Bone marrow and histochemical features of malignant histiocytosis

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ABSTRACT

Objectives: To study the hematological and histochemical features of malignant histiocytosis cases diagnosed at King Khalid University Hospital. **Materials and methods:** This is a retrospective analysis of malignant histiocytosis cases diagnosed by bone marrow examinations at the Hematology Section, Department of Pathology, King Khalid University Hospital. The medical records were evaluated for clinical symptoms and signs at presentation and peripheral blood count. Bone marrow aspirates and biopsies were reviewed for morphological features. Immunohisto-chemical staining of bone marrow trephine biopsies was performed. **Results:** Over 11 years, from February 1984 to March 1995, four cases of malignant histiocytosis were diagnosed at King Khalid University Hospital (KKUH) in Riyadh. They were two males and two females. The age range was 25-56 years. The predominant symptoms at presentation were fever and fatigability. All patients had hepatomegaly and three had splenomegaly. One patient had localized lymphadenopathy and skin involvement. Three patients had pancytopenia while one patient had anemia, thrombocytopenia and leukocytosis. Immunohistochemical stains on three cases showed positivity with α1 antitrypsin and lysozyme. One case showed CD8 (T cell marker) positivity by flow cytometry. The clinical, hematological and immunohistochemical staining findings are described.

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Malignant histiocytosis (MH) is a rare and rapidly progressive systemic illness characterized by fever, hepatosplenomegaly, lymphadenopathy and pancytopenia.[1] It was originally described by Scott and Robb-Smith in 1939 [2] and was subsequently termed malignant histiocytosis by Rappaport in 1966.[3] The disease is characterized by proliferation of histiocytes with cytologic atypia and infiltration of lymph nodes, bone marrow and various tissues and hemophagocytosis is a prominent pathological finding. Distinction of this disorder must be made from infection associated hemophagocytic syndrome,[4] erythrophagocytic T-cell lymphomas[5] and diffuse large cell lymphomas, especially the anaplastic large cell lymphomas (ALCL). We describe the clinical and hematological features of four cases diagnosed in our hospital.

Material and methods The records of four cases diagnosed as MH at KKUH, Riyadh, in the period February 1984 - March 1995 were reviewed. The diagnosis in these cases was based on the clinical features, the rapidly fatal course and the histiocytic infiltrate of the bone marrow with atypia and hemophagocytosis. The records were reviewed for symptoms and signs at presentation.

Hematological evaluation included complete blood count (CBC), white blood cell differential, bone marrow aspirate and trephine biopsy examination.

Cytochemical stains (periodic acid Schiff [PAS], Sudan black B [SBB], α-naphthy acetate esterase [ANAE] and acid phosphatase [AP]) results were available for two cases. Immunohistochemical staining using the following monoclonal reagents: S-100, CD20 (B-cell marker), CD3 (T-cell marker), leukocyte common antigen (LCA), α1 - antitrypsin and CD68 (macrophage/monocyte marker) was performed on paraffin embedded sections of the bone marrow trephine biopsies of three cases and the skin biopsy in one of the three cases. In the fourth case the number of malignant

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Table 1 - Symptoms and signs at presentation

	Patient 1	Patient 2	Patient 3	Patient 4
Age (yrs)	32	56	25	49
Sex	F	M	F	M
Nationality	Saudi	Saudi	Sudanese	Egyptian
Presenting symptoms	Fever, diarrhea, vomiting, drowsiness	Fever, fatigue	Fever, abdominal pain	Fever, fatigue
Hepatomegaly	+	+	+	+
Splenomegaly	-	+	+	+
Lymphadenopathy	-		-	+ (cervical)
Other tissue involvement	-	-		+ (skin)
Bleeding	-		+	+
Diathesis	-	-	+	+
Jaundice	-		-	-
Infection	(E coli), septicemia	(Klebsiella pneumoniae pneumonia)		
Fever, diarrhea, vomiting, drowsiness				
Patient no				
WBC (x10⁹/l)				
Hb (g/L)				
Platelet (x10⁹/l)				
Neutrophils (%)				
Lymphocytes (%)				
Circulating malignant cells (%)				

cells in the biopsy was small.

Results The cases were two males and two females. Two were Saudi nationals and two were non-Saudi Arabs (one Sudanese and one Egyptian). Their age range was 25-56 years. Symptoms and signs at presentation are shown in Table 1. The duration of symptoms was generally short, approximately 1 month in patients 1, 2 and 4 and 6 months in patient 3. All patients died 2-20 days after admission. Patients 1 and 2 died before treatment was started. Because of poor general condition, patient 3 received only prednisone and vincristine and patient 4 received CHEP (cyclophosphamide, doxorubicin, eroposide and prednisone).

Hematological evaluation showed anemia and thrombocytopenia in all patients. Three patients had leukopenia while the fourth had leukocytosis. Blood counts and the presence of circulating malignant cells are shown in Table 2. Bone marrow aspirate evaluation revealed hypercellular marrow in all four cases with malignant cells ranging from 2% to 65% of all nucleated cells (Fig. 1). These cells displayed atypia and hemophagocytosis. Cytochemical stain results were available for two patients and show positivity for the ANAE (inhibited by NaFl) and for acid phosphatase. Trephine biopsy sections showed hypercellularity. There was diffuse infiltration by malignant cells in patients 1 and 4. Patient 2 revealed patchy infiltration while patient 3 showed few scattered malignant cells. Reticulin fibers were increased in all cases. Immunohistochemical staining results are shown in Table 3.

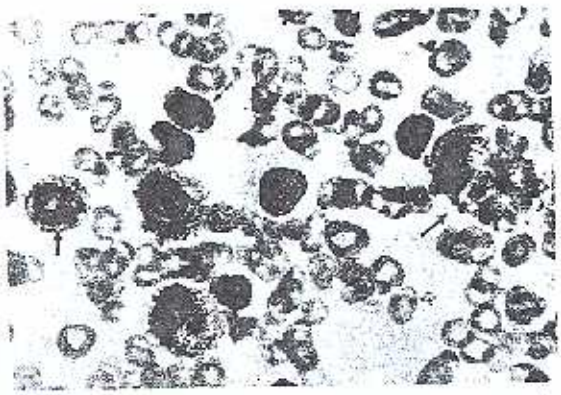
Table 2 - Bone marrow aspirate: atypical histiocytes and blastoid cells (small arrows) and hemophagocytic cells (big arrow)-case no. 1 (May-Giems) x 1000)

Patient No.	WBC (x10⁹/l)	Hb (g/L)	Platele (x10⁹/l)	Neutrophils (%)	Lymphocytes (%)	Circulating Malignant Cells
1	1.3	62	18	18	50	15
2	2.3	86	43	58	35	0
3	2.8	94	52	52	37	0
4	19.9	95	4	0	13	75

Table 3 - Immunophenotyping results of patients 1, 2 and 4.

Patient No	X,-anti trypsin	S-100	Lysozyme	CD68	CD3	CD20	LCA
1	+	-	+	+	±	-	-
2	-	+	+	+	-	-	-
4	+BM -Skin	ND	-BM +Skin	+BM +Skin	±BM ±BM	-BM -Skin	ND

+ : positive, - : negative, ± : weak staining, ND : not performed



Legend 1 - Bone marrow aspirate: atypical histiocytes and blastoid cells (small arrows) and hemophagocytic cells (big arrow: case no. 1

Discussion Malignant histiocytosis (MH) is characterized by proliferation of atypical histiocytes with infiltration of the reticuloendothelial system. The clinical picture is dominated by fever, hepatosplenomegaly, lymphadenopathy and manifestations of cytopenias e.g. bleeding.[1,6,10] Our cases showed similar clinical features although lymphadenopathy was not prominent. In addition, one case demonstrated skin infiltration. Involvement of various tissues in MH have been described, most commonly skin.[1] The main hematological manifestation is pancytopenia.[1,6,10] In less than 10% of cases circulating abnormal histiocytes are seen in the peripheral blood.[1,5,6] In some cases, there is marked involvement of the peripheral blood with leukocytosis. This probably represents a leukemic phase of the disease.[11-14] This entity simulates acute monocytic leukemia (AML-M5). Two of our cases showed circulating malignant cells. In one case this was associated with leukocytosis and marked bone marrow involvement.[15]

The degree of bone marrow involvement in MH is variable and the number of atypical histiocytes is reported between 2-75%.[10,16] This is in contrast to AML-M5 which usually shows more extensive involvement. The degree of atypia is also variable. Cells resembling blasts - blastoid cells as well as giant multilobulated - and Hodgkin's-like cells have been reported.[6,7] There is usually marked hemophagocytosis which is more frequently observed in the more differentiated histiocytes than in the less differentiated or blast-like cells.

By cytochemical staining the cells of MH usually show a macrophage histiocytic pattern with strong positivity for both ANAE (with NaFl inhibition) and AP.17,[18] However, in some cases, the staining with ANAE is weak.[16] The cells are usually negative with SBB and CAE, a feature that is helpful in differentiating MH from AML.

Immunohistochemical staining pattern in MH is variable. The cells are usually positive for lysozyme, ∂l -antitrypsin and CD68 as in our cases and negative for B cell markers.[7,14] The staining with LCA and S-100 is variable. By flow cytometry, the cells usually express the macrophage/ monocytic markers CD13, CD11b, CD11c, CD14 and HLADR.

Several cases diagnosed as MH also expressed T cell markers with positivity CD3, CD5 and UCHL1.[7,15,20,21] The presence of T cell markers in MH is controversial. Many believe that these cases are actually T cell lymphoid malignancies. Indeed, many of the cases diagnosed originally as MH have been found with immunohistochemical stains to be Kil+ALCL. [20,21] However, cases of MH expressing both T cell and macrophage/monocytic markers have been reported. This suggests that some cases of MH might be biphenotypic.

MH is a rare disorder of histiocytic cells. Clinically and morphologically, this entity can be confused with other hematological disorders. These entities include Kil+ALCL. The positivity for Kil (CD30) and the lack of macrophage-associated antigen is helpful in diagnosing Kil+ALCL. Infection-associated hemophagocytosis shows a similar clinical picture and profound hemophagocytosis. However, the cells usually show no significant atypia. MH can also be misdiagnosed as acute myeloid leukemia (AML) and in particular AML-M5 which shares many clinical and morphological features with MH. The two entities may be distinguished by the presence of abundant malignant cells in AML-M5 and the greater degree of extramedullary tissue infiltration in MH. In addition, the cell population in MH includes all stages of maturation, while in AML M5 the cell population is usually uniform. However, the distinction may not always be possible. The most important diagnostic feature in diagnosing MH is the demonstration of phagocytosis in cytologically atypical histiocytes. In addition, cytochemical, immunophenotypic, ultrastructural and molecular studies are helpful in establishing the diagnosis.

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