Malignant Histiocytosis. Clinicopathologic Review of 18 Cases with Immunohistochemical Study

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We reviewed clinical and pathologic characteristics of 18 cases of malignant histiocytosis including 2 autopsy cases with special interest on their immunohistochemical characteristics. We report 3 cases of unusual immunohistochemical finding and postulate these cases may be a supportive evidence of the view that dendritic cells share common precursor with those of mononuclear phagocytic system. More accumulated cases in the future and careful analysis would be needed to answer the basic question about the origin of malignant histiocytosis.

Key Words: Malignant histiocytosis, Immunohistochemistry, Histiocytic medullary reticulosis

INTRODUCTION

The malignant histiocytosis is a rare, fatal systemic disorder which is characterized by fever, wasting, generalized lymphadenopathy, hepatosplenomegaly, pancytopenia, and preterminal jaundice with progressive proliferation of atypical histiocytes showing marked erythrophagocytic activity. Since the initial description of four cases by Scott and Robb-Smith in 1939 under the name of 'Histiocytic Medullary Reticulosis', which was replaced by the term 'Malignant Histiocytosis' by Rappaport in 1966, many reports on its clinical and pathologic aspects have been introduced.

In this review, we summarized clinicopathologic feature of 18 cases that were diagnosed as histiocytic medullary reticulosis or malignant histiocytosis in our institution during the recent ten years and tried to analyze the origin of neoplastic histiocytes with immunohistochemical staining using peroxidase-antiperoxidase method for lysozyme, alpha 1 antitrypsin, and S-100 protein.

MATERIALS AND METHODS

The clinical records and histologic materials from 18 patients including two autopsy cases diagnosed as histiocytic medullary reticulosis or malignant histiocytosis in Seoul National University Hospital during January, 1978 to July, 1987 have been reviewed. There were two autopsies and 16 biopsy cases. Every biopsy case was diagnosed with specimens from organs or tissue other than bone marrow.

Clinical informations were collected from medical record review. Laboratory findings regarded as abnormal were also summarized. Histologic sections were reviewed without prior information on the bone marrow involvement. Data on survival was based on fifteen cases for whom adequate follow ups were possible and development of signs and symptoms that could not be explained by other reasons than malignant histiocytosis was regarded as beginning of the disease.

Seventeen cases out of 18 cases were available for the study of immunohistochemical staining. Stains for lysozyme, alpha 1 antitrypsin, and S-100 protein were performed using peroxidase-antiperoxidase method.

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RESULTS

Clinical Findings

1. Age and Sex Distribution (Fig.1)

Age of the patients ranged from 6 years to 55 years but more than two thirds of the patients were young adult population within their second to fourth decades and the mean age was 28 years. Among them, only three cases were female, thus revealing a marked male preponderance with the male to female ratio of 5:1.

Table 1. Initial symptomatic manifestations of malignant histiocytosis (n=18)

Manifestations	No. of cases (%)
Fever	15 (83%)
General weakness	9 (50%)
Headache	8 (44%)
Cough	5 (28%)
Weight loss	4 (22%)
Lumbago	4 (22%)
GI symptoms	3 (17%)
Easy bruisability	3 (17%)

Fig. 1. Age and sex distribution of malignant histiocytosis (n=18)

2. Initial Symptoms (Table 1)

Unexplained high fever was the most common presenting manifestation. Those nonspecific symptoms such as general weakness, headache, cough, weight loss, and gastrointestinal symptoms were also frequently observed. In four patients, lumbago was among major clinical presentations.

3. Physical Findings (Table 2)

Variable degree of hepatomegaly was present in seventeen patients. Splenomegaly and lymphadenopathy were also commonly found. Clinically detected jaundice was present in only three cases. Repeated bouts of pleural effusion and pitting edema were pre-

sent in two case and these patients had decreased level of serum protein. Erythematous skin lesions were

Table 2. Physical findings of malignant histiocytosis (n=18)

Findings	No. of cases (%)
Hepatomegaly	17 (94%)
Splenomegaly	14 (78%)
Lymphadenopathy	10 (56%)
Petechia, purpura	6 (33%)
Jaundice	3 (17%)
Pleural effusion	2 (11%)
Pitting edema	2 (11%)
Erythematous skin lesion	2 (11%)

observed in extremities of two patients.

4. Laboratory Findings (Table 3)

Marked decrease in blood cell population, elevation of SGOT and SGPT, hyperbilirubinemia, and hypoproteinemia were major abnormal findings. Thrombocytopenia, anemia, and leukopenia were found in over a half of the patients and only one patient had persistent leukocytosis over of 25,000/mm³. Erythrocyte sedimentation rate was elevated in 50 per cent of the patients and abnormal histiocytes were identifiable in peripheral blood smears in three patients.

Table 3. Abnormal laboratory findings of malignant histiocytosis (n=18)

Findings	No. of cases (%)
Thrombocytopenia (<130,000/mm ³)	15 (83%)
Anemia (<Hb 12 g/dl)	14 (78%)
Abnormal LFT	14 (78%)
Hyperbilirubinemia (>1.2 mg/dl)	12 (67%)
Hypoproteinemia (<Prot./alb. 6.0/3.3 g/dl)	10 (56%)
Leukopenia (<4,000/mm ³)	9 (50%)
Elevated ESR (>20 mm/hr)	9 (50%)
Peripheral blood histiocytosis	3 (17%)
Leukocytosis (>10,000/mm ³)	1 (6%)

Pathological Findings

1. Autopsy cases

The findings and clinical course of the two autopsy cases are summarized in Table 4.

Case 1 (A80-14): This was a case of a six years old boy presented with high fever and left submandibular swelling. Anemia and leukopenia were found during hospitalization for exploratory laparotomy due to intestinal hematoma after abdominal trauma that was sustained six months ago. Bone marrow biopsy revealed infiltration of atypical immature cells, and under the impression of metastasis of malignant lymphoma, he received chemotherapy with cytoxan, prednisolone, and vincristine. Although general condition got slightly improved, subsequent lymph node and liver biopsies showed histiocytic proliferative disorder. After a

few months, he developed a marked respiratory difficulty and high fever, and eventually died of respiratory failure. Postmortem examination revealed extensive fibrinous bronchopneumonia and involvement of multiple organs were found. Major microscopic finding was atypical histiocytic proliferation in lymph nodes, spleen, submucosa of esophagus, small intestine, liver, lungs, adrenals, kidneys, and bone marrow. Some of these atypical histiocytes showed prominent, strong erythrophagocytic activities. While diffuse pattern of involvement with marked sinusoidal distension was observed in lymph nodes and liver, atypical cells in kidneys and adrenals were present mainly as perivascular infiltrates around small blood vessels. In small intestinal and colonic mucosa, scattered atypical cell infiltration was observed in lamina propria and lymphoid tissue. Besides confluent fibrinous bronchopneumonia, opportunistic infections of candida and mucormycosis were present in the small intestine.

Case 2 (A87-3): This was a 25-year-old male patient who found easy bruisability during his military service. About one year later, dizziness and purpuric skin lesions developed, so he visited a general hospital, where splenomegaly and pancytopenia were found. Splenectomy was performed to correct his hypersplenism. During operation, reddish mucosal lesion was found in the terminal ileum and segmental resection of ileum was performed. The splenic weight was 950 gm and microscopic features of spleen and ileal lesion were typical findings of malignant histiocytosis. Despite subsequent multiagent chemotherapy, he died of massive gastrointestinal bleeding associated with sepsis. On postmortem examination, the liver was diffusely enlarged and weighed 2130 gm. The cut surface was rusty brown and showed mild cholestasis. Microscopically, hepatic sinusoids contained atypical histiocytes with intracytoplasmic red blood cells or hemosiderin pigments (Fig.2). Bone marrow and all lymph nodes were involved by neoplastic histiocytes with marked erythrophagocytic activity and their cut surfaces had characteristic brown hue. Bone marrow sections revealed hypercellular marrow involved by bizarre, atypical histocytes, and multinucleated giant cells. (Fig.3) Clusters of residual hemopoietic components were scattered. Reactive proliferation of megakaryocyte resembled tumor giant cells. Some of those atypical cells had abundant, foamy to bubbly cytoplasm. Sections from lymph nodes showed sinusoidal involvement with architectural effacement. (Fig.4) In the stomach, a diffuse elevated lesion with superficial ulceration was noted along the greater curvature.

Table 4. Clinical and pathological summaries of two of autopsy cases of malignant histiocytosis

	CASE 1 (A80-14)	CASE 2 (A87-3)
Sex/Age	M/6	M/25
Initial presentation	anemia, leukopenia	easy bruisability
Physical findings	fever, hepatosplenomegaly generalized lymphadenopathy purpura	hepatosplenomegaly fever, purpura preterminal jaundice
Lab. findings	pancytopenia blood culture; S.aureus alpha hemolytic streptococcus	pancytopenia hypoproteinemia abnormal LFT postmortem blood culture; E.coli, Paeruginosa, S.viridans
Organs involved	spleen, liver, lung, adrenal, kidney, bone marrow esophagus, small intestine lymph nodes	spleen, ileum, bone marrow liver, lymph nodes
Associated lesions	candidiasis, duodenum mucormycosis, ileum	clonorchiasis, liver occult papillary carcinoma, thyroid Herpes simplex, skin adrenal cortical nodule CHOP#2, COPP#2 COP-BLAM#2
Treatment	cytoxan-Pd-vincristine #2	
Survival	9 months	30 months
Cause of death	fibrinous bronchopneumonia	sepsis and associated GI bleeding

Fig.2. Every hepatic sinusoids contains plump, erythrophagocytic histiocytes (arrow).

Fig.3. Marrow space is involved by immature cells having abundant foamy cytoplasm.

Fig.4. Marked distension of sinusoids with architectural effacement in lymph node.

The lesion was intramural hematoma without evidence of tumor infiltration on microscopic examination. Entire gastrointestinal tract contained tarry, bloody material and showed foci of submucosal or intramural hemorrhage. Incidentally, *clonorchis sinensis* infestation in the liver and occult papillary carcinoma of the thyroid were found.

2. Biopsy cases

Majority of specimens were from liver and lymph nodes. Other sites included spleen, nasopharynx, and skin.

Liver: Liver sections were available in ten cases. Representative finding was prominent sinusoidal dilatation in which atypical histiocytes with large vesicular nuclei, foamy to abundant amphophilic cytoplasm. Variable degree of erythrophagocytic activities was observed. Sometimes numerous intracytoplasmic erythrocytes mimicked sinusoidal congestion. Among neoplastic histiocytes, population with benign looking, eccentrically located nucleus and abundant cytoplasm showed more marked hemophagocytic activity. In about half of the cases, widened portal space was also infiltrated by large atypical cells with hyperchromatic nuclei and variable amount of cytoplasm. Overt intrahepatic cholestasis was also present in two cases. Despite rather frequent elevation of hepatic en-

zymes in the patients, microscopic evidence of parenchymal necrosis was not present.

Lymph nodes: All lymph nodes of eight cases showed diffuse effacement of nodal architecture, with marked widening of subcapsular and medullary sinus. Normal follicles were nearly absent. patchy necrosis was found in one case and definite pericapsular spill out of atypical cells was present in two cases. The degree of maturation or differentiation of individual histiocyte varied markedly and binucleated giant cells were not uncommon. Active erythrophagocytosis by benign looking cells was also evident.

Spleen, nasopharynx, skin, and others: Microscopic features of individual cells were basically identical. Most of biopsy specimens showed focal or patchy background necrosis.

3. Immunohistochemistry (Table 5)

Results of PAP immunohistochemistry for lysozyme, alpha 1 antitrypsin, and S-100 protein in seventeen cases are summarized in table 5. Moderate to strong cytoplasmic staining of scattered tumor cells was observed in seven cases for S-100 protein (Fig.5). The four cases that showed positive staining for lysozyme or alpha 1 antitrypsin were completely negative for S-100 protein. In three cases, neoplastic cells were negative for all three markers.

Fig.5. In section from lymph node biopsy, atypical cells showed positive staining only for S-100 protein.

The remaining three cases showed weak to moderate but definitely positive staining for both S-100 protein and lysozyme or alpha 1 antitrypsin (Fig.6,7). Among these four groups with different immuno-histochemical characteristics, there was no notable difference in histologic features such as cellular atypism, erythrophagocytic activity, and pattern of involvement.

Duration of Survival, Treatment, and Bone Marrow Involvement (Table 6).

The data on survival was based on 15 cases for whom adequate follow up was possible. Those excluded cases were a 50-year-old male who was relatively well until 1 year after, but then who was lost to follow up. Two recent cases had too short period of follow up. The duration of survival ranged from 1 month to 7 years with median survival of 5 months and mean survival of 13.5 months. Though mean survival was 13.5 months, twelve patients out of fifteen died within one year. Three patients lived more than 30 months. It was interesting to note that these patients of long survival were common in that severe splenomegaly was the initial presentation. Bone marrow involvement was present in ten cases. There was no significant difference between groups according to therapeutic modalities.

DISCUSSION

The age and sex distribution in this series implies that the malignant histiocytosis is principally a disease of young adults and especially of male. This result coincides with those of previous studies (Warnke et al., 1975, Marshall, 1956, Ahn et al., 1984, Lee et al., 1986), though male preponderance is more exaggerated. Selection bias of patients in our institution as nation wide tertiary hospital may have played a minor role for the male preponderance because more males were admitted during this period. However, it seems true that malignant histiocytosis is more frequent in male as are all types of leukemias and histiocytosis.

In the laboratory findings, hypoproteinemia was frequently found than expected with decrease in both total protein and albumin level. Report of protein losing enteropathy in malignant histiocytosis (Clark et al., 1969) advocates the mechanism as direct involvement of intestinal mucosa by neoplastic cells and authors observed histiocytic proliferation in the lamina propria of small intestine. In the present study, one of two autopsies had a mild decrease in serum protein level and small bowel mucosa was infiltrated by atypical cells. These atypical cells were scattered among other

Fig.6,7. Scattered immature cells show cytoplasmic staining for both alpha 1 antitrypsin (Fig.6) and S-100 protein (Fig.7).

inflammatory cells in the lamina propria and lymphoid tissue of small intestine. The other autopsy case showed no mucosal involvement but the serum protein level was lower than the first case. Though intestinal villi showed mild to moderate edema in both cases, neither of them showed features of celiac disease such

Table 5. Immunohistochemistry findings done on 17 cases of malignant histiocytosis

Material	Alpha 1 antitrypsin	Lysozyme	S-100 protein	Remark
Lymph node	-	-	+	Biopsy
Liver	-	-	+	Biopsy
Liver, spleen	-	-	+	Necropsy
Liver, spleen, heart	-	-	+	Necropsy
Skin	-	-	+	Biopsy
Lymph node	-	-	+	Autopsy
Lymph node	-	-	+	Biopsy
Lymph node	+	-	+	Biopsy
Liver, spleen, lymph node	+	-	+	Biopsy
Liver	-	+	+	Biopsy
Lymph node	+	+	-	Autopsy
Lymph node and liver	+	+	-	Biopsy
Lymph node and nasopharynx	-	+	-	Biopsy
Lymph node	-	-	-	Biopsy
Liver	-	-	-	Biopsy
Liver	-	-	-	Necropsy

Table 6. Duration of survival, treatment, sites of diagnosis, and bone marrow involvement in malignant histiocytosis

No.	Age	Sex	Sites of diagnosis	Bone marrow involvement	Treatment	Survival
1.	29	F	liver	+		1 month
2.	19	M	lymph node	-	antibiotics	1 month
3.	31	M	lymph node	+	C-MOPP	2 months
4.	32	M	liver	-	BVP	2 months
5.	30	F	liver, spleen	-	antibiotics	2 months
6.	22	M	lymph node	-	antibiotics	3 months
7.	13	M	skin	+	pd, vincristine	3 months
8.	33	M	lymph node	+	C-MOPP #2	5 months
9.	39	M	liver	-	antibiotics	6 months
10.	55	M	liver	-	antibiotics	8 months
11.	6	M	liver, lymph node	+	cytoxan, pd #2 vincristine	9 months
12.	47	M	liver	+	CHOP	10 months
13.	25	M	liver lymph node	+	CHOP#2, COPP#2 COP-BLAM#2	30 months
14.	16	F	liver, spleen, lymph node	+		3 years
15.	14	M	liver, spleen, lymph node	-	pd	7 years
16.	50	M	lymph node, nasopharynx	+	C-MOPP#3	1 year well
17.	32	M	liver	+	CHOP#3	10 months-
18.	20	M	lymph node, liver	-	CHOP	4 months-

median survival: 5 months
mean survival: 13.5 months
* bone marrow involvement: 55.6%

as villous atrophy (Isaacson et al., 1982). Other possible etiologic factors for the hypoproteinemia might be hepatic failure due to involvement or malnutrition due to debilitating clinical course though not proven.

All the patients lived more than 30 months had common features. These were relatively chronic indolent clinical course and their initial presentation with marked splenomegaly for sufficiently long duration when compared with other cases. Evaluation of the splenic weight was possible in only one case who had splenic weight of 950 gm for whom autopsy was performed. He lived about 30 months since the beginning of the disease. Remaining two cases were a 14-year-old male and a 16-year-old female whose initial presentations were only splenomegaly and intermittent high fever. Three years and seven years have passed until more systemic, generalized symptoms with rapidly deteriorating clinical course developed. We think that these cases are chronic form of malignant histiocytosis associated with initial presentation with marked splenomegaly as previously reported cases of Vardiman et al (1975). But even these cases did not differ from other cases in clinical course once aggressive systemic symptoms developed. Their final course and pathologic findings didn't show any remarkable difference with other cases. It is interesting that initial involvement of spleen is a favorable prognostic factor in malignant histiocytosis of which marked erythrophagocytic activity of atypical histiocytes is characteristic feature and spleen is the major site where senescent red blood cells are phagocytized by macrophages.

Various cytochemical and immunohistochemical markers for histiocytic proliferative disorders have been introduced. Among these we selected lysozyme and alpha 1 antitrypsin for histiocytes of mononuclear phagocytic system origin and S-100 protein for those belonging to dendritic cells or so called T-zone histiocytes. With these three immunohistochemical markers, we analyzed 17 cases in our study.

Recently, Watanabe et al (1983), in their analysis of 14 cases of malignant histiocytosis and Letterer-Siwe disease, used S-100 protein as a valuable marker and proposed the concept of neoplasms of T-zone histiocytes with S-100 protein. They explained that malignant histiocytosis has at least dual origins, from S-100-/lys+/NCA+(S-100 protein/lysozyme nonspecific cross reacting antigen with carcinoembryonic antigen) mononuclear phagocytic system and S-100+/lys-/NCA- so called T-zone histiocytes.

The lysozyme and alpha 1 antitrypsin have been introduced by many authors as helpful markers in the

diagnosis of malignant histiocytosis. Mendelsohn et al (1980) observed difference in stainability on immunohistochemical staining for lysozyme among ten cases of malignant histiocytosis according to degree of cytologic atypia and hemophagocytic activity. Most poorly differentiated or dedifferentiated neoplastic cells were negative while cases with minimal cytologic atypia were moderately to strongly positive for lysozyme.

Our result of immunohistochemical findings is somewhat confusing in some aspects. Among 17 cases, 7 cases were positive for S-100 protein only with diffuse moderate to strong cytoplasmic positivity and 4 cases were only positive for lysozyme or alpha 1 antitrypsin with variable stainability and 3 cases were negative for all 3 kinds of antibodies.

The remaining 3 cases showed unexpected results. In these cases, scattered neoplastic cells were weakly to moderately but definitely positive not only for S-100 protein but also for lysozyme and/or alpha 1 antitrypsin. We are not aware of any report of malignant histiocytosis that showed above mentioned pattern of immunohistochemical finding. How can we explain this unusual finding? Though definitive and precise interpretation of the result may be impossible now, a kind of suggestion can be made. In a given cell, antigenic expression is a reflection of certain function or biologic feature of the cell that may precede or follow morphologic change. In this sense, lysozyme and S-100 protein are representative expressions for 2 major functions of histiocytes, phagocytosis and antigen presentation to lymphocyte, respectively. Malignant histiocytosis is a proliferative disorder of immature histiocytes lying in between those of monocyte and mature macrophage and through the dedifferentiation process neoplastic histiocytes may acquire or lose their initial phenotypes as in other common tumors. Though our present knowledge about macrophages and S-100 protein positive dendritic cells is incomplete, informations from study of Langerhans cells, the most extensively studied of all dendritic cells, raise the possibility that dendritic cells may share common precursor with mononuclear phagocytic system.

The concept of malignant histiocytosis of T-zone histiocytes with S-100 protein is still valid for our cases which showed positivity for only S-100 protein. But we didn't see any notable morphological difference in this group and others, even in hemophagocytic activity. Three cases that showed no reaction for all markers may be understood in the spectrum mentioned in report of Mendelsohn et al, that is to say, tumor cells in these cases may have lost their antigenic expres-

sion through dedifferentiation to the level that can not be detected with immunohistochemical method.

Malignant histiocytosis is still a rapidly fatal disorder of unknown etiology and no effective therapeutic modality is present. It arises from malignant proliferation of histiocytes of mononuclear phagocytic system and dendritic cells and possibly from intermediate precursor cells between the two. The involved cell level is usually immature macrophage but even basic stem cell abnormality may be present especially in the cases of malignant histiocytosis associated with acute lymphocytic leukemia as authors postulated in their reports (Shreiner, 1975, Skoog et al., 1978).

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