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Malignant Histiocytosis: A Reassessment of Cases Formerly Classified as Histiocytic Neoplasms and Review of the Literature

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Malignant histiocytosis (MH) and true histiocytic lymphoma (THL) are hematopoietic malignancies of the mononuclear phagocytic system distinguished from each other by clinical presentation and presumed cell of origin. THL present as a localized mass derived from the fixed tissue histiocyte which may or may not disseminate. MH originates from the circulating monocyte or tissue macrophage and is characterized by a syndrome of systemic symptoms, pancytopenia, adenopathy, hepatosplenomegaly, and wasting. The distinction between MH and THL is at times arbitrary and overlap exists between these syndromes. The clinicopathologic studies that defined these entities were performed prior to the development of immunophenotyping and other molecular techniques currently used to ensure proper classification of hematopoietic malignancies. Nine patients from the University of Minnesota originally diagnosed with MH were retrospectively analyzed using a panel of antibodies reactive against T cell, B cell, and myelomonocytic antigens. Only one patient was reclassified as a possible histiocytic malignancy after reevaluation. Similar immunophenotyping studies have also shown cases previously diagnosed as MH or THL express lymphoid antigens, and would now be classified as Ki-1 positive anaplastic large cell lymphoma (ALCL) or some other hematopoietic neoplasm. These results indicate true histiocytic neoplasms are extremely rare, and previous concepts concerning clinical presentation and therapeutic outcome of the entities are inaccurate. In this paper we summarize the results of multiple retrospective analyses of cases previously diagnosed as MH or THL, including our experience at University of Minnesota, to illustrate the overall rarity of these entities. The current literature on malignant histiocytic disorders is reviewed, and the clinical presentation of patients determined to have histiocytic malignancies using contemporary analytical techniques is discussed.

Key words: malignant histiocytosis, anaplastic large cell lymphoma, neoplasm

INTRODUCTION

Tumors of presumed histiocytic origin are a controversial subset of hematopoietic malignancies including true histiocytic lymphoma (THL) and malignant histiocytosis (MH). THL is defined as a focal proliferation of malignant histiocytes which may or may not disseminate. MH is characterized a syndrome of fever, wasting, pancytopenia, hepatosplenomegaly, adenopathy, and a systemic proliferation of malignant histiocytes [1]. The disease occasionally presents with isolated involvement of the gastrointestinal tract [2]. The distinction between MH and THL is at times arbitrary and the clinical syndromes may merge.

The clinicopathologic studies which defined histiocytic neoplasms were performed prior to the development of immunologic and molecular techniques now used to properly classify hematopoietic malignancies. We evaluated nine patients from the University of Minnesota originally diagnosed with MH using a broad panel of antibodies reactive with B cell, T cell, and myelomonocytic antigens. Only one of nine patients analyzed was reclassified as a possible histiocytic malignancy [3]. Similar immunophenotyping studies also have shown most cases previously diagnosed as MH or THL by clinical and morphologic criteria are in fact Ki-1 anaplastic large cell

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TABLE I. Criteria Used for Diagnosis of True Malignant Histiocytosis

Immunophenotyping
Cells are negative for T and B cell-associated antigens, and express antigens associated with monocyte/macrophage origin including
Myelomonocytic antigens:
CD11b, CD11c, CD13, CD14, CD15, CD33, lysozyme
Monocyte–macrophage antigens:
CD36, CD68, MAC-387, α_1-antitrypsin, α_1-antichymotrypsin
Antibodies associated with other lineages which may show reactivity with cells of monocyte/macrophage lineage:
HLA-DR, CD43, CD45RO, CD45 (LCA), CD74
Gene rearrangement studies[a]
Negative B immunoglobulin and T cell antigen receptor gene rearrangement studies

[a]It is generally assumed that Ig and TcR gene rearrangements are only functional in B and T cells, respectively. We also have used this as criterion. Nevertheless, we are aware of the fact that such rearrangements have been described to occur occasionally in cells from other lineages as well, known as cross-lineage rearrangements.

lymphoma (ALCL) or some other hematopoietic neoplasm [4–13]. While these results point to the rarity of these entities, sporadic cases exist which meet contemporary criteria for a malignant histiocytic disorder [14–18].

As most cases of MH and THL are now proven to be a heterogeneous group of other hematologic disorders, the clinical features traditionally associated with these syndromes should also be questioned. In this article we review the current literature on histiocytic malignancies, including our experience at University of Minnesota and other reevaluation studies, to illustrate the overall rarity of these neoplasms. The clinical presentation of patients determined to have true histiocytic malignancies by contemporary criteria are evaluated and discussed. Given the frequent overlap of these entities, the presenting feature of THL and MH will be discussed together under one category of true histiocytic malignancies.

MATERIALS AND METHODS

Reevaluation of Patients From University of Minnesota Previously Diagnosed With Malignant Histiocytosis

From 1967 to 1992 14 patients were diagnosed with MH at the University of Minnesota. The diagnosis was originally made by clinical examination, laboratory findings, radiographic studies, and morphologic interpretation of hematoxylin and eosin-stained biopsy sections.

In 1992 we reanalyzed the pathologic characteristics of these patients incorporating a large panel of immunoperoxidase antibody stains reactive against B cell, T cell, and myelomonocytic antigens on archival paraffin-embedded tissue. Detailed results of this study are published elsewhere [3].

In brief, the antibodies used included CD30 (ber H2/Ki-1), EMA (epithelial cells, some lymphomas), CD45 (pan hematopietic), CD20 (B cell), CDw75 (B cell), CD74 (B cell), MB-2 (B cell), κ, λ, CD45RO (T cell), CD3 (T cell), MT-1 (T cell), lysozyme (myelomonocytic), α_1-antitrypsin and α_1-antichymotrypsin (monocyte/macrophage), CD68 (monocyte/macrophage), CD36 (monocyte/macrophage), CD15 (myelomonocytic, Reed Sternberg cells), and S-100 (neural origin cells, Langerhans cells). Frozen material for gene rearrangement studies was unavailable.

Literature Review and Criteria for Inclusion as True Histiocytic Malignancy

A medline computerized search was conducted to identify studies and case reports of MH or THL. Patients were determined to have a true histiocytic malignancy only when strict criteria was met as outlined by Weiss and others [19,20] (Table I). Histiocytic malignancies are negative for pan B and T cell markers by immunophenotyping and show expression of multiple monocyte/macrophage associated antigens including CD11b, CD11c, CD13, CD14, CD15, CD33, CD36, CD68, and MAC-387. Cytoplasmic enzymes such as α_1-antitrypsin, α_1-antichymotrypsin, or lysozyme are often present but are not specific enough to determine histiocytic lineage [16]. Isolated reactivity with antibodies associated with B or T lineage known to crossreact with cells of monocyte/macrophage lineage is acceptable, but expression of multiple B or T cell markers suggests lymphoid lineage. When air-dried material is available, the cells are positive for nonspecific esterase, and negative for myeloperoxidase.

As lymphomas lacking T or B cell antigens, with or without expression of histiocytic markers, may show evidence of lymphoid lineage by gene rearrangement studies [4,7,8,21], cases lacking gene rearrangement analysis were not included [22–27]. Patients developing acute monocytic leukemia after an initial diagnosis of MH or THL were excluded as these most likely represent granulocytic sarcomas [28,29]. Patients diagnosed with a malignant histocytic disorder who had evidence of B or T cell lineage by immunophenotyping or gene rearrangement studies were also excluded [30].

RESULTS

Reevaluation of Patients From University of Minnesota Previously Diagnosed With Malignant Histiocytosis

Nine of 14 patients diagnosed with MH at the University of Minnesota had complete clinical and pathologic data available for review. Eight of the nine patients originally diagnosed with MH were reclassified as having other hematologic malignancies based on the immunoperoxidase antibody studies. The results of this study are summarized in Table II and discussed below along with other reevaluation studies. One patient had a neoplasm of possible histiocytic origin by immunophenotyping. However, gene rearrangement studies were not performed and the true lineage is therefore uncertain.

Summary of Literature Review of the Reevaluation Studies

Eleven studies, including ours, have retrospectively analyzed and reclassified cases previously diagnosed as histiocytic malignancies using immunophenotyping or gene rearrangement analysis. The results of these studies are summarized in Table II. Approximately 164 cases of MH or THL have been analyzed with the majority of cases being reclassified into Ki-1 ALCL (114 cases), T or B cell lymphomas (24 cases), or some other category of hematopoietic disorder (7 cases). Nineteen cases retained the diagnosis of MH/THL after reevaluation. These cases were negative for B and T cell markers and expressed monocyte–macrophage-associated antigens by immunophenotyping. Gene rearrangement studies, however, were not performed and the possibility of a B or T cell lymphoma cannot be ruled out. Nine cases were reclassified as Ki-1 lymphoma of possible histiocytic lineage. These cases were negative for B and T cell markers and expressed monocyte–macrophage-associated antigens in addition to CD30 (Ki-1 antigen). With the exception of one case, gene rearrangement studies were not performed and a lymphoid lineage for these lesions cannot be ruled out [9]. Tumor cells in the case with gene rearrangement studies expressed histiocytic antigens and lacked evidence of B or T cell lineage by immunophenotyping or gene rearrangement studies. This case is discussed below under Ki-1 positive lymphomas of possible histiocytic lineage.

Clinical Presentation of Patients With True Histiocytic Malignancies Determined by Contemporary Diagnostic Techniques

Application of the criteria for true histiocytic tumors to published cases of MH or THL reveals several cases which appear histiocytic in origin by immunophenotyping, but marked paucity of cases where B or T lineage has been excluded by gene rearrangement studies.

The clinical features of patients meeting all criteria for true histiocytic neoplasms are listed in Table III. Most patients presented with one or two sites of focal involvement with a high incidence of extranodal presentation. Cytopenias and systemic symptoms were sporadically noted. Hepatosplenomegaly was absent with isolated splenomegaly noted in 2 patients. Only one of seven patients presented with a clinical syndrome resembling MH including splenomegaly, lymphadenopathy, pancytopenia, fever, and systemic symptoms.

Of the several published studies excluded for lack of gene rearrangement analysis, two studies warrant further discussion given the large numbers of patients in those series. Sonneveld et al. [11] described 12 patients who retained the diagnosis of MH after reevaluation by immunoperoxidase studies. These patients presented with a clinical syndrome resembling MH, including lymphadenopathy (92%), splenomegaly (100%), hepatomegaly (75%), thrombocytopenia (92%), anemia (92%), leukocytopenia (67%), and fever. A similar retrospective study of seven patients reclassified as MH by immunophenotyping reports a lower incidence of presenting features associated with MH [12]. All patiens had fever and generalized lymphadenopathy and 50% reported weight loss. Splenomegaly was noted in 42% and hepatosplenomegaly in 28%. No comment was made on hematologic data. While these last two studies may represent true histiocytic neoplasms, generalizations concerning these data should be guarded. Gene rearrangement studies were not performed and a lymphoid lineage is not entirely ruled out.

Clinical Presentation of Patients With CD30 positive (Ki-1 Associated Antigen) Lymphomas of Histiocytic Lineage by Contemporary Diagnostic Techniques

Patients with Ki-1 positive anaplastic lymphoma generally show evidence of T or B cell lineage with some patients demonstrating a mixed or indeterminate lineage. Review of the literature reveals an unusual subset of $CD30^+$ lymphomas with expression of monocyte–macrophage-associated antigens which lack evidence of T or B cell lineage by immunophenotyping or gene rearrangement studies [9,15,31,32]. The clinical features of this group were further evaluated to determine if this category of neoplasms is clinically unique.

As seen in Table IV, most patients presented with one or more sites of focal involvement with a high incidence of lymph node and extranodal involvement. Except for one patient, hepatosplenomegaly was not a feature of these patients and systemic features were sporadically reported. Hematologic data were not provided. One patient presented with a clinical syndrome resembling MH including hepatomegaly, lymphadenopathy, systemic symptoms, and a disseminated neoplasm.

TABLE II. Results of Malignant Histiocytosis Reevaluation Studies*

Reference	Number of cases	Method of reevaluation	New diagnosis
Stein et al., 1985 [4][a]	45	Immunophenotyping, limited gene rearrangement studies	35 Ki-1 lymphoma, T cell type 7 Ki-1 lymphoma, B cell type 3 Ki-1 lymphoma, uncertain or mixed lineage
Weiss et al., 1985 [5][b]	6	Immunophenotyping, gene rearrangement studies	4 T cell lymphoma 1 B cell lymphoma 1 unclassified (possible IR)
Isaccson et al., 1985 [6]	4	Immunophenotyping gene rearrangement studies	1 unclassified 3 T cell lymphoma
Delsol et al., 1988 [7][c]	27	Immunophenotyping	12 Ki-1 lymphoma, T cell type 4 Ki-1 lymphoma, B cell type 11 Ki-1 lymphoma, uncertain or mixed lineage
Cattoretti et al., 1990 [8]	10	Immunophenotyping gene rearrangement studies	5 T cell lymphoma 5 Ki-1 lymphoma, uncertain lineage
Van der Valk et al., 1990 [9][d]	12	Immunophenotyping gene rearrangement studies	2 B cell lymphomas 1 probable B cell lymphoma 1 T cell lymphoma 1 unclassified 4 Ki-1 lymphoma, T cell type 2 Ki-1 lymphoma, probable T cell type 1 Ki-1 lymphoma, possible histiocytic lineage
Wilson et al., 1990 [10]	15	Immunophenotyping	3 T cell lymphoma 2 B cell lymphoma 6 Ki-1 lymphoma, T cell type 2 Ki-1 lymphoma, uncertain lineage 1 IAHS 1 unclassified
Sonneveld et al., 1990 [11][e]	12	Immunophenotyping	12 malignant histiocytosis
Hsu et al., 1991 [12][f]	13	Immunophenotyping limited gene rearrangement studies	6 malignant histiocytosis 7 Ki-1 lymphoma, histiocytic lineage
Nezelof et al., 1992 [13][e]	11	Immunophenotyping	1 Ki-1 lymphoma, possible T cell type 9 Ki-1 lymphoma, histiocytic lineage 1 unclassified (questionable Ki-1 positivity)
Own patients [3]	9	Immunophenotyping	1 Ki-1 lymphoma, T cell type 2 Ki-1 lymphoma, B cell type 2 Ki-1 lymphoma, lineage indeterminate 2 AML (FAB M5) 1 unclassified 1 possible histiocytic neoplasm

*IAHS, infectious associated hemophagocytic syndrome; IR, interdigitating reticulum cell.
[a]Majority of cases originally diagnosed as MH, exact number not stated. Evaluation for immunoglobulin heavy chain rearrangement only.
[b]CD30 studies were not done.
[c]Only 27 of 63 cases had complete immunophenotyping data. The exact number of these cases which were previously diagnosed as MH is not stated.
[d]Includes one case of Ki-1 positive lymphoma with expression of monocyte–macrophage numbers by immunophenotyping (IP) and lack of T cell or B cell differentiation by IP or gene rearrangement studies. This case is included in Table IV.
[e]Possibility of T or B cell lineage not ruled out by gene rearrangement studies.
[f]Malignant cells lack T and B cell markers and express histiocytic antigens. Gene rearrangement studies done in only 5 of 13 cases; exact cases not specified.

One study excluded from Table IV due to lack of gene rearrangement studies warrants further discussion given the large number of patients in this series [13]. The clinical features of 20 patients with $CD30^+$ lymphoma of histiocytic lineage by immunophenotyping are described. Patients in this group presented with a high incidence of lymphadenopathy (95%) and systemic symptoms (75%). Splenomegaly, hepatomegaly, and pancytopenia were noted in 30 to 40% of patients. As stated in the previous section, while cases from this study may represent

TABLE III. Clinical Features at Presentation of Patients With Possible Histiocytic Malignancies*

Study/case number	Sex/age	Fever and/or systemic symptoms	Pan	Hep	Spl	Lym	Pos Biop	BM	Rx	Survival
Ralfkiaer et al., 1990 [14]										
2	M/73	No	No	−	+/−	−	Sk	+	Chemotherapy	6 months
3	M/75	No	No	−	−	−	Sk, Lu	−	None	0.5 months
4	M/57	No	No	−	−	−	Sk	−	Chemotherapy	5 months
Levine et al., 1991 [5]										
2	M/30	Yes	NA	−	−	−	Med	−	Chemotherapy ABMT	18 months
Kamesaki et al., 1988 [16]										
1	F/41	Yes	Yes	−	+	+	Lym	−	Chemotherapy	3 months
Milchgrub et al., 1992 [17]										
1	M/60	NA	NA	−	−	+	Il mass	−	Chemotherapy	DF 2 years
Franchino et al., 1988 [18]										
1	M/38	No	Yes	−	+	−	Spl	−	Splenectomy	DF 13 months

*Includes only patients with expression of monocyte–macrophage-associated antigens, lack of T or B cell antigens, and negative T and B cell gene rearrangement studies. Pan, pancytopenia; Hep, hepatomegaly; Spl, splenomegaly; Lym, lymphadenopathy; Pos Biop, positive biopsy; BM, bone marrow; Rx, treatment; Sk, skin; Lu, lungs; Med, mediastinum; Il, ileal; ABMT, autologous bone marrow transplantation; DF, disease free; NA, not addressed.

TABLE IV. Clinical Features at Presentation of Patients With Possible Histiocytic Malignancies Expressing CD30 (Ki-1)-Associated Antigen*

Study/case number	Sex/age	Fever and/or systemic symptoms	Pan	Hep	Spl	Lym	Pos Biop	BM	Rx	Survival
Levine et al., 1991 [15]										
4	F/42	No	NA	−	−	+	Gl mass Lym	−	Chemotherapy	DF 4 months
6	M/68	No	NA	−	−	+	tongue Lym	−	Chemotherapy	Cr, NA
7	F/10	No	NA	−	−	−	Sk	−	Chemotherapy	Multiple recurr 8 years
Carbone et al., 1990 [31]										
2	M/18	Yes	No	−	−	+	Lym	−	Chemotherapy	DF 23 months
Banks et al., 1990 [32]										
1	F/52	Yes	NA	+	−	+	Lym, hep, kidney, ovaries	−	Chemotherapy	Expired no response at all
Van der Valk et al., 1990 [9]										
10	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

*Includes only cases with expression of monocyte–macrophage-associated antigens, lack of T or B cell antigens, and absence of T and B cell receptor and B cell immunoglobulin gene rearrangement. Pan, pancytopenia; Hep, hepatomegaly; Spl, splenomegaly; Lym, lymphadenopathy; Pos Biop, positive biopsy; BM, bone marrow; Rx, treatment; Sk, skin; Gl, gluteal; ABMT, autologous bone marrow transplantation; DF, disease free; NA, not addressed.

true histiocytic neoplasms, generalizations concerning these data should be guarded as B or T cell lineage is not ruled out.

DISCUSSION

The results of our study and multiple other studies analyzing archival tissue of cases previously diagnosed malignant histiocytosis/histiocytic lymphoma demonstrate the overall rarity of these entities. Prior to the availability of immunophenotyping and molecular techniques now used to classify hematopoietic neoplasms, MH was diagnosed on the basis of a syndrome of fever, wasting, pancytopenia, hepatosplenomegaly, lymphadenopathy, and a systemic proliferation of malignant appearing histiocytes. The majority of these cases are now

known to be Ki-1 anaplastic large cell lymphoma or some other hematologic disorder. The clinical features traditionally associated with histiocytic neoplasms should also be questioned and necessitates further evaluation.

While these studies demonstrate the overall rarity of MH and THL, a small number of cases exist in the literature which appear to be of histiocytic origin using current nosologic concepts of lymphoma and contemporary analytic techniques. These cases express surface antigens associated with monocyte-histiocyte origin and lack evidence of T or B cell lineage by immunophenotyping or gene rearrangement studies. A group of related neoplasms exists which appear to be of histiocytic origin but in addition express the Ki-1-associated antigen. The presenting clinical features of these two groups were further evaluated to determine the clinical features associated with true histiocytic neoplasms diagnosed by contemporary techniques.

Although numbers are limited, the clinical presentation of patients with histiocytic neoplasms is heterogeneous and lacks a consistent clinical syndrome. These patients have one or more focal lesions with frequent extranodal proliferations. Fever, systemic symptoms, and cytopenias were sporadically reported. Patients with neoplasms of histiocytic lineage with CD30 antigen expression are similar and presented with one or more focal sites of involvement with frequent nodal and extranodal proliferations. Systemic symptoms were noted in two patients. Hematologic data were not given. Only one patient from each group presented with clinical features resembling MH.

These results must be viewed as preliminary as large numbers of patients with histiocytic neoplasms by immunophenotyping were excluded from evaluation due to lack of gene rearrangement studies. We feel this exclusion criteria is valid as studies have shown lymphomas indeterminate for B or T cell lineage by immunophenotyping studies may have clonal T cell antigen or B cell immunoglobulin gene rearrangements. Some of these cases lacked B and T cell-associated antigens, express histiocytic antigens, and would have been misclassified as a histiocytic neoplasm in the absence of gene rearrangement studies [5,8,9,21,33]. We recognize that gene rearrangements are not specific exclusively to lymphoid lineage and occasional myeloid tumors show gene rearrangements. However, given the history of misdiagnosis of this entity, in this manuscript we recommended a diagnosis of MH/THL be made only in cases where immunophenotyping results support a histiocytic lineage and the cells lack T cell or B cell related gene rearrangements [19].

It is of interest that most cases previously diagnosed as MH are Ki-1 positive anaplastic large cell lymphoma. While lymph node and/or skin involvement is the most common presentation of Ki-1 lymphoma, a small subset of patients present with pancytopenia, hepatosplenomegaly, lymphadenopathy, fever, and wasting [8,13,34]. Some authors theorize the clinicopathologic syndrome previously described as MH may in fact represent a subset of Ki-1 lymphoma, and suggests this subtype is recognizable on the basis of a 5q35 cytogenetic abnormality [35]. This theory is speculative and needs confirmation by further studies. Cases of Ki-1 lymphoma have been reported with the 5q35 cytogenetic abnormality which do not present with this syndrome [36,37].

The possibility that the present cases of histiocytic neoplasms may be related to a localized form of monocytic leukemia (AML M5b) cannot be excluded. It is known monocytic leukemia may present as a extramedullary mass without blood and marrow involvement [38–40]. Results of immunophenotyping and gene rearrangement studies would be similar in monocytic leukemia and histiocytic lymphomas. Morphologically AML M5b is composed of monoblasts, promonocytes, and monocytes. True histiocytic malignancies are reportedly composed of malignant appearing monocytes with greater variation in cell size and nuclear morphology [1,14], a distinction which may be difficult and arbitrary. Careful consideration must be given to this possibility before a histiocytic neoplasm is diagnosed.

It is clear much work in the area of histiocytic malignancies remains to be done. A diagnosis of a true histiocytic neoplasm should not be considered unless strict pathologic criteria are met as outlined in this paper. Only until appropriate pathologic techniques are used on all cases can progress be made in identifying these patients and determining the cell of origin, the clinical presentation, appropriate treatment, and outcome. Once a unified approach in diagnosis is used the true nature of these neoplasms can be uncovered.

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