by WHO Committee on Histiocytic/ Reticulum Cell Proliferations

Disorders of varied biologic behavior
Dendritic cell related
Langerhans cell histiocytosis
Secondary dendritic cell processes
Juvenile xanthogranuloma and related disorders
Solitary histiocytomas of various dendritic cell phenotypes
Macrophage related
Hemophagocytic syndromes
Primary hemophagocytic lymphohistiocytosis (familial and sporadic; commonly elicited by viral infections)
Secondary hemophagocytic syndromes
Infection associated
Malignancy associated
Others
Rosai-Dorfman disease (sinus histiocytosis with massive lymphadenopathy)
Solitary histiocytoma with macrophage phenotype
Malignant disorders
Monocyte related
Leukemias (FAB and revised FAB classifications)
Monocytic leukemia M5A and B
Acute myelomonocytic leukemia M4
Chronic myelomonocytic leukemia
Extramedullary monocytic tumor or sarcoma (monocytic counterpart of granulocytic sarcoma)
Dendritic cell-related histiocytic sarcoma (localized or disseminated)
Specify phenotype, follicular dendritic cell, interdigitating dendritic cell, etc.
Macrophage-related histiocytic sarcoma (localized or disseminated)

Since then, there has been break through regarding molecular mechanism in pathogenesis of many histiocytosis – especially pertaining to LCH & ECD. [Table 1.2]

(RAS/MAPK Pathway) which made way to the new classification by Emile et al in 2016. (3)[Table 1.3]

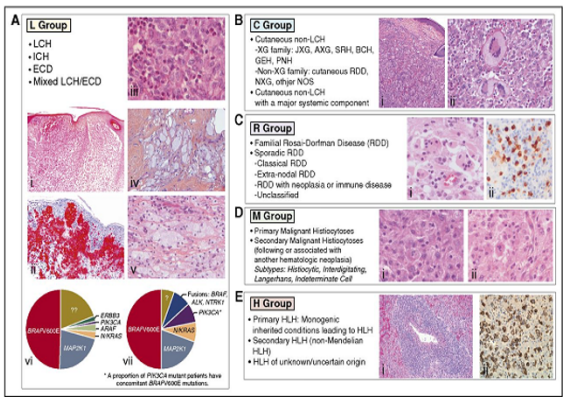
Table 1.2

2016 Revised classification of histiocytoses and neoplasms of the macrophage-dendritic cell lineages based on clinical, radiographic, pathological, phenotypic, genetic, and/or molecular features

L group histiocytoses
Langerhans cell histiocytosis
Indeterminate dendritic cell tumor
Erdheim-Chester disease
Mixed Langerhans cell histiocytosis/Erdheim-Chester disease
C group: non-Langerhans cell histiocytosis of skin and mucosa
Cutaneous non-Langerhans cell histiocytosis
Xanthogranuloma family:
Juvenile xanthogranuloma granuloma
Adult xanthogranuloma granuloma
Solitary reticulohistiocytoma
Benign cephalic histiocytosis
Generalized eruptive histiocytosis
Progressive nodular histiocytosis
Non-xanthogranuloma
Cutaneous Rosai-Dorfman disease
Necrobiotic xanthogranuloma
Cutaneous histiocytosis not otherwise specified
Cutaneous non-Langerhans cell histiocytosis with a major systemic component
Xanthogranuloma family: xanthoma disseminatum
Non-xanthogranuloma family: multicentric reticulohistiocytosis
R group: Rosai-Dorfman disease and miscellaneous noncutaneous, non-Langerhans cell histiocytoses
Familial Rosai-Dorfman disease
Sporadic Rosai-Dorfman disease
Classical (nodal) Rosai-Dorfman disease
Extranodal Rosai-Dorfman disease

[Table 1.3]

Revised classification of histiocytoses and neoplasms of the macrophage-dendritic cell lineages



Upto our knowledge, Rosai Dorfman's disease affecting the soft tissue of the back has not been reported and Erdheim Chester presenting with asymmetric bone lesion and Langerhan cell histiocytosis affecting the scapula in extremely rare. Identifying genetic mutations has leads to targeted therapies to many of these lesions. It is essential to design clinical trials to determine which patient populations might benefit from these targeted therapies to abnormal genes.

METHODS:

This study is retrospective study of rare histiocytic disorders of bone over a period of 4 years from January 2016 to Jan 2020. As this is a case series, we chose to describe cases received during this period at Karuna Medical College, Palakkad and HISTOLAB, Coimbatore.

Case Reports:

19 years old female presented with a mass in the back chest of a short duration with no associated fever or loss of weight. MRI showed no bony involvement with skin and underling muscle free of tumour. Clinical diagnosis was soft tissue sarcoma and incisional biopsy was done and sent for HPE which showed polymorphous inflammatory infiltrate with histiocytes and emperipolesis with increase in plasma cells. A differential diagnosis of Rosai Dorfman's disease / Plasma cell granuloma was made and tissue was taken up for IHC and diagnosis of Rosai Dorfman's disease was made(FIG 1 A,B,C,D&E).

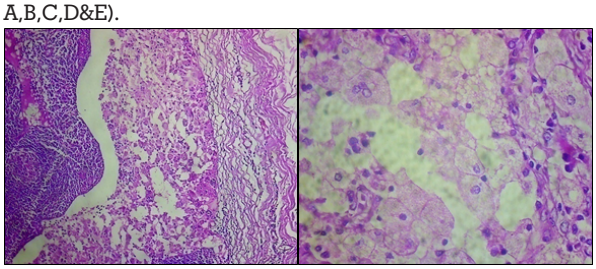


FIG 1A (10x)&B (40x) (Dilated spaces with macrophages)

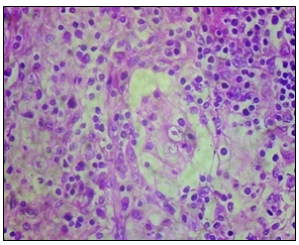


FIG 1C (40x) (Macrophages with emperipolesis)

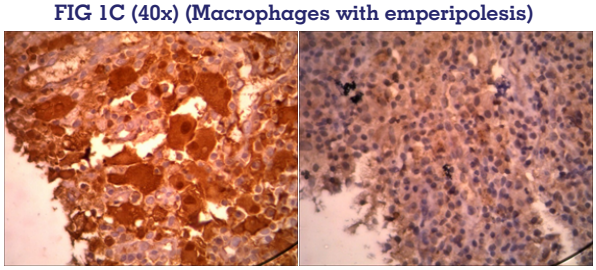


FIG 1D (40x) (S100 positive) FIG1 E (40x)(CD1a negative)

(2) 62 years male presented to orthopedic OP with lytic lesions in the right iliac crest and right femur. No other significant bone lesions was seen and with clinical diagnosis of metastasis / plasma cell disorder, biopsy material was sent from iliac bone and femur. Biopsy material showed sclerotic bone and intervening spaces with fibrosis and dense infiltrates of foamy histiocytes, lymphocytes, plasma cells and occasional touton giant cells along with marrow elements. IHC was done and foamy cells were positive for CD 68 (PGM – 1) and negative for S – 100 and CD 1a and a diagnosis of Erdheim Chester disease was made.(FIG 2 A,B ,C &D)

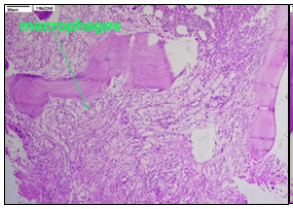


FIG 2A (scanner)

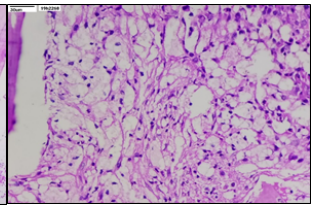
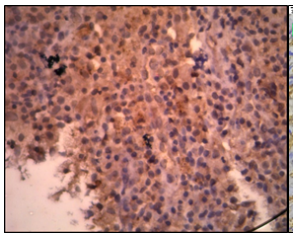


FIG 2B (10x)



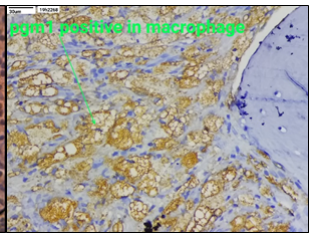


FIG 2C (40x) (CD1a negative) FIG 2D (10x)(Pgm1 positive)

(3) 35 years old male presented to dental OP with loosening of left lower premolars with pain along the jawbone. X-Ray revealed a lytic lesion in the underlying bone. Biopsy material showed inflammatory cells, foamy histiocytes and eosinophils which on IHC confirmed Langerhan's cell histiocytosis. In view of polyostotic / multisystemic nature of the lesion, the patient was taken up for extensive work up and was found to have multiple osteolytic lesions in skull, scapula and iliac bone and a diagnosis of polyostotic LCH was made.

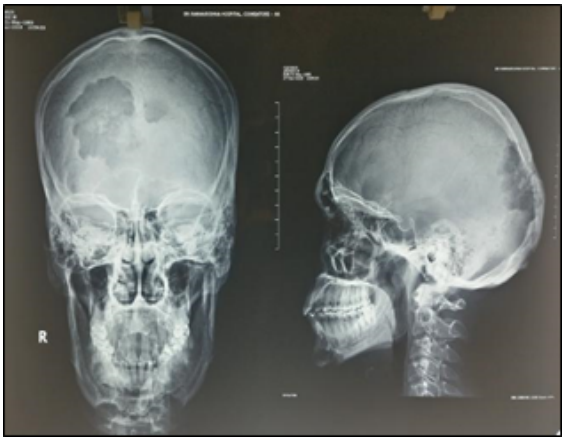


FIG 3A (multiple osteolytic lesions in skull)

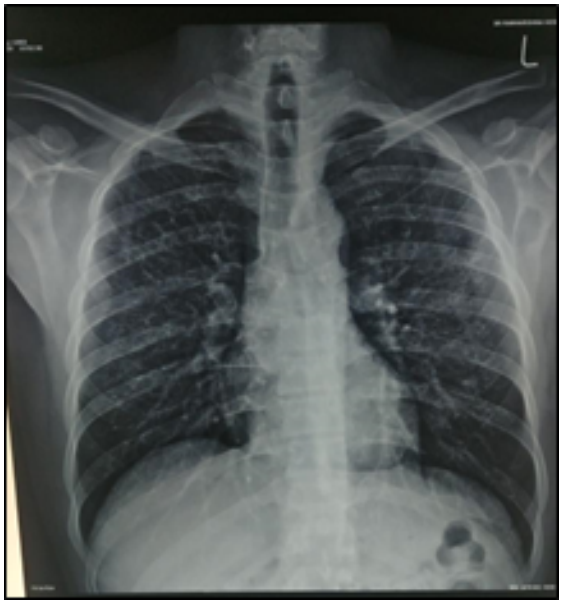
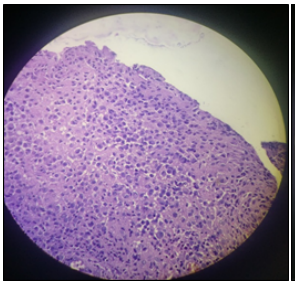


FIG 3(multiple osteolytic lesions in scapula)



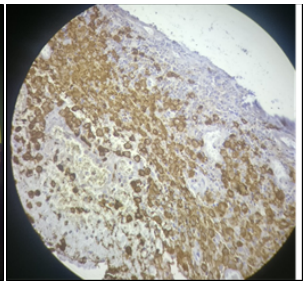


FIG 3C (10x) FIG3D (10x) (CD1a positive)

DISCUSSION:

WHO classifies histiocytic disorders as [Table 2]:

Table 2

1997 Contemporary classification of histiocytic disorders: by WHO Committee on Histiocytic/Reticulum Cell Proliferations

Disorders of varied biologic behavior
Dendritic cell related
Langerhans cell histiocytosis
Secondary dendritic cell processes
Juvenile xanthogranuloma and related disorders
Solitary histiocytomas of various dendritic cell phenotypes
Macrophage related
Hemophagocytic syndromes
Primary hemophagocytic lymphohistiocytosis (familial and sporadic; commonly elicited by viral infections)
Secondary hemophagocytic syndromes
Infection associated
Malignancy associated
Others
Rosai-Dorfman disease (sinus histiocytosis with massive lymphadenopathy)
Solitary histiocytoma with macrophage phenotype
Malignant disorders
Monocyte related
Leukemias (FAB and revised FAB classifications)
Monocytic leukemia M5A and B
Acute myelomonocytic leukemia M4
Chronic myelomonocytic leukemia
Extramedullary monocytic tumor or sarcoma (monocytic counterpart of granulocytic sarcoma)
Dendritic cell-related histiocytic sarcoma (localized or disseminated)
Specify phenotype, follicular dendritic cell, interdigitating dendritic cell, etc.
Macrophage-related histiocytic sarcoma (localized or disseminated)

Rosai Dorfman Disease (Extranodal)

Rosai Dorfman Disease (Massive sinus histiocytosis with lymphadenopathy / lymphadenitis with massive haemophagocytic sinus histiocytosis of Lennert) is a rare, non neoplastic, Class II histiocytic disorder, which was described first in 1965 by Destombes in 1966 by Azonry and Reed and in 1969, it was described as a clinicopathologic entity by Rosai and Dorfman (4, 5). RDD usually affects young people with

slight male predominance with increased incidence in African descents. (Our patient is a young female).

RDD is classified as Nodal or Systemic with latter further classified as cutaneous, respiratory and osseous (6). Nodal involvement is usually cervical followed by inguinal, axillary and mediastinal and patients may have fever, leukocytosis, elevated ESR and polyclonal hypergamma globulinemia. Extranodal presentation has been described with most common sites being skin and nasal sinuses. Soft tissues with bone involvement is very rare. Longest study of RDD was conducted by Foucar, Rosai and Dorfman in 1990, which included 423 cases (7, 8, 9) of which 43% had extranodal disease with soft tissue involvement with only 3% having soft tissue involvement without lymphnode involvement (10, 11, 12). This study showed a male predominance with younger age involvement with anatomic location being lower extremity followed by upper extremities and head and neck. (13, 14) THERE IS NO CASE REPORT OF RDD IN BACK OF CHEST, UPTO OUR KNOWLEDGE AND SEARCH.

Etiology of RDD is not known though viral. Etiology is thought to play a role probably by dysregulation of the immune system. Viruses like Human Herpes Virus 6, Epstein Barr Virus and Rubella Virus were detected by In Situ hybridisation in few cases (15, 16). Yoon and colleagues theorized that (17, 18,) initiation of monocytes colony stimulating factor mediated histo proliferation in RDD is abnormal response to infections. However pathogenesis is still poorly understood and may be multifactorial as some patients present with auto Immune disorders. It is rarely seen in identical twins or family members with a rare genetic syndrome called Faisalabad histiocytosis, characterised by sensorineural deafness, short stature and joint contractures associated with lymphadenopathy.

Prognosis is fairly good with spontaneous regression and surgical resection if there is no regression. Symptomatic patients are treated with steroids, alkylating agents and IFN. Role of radiotherapy and chemotherapy is poorly understood. Rarely death has been reported. (19)

When presenting as a soft tissue mas with bone involvement, it is very difficult to differentiate from soft tissue sarcoma as it can appear malignant on PET scan, due to its hypermetabolic state. Histopathological examination on wide excision material with Immunohistochemistry is essential for definite diagnosis.

RDD of soft tissue in the back of chest has not been reported upto our knowledge and search conduted and patient is doing well on follow up for three years.

Erdheim Chester Disease

Erdheim Chester Disease also called polyostotic sclerosing histiocytosis is extremely rare disorder with only 500 cases being reported in literature. It is a non-familial, neoplastic, xanthogranulomatous non Langerhan's cell histiocytosis, which was first described in 1930 by William Chester and Jakob Erdheim. It was previously thought to be inflammatory, but now recognised as a neoplasm by WHO and classified under 'L' group of histiocytic disorders.

ECD is a systemic disease with frequent involvement of bones with other sites involved being retroperitoneum (hairy kidney, coated aorta), orbit (leading to exophthalmos), lymphnodes (diabetic insipidus), lung and cutaneous (xanthelsma). Rarely thyroid and lymphnodes can be involved. (20)

Skeletal involvement is usually bilateral and symmetrical with cortical osteosclerosis of diaphysis and metaphysis of long bones, usually femur and tibia. Our patient had lytic lesions in the iliac bone and femur, but lesions were not symmetrical and hence an unusual presentation. The patients can also have general symptoms like fever, malaise, weight loss and night sweats.

In retrospective study of 59 cases of ECD in 1996, Veyssier - Belot et al (21) reported that 5 -8% of patients in this study had lytic lesions in flat bones and long bones. In 2002, Oweisity et al reported that 30% of ECD can exhibit osteolytic lesions (22).

Histological appearance of bland appearing histiocytes with foamy cytoplasm and fibrosis with Touton's giant cells and lymphohistiocytic infiltrate offer a differential diagnosis of LCH, ECD, RDD, reactive histiocytosis and Juvenile xanthogranuloma. IHC positivity of CD 68 and negativity of CD 1a and S 100 confirmed the diagnosis of ECD. AS ECD may be associated with other histiocytic neoplasms like LCH and RDD, adequate biopsy material is essential. Molecular Genetics plays a very important role in 90% of the patients having MAPK mutation and BRAF V600E mutation. (23)

Diagnostic criteria of ECD as per orphanet Journal of Rare disease is as follows: [Table 3]

Table 3

Radiology	Radiography	Bilateral symmetric diametaphyseal osteosclerosis of long bones
	^{99m}Tc Bone Scintigraphy	Symmetric and abnormally strong 99mTc labeling of the distal ends of the long bones
Histology	Microscopic Environment	Non Langerhans histiocytes with foamy or eosinophillic cytoplasm, polymorphic granulomae and fibrosis, xanthogranulomatosis, proliferating fibroblasts, lymphocytic aggregates, Touton giant cells
	Histiocyte Immunostaining	**CD68(+), CD1a(–), S-100(negative/low)** *
	Histiocyte Ultrastructure	Lack of Birbeck granules

Etiology of ECD is attributed to mutation of mitogen activated kinase (MAPK) pathway leading to tissue acumination of histiocytosis with increased expression of cytokines. (24)

Seven of ECD patients demonstrate an unique inflammatory cytokine signature with elevated levels of interferons (α I FN), interleukin 12, Monocyte chemotactic protein 1 and reduced IL 4 – which is suggestive of Th – 1 mediated systemic immune response. (25)

Increased prevalence of myeloid neoplasms among ECD patients hints that this may be clonally related – suggestive of a clonal haematopoeitic precursor.

Oncomap, which tested 983 specific alleles in 115 cancer related genes analysed the causes of LCH and ECD, discovered that mutation of BRAF C600 E was seen in over 50% of ECD patients, suggesting a neoplastic etiology of ECD.

Treatment of ECD is Immunodulation and Zelboraf (Vemurafenib), the latter indicated to treat patients whose tumour cells have specific genetic mutation BRAF V600. The other treatment options include surgical debulking, high dose corticosteroids, cyclosporin, alpha interferon, chemotherapy and radiotherapy. Prognosis is not very good with survival rate below 50% at 3 years from diagnosis (26) and now with interferon therapy and Nemurafenib, long term survival is more promising. (27)

The diagnosis of ECD can be difficult, owing to its rarity and protean manifestations and histologic findings with IHC is mandatory for identification of ECD.

Langerhan Cell Histiocytosis:

Langerhan cell histiocytosis (LCH) was first described by Paul Langerhan's in 1868, (28) but described as epidermal dendritic cells and in 1950, Lichenstein noted that Litterer Siwe disease (multifocal multisystemic disease), Hand Schuller Christian disease (multifocal unisystem disease), eosinophilic granuloma (unifocal) and Hashimoto's – Pritzker disease (congenital, soft healing reticulohistiocytosis)

described earlier demonstrated a common histologic appearance and hypothesis with common cell origin (29) and called it histiocytosis x where x meant to represent the unknown cell of origin. Until Nezelof's (30) discovery of Birbeck's granules in 1973, that is associated with Langerin (CD 207), LCH was called histiocytosis x. However Risdall coined the name Langerhans cell histiocytosis, which was endorsed in 1987 by the histiocytic society and in 'L' group by Emily et al in 2016. (31)

Bone involvement manifests usually as an asymptomatic solitary osteolytic lesion or multifocal with or without multiorgan involvement, though the former is more common. Our case is polyostotic without multiorgan involvement which is rare and scapular involvement as in our case is extremely rare. Also this picture is usually seen in patients less than 15 years old, but our patient is 35 years old.

Scapula is the site of 3% of bone tumours and LCH is least common with only 4 cases reported in literature.

The Pathogenesis is varied too. Initial hypothesis suggests that LCH might be an inflammatory disorder. This notion was supported by documented cases of spontaneous remission even in advance and aggressive diseases like Letterer Siwe disease (32). Reports of association with Epstein Barr virus, cytomegalo virus, HHV – 6 and Merkel Cell Polyoma virus (33) is not confirmed and auto Immune etiology was suspected too due to high level of cytokines like GM – CSF, M – CSF, FLT – 3L and IL – 17A, (34). In 1994, 2 reports described the use of human androgen receptor gene based chromosomal inactivation assay (HUMARA assays) to demonstrate that the abnormal histiocytes in LCH are clonal, thus confirming the neoplastic etiology. (35)

Identifying recurrent genetic or epigenetic abnormalities in LCH has been far more challenging as assays for single nucleotide variants (SNVS), copy number variations (CNVS), translocations or epigenetic modifiers of DNA require abundant amount of tissue which was not available for study.

A customised version called Oncomap (36) which testes 983 specific alleles in 115 cancer related genes, analysed 61 archived LCH cases and demonstrated presence of ongogenic mutation encoding the BRAF V600E mutation in 57% of samples (37) confirming the neoplastic nature of LCH.

Treatment of LCH is based on New clinical score of LCH and is very useful to assess the prognosis and treatment protocols. (38)[Table 4]

Table 4

New clinical scores of Langerhans cell histiocytosis at diagnosis.

Variable	Score
Fever (38.5°C)	1
Skin rash	1
GI involvement	1
Endocrine involvement	1
CNS-risk lesion involvement	1
Lymphadenopathy	1
Bone involvement	
Single	1
Multifocal	2
Hematopoietic involvement (with or without bone marrow involvement[a])	
Anemia: hemoglobin <10 g/dL, infants <9 g/dL (exclusion of iron deficiency)	1
Leukocytopenia: leukocytes $<4.0\times10^9$/L	1
Thrombocytopenia: platelets $<100\times10^9$/L	1
Spleen involvement	
Enlargement ≥2 cm below costal margin	3
Liver involvement	
Enlargement >3 cm below costal margin and/or liver dysfunction (hyperbilirubinemiam, hypoalbuminemia, transaminases, ascites, edema) and/or histopathologic diagnosis	3
Lung involvement	
Typical changes on high-resolution computed tomography and/or histopathologic diagnosis	3

[a]CD1a positivity.

In this study on LCH at Asan Medical Centre, Korea, Han Yang University Hospital, Korea and Department of Surgery, University of Pittsburg, USA, between March 1998 and February 2009 – 133 patients out of 159 were chosen and based on their clinical scoring, it was observed and treatment protocol was planned as below.[Table 5]

[Table 5 Therapeutic approach according to the new clinical scores.

	1-2 (N=101)	3-5 (N=21)	≥6 (N=11)
Wait and see, n (%)	6 (5.9%)	0 (0%)	0 (0%)
Local therapy, n (%)	39 (49.5%)	0 (0%)	0 (0%)
Systemic therapy, n (%)	56 (55.4%)	21 (100%)	11 (100%)

6 patients who were not treated and on follow up study had resolution of the lesions and 39 patients who had single bone involvement and who received local therapy as curettage were in the score 1 or 2. All other patients with score more than 3 were treated with systemic chemotherapy, whereas only 5% of patients with score 1 or 2 received chemotherapy.

When treatment response was analysed after 6 weeks, 93% pf patients with score 1 and 2 had better response and complete resolution to regression and none of the patients with score above 6 had complete resolution.[Table 6]

Table 6 Treatment response at 6 weeks according to the new clinical scores.

	1-2 (N=101)	3-5 (N=21)	≥6 (N=11)
Better			
Complete resolution	44 (43.6%)	8 (38.1%)	0 (0%)
Regression	50 (49.5%)	8 (38.1%)	3 (27.3%)
Intermediate			
Mixed	1 (0.9%)	0 (0%)	2 (18.2%)
Stable	2 (2.0%)	5 (23.8%)	2 (18.2%)
Worse	4 (4.0%)	0 (0%)	4 (36.3%)

Involvement of spleen, lung, liver or haematopoeitic system contributed to poor prognosis. In one large study of 101 children with LCH, the overall survival rate was 79% at 1 year, 74% at 3 years and 71% at 5 years. However in patients with liver or splenic involvement, the 1 year survival was 33% and 5 years survival was 25% only. (39)

This quantitative disease activity scoring can help in therapeutic disease management, especially in complex situations with multiple bone and organ involvement with treatment response classified as Better (complex resolution, regression) and worse with an intermediate zone (stable and mixed).

The most commonly used therapy consists of steroids and vinblastine with Etoposide useful in multiorgan involvement. Target therapy to mutated genes is not yet established.

Despite major advances in understanding LCH, it remains strange with its diverse symptoms, variable organ involvement and mysterious etiology and remains a challenge for clinicians.

CONCLUSION:

The histiocytic disorders of bone are group of disorders that have diverse symptoms, variable organ involvement, mysterious etiology, vague biological findings and genetic alterations. Though overall treatment varies from observations alone for spontaneous regression, bone curettage and grafting, low dose irradiation with targeted x-rays, corticosteroids, chemotherapy targeted therapies, new ideas are being tested to determine the cause and to understand why some patients respond better to treatment than others. It is essential to design clinical trials to determine the response of targeted therapies to abnormal genes and decision regarding treatment should be based on type, site and extent of disease, organs involved, biological findings, genetics of the disease, degree of risk involved and host of other factors. Despite major advances in understanding few of

them, it remains challenging for orthopaedicians as to how to manage these patients.

ABBREVIATIONS:

LCH – Langhern's cell histiocytosis
ECD – Erdheim Chester Disease
RDD – Rosai Dorfman's Disease

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