caso clinico

The controversial issue of malignant histiocytic disorders personal observations and review of the literature

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Abstract. The Authors describe two cases, initially diagnosed on morphological and clinical grounds, as malignant histiocytic proliferations, in which cytochemical, immunocytochemical and genotypic investigations demonstrated a probable histiocytic malignancy in one case and a B lymphoma in the other.
While the results of the studies on IgG and TCR rearrangements have not provided a definite answer with regards to their usefulness in separating lymphoid proliferations from the so-called histiocytic disorders, a panel of immunocytochemical techniques, especially that employed for demonstrating lysozyme, together with a number of cytochemical reactions may be helpful in establishing a correct diagnosis towards one disorder rather than another.
The Authors outline all the diagnostic problems which underline hystiocytic proliferations and take the opportunity for a critical review of the most recent literature.

Introduction

There are few disease entities so confusing as those related to the histiomonocytic cells and their malignant proliferations, defined either as Malignant Histiocytosis or histiocytic lymphoma. Both terms have been considered synonymous and employed indifferently by most Authors, although certain differences in the clinical manifestations have sometimes been outlined.
The term "malignant-histiocytosis" was applied to a hematological condition first described by Scott and Robb-Smith [1] as histiocytic medullary reticulosis on the basis of its clinical features. Rappaport [2] introduced the term "malignant histiocytosis**"** in 1966 and reviewed the pathological features of this condition. Malignant histiocytosis has been considered a most aggressive disease. It was characterized by the systemic proliferation of malignant cells [3] and presented with fever, wasting, pancytopenia, hepatosplenomegaly and adenopathy.
Reevaluation of cases formerly considered malignant histiocytosis, however, disclosed that the malignant cells were not histiocytes but various other cell types, including T-cells, B-cells, CD30+ anaplastic lymphoid cells and possibly others [4-5-6-7-8-9-10-11-12].
Notwithstanding these results, there remain case reports and descriptions of small series of lymphomas with features suggestive of a true histiocytic derivation [13-14-15-16-17-18].
In view of these conflicting reports, it seems justifiable to provide further contribution to this intriguing issue and to attempt a definition of the biological and clinical features which characterize these unusual and atypical malignant proliferations.
A substantial improvement in the recognition and definition of these histiocytic disorders derives from the results of a study carried out by a group of Pathologists and haematologist/oncologists who have recently proposed an updated classification of the proliferative histiocytic disorders of childhood, which replaces that of the Histiocyte Society, published a decade ago [19].
According to these Authors, under the heading of "histiocytes" are included both macrophages and monocytes as "antigen processing cells" and dendritic cells as "antigen presenting cells" of the mononuclear phagocytic system (MPS). The Authors furthermore propose the abandoning of the confusing terms "histiocytic lymphoma" and "malignant histiocytosis".
Lymphomas are malignant tumours of different lymphoid cell types and therefore cannot be "histiocytic". There are instead very rare tumors that may mimic large cell anaplastic lymphomas (LCAL) by morphology but the tumor cells show clear markers of monocytes and/or macrophages without any lymphoid properties. They should be designated as monocytic- or macrophage-related histiocytic sarcomas (MMHS) [20].
These different entities differ only in phenotype, so that the signs and symptoms of these rare malignant histiocytic disorders cannot be differentiated on the

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basis of the limited number of reports available for a critical review. The problem is further complicated by the fact that many cases, diagnosed as "malignant reticulosis " were actually cases of large cell anaplastic lymphomas.
In general, it may be stated that the clinical manifestations, according to the most reliable descriptions, include generalized and localized lymphadenopathies, skin rashes, hepatosplenomegaly, jaundice, pancytopenia, cutaneous and pulmonary localizations. Despite the wide-spread dissemination of the condition, bone-marrow involvement is present initially in only a small number of patients. Patients suffer from weight loss, fever, general weakness and occasionally from hemolytic anaemia.
The exact frequency of the various symptoms reported is uncertain on account of the rarity of the condition. However, malignant histiocytic disorders do not differ clinically from advanced non Hodgkin lymphomas, although most probably extra-nodal and cutaneous involvement are more frequently observed.
Generalized symptoms are not well defined for the dendritic cell related malignancies, which are more often localized to the skin or lymphnodes or both and do not have a tendency to disseminate unlike in monocytic or macrophage-related histiocytic sarcoma (MMHS).
To exemplify the considerable difficulties which may be encountered in diagnosing a case of a malignant histiocytic proliferation, we describe two cases. Initially diagnosed on histological and clinical grounds, as true histiocytic sarcomas in which subsequent cytochemical, immunocytochemical and genotypic studies revealed a true histiocytic malignancy in one case and a B cell lymphoma in the other.

Patients and methods

CASE 1: a 14 years old boy, who was admitted to our unit because of persistent fever, weight loss, diffuse muscular and bone pains.
Laboratory investigations showed an increase in both transaminases, alkaline phosphatase and gammaglutamyl-transpeptidase. Ultrasonography showed the presence of spleno-hepatomegaly and the presence of focal lesions in the context of the latter organ; lymphnodes were not enlarged.
Antibodies anti-hepatitis, both B and C were absent. Bilirubin was normal. A blood count showed a slight degree of normocytic-normochromic anaemia, leucocytosis (WBC 15 10^9/L) but a normal differential count. All other laboratory test were normal. Both liver and bone marrow biopsy were carried out soon after admission. Histological examination of liver and bone marrow sections indicated the presence of neoplastic cells, compatible with a diagnosis of histiocytic lymphoma.
The patient was given six courses of Promyce-CytaBom which induced a clinical remission lasting several months. At relapse, the patient was given further courses of chemotherapy according to the MIPE schedule; however death supervened 1 year after diagnosis.

CASE 2: a 51 years old man with a five years history of chronic renal failure. He was admitted to our Medical Unit because of high temperature, nausea and vomiting, right upper quadrant abdominal pain and jaundice. Laboratory exames showed increased levels of transaminases, alkaline phosphatase, glutamyl transpeptidase and lactic dehydrogenase. Total bilirubin was 21.4 mg/100mL; haemoglobin was 8.4 g/100mL; WBC 9.2 10^9/L with a normal differential count. Blood urea 294 mg/100mL, serum creatinin 6.7 mg/100mL. Antibodies against Epstein Barr virus and Cytomegalovirus were negative.
Serological studies and a search for parasitic, bacterial and viral agents failed to identify any infectious cause. Physical examination revealed hepato-splenomegaly but no lymph-node enlargement.
Abdomen ultrasonography and computerized tomography confirmed liver and spleen enlargement without focal lesions. No dilation of the biliary tract was observed. The patient underwent liver and bone marrow biopsy. On the basis of liver histology and bone marrow cytology a diagnosis of malignant histiocytosis was put forward.
The patient was given chemotherapy according to the Promice-CytaBom schedule but his clinical conditions rapidly deteriorated with progressively marked liver and renal failure and died in a few days.
In both cases bone marrow slides were stained by May-Grünwald-Giemsa and by the following cytochemical methods: periodic-acid Schiff (PAS), peroxidase, acid phophatase, sudan black B, a-naphthyl butyrate esterase, naphtol AS-B Chloracetate esterase, according to the techniques described by Hayhoe and Quaglino [21].
Immunocytochemical investigations were carried out both on formalin-fixed and paraffin-embedded liver biopsy specimens, and bone marrow preparations. The following panel of monoclonal antibodies were employed: CD3, CD20, CD43, CD68, GPIIIa, CD45RA, S-100, vimentine, MAC387. Lysozyme was demonstrated on paraffin embedded sections using a polyclonal antibody, according to the technique of Mason [22]. The immunocytochemical techniques employed were based on the use of the PAP and APAAP methods as described in Hayhoe and Quaglino [21]. Ig and TCR gene rearrangement studies were carried out in both cases with the Southern Blotting technique [23].

Figure 1. Presence of neoplastic cells gathered in nodular structures, infiltrating normal liver tissue. Case 1. Bone marrow biopsy. Hematoxylin-Eosin.

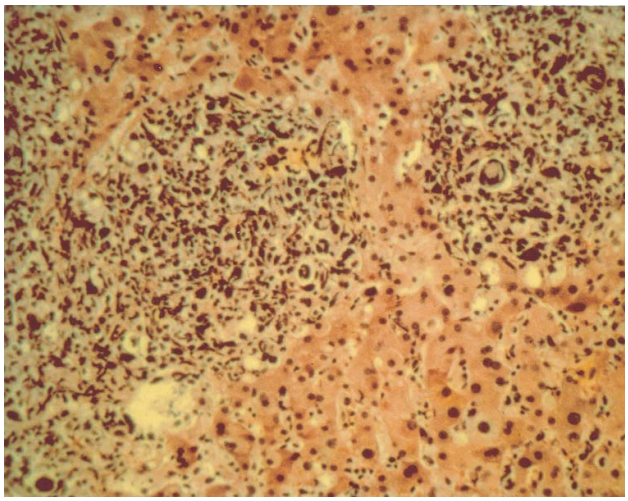


Figure 2. Extensive infiltration of the liver in case 2 by neoplastic cells with atypical morphological features. Bone marrow biopsy. Hematoxylin-Eosin

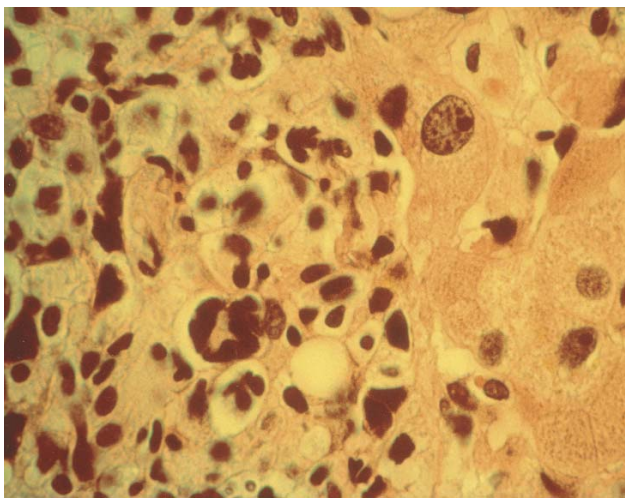


Figure 3. Presence of neoplastic cells, with bizzarre cytological features, dispersed among normal myeloid cells. Bone marrow biopsy of case 2. MGG

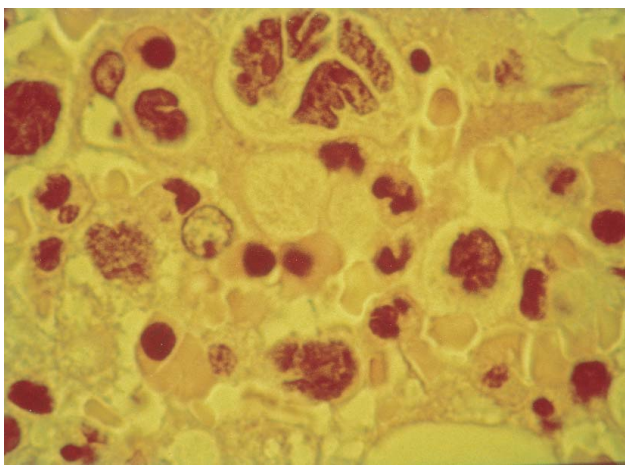


Figure 4. Three neoplastic cells, with irregular nuclear outlines and clumped chromatin present in the bone marrow of case 2. MGG

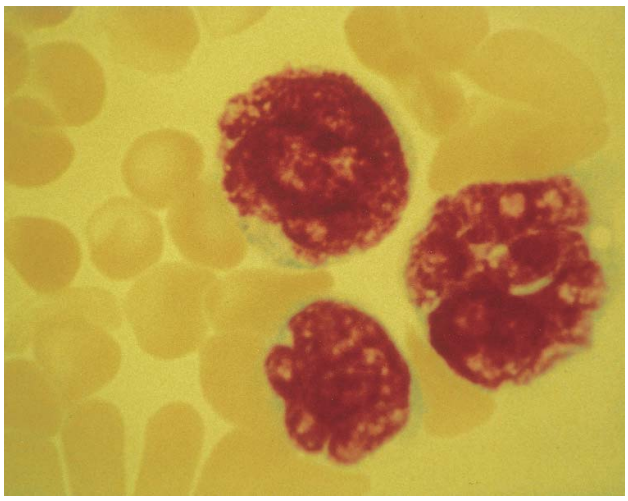


Figure 5. PAS reaction in two neoplastic cells of case 2, showing strong diffuse positivity in one and fine peripheral granular reaction in another. Bone marrow biopsy

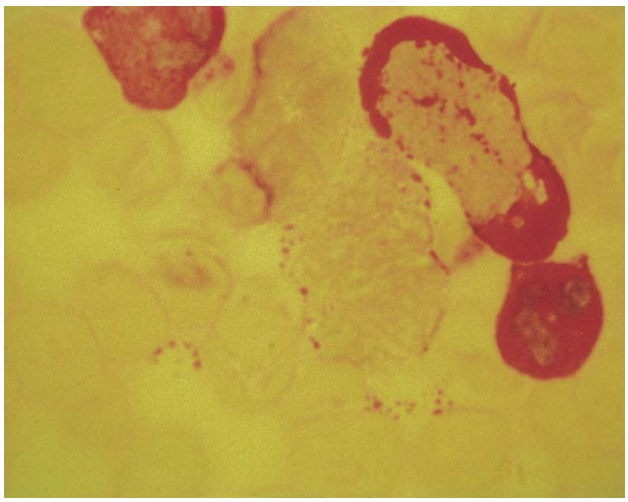


Figure 6. Strong granular Acid Phosphatase positivity in a neoplastic cell present in the bone marrow of case 2.

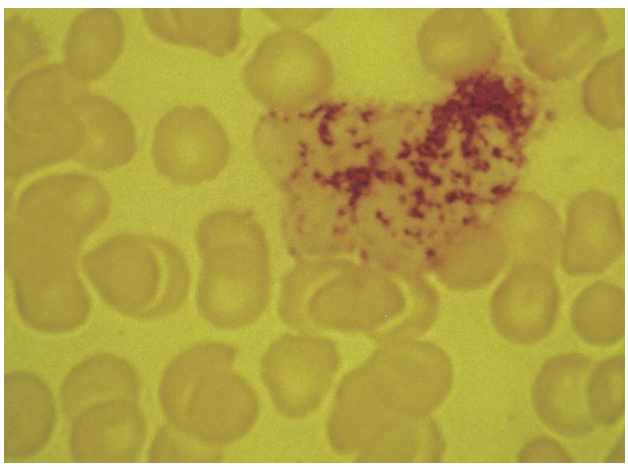


Figure 7. Alpha Naphthyl Butyrate Esterase reaction in a neoplastic cell, present in the bone marrow of case 2. Together with other myeloid cells.

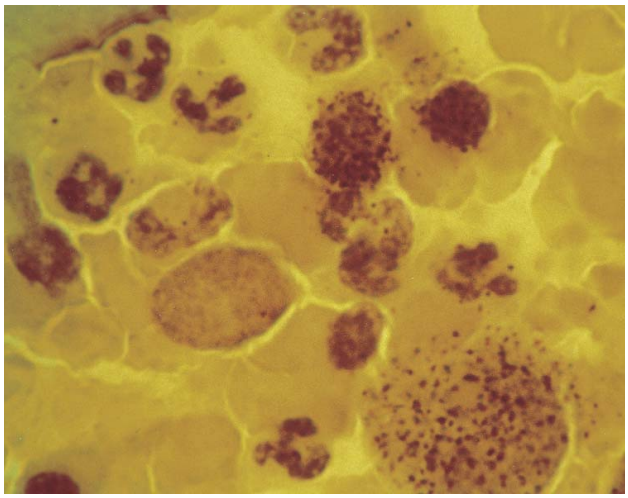


Figure 8. Immunohistochemical reaction for the demonstration of CD20 in neoplastic cells present in the bone marrow of case 1.

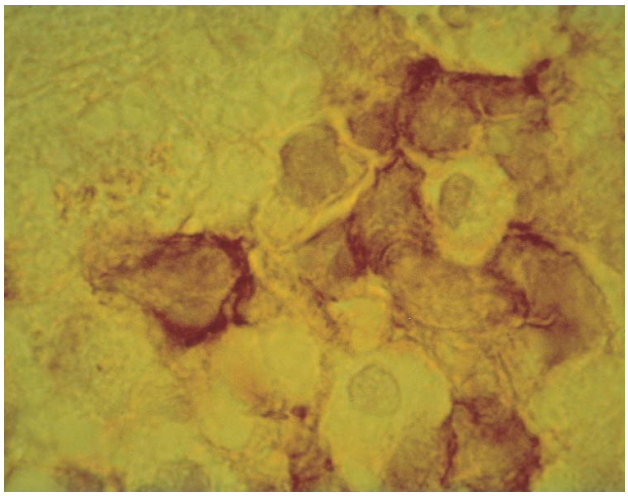


Figure 9. Immunohistochemical demonstration of CD68 in neoplastic cells present in the bone marrow of case 2. All cells display strong cytoplasmic positivity.

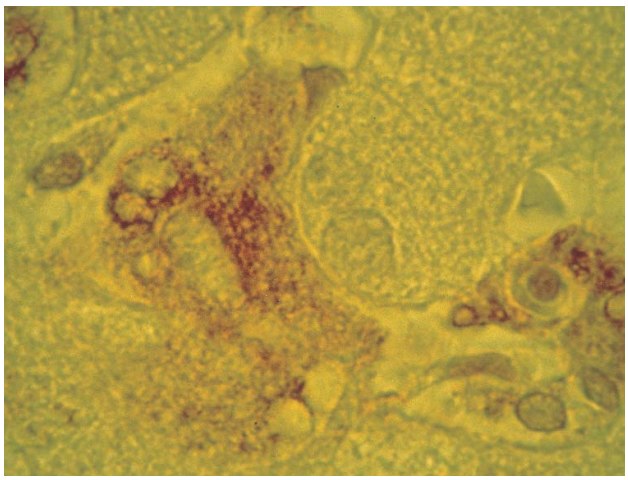


Figure 10. Immunohistochemical reaction for the demonstration of lysozyme in a liver section. Neoplastic cells show intense positivity. Case 2

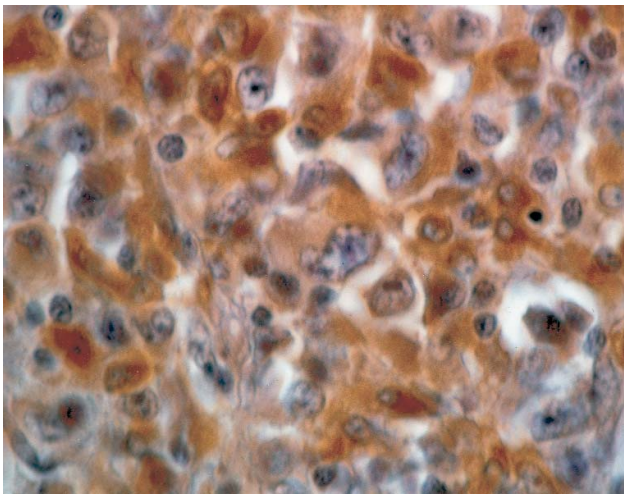


Figure 11. Another immunohistochemical preparation for the demonstration of lysozyme in neoplastic cells present in another area of a liver section. Intense positivity in all neoplastic cells. Case 2

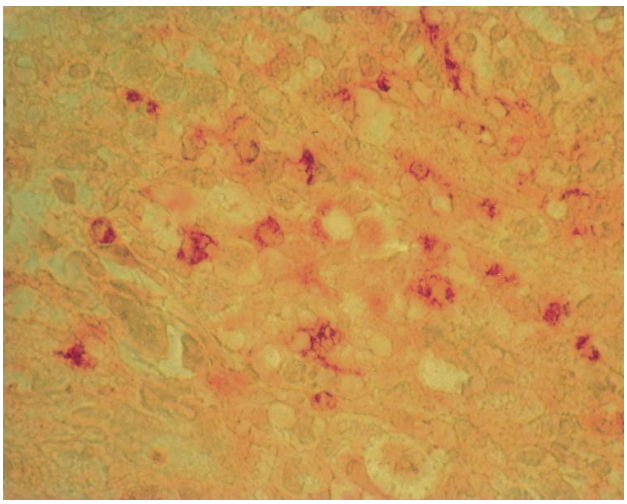
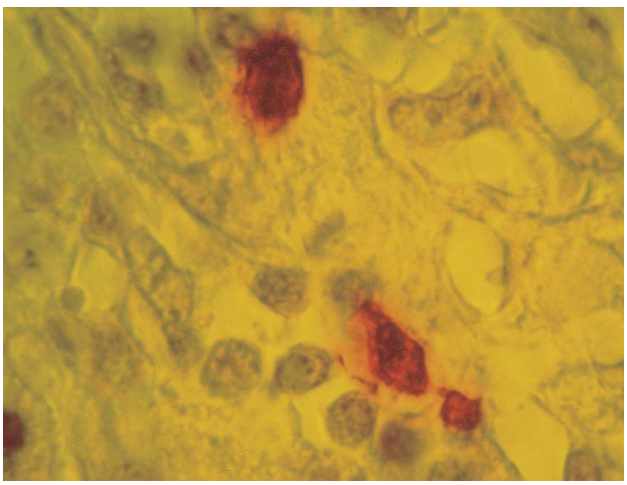


Figure 12. Immunohistochemical reaction for demonstrating the presence of MAC 387 in the neoplastic cells of case 2. Bone marrow section.



Results

Histological and cytological findings

CASE 1:

• **Histology**

Liver biopsy showed the presence of an extensive neoplastic infiltration with replacement of large areas of liver tissue. Neoplastic cells were gathered in nodular structures (Figure 1), presented a round or oval shape or were irregularly elongated, thus displaying a morphological appearance compatible with a histiocytic lymphoma.

• **Cytology**

A bone marrow biopsy disclosed the presence of a relatively low number of neoplastic cells, the majority of which were large, with irregularly shaped nuclei, sometimes bilobed, with fine chromatin and one or two nucleoli; cytoplasm was intensely basophilic and showed an irregular outline.

CASE 2:

• **Histology**

Examination of sections from a liver biopsy disclosed the presence of a plurifocal proliferation of neoplastic histiocytes, some dispersed, but others gathered in clumps with a cohesive growth pattern (Figure 2). The histio-monocytic cells showed a variable morphological aspect from bizarre and pleiomorphic blast cells to more mature cells of the same cellular line, showing evidence of erythrophagocytosis.

• **Cytology**

Examination of bone marrow sections and slides obtained from the iliac crest and stained both by Hematoxylin-Eosin and by May-Grünwald Giemsa showed the presence of medium-size to large cells, irregularly interspersed among non-neoplastic myeloid cells (Figure 3). The tumor cells showed a gray-blue or sometimes a deep-blue cytoplasm.

The chromatin was somewhat irregularly clumped and not uniformly fine as that of the normal macrophages, dispersed among the tumor cells. There were also binucleate and multinucleate giant cells and numerous mitotic figures, sometimes polyploid. A small number of tumor cells showed evidence of erythrophagocytosis.

The nuclei were round or oval, but not infrequently polymorphic, containing medium-sized irregular central nucleoli, sometimes only hardly recognizable, in contrast to those of Reed-Sternberg cells (Figure 4).

Results of cytobiological investigations

Cytochemically neoplastic cells of case 2 were characterized by strong PAS positivity (Figure 5) Acid Phosphatase (Figure 6) and Naphthyl Butyrate Esterase (Figure 7) while these reactions were negative in case 1. From the immunohistochemical point of view, malignant cells from case-1, were substantially negative for all histiocytic markers, stained strongly with the CD20 antibody (Figure 8), which recognizes a B cell antigen, whereas neoplastic cells from case-2 were characterized by both cytochemical and phenotypic markers of histiocytic lineage: CD68 (Figure 9), Lysozyme (Figure 10-11), and MAC387 (Figure 12). Genotypic studies revealed a germ line configuration in both cases for the heavy immunoglobulin chain and TCR genes.

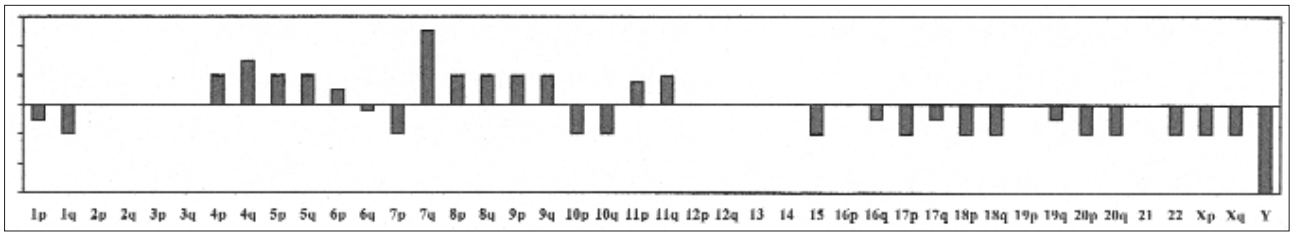
Cytogenetic analysis in case 2

Cytogenetic analysis on this patient has shown the presence of a complex karyotype in neoplastic cells with chromosomal number ranging from 72 to 131 and modal number of 78. In table 1 description and frequency of some identified chromosomal markers found are reported. These data indicate a high genetic heterogeneity as some markers (M2, M3, M5, M11 and M12) are present in all neoplastic cells, while other markers were found with lower frequency. Finally, even if in this situation of genetic heterogeneity it is difficult to determine the chromosome copy number, in (Figure 13) we have tried to describe the karyotype balance, demonstrating that some chromosomal regions, such as chr. 4, 5, 7q, 8, 9, and 11, are over-represented in comparison with a near-triploid state, while others 1q, 7p, 10, 15, 17p, 18, 20, 22 and sex chromosomes seem to be partially lost.

Discussion

The two cases described, initially considered examples of malignant histiocytic proliferations, were

Figure 13. Karyotype balance, showing overexpression of some chromosomes and partial loss of others.



subjected to further investigation, characterized by a completely different cytochemical, phenotypic and genotypic profile.

Case 1, in view of the strong and diffuse positivity in liver sections, indicative of a B cell phenotype, as well as the presence of negative reactions for CD68 and My-9, may be, with considerable confidence, ascribed to a non Hodgkin lymphoma, recently defined by Harris and colleagues [24] as a diffuse large B cell lymphoma, which according to the old nomenclature of Rappaport [2] would have been designated as diffuse histiocytic and according to the Kiel Classification [25] as B immunoblastic or large cell anaplastic (B cell) lymphoma.

The morphology of this subtype may vary from large cells with vesicular nuclei, prominent nucleoli and basophilic cytoplasm to large cleaved, multilobulated or anaplastic large cells.

In **Case 2**, the cytochemical and immunohistochemical studies which show strong CD68, MAC 387 and lysozyme positivity, as well as the results of genotypic studies, which reveal a germ-like configuration of the genes for the heavy immunoglobulin chain and the TCR genes, support a histiocytic derivation for the cells infiltrating both the liver and the bone marrow.

Although the problem of Ig and TCR gene rearrangements in histiocytic proliferations is still a matter for controversial arguments, according to same Authors [12-18-26], a non B, non T genotype is invariably associated with histiocytic malignancies.

On the contrary, other Authors [27-28-13] believe that in the presence of a phenotype typical for histiocytic proliferations, the rearrangement of Ig genes, especially if limited to the genes coding for the heavy chain, or for those of the T cell receptor, are not incompatible with a diagnosis of a histiocytic disorder, since these rearrangements, although indicative of clonality, are not sufficiently reliable for determining the nature of a differentiating line in a malignant neoplasm.

In keeping with these considerations, non lymphoid tumors have been described, in which these rearrangements have been observed [29-30] and on the other hand the presence of Ig gene rearrangements in T cell lymphomas or T cell receptors in B cell lymphomas have occasionally been described [31-32].

There is no single immunophenotypic marker that identifies with certainty a cell as a histiocyte. Negative immunohistochemical reactions for CD3 on preparations of supposed histiocytic derivation, do not argue against a T cell lineage, since CD3 is expressed relatively late in the T cell differentiation pathway, (mature thymocytes). Furthermore, CD68 is not unfortunately an absolute distinctive marker for histiocytes. Activated T cells are able to express both CD68 and other markers that are more or less characteristic for monocytes and macrophages. T cells, however, are never positive for lysozyme, which should therefore be considered a strong distinctive feature of monocytes/macrophages.

When employing any histiocytic marker, it is important to be aware of the extremely high numbers of reactive macrophages which may be present in B and T cell lymphomas, especially large cell anaplastic lymphoma, which also for this reason, was frequently misdiagnosed as a histiocytic neoplasm.

In fact in about 20% of all large cell anaplastic lymphomas, the cell of origin remains unclear [33]. It is in this group of tumors with unresolved lineage of aberrant cells that lies the major cause for confusion, by concealing and compassing at the same time histiocytic neoplasia [34].

In contrast to lymphoid cells, very little is known about the physiological differentiation pathway of histiocytic cell lineages, for which there are no good markers that are able to establish clonality [35].

Another cause for diagnostic uncertainty may lie in the similarities between a malignant histiocytic proliferation and the viral associated hemophagocytic syndrome (VAHS), in which the patient presents clinical features, such as fever, systemic symptoms, jaundice, multiple organ failure and occasionally ra-

Table I: Description and frequency fo some identified chromosomal markers

MARKER	DESCRIPTION	%	MARKER	DESCRIPTION	%
ml	der(6)t(4;6)(q28;q23)	**83**	**m10**	del(3q)	**83**
m2 (x2)	i(7q) ?	**100**	**m11**	der(13)t(6;13)(p21;p11)	**100**
m3	der(11)t(1;11)(p32;p15)	**100**	**m12**	i(21q)	**100**
m4	?	**42**	**m13**	?	**83**
m5	der(7)t(7;?)(q31;?) o del(7)(q31.2q31.3)	**100**	**m14**	rob(14;21)	**75**
m6	5p-	**33**	**m15**	der(5)8t(5;?)(p12;2)	**17**
m7	der(19)t(19;?)	**92**	**m16**	t(2;3) o t(2;11)	**17**
m8	der(16)t(16;?)	**42**	**m17**	der(19)t(17;19)(q21;q13)	**83**
m9	?	**?**			

pidly fatal outcome. This disorder is more frequently encountered in children and is often associated with bacterial infection or with viruses such as Epstein Barr virus, Cytomegalovirus and Herpes virus. The largest series of cases of "fulminant" hemophagocytic syndrome have been reported from Asia, where virus infection is the usual inciting stimulus. However, the histiocytes of viral associated hemophagocytic syndrome are usually of mature appearance, without nucleoli and ample pale cytoplasm and generally displaying a more conspicuous phagocytosis of erythrocytes and other formed elements of the blood.

In histiocytic neoplasms, instead, neoplastic cells are more cytologically pleomorphic with at least some showing a high nuclear/cytoplasmic ratio, basophilic cytoplasm, prominent nucleoli and less frequent phagocytic activity. The distinction is important, although sometimes difficult, because VAHS may respond to active treatment of the associated infection with acyclovir or other appropriate agents, while malignant histiocytic disorders require aggressive cytotoxic therapy, which however is not always effective.

As stated in the introduction, the place of histiocytic malignancies among the lymphomas has become equivocal with the demonstration by surface marker techniques that most of the lymphomas earlier regarded as histiocytic are in fact either B or T cell lymphomas. There are, nevertheless, some rare cases of true histiocytic proliferations, with predominance of cells showing certain of the characteristic histiocytic features of phagocytic activity, usually manifest by erythrophagocytosis, strong cytochemical positivity for acid phosphatase and acetate or butyrate esterase and cytochemical or immunocytochemical positivity for membrane lysozyme and a-1 antitrypsin. Additional confirmatory evidence may be obtained employing monoclonal antibodies, which give negative reactions for T and B cell antigens, such as CD3, CD19, CD20 and positive reactions with a panel of antibodies for the monocyte-macrophage cell line, such as CD64, CD68, MAC387.

The detection of a germ-line configurations for the IgG heavy chains and TCR genes, while not conclusive, is certainly suggestive of a histiocytic derivation.

In conclusion, on the basis of the data from the literature and our, although limited, observations it may presumed that the majority of the so called histiocytic lymphomas or malignant histiocytosis are in reality either T or B cell lymphomas, although there are little doubts regarding the existence of a minority of cases, which might be the expression of a clonal proliferation of histiocytic cells, the diagnosis of which requires stringent histological and immunophenotypic criteria. The skin and the intestinal tract appear to be the favored sites of origin.

The prognosis of histiocytic malignancies is unpredictable. Some cases are characterized by a rapidly fatal course [17] (as in our case), whereas others appear to respond favorably to chemotherapy [18-16].

The treatment experience is however limited to either case reports [36-37] or to small series [3 8-39], the results being often equivocal and misleading because of the intermixture of cases of LCAL amongst true histiocytic proliferations.

As further cases are recognized and diagnosed with certainty, it is to be hoped that rational treatment regimens will emerge.

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