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Case Reports

MALIGNANT HISTIOCYTOSIS: A CASE REPORT AND REVIEW OF THE LITERATURE

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ABSTRACT

Malignant histiocytosis (MH) is a rare hematologic malignancy, especially in the first decade of life. The disease is clinically characterized by fever, hepatosplenomegaly, lymphadenopathy, pancytopenia and jaundice, and histologically by systemic proliferation of malignant histiocytes and hemophagocytosis. The prognosis is poor and often the diagnosis is not made before death. Because of the rarity of this disease, it is unusual for practitioners to diagnose it by bone marrow aspiration (BMA) alone.
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INTRODUCTION

MH was introduced in 1966 by Rappaport, although this disease was originally described in 1936 by Scott and Robb-Smith under the name of histiocytic medullary reticulosis.

The disease is classified as class III of the histiocytosis syndrome[4,19] and is a rare, nonfamilial, rapidly progressive and fatal neoplasm of true histiocytes that affects children and adults[12,19] with a mean age of 31 years.[18] It accounts for less than 10% of hematopoietic malignancies with an average of one case per year.[6] The male to female ratio is 2.2[18] and it may be associated with primary mediastinal germ cell tumors in males.[10]

CASE REPORT

A 5 year old girl was referred to our hospital with fever and knee pain of 2 days' duration and constipation. On admission there were no abnormal physical findings except fever (axillary temperature=38.5°C) and limping. Her general appearance was good. Routine laboratory examinations revealed only mild normocytic, normochromic anemia (Hct= 33%), abnormal ESR (110 mm/h) and a positive CRP.

During the hospital stay arthralgia subsided, and all other examinations and cultures were negative. Radiography of the knees showed leukemic translucent lines. The peripheral blood smear was normal. Bone marrow aspiration was performed and reported as acute undifferentiated leukemia.

Her parents refused chemotherapy. 5 months later, she developed hepatosplenomegaly, massive cervical lymphadenopathy and infraorbital soft tissue swelling and echymoses. Trismus had been present for 1 month and abdominal pain for 2 weeks. Her general condition deteriorated and there was weakness and wasting. Laboratory findings are summarized in Table I.

The second BMA was reported as ALL(L_3), and the patient was treated by the standard ALL protocol. At the end of induction of remission she was admitted for the 3rd time with intractable bleeding from buccal ulcers, abdominal pain, diarrhea and melena. Upon physical examination she was very ill with severe weight loss and cachexia. Cervical

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Table I. Lab findings.

Exam.	Normal Range	Results
WBC count		2,300/μl
Platelet count		87000/μl
Hct		27%
ESR		87 mm/h
LDH	100-500	4740 U/L
Ca	9-11	9.7 mg/dl
P	4-7	3.2 mg/dl
Uric acid	2.5-6	9.6 mg/di
Urea	17-50	23 mg/dl
Creatinine	0.9-1.6	0.8 mg/dl
Reticulocytes		0.1%
CSF cytology		neg. for malignancy
ALP	up to 250	117 U/L
ACP	5-11	8 U/L

lymph nodes, liver and spleen were palpable but smaller than before. A surprising finding was ascites and abdominal distention.

BMA and peripheral blood smear indicated no response to treatment, therefore the original aspirate specimens were reviewed and prominent hemophagocytosis with atypical, blast-like histiocytes was noticed (Figs. 1,2,3) which was unappreciated initially. Non-specific esterase staining of the cells was positive, thus the diagnosis of MH was made based on BMA findings. The peripheral blood smear showed atypical histiocytes (Fig. 4).

COPAD regimen was used for chemotherapy but on the second day of therapy, the patient suddenly developed periorbital edema and died. Autopsy was restricted only to needle biopsies of the liver and spleen. The liver specimen was normal but the spleen biopsy was compatible with MH (Figs. 5,6,7).

DISCUSSION

Etiology

MH is a nonhereditary disease of unknown etiology. Although aneuploidy and some complex chromosomal abnormalities have been reported [t (8:16) (p11, p13) and t(5:6) (5q35:6p21)], there is no significant genetic abnormality.[5,8,17,19]

Clinical manifestations

Fever, localized or generalized frequently tender lymphadenopathy and weakness are the most common initial presentations.[18,19] Hepatosplenomegaly, skin lesions, back, chest and abdominal pain, sweating and a soft tissue mass are also frequent findings.[5,6,12,13,17,19] Jaundice is seen later in the course of disease.[6,12,13,17,19]

Skin lesions are often nonpruritic, macular, erythematous and blanching but may change to raised nodular lesions.[17] Other less frequent presentations include CNS involvement with positive CSF cytology, respiratory symptoms, GI symptoms (GI bleeding & diarrhea), buccal ulceration and

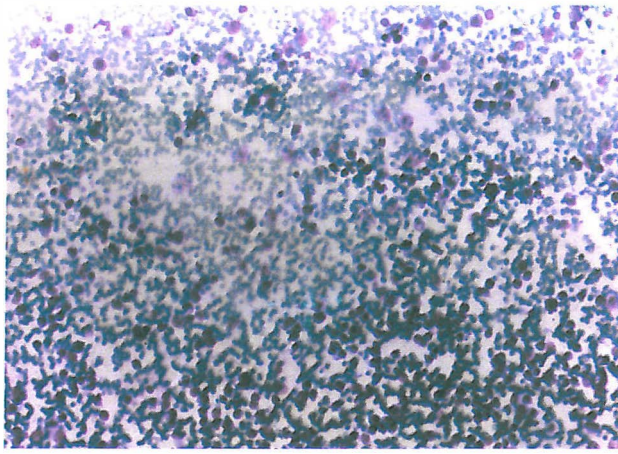

Fig. 1. Bone marrow aspiration (magnification × 10).

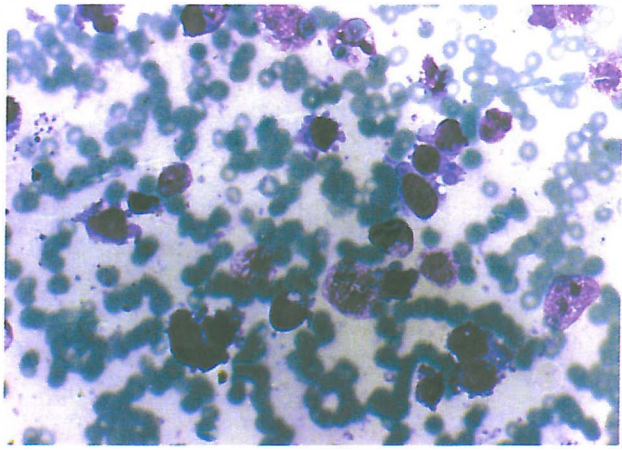

Fig. 2. Bone marrow aspirate with atypical histiocytes and hemophagocytosis (magnification × 40).

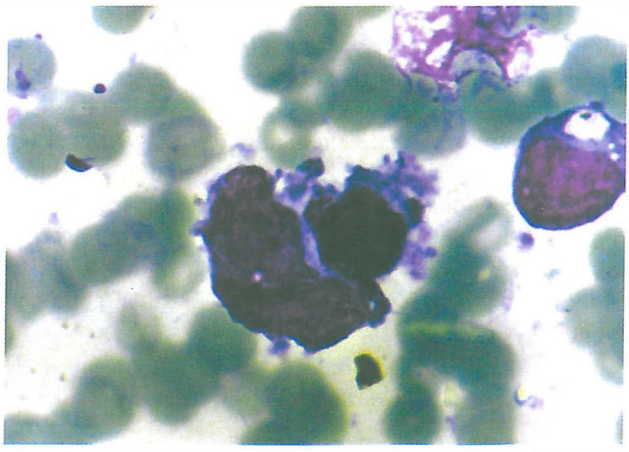

Fig. 3. Bone marrow aspirate showing atypical histiocyte (magnification × 100).

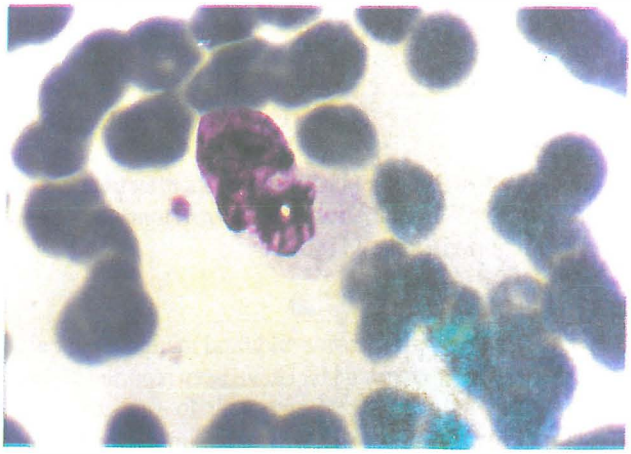

Fig. 4. Peripheral blood smear revealing an atypical histiocyte.

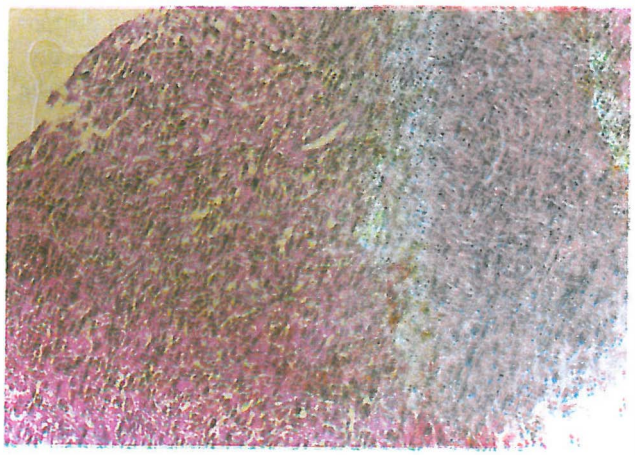

Fig. 5. Spleen (H&E stain, magnification × 5).

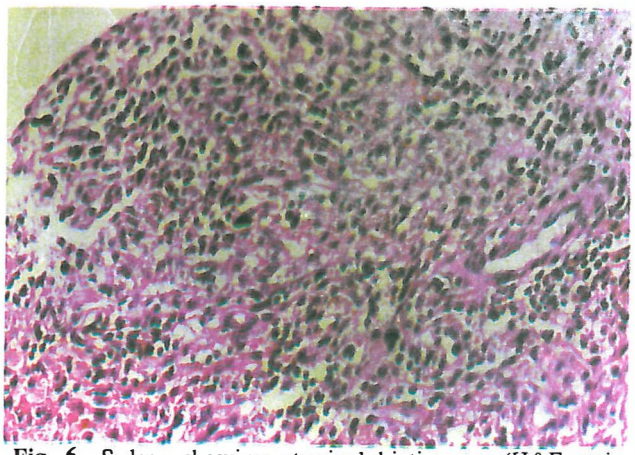

Fig. 6. Spleen showing atypical histiocytes (H&E stain, magnification × 10).

pleural effusion.[6,17,19] Bone lesions[11,13] and ascites[19] are also rarely reported. The lung is the most common site of extranodal involvement.[17]

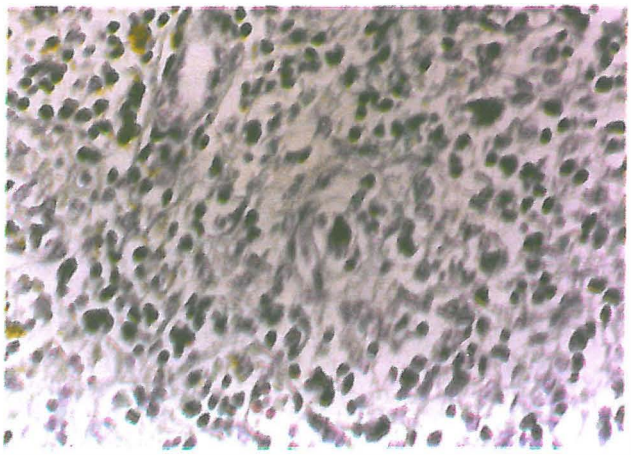

Fig. 7. Spleen showing atypical histiocytes (H&E stain, magnification × 40).

Laboratory findings

Hematologic: Anemia is the most frequent finding (75%) followed by thrombocytopenia (58%), leukopenia and pancytopenia (21%).[14,17-19] Coombs' positive hemolytic anemia, thrombocytosis, leukocytosis, monocytosis, circulating histiocytes and fibrinopenia are infrequent findings.[6,14,18]

Biochemical: Liver enzymes are often increased, especially LDH (33%).[17,19] Serum bilirubin levels above 2 mg/dl are present in about 29% of patients.[17] Hypoalbuminemia, hyponatremia (<130 mEq/L) and hyperuricemia are other infrequent findings.[6,17] Hyperferritinemia may be a significant indicator of MH.[15]

Radiologic: Abnormal CXR has been reported in 33% of cases, although overt respiratory symptoms are rare.[17] CXR findings include pleural effusion, hilar adenopathy and reticular patterns.[6] Periosteal reactions and translucent zones have rarely been reported.[16]

Immunology and immunohistochemistry: Positive RF, increased IgA and polyclonal hypergammaglobulinopathy have been reported by some authors.[6] Histiocytes react with alphanaphtyl esterase and acid phosphatase and are inhibited by NaF and tartarate, respectively.[9,16,17,19] Sudanophilia, PAS positivity and free iron staining which probably arise largely from phagocytic activity are also increased.[9] The malignant cells also react with alpha antichymotripsin and antibodies directed against EMA, HLA-DR antigens, CD 25, CD 30, CD 68, CD 71,[14] and S-100 protein.[5,15] There are neither B- nor T-cell antigens.[14] The degree of cytologic atypia and phagocytic activity is indirectly related to the quantity of lysozyme within the cells.[13]

Diagnosis

Diagnosis is based on biopsy and erythrophagocytosis in the bone marrow, liver and spleen and histiocyte infiltration

Table II. Complementary lab examinations.

Exam.	Normal Range	Results
WBC		1500 (16 L, 60 P, 6 M, 18 B)
Hct		24%
Platelets		12000/µl
ESR		20 mm/h
Coombs' test		negative
Total bilirubin	0.3-1	0.86 mg/dl
D. bilirubin	0.1-0.4	0.25 mg/dl
Ind. bilirubin	0.1-0.6	0.61 mg/dl
S. ferritin	200	900
Triglycerides		400
Cholesterol		136
CXR		normal
Schüller rad.		normal
Brain CT scan		mild brain atrophy
LDH	120-300	3/20 U/L
CSF cytology		negative
T_{11}*		20.8%
B_4*		4.2

* analysis of area with high possibility of tumoral cells.

of subcapsular and medullary regions of lymph nodes, splenic red pulp or hepatic sinusoids.[4,5,12,17,18] Although phagocytosis is essential for the diagnosis of MH, phagocytosis may not be histologically evident in all cases.[13, 18] and may often be seen in benign-looking histiocytes.[19]

Plasma cells are increased in 78% of cases.[17] Skin, lung, CNS, pericardium, bone, soft tissue, intestinal tract and meninges are other frequent sites of infiltration.[4, 6,17] Nasal and paranasal sinuses and the kidney are rare sites of involvement in MH.[6,17]

Malignant cells are atypical with deep blue cytoplasm, high cytoplasmic/nuclear ratios, prominent nucleoli and frequent mitoses. Cellular atypia increases with time.[18,19]

Bone marrow biopsy is positive in 27% of cases and bone marrow aspiration in 33%;[17] therefore BMA is more diagnostic than BMB.

Differential diagnosis

MH must be differentiated clinically and histologically from undifferentiated carcinoma, non-Hodgkin's lymphoma, Hodgkin's disease, infection induced hemophagocytic syndrome, hemophagocytic lympho-histiocytosis, T-cell lymphoma, AML, histiocytosis X, sinus histiocytosis with massive lymphadenopathy, hairy cell leukemia and myeloproliferative disease.[6,7,13,16,19]

Treatment

Multi-agent chemotherapy with cyclophosphamide, doxorubicin, vincristine, prednisolone or etoposide and cytosine arabinoside may improve survival.[2,14]

Some effective regimens which have been used with relatively good results include COPAD, ACOP, CHOP, CVP and BACOP.[1,6,12,16,17]

CNS prophylaxis may be done but its effectiveness is controversial.[1,12,17] Autologous bone marrow transplantation has been reported with good results.[3]

Outcome

MH is a rapidly progressive and fatal malignancy; only a few cases of long-term survival have been reported.[6] Most patients die within a year of disease.[19] In one series the median survival was 4 months with a maximum duration of 25 months.[6] Hepatic and pulmonary dysfunction[6] and platelet counts < 150000 at presentation indicate a poor prognosis.[17]

The dose of drug delivered is another important prognostic factor.[17] Age, sex, stage and site of disease, WBC count and LDH and bilirubin levels do not seem to be important in outcome.[6]

Overall mortality rate is 68%[5] and all untreated patients die within weeks to months.[16,19] Common causes of death are cerebral hemorrhage and pneumonia.[6]

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