Original Article

Childhood Histiocytic Disorders — A wolf in Sheep's Clothing : Experience from a Cancer Institute in south India

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Background : Histiocytic disorders are uncommon entities which arise from the cells of the mononuclear phagocyte system. Most common amongst these are Langerhans Cell Histiocytosis (LCH) and Rosai Dorfman Disease (RDD).

Objective : To study the spectrum and the clinicopathological profile of histiocytic disorders in children at a tertiary cancer institute in south India.

Methods : This retrospective descriptive study included children aged ≤16 years diagnosed with a histiocytic disorder according to the recent World Health Organisation classification of Haematolymphoid and Paediatric tumours during a two- and half-year period from January, 2020 to July, 2022.

Results : This study included 23 children with a mean age of 6.7 years, comprising of 14 Boys and 9 Girls. We encountered 12 cases of LCH, six cases of RDD, single case each of Histiocytic sarcoma, Erdheim Chester disease (ECD) and Juvenile Xanthogranuloma (JXG) and two cases of unclassified histiocytic neoplasms. Four cases showed recurrence, with three of them showing ambiguous histomorphology on recurrence. Our cohort had two children who were first degree relatives with different histiocytic disorder/neoplasms.

Discussion : LCH was encountered mostly in bone with all our cases expressing CD1a and S100 as in other studies. Histiocytic sarcoma is an aggressive neoplasm which showed recurrence in our study. In concordance with the literature, the case of ECD presented with bilateral bone lesions.

Conclusion : Histiocytic disorders/ neoplasms can rarely have familial predisposition and present with ambiguous histomorphology when they recur. These recurrent tumours carry poor prognosis.

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Key words **: Histiocytic disorders/ neoplasms, Langerhans cell histiocytosis, Rosai Dorfman Disease, Histiocytic sarcoma, Erdheim Chester disease.**

Histiocytic and dendritic cell neoplasms include clonal inflammatory disorders and overtmalignancies which are known to show differentiation towards monocytes, macrophages, or dendritic cells. They account for <1% of all lymph node and soft tissue tumours[1]. The World Health Organisation (WHO) Paediatric Tumour classification online blue book incorporates in its histiocytic disorders classification, LCH, Juvenile Xanthogranuloma (JXG), Erdheim Chester Disease (ECD), Rosai Dorfman Disease (RDD) and histiocytoses of uncertain malignant potential[2] whereas, the 5th edition of WHO classification of Haematolymphoid tumours also includes Langerhans cell sarcoma, Interdigitating dendritic cell sarcoma (IDCS), ALK – positive histiocytosis and Histiocytic Sarcoma (HS) in addition to the above mentioned entities. Follicular Dendritic Cell Sarcoma (FDCS) and Fibroblastic reticular cell tumour are no longer considered as histiocytic neoplasms[1]. Histiocytic disorders/ neoplasms mimic a variety of reactive processes and a deep insight is vital to avoid misdiagnosis.

Editor's Comment :

- Histiocytic disorders neoplasms are rarely encountered clonal proliferative disorders/ neoplasms. They can be confused with a variety of benign and inflammatory conditions. Infrequently, they can recur and behave aggressively. Familial predisposition is also documented in a minority of cases.

Extensive literature is available on individual histiocytic disorders, but a collective study encompassing all entities are limited[3]. We aimed to study the spectrum of histiocytic disorders and analyse their clinicopathological and immunohistochemical characteristics in children aged ≤16 years. In addition, we intend to discuss the diagnostic challenges faced by the pathologists.

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Materials and Methods

This retrospective descriptive study was carried out in the Department of Pathology at Kidwai Memorial Institute of Oncology, Bengaluru, Karnataka, India. As this was a retrospective study and did not involve any intervention, an exemption from the Institutional Ethics Committee was taken and a broad consent was taken for all procedures. All cases aged ≤16 years diagnosed with a histiocytic disorder/ neoplasm from January 2020 to July 2022 were included in the study.Cases diagnosed as FDCS or plasmacytoid dendritic cell neoplasms were excluded from the study. Case details were collected from the Medical Records Department. Haematoxylin and Eosin (H&E) and immuno-histochemical slides were retrieved from the departmental archives and reviewed. Immuno-Histochemistry (IHC) panel done wereS100 (4C49, TBS), CD68 (CD68/G2, BGX), CD1a (010, BGX), BRAF(v600e, Roche). Demographic details, sites involved, Bone Marrow (BM) involvement, IHC profile and additional clinical findings were collected. Qualitative and quantitative variables are expressed as frequency with percentage and mean± standard deviation or median with range respectively.

Results

Our study included 23 Indo Asian children comprising of 14 (60.9%) Boys and nine (39.1%) Girls. LCH accounted for majority of the cases (52.17%) followed by RDD (26.09%). Two cases were diagnosed as unclassified histiocytic disorder, as the immuno-morphology did not allow definitive categorization. Spectrum of histiocytic disorders in this study is listed in Table 1.

Table 1 — *Spectrum of histiocytic disorders in children ≤16 years in this study*

Diagnosis	Number (%)
Langerhans cell histiocytosis	12 (52.17)
Rosai Dorfman disease	6 (26.09)
Erdheim Chester Disease	1 (4.35)
Histiocytic sarcoma	1 (4.35)
Juvenile Xanthogranuloma	1 (4.35)
Histiocytic disorder – unclassified	2 (8.69)

The age of the children ranged from 5 months to 16 years with a median of 3 years. The mean age of the children with LCH and RDD were 59.3±78.2 and 82±51.2 months respectively. Male to female ratio was 2:1 in LCH and RDD. HS was encountered in six-year-old child while children with ECD and JXG were 3 years old. Both the cases of unclassified histiocytic disorder were 16 years old.

Out of the 12 LCH cases, 5 were Single system LCH(SS - LCH) and 7 were multisystem LCH (MS - LCH). All the cases of SS – LCH showed unifocal bone involvement with frontotemporal bone being the most common site. MS – LCH involving skin, bone, lymph nodes, Central Nervous System (CNS) in various combinations were encountered in four cases. Three cases of MS – LCH involving liver, spleen, or BM were stratified as MS -LCH high risk. One of the LCH cases was a known case of Immune Thrombocytopenic Purpura (ITP). The child with ECD presented with bilateral symmetrical bone lesions.Isolated orbital soft tissue involvement was seen in the child with JXG.The sites of involvement are summarized in Table 2.

BM performed in all the cases of LCH, ECD and JXG were not involved by the tumour. However, the BM of a 5-month-old baby with LCH showed myeloid hyperplasia with histiocytic aggregates and giant cells, raising suspicion of involvement. However, it was rendered uninvolved as CD1a was negative.

Our small cohort had two siblings born of first-degree consanguineous marriage. The elder girl was diagnosed with HS and the younger boy was diagnosed with LCH.

Histologically, all LCH cases showed inflammation with histiocytes having grooved nuclei (Fig 1a). RDD cases showed emperipolesis in almost all cases (Fig 1b). Biopsy of the femur lesion in ECD showed foamy histiocytes and inflammation (Fig 2a). Morphologically, HS was characterized by sheets of plump epithelioid cells (Fig 2b). JXG was composed of sheets of spindled and foamy macrophages with dense inflammation and giant cells (Fig 3a). Among unclassified histiocytic disorders, one case hadan epithelioid foamy appearance and other had a spindly morphology (Fig 3b).

Table 2 — *Sites of involvement of histiocytic disorders in this study*

Langerhans cell histiocytosis (N = twelve)		Rosai Dorfman Disease (N = six)	
Single system (unifocal)- Craniofacial bones	Five cases (41.67%)	Cervical Lymph node only	Three cases (50%)
Multisystem- Skin, bone, lymph node, CNS	Four cases (33.33%)	Central nervous system involvement (dural) only	Two cases (33.3%)
Multisystem High Risk-with liver and spleen	Three cases (25%)	Intracranial location and lymph nodes	One case (16.7%)
Erdheim Chester Disease	- Bone: bilateral femur, iliac blades		
Histiocytic sarcoma	- Bone, skin, lymph nodes		
Juvenile Xanthogranuloma	- Periorbital region		
Histiocytic disorder-unclassified	- Thoracic vertebra and cervical lymph node respectively (single system in both cases)		

N = total number of cases

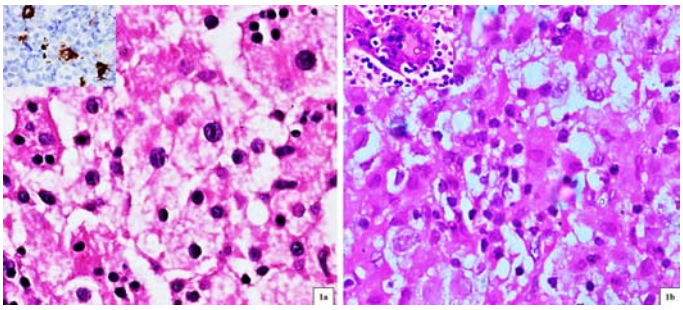

Fig 1 — a. Langerhans cell histiocytosis – histiocytes with grooved nuclei, H&Ex200. Inset: CD1a x200. b. Rosai Dorfman Disease– sheets of histiocytes with emperipolesis H&E x200. Inset: multinucleated giant cell exhibiting emperipolesis

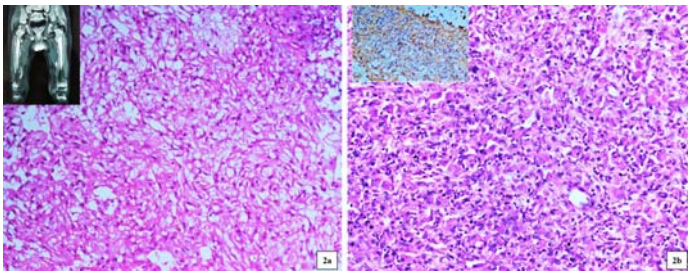

Fig 2 — a.Erdheim Chester Disease– histiocytes with xanthomatous change, H&E x50. Inset: Magnetic resonance imaging showing bilateral symmetrical altered intensities in femur. b. Histiocytic sarcoma–sheets of plump histiocytes, H&E x50. Inset: CD68 x50.

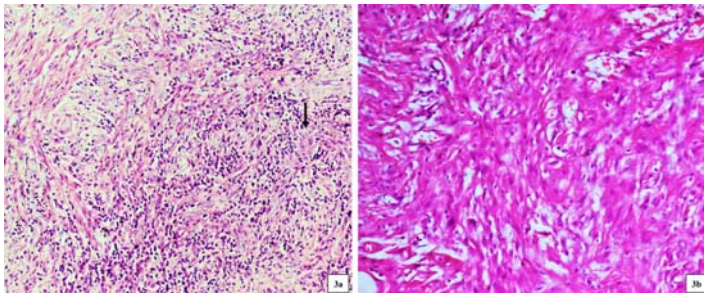

Fig 3 — a. Juvenile Xanthogranuloma – sheets of histiocytes dispersed amidst inflammatory cells. indicates multinucleated giant cell, H&E x50. b. Histiocytic disorder – unclassified: sheets and fascicles of histiocytes with spindled morphology, H&E x50.

Diagnoses of LCH was made based on morphology and immunoreactivity for CD1a, (Fig 1a inset) S100 and/ or CD68. Ki67 ranged from 3-30%. The immunoprofile of these cases are summarized in Table 3. The histiocytes in RDD cases were at least focally positive for S100and CD68. JXG was positive for CD68 and negative for CD1a and ALK.

ECD was diagnosed based on the classic clinical presentation, histomorphology and immunoreactivity for CD68. A diagnosis of HS was rendered after ruling out the possible morphologic differentials by using a panel of IHC markers. The neoplastic cells were positive for S100, CD68 (Fig 2b inset) and negative for CD23, SMA, CD34 etc, with Ki67 index of 20%.

Two cases with atypical morphology, one with an epithelioid appearance and other with a spindly morphology were categorized as unclassified histiocytic disorders as they were positive only for CD68 and negative for S100,CD1a andBRAF.

All LCH cases and HS were treated with chemotherapy. Mean follow up period was 14.7 months with a range of 1-30 months. During this period, four out of 23 cases recurred, which included two RDD cases (at two and six months of diagnosis), one case of LCH with ITP (after 27 months) and HS (after two months). Disease recurrence was observed in both siblings with RDD and HS.Ki67was high (60%) upon recurrence in HS. The immuno-morphology of the both the recurrent RDD cases were different from the primary immuno-morphology wherein, one case showed focal positivity for CD1a, and the other case revealed atypical histiocytic proliferation. An infant with MS-LCH high risk succumbed to the illness within three weeks of diagnosis.

Discussion

Histiocytic neoplasms are commonly encountered in children and rarely in adults. The classification of histiocytic disorders has evolved over the years, from comprising of three categories in 2004 – L group (LCH, Indeterminate cell tumour, ECD, mixed LCH and ECD), C group (JXG, Adult xanthogranuloma, cutaneous RDD) and the M group (primary and secondary Malignant histiocytosis) to including two other categories namely the R group (RDD and its types) and the H group (primary and secondary Haemophagocytic Lymphohistiocytosis) in 2016 by the Histiocyte Soceity[4] to the current 5th edition WHO classification of Haematolymphoid tumours.

LCH is the most common disorder among histiocytic disorders accounting for approximately 5 cases/ million population per year with a male predominance[5]. In par with the literature, LCH constituted the bulk of the cases in this study (52.17%) showing a male predominance. LCH presents either as SS- LCH or MS- LCH and each account for 50% of cases[6]. In contrast, MS-LCH was slightly more common in this study (58.3%). According to a systematic review, skull bones (42.2%), chest wall (23.4%) are the frequently affected sites followed by the spine (9.4%) and pelvis (9.4%)[7]. Similarly, in this study, craniofacial bones were commonly involved with a rare case involving iliac bone. Other sites involved included skin, hematopoietic system, lung, and CNS[6]. In this study, BM of one LCH case was highly

Table 3 — *Immunoprofile of Langerhans cell histiocytosis cases*

Case	CD68	S100	CD1a
Case 1	Focal Positive	Focal Positive	Positive
Case 2	Positive	Focal Positive	Positive
Case 3	Focal Positive	Non-Contributory	Positive
Case 4	Not Done	Positive	Positive
Case 5	Negative	Positive	Positive
Case 6	Not Done	Positive	Positive
Case 7	Focal Positive	Focal Positive	Focal Positive
Case 8	Not Done	Positive	Positive
Case 9	Not Done	Positive	Positive
Case 10	Positive	Positive	Positive
Case 11	Focal Positive	Positive	Positive
Case 12	Not Done	Focal Positive	Positive

suspicious of involvement but was rendered uninvolved as it was negative for CD1a. However, a study by Galluzzo ML, *et al* showed histiocytic clusters in 40.9% LCH cases, but only 14% cases showed CD1a immunoreactivity[8]. If these findings are taken, then this case may be considered to be involved. More studies are needed to determine the importance of histiocytic aggregates without CD1a expression in BM of LCH cases. A rare case of a child with ITP presenting with MS - LCHat adulthood has been reported, which was also the scenario in one of the cases[9]. Although, no theories related to this association are available at present, future studies might elicit relation between these two entities.

The diagnosis of LCH is supported byfocal or strong expression of CD1a, S100 and CD68 which was the case in our study as well[2]. Despite being known as a specific marker for LCH, CD1a can also be expressed in JXG, HS and RDD[10]. Ki67 performed in few cases in our study, was as high as 30%. Ki67upto 40% has been reported in literature and high Ki67 correlates with poor prognosis[10,11]. BRAF immunoreactivity, an indicator of MAPK pathway mutation is seen in >85% LCH cases[10]. Despite chemotherapy, the girl with ITP and MS-LCH involving the CNS presented with recurrent disease at a different site after two years. An infant diagnosed with MS-LCH high risk expired within few weeks of initiating treatment.The dismal prognosis of recurrent MS-LCH cases is well studied[12].

The global incidence of RDD (Sinus Histiocytosis with massive lymphadenopathy) is largely unknown[1,5]. Although, rare studies demonstrated a slight female preponderance, RDD is more common amongst males and this study consisted of four males and two females[13,14]. Clinically RDD can be nodal or extra nodal and they were seen in equal number of cases in this study as in literature. Extra nodal manifestations include cutaneous, intracranial, spinal, head and neck and intrathoracic sites[15]. CNS RDD accounts for <5% of involved cases in literature and we had two cases of CNSRDD[15]. Although rare, relapses do occur in RDD with soft tissue and CNS involvement[13]. In this study, recurrence was observed in two multisite disease cases and one among them had a familial background as well. Classic morphology include slymphocytic emperipolesis, increased histiocytes with mild atypia and mitoses[16]. Atypical histiocytic proliferation was observed in one of the recurrent cases. The other recurrent case expressed only CD1a upon recurrence and this raised suspicion as to whether an overlap disease (RDD – LCH) was present initially or just the mere infrequent expression of CD1a in a RDD case[10,14].

HS, a diagnosis of exclusion can present in variable age groups and the exact incidence is presently unknown due to changes in classification[5]. This can present either denovo or in association with other lymphoid neoplasms and may have an aggressive clinical course[17]. Available literature shows a slight male predominance whereas in this study, HS was diagnosed in a young girl[1]. Lymph nodes are usually affected in HS, but any extra nodal site like gastrointestinal tract, spleen, soft tissue, skin, CNS or orbit may be affected[1]. The child in this study had multisystem disease involving skin, bone and lymph nodes. The diagnosis was rendered after excluding various morphologic differentials like FDCS, IDCS, Langerhans cell sarcoma, inflammatory pseudotumor, Anaplastic Large cell lymphoma, melanoma etc,[18]Despite chemotherapy, this child presented with recurrent disease within two months[17].

Hereditary predisposition in RDD is due to germline mutations in SCL29A3 gene or TNFRSF6 gene[2,19]. No known hereditary factor has been implicated in HS as of now upon extensive literature search. A possibility of germline mutations in MAPK pathway may be considered due to its versatile role in histiocytic disorders[1]. As the siblings in this study had different histiocytic disorders, namely RDD and HS,further studies are required to adequately study the familial background in these disorders.

Fewer than 1000 cases of ECD have been reported in literature[5]. ECD often presents with a male preponderance between 46-56 years[20]. Paediatric cases infrequently show the classic adult clinical presentation of bilateral bone lesions[2]. The diagnosis of ECD is aided by the constellation of clinical (bone pain), radiographic (bilateral cortical sclerosis) (Fig 2a inset) and histological (foamy histiocytes which are negative for CD1a) findings, which was observed in the child in this study[21]. BRAF p.V600E mutation is seen in >50% of these tumours[2]. However, this case was negative for BRAFIHC[21].

JXG is a paediatric histiocytic disorder having excellent prognosis, seen confined to skin of head and neck usually[2]. It accounts for 1 case/ million children and can undergo spontaneous resolution[22]. We had one case of JXG with a solitary lesion in the orbit expressing CD68. ECD is a mimicker of JXG and hence, the diagnosis should be made only in the appropriate radiographic and clinical context.

Rarely, histiocytic lesions can have ambiguous morphology and express only CD68. Tissue fixation and IHC pitfalls are key areas to be pondered in these unclassified cases. Overlap diseases like LCH – ECD do exist and awareness of these are vital for arriving at a correct diagnosis[23].

Conclusion

Histiocytic neoplasms are rare entities which can involve multiple systems. They can have overlapping histomorphology with various benign and reactive conditions thereby posing diagnostic challenges to the Pathologist. Familial RDD is well known, but further studies are required to identify familial relationship between these distinct entities. Although considered indolent, these entities can have a poor prognosis. Although there are many case reports and series, large scale Indian studies are still lacking and our study is one such initiative to collectively look upon the clinico-pathological and IHC profile of these histiocytic neoplasms.

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