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Childhood Histiocytoses: A Review of Twenty Two Cases

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Histiocytoses are a group of uncommon disorders characterized by proliferation of cells of the mononuclear phagocyte system and the dendritic system(l). Each of the histiocytoses of childhood is characterized by localized or generalized, reactive or neoplastic proliferation of cells similar if not identical to one of these cell types(2). As per Writing Group of the Histiocyte Society(3), various histiocytoses of childhood have been classified into Class I, Class II and Class **III.** In case of Class I Histiocytosis, the proliferation cell is the Langerhans cells(2). We present 22 cases of childhood histiocytosis diagnosed over a span of 10 years (1985-95). This is a retrospective study emphasizing the clinicopathological features alongwith a brief review of literature.

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Subjects and Methods

Twenty two children were diganosed as histiocytosis at the Lok Nayak Hospital,

New Delhi, during the period 1985-1995. The age of these cases ranged from 3 months to 12 years. There were 14 males and 8 females.

Pathological diagnosis was made on bone marrow aspiration (15 patients), fine needle aspiration cytology (8 patients), and/or tissue biopsy (16 patients). Hemograms were done in all cases. Special stains (PAS and Oil Red 0) were done whenever required.

Results

Of these 22 patients, 12 patients were anemic, 13 showed leucopenia, 16 had thrombocytopenia while 12 had pancytopenia. The clinical and hemotological profile of these patients are summarized in *Tables I, II* and *III*. The morphological

TABLE I–*Clinico hematological Profile and Diagnostic Criteria in 10 Cases of Langerhans Cell Histiocytosis*

Features		No
Clinical		
Fever		8
Lymphadenopathy		2
Hepatomegaly		2
Splenomegaly		5
Hepatosplenomegaly		4
Soft tissue mass		4
Scalp	2	
Front of trunk	1	
Back of trunk	1	
Lytic lesions in bone		6
Unifocal	3	
Multifocal	3	
Skin rash		2
Hematological		
Leucopenia		6
Thrombocytopenia		7
Pancytopenia		6
Positive Diagnostic Criteria		
Bone Marrow involvement		3
FNAC and biopsy lymph node		2
Soft tissue biopsy		4

TABLE II *Clinico-hematological Profile and Diagnostic Criteria in 9 Cases of Hemophagocytosis*

Profile		No
Clinical		
Fever		9
Lymphadenopathy		9
Hepatosplenomegaly		9
Hematological		
Leucopenia		5
Thrombocytopenia		7
Pancytopenia		5
Positive Diagnostic Criteria		
Bone Marrow involvement		9
with LD bodies	3	
with *P Falciparum*	1	

TABLE III–*Clinico hematological Profile and Diagnostic Criteria in 3 Cases of Malignant Histiocytosis*

Feature	No
Clinical	
Fever	3
Lymphadenopathy	3
Hepatosplenomegaly	3
Hematological	
Leucopenia	2
Thrombocytopenia	2
Pancytopenia	1
*Diagnostic Criteria**	
LN FNAC	3
LN biopsy	3
BM Aspiration	3
BM biopsy	3

* All were positive for malignant histiocytosis
LN = lymph node, BM = Bone marrow

features of these 22 cases were as follows: *(i)* Class I Langerhans cell histiocytosis-10; *(ii)* Class II Hemophago-cytic syndrome-9; and *(iii)* Class HI Malignant histiocytosis—3.

Langerhans cell histiocytosis: Diffuse histiocytic proliferation was observed in all the 10 cases. Cells demonstrated abundant eosinophilic to foamy cytoplasm with large vesicular nucleus. There were binucleate and multinucleate forms as well. These sheets of histiocytes, were seen admixed with polymorphs, lymphocytes, eosinophilis and plasma cells. Eosinophilic infiltrate was variable, being marked in 4 cases diagnosed as eosinophilic granuloma and sparse in 4 cases of Letterer-Siwe disease. These latter patients showed preponderant proliferation of histiocytes. In 2 cases, a diagnosis of Hand-Schuller-Christian disease was made. All these cases of Class I histiocytosis showed rare mitotic figures and occasional histiocyte with phagocytic activity *(Fig. 1).*

Hemophagocytic syndrome: These 9 cases showed marked increase in histiocytes with significant phagocytosis of platelets, erythroid and myeloid cells *(Fig. 2).* Hemopoiesis was diminished to a variable degree and 7 cases showed decreased myelopoiesis while 5 cases each showed decreased megakaryopoiesis and erythropoiesis. Parasitic infestation was concomitantly present in 4 cases of which 3 had associated leishmaniasis and 1 had falciparum malaria. All of these 4 patients snowed pancytopenia.

Malignant histiocytosis: Only three cases of this entity were encountered. They showed sheets of histiocytes with marked pleomorphism. Highly cellular tumor masses were seen with atypical histiocytes showing high mitotic activity and large areas of necrosis. Few multinucleate forms were seen. Clusters of pleomorphic cells were found to be rimmed by fibrosis *(Fig.* 3).

Discussion

Of the 3 classes of histiocytosis in childhood, the 2 most often encountered forms are Langerhans cell histiocytosis (LCH) and hemophagocytic syndrome (HPS) while malignant histiocytosis (MH) is rare(4). In our series also, MH was least common. However, a series of 120 cases of histiocytosis in children documented 54 cases of Class I, 9 of Class II and 47 of Class III histiocytosis(5). In our series, Langerhans cell histiocytosis (LCH) was the commonest while malignant histiocytosis was the least common in contrast to the above study where almost an equal number of cases were seen in Class I and Class III types.

Regarding the epidemiology of LCH, very limited data is available largely because of its relatively low incidence(6). LCH can present at any age from newborn to elderly with a peak incidence between 1 and 4 years(7). It has a wide clinical spectrum and the prognosis varies accordingly^). Traditional classification of clinical variants of LCH has been based on patterns of organ involvement(8). Eosinophilic is characterized by uni-or multifocal bone lesions in the absence of organ involvement^). All 4 cases of eosinophilic granuloma in our study had lytic bone lesions (unifocal in 3 and multifocal in 1). Letterer-Siwe disease on the other hand presents primarily with visceral involvement(lO). The organs commonly affected are liver, spleen, lymphnodes, bone, skin and/or bone marrow(9). Involvement of the CNS is seen less commonly(lO). In our series 3 of the 4 patients with Letterer-Siwe disease had hepatomegaly and 2 cases presented with lymphadenopathy and characteristic skin rash. Bone marrow involvement was observed in 3 subjects. The triad of multiple bone lesions, exophthalmos and diabetes insipidus constituting Hand-Schuller-

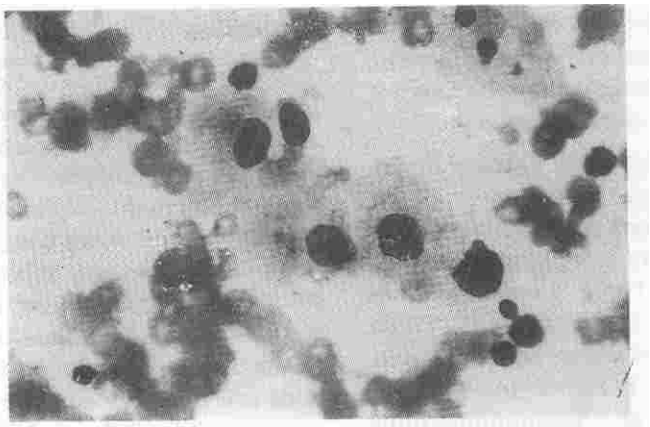

Fig. 1. Cluster of large histiocytes with foamy abundant cytoplasm (Giemsa × 1000).

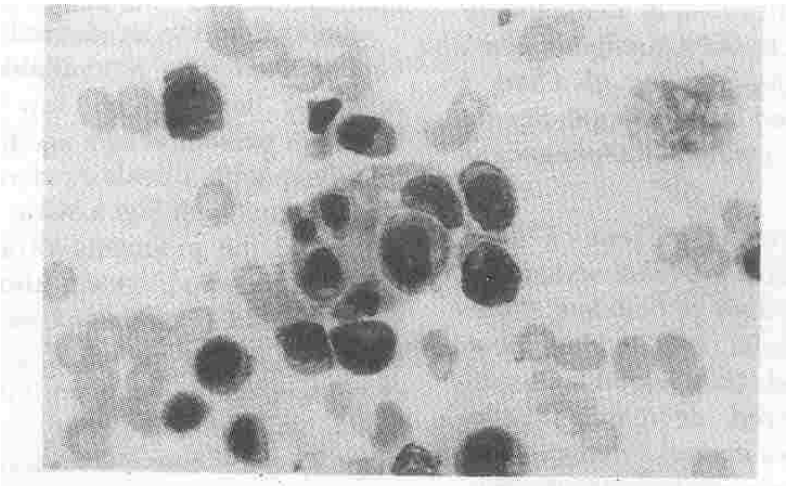

Fig. 2. Bone marrow aspiration smear with a single histiocyte showing marked hemophagocytosis (Giemsa × 1000).

Christian (1156356(9), was observed in 2 of our cases. Seperation characterized by visceral involvement has proved to be useful prognostically. However, distinction between Letterer-Siwe and Hand-Schuller-Christian diseases is subtle and clinically irrelevant^).

Pressumptive diagnosis of LCH is based on light microscopic features(2). However, the definitive diagnosis requires in addition demonstration of Birbeck granules by electron microscopy and/or positive stain for CDIa antigen by immunohistochemistry(2) which could not be done in our cases.

Clinical picture is usually very different in hemophagocytic syndrome. Clinical manifestations of this entity relate to infiltration of multiple organs, especially those of the reticulo-endothelial system(9). Common presenting features are fever, splenomegaly, lymphadenopathy, hepato-

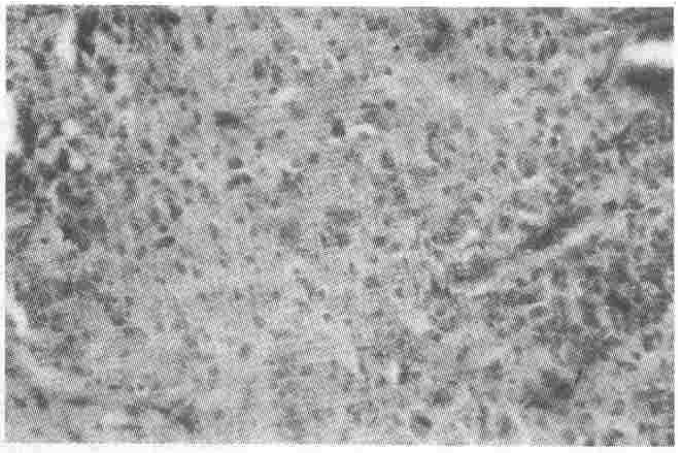

Fig. 3. Malignant histiocytosis showing aniso-cytosis and aniso-nucleosis with increased mitotic activity (H&E ×400).

megaly and bone marrow involvement(11). All nine patients of HPS in our study had all of the above features. The clinical profile among familial and sporadic forms are similar and can be distinguished from other forms of histiocytosis(9). Skin rash and bone diseases are hardly ever seen in HPS.

The morphological features are similar in both types of HPS, most prominent being proliferation of benign histiocytes displaying a striking degree of hemophagocytosis(12). Infiltrates occur primarily in lymphnode sinuses and medullary cords, liver sinusoids and portal areas, splenic red pulp and bone marrow. Variable degree of cytopenias are seen in these patients. Presence of increased numbers of phagocytic histiocytes should precipitate an exhaustive search for underlying infection or malignancy (9). In the present study 3 patients had leishmaniasis and there was one patient of falciparum malaria which were treated accordingly. Other 5 patients were treated with broad spectrum antibiotics and steroids. All of these patients showed good response to treatment. Management of infection associated HPS is directed towards specific treatment of infections, broadspectrum antimicrobials, supportive care and steroids. These patients in particular show excellent response to steroids.

Malignant histiocytosis is quite rare in children. The cardinal features for distinguishing between patients with malignant histiocytosis from other hematologic neoplasma is early widespread involvement of multiple organs and tissues of the reuculoendothelial system and extranodal sites such as lung and skin(9). We encountered 3 patients of malignant histiocytosis who presented with fever and variable degree of hepatosplenomegaly and lymphadenopathy. The involved lymphnodes show the characteristic findings(13). The cellular composition of the infiltrate is variable but they demonstrate large atypical malignant cells with frequent mitoses *(Fig. 3)*. The degree of cytologic atypia is variable with nuclei having round, clefted, lobulated or bizarre shapes and one or more prominent nucleoli(9).

In all such cases of histiocytosis, it is suggested that clinical features, bone mar-

row findings and tissue biopsy features (lymph node/liver/spleen/local site) must be correlated to subtype the class of histiocytosis for adequate management.

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Immunization Coverage in Bihar

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The National Family Health Survey (NFHS) in 1993 reported a low coverage level of immunization for children and mothers for the State of Bihar, using a properly designed random survey methodology(1). This is in contrast to a high coverage level as reported by the State Government, which generated lot of controversy.

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