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HISTIOCYTIC SYNDROMES IN CHILDREN*

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The "histiocytes" are a group of proliferative disorders of the mononuclear phagocyte system whose etiologies are basically unknown. The majority of childhood histiocytoses are expressions of excessive numbers of Langerhans cells, representing so-called Langerhans cell histiocytosis. Fifteen patients who were diagnosed with histiocytosis syndrome at the Pediatric Hematology and Oncology Department of Ege University Hospital between October 1986 and January 1995 were included in this study. The majority of the patients had Langerhans cell histiocytosis (LCH), and skeletal involvement was the most common manifestation. A good response to radiotherapy and chemotherapy was obtained by our patients with unifocal and multifocal involvement of LCH. Two patients with disseminated LCH died with progressive disease. In the patient with Rosai-Dorfman disease, a partial response was obtained with prednisone. The patient with malignant histiocytosis died during a relapse at the end of one year. Organ dysfunction and the patient's age are important factors affecting the outcome of the disease. *Key words: Langerhans cell histiocytosis, chemotherapy, radiotherapy, "histiocytosis syndrome".*

The "histiocytes" are a group of proliferative disorders of the mononuclear phagocyte system whose etiologies are basically unknown, although there are selected instances of a clinical association with primary immunodeficiency states. The majority of childhood histiocytoses are expressions of excessive numbers of Langerhans cells, representing so-called histiocytosis X or the preferred appellation, Langerhans cell histiocytosis[1]. Etiologies vary; the response to infection, immunologic stimulation, genetic abnormality and clonal malignant proliferation are all associated with proliferation of histiocytes[2-4]. There are three classes of histiocytic syndromes. Langerhans cell histiocytosis (LCH-Class I) embraces disorders previously referred to as "Histiocytosis X" (including eosinophilic granuloma of bone, Letterer-Siwe and Hand Schüller-Christian syndrome). The hemophagocytic syndromes (Class II) include familial hemophagocytic lymphohistiocytosis, infection-associated hemophagocytic syndrome, and sinus hystiocytosis with massive lymphadenopathy (Rosai-

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Dorfman disease). The malignant histiocytosis (MH) syndromes (Class III) comprise acute monocytic leukemia, malignant hystiocytosis and hystiocytic lymphoma[2,3,5].

Classes II and III are rarely seen in childhood. LCH can occur in persons ranging in age from newborn to elderly; the peak incidence occurs between one and four years of age. LCH is probably underdiagnosed, the bone lesions being symptomless[6]. According to the site of infiltration, osteolytic lesions may appear, while various other organs may also be involved in LCH. The role of cytokine expression and the production of LCH cells has also been documented, reflecting the activated state of these cells and probably explaining some of the clinicopathological changes[7-10].

In this study, we investigated the classes of histiocytosis stages of LCH and their treatment and prognosis in our clinic.

Material and Methods

Fifteen patients who had been admitted to the Pediatric Hematology and Oncology Department of Ege University Hospital between October 1986 and January 1995 and diagnosed with histiocytosis syndrome by histopathological examination were retrospectively evaluated for epidemiologic, clinical, therapeutic and prognostic factors.

Radiographic investigations, skeletal surveys, complete blood counts as well as liver and kidney function tests were performed on all patients. Most patients were diagnosed by bone, skin or lymph node biopsy. The patient with malignant histiocytosis was recognized on splenectomy.

Organ dysfunction was evaluated using the criteria of Lahey, as shown below[11]:

Hematopoietic: Hemoglobin < 10 g/dl (in the absence of other causes), neutrophils < 1,500/mm^3, platelets < 100,000/mm^3.

Hepatic: Total bilirubin > 1.5 mg/dl, total protein < 5.5 g/dl, albumin < 2.5 g/dl, edema or ascites.

Pulmonary: Tachypnea, dyspnea or cyanosis, pneumothorax, pleural effusion. The staging and classification of LCH were made as shown in Table I[4-11].

Group IA: Unifocal involvement (those with a single bone lesion, with or without an associated soft tissue mass or regional lymph node involvement).

Group IB: Multifocal involvement (patients with two or more bone or soft tissue lesions, with or without skin rash, diabetes insipidus or both).

Group II: Acute disseminated form (patients with organ dysfunction) Histopathological evaluation was performed in the Department of Pathology, Ege University Faculty of Medicine.

Table I: Clinical Staging System for LCH

Variable	No. of Points
Age at presentation	
> 2 years	0
< 2 years	1
Number of organs involved	
< 4	0
> 4	1
Presence of organ dysfunction	
No	0
Yes	1
Stage	Total points
I	0
II	1
III	2
IV	3

Results

This retrospective study involved 15 patients with histiocytic syndrome. There were six girls and nine boys whose ages ranged between 14 months and 14 years (mean 6 years). Thirteen had class I (LCH Fig. 1), one had class II (NLCH Fig. 2) and one had class III (MH Fig. 3) histiocytosis.

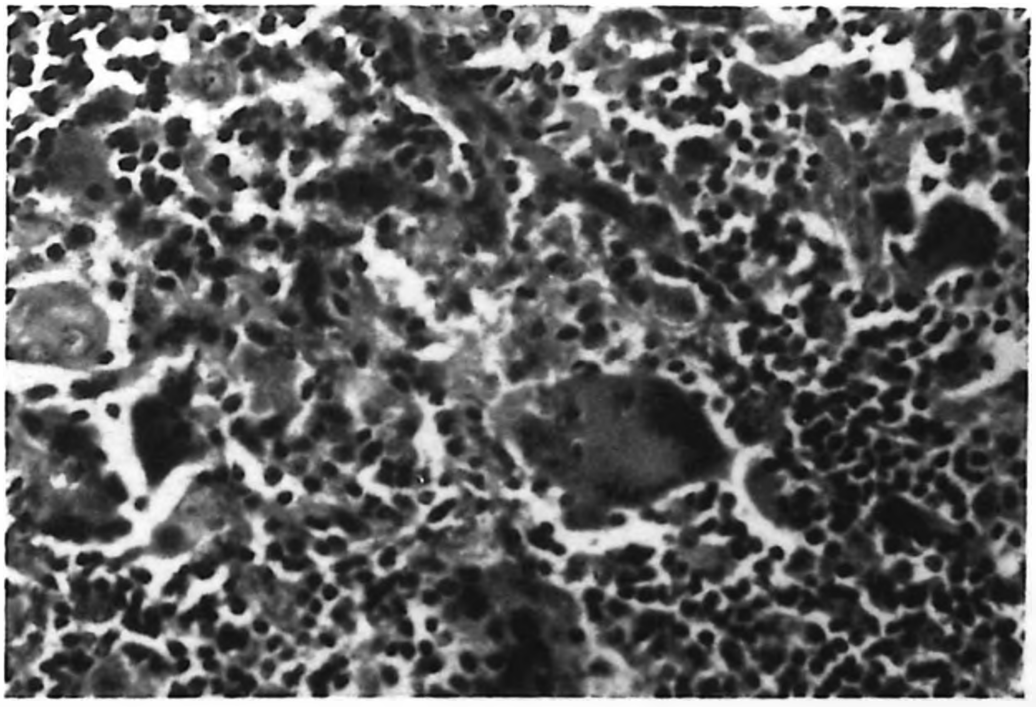

Fig. 1: Langerhans cell histiocytosis (LCH-Class I).

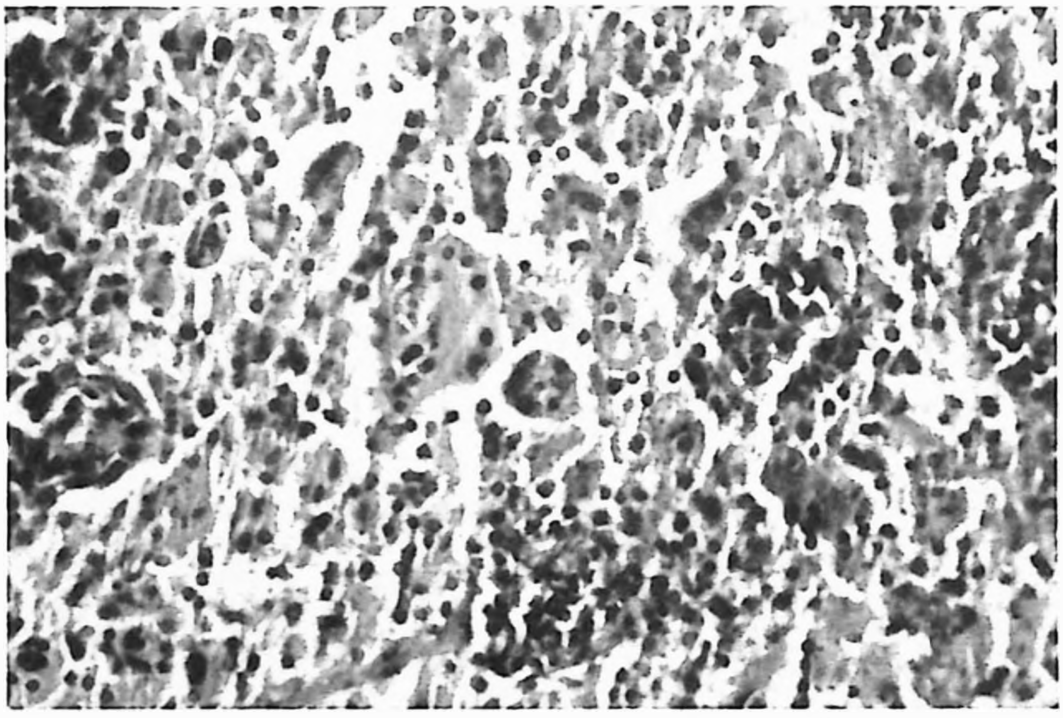

Fig. 2: Rosai-Dorfman disease (sinus histiocytosis with massive lymphadenopathy).

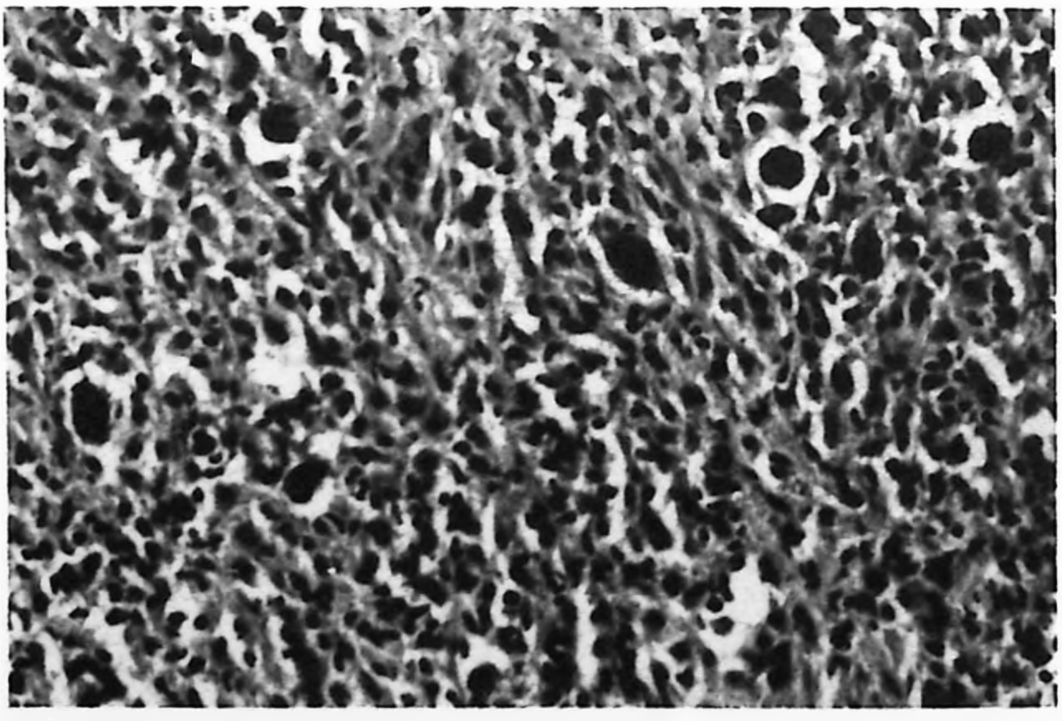

Fig. 3: Malignant histiocytosis (LCH-Class III).

The male-to-female ratio was two to one for the patients with LCH. The majority of patients had multifocal involvement (61.5% Group IB), 23 percent had unifocal involvement (Group IA) and 15.5 percent had disseminated disease (Group II). The clinical manifestations and distribution of bone lesions are listed in Table II.

Surgery, radiotherapy (1600-2000 cGy) or single- or double agent chemotherapy (prednisolone, vinblastine [VBL] or cyclophosphamide [CYC]) was administered for treatment of patients with unifocal involvement in the years 1986 to 1990. Combined chemotherapy (prednisolone + VBL or vincristine [VCR] or CYC) was administered to patients with multifocal involvement. Between 1991 and 1994, single or multiple chemotherapeutic agents including prednisolone, VBL, etoposide (VP-16), methotrexate (MTX), CYC and radiotherapy (if necessary) were administered to patients with LCH. Prednisolone was used for the patient with Rosai Dorfman. The patient with MH was treated with intensive chemotherapy. The results of treatment are shown in Table III.

Table II: Clinical Manifestations of Langerhans Cell Histiocytosis

System	n	(%)
Bone lesions*	10	67
Skin and mucous membranes	2	13
Lymphadenopathy	3	20
Pulmonary manifestations	3	20
Central nervous system (D. insipidus)	2	13
Chronic otitis media	1	7

* Distribution of bone lesions:
Skull 40%, Innominate bone 20%, Ribs 20%, Femur 13%, Vertebra 7%.

Table III: Treatment Results of Patients with Histiocytosis Syndrome

Patients (n)	Results
Class I	
Unisystem unifocal involvement (3)	Remission
Unisystem multifocal involvement (8)	Remission
Systemic involvement (2)	Exitus (6 months and 1 year later)
Class II	
Sinus histiocytosis with massive lymphadenopathy (1)	Partial response
Class III	
Malignant histiocytosis (1)	Exitus (1 year later)

Discussion

The histiocytoses are characterized by infiltration and proliferation of histiocytes. Their biologic diversity extends from the clearly benign to the fulminantly malignant, with uncertain lesions in between[2]. LCH is a nonmalignant disorder of immune regulation. There are several well-established clinical syndromes that

herald the presence of LCH in a child between the newborn period and late adolescence. Regardless of the severity of clinical manifestations, the basic histopathologic findings are essentially identical, whereas the number of affected organs and associated dysfunction are the principal determinants of prognosis[1]. According to the site of infiltration, osteolytic lesions appear, and various other organs may be involved[5, 7, 12]. Patients with localized disease have a good prognosis, and spontaneous healing of the lesions, especially of the skeletal and cutaneous ones, may be observed[3, 5, 7, 13]. Moreover, patients can experience spontaneous remissions and exacerbations. Careful classification and staging would partly overcome the difficulty of comparing the response to therapy in a disease that has variable and heterogeneous clinical manifestations[14].

The majority of our patients had LCH, and skeletal involvement was the most common manifestation (Table II). In addition, nondisseminated involvement was established in 11 of the patients with LCH.

A variety of radiation doses and many different drugs and drug combinations, including vincristine, vinblastine, prednisone, mercaptopurine, methotrexate, cyclosphosphamide, chlorambucil and etoposide have been employed[3-5, 15, 16]. A good response was obtained to radiotherapy and single-agent or double-agent chemotherapy (VCR, VBL, Pred, CYC) in the patients in groups IA and IB. Remission was achieved after six weeks. VP-16 and MTX were added to the chemotherapy regimen of the patients who had recurrences, and complete remission was achieved in this patient group as well. Desmopression was used for the patient with diabetes insipidus. The first evidence of the efficacy of Cyclosporin-A (CSA) in LCH was provided by Mahmoud et al.[17], who showed that all three untreated LCH patients had a favorable response to CSA associated with vinblastine and steroids.

Children with disseminated disease may have a more severe clinical picture, at times, progressing to a life-threatening condition. Despite several therapeutic approaches including steroids and cytotoxic drugs, no individual treatment has proven to be superior. The optimal treatment for disseminated LCH has not yet been established. Disseminated LCH may become life-threatening, and immediate clinical improvement may be critical. CSA is also effective for the treatment of LCH in pretreated children with progressive disease, including life-threatening organ dysfunction[17, 18], as supported by recent evidence of massive cytokine production (IL 1, PGE2, etc.) within the lesional tissue in the course of LCH and from isolated LCH cells[18, 19]. Previous authors have used the specificity of a monoclonal antibody directed against the CD1a antigen on Langerhans cells[6]. In our patient with disseminated disease and lung dysfunction, refractory LCH was pretreated with multiple agents including VBL, MTX, VP-16 and CYC, which led to a partial remission for six months. However, the patient

relapsed at the end of this period and was given CSA. The patient died of progressive disease at the end of the first month. Another patient was less than two years of age at the time of diagnosis. He did not respond to multiagent chemotherapy and died after six months.

Although sinus histiocytosis with massive lymphadenopathy (Rosai-Dorfman disease) is not considered a malignant disorder, considerable mortality and morbidity can result. Both radiotherapy and chemotherapy have been used with some success, and in some cases the lesions spontaneously regress[3, 4, 20-22]. Prednisone were given to our patient with Rosai-Dorfman disease; partial remission was obtained, and the patient was still alive with the disease as of this writing.

Malignant histiocytosis is a syndrome of fever, wasting, pancytopenia, hepatosplenomegaly, adenopathy and systemic proliferation of malignant histiocytes. The disease occasionally presents with isolated involvement of the gastrointestinal tract. The majority of affected cases are now known as having Ki-I anaplastic large cell lymphoma or some other hematological disorder[23, 24]. Our patient with MH was treated as a case of histiocytic lymphoma. He had a complete remission, but died during a relapse at the end of the first year.

In conclusion, the outcome of localized LCH and of LCH with multifocal involvement are generally good. The two key factors appear to be age at the time of diagnosis and the degree of organ involvement. Children younger than two years of age at the time of diagnosis have a higher mortality rate than do older children. Involvement of multiple organ systems and the presence of organ dysfunction have been found to be poor prognostic signs. The treatment of patients with organ dysfunction is still a big problem. New prospective clinical trials should be designed to determine the optimal therapy in class I and II patients.

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