Is macrophage activation syndrome a new entity?

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Received on February 5, 2002; accepted on February 11, 2002.

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In 1985, Hadchouel, Prieur and Griselli described a syndrome characterized by hematologic, neurologic and hepatic abnormalities in association with systemic onset JRA (1). Although such an association was known and individual case reports had been written by others, these authors recognized the similarities of this syndrome to Familial Hemophagocytic Syndrome and Chediak-Higashi syndrome in which macrophages play an important role. Therefore the authors suggested the term Macrophage Activation Syndrome (2). This name is now well-entrenched in pediatric rheumatology (3, 4).

The same name, Macrophage Activation Syndrome (MAS), is presently applied by rheumatologists to the other reactive forms of hemophagocytic syndrome, which could suggest that this represents a unique, hitherto unknown syndrome. Consequently, specialists in other fields (such as infectious diseases and hematology) who are very familiar with the syndrome are often unaware of the rheumatology literature on this subject. For example, a recent review of secondary hemophagocytic lymphohistiocytic syndromes in a monograph on histiocytic disorders published in 1998 did not mention the word MAS anywhere (5). In this essay I suggest that MAS be placed in terms of nosology and classification where it belongs – namely, among the histiocytic disorders. This should facilitate better communication between different specialties, and help in the development of uniform diagnostic criteria and, hopefully, uniform treatment strategies.

The term "histiocytes" includes two groups of immune cells – the antigen-presenting dendritic cells and the antigen-processing macrophages. Conditions characterized by the proliferation and accumulation of macrophages and dendritic cells are grouped under the classification of histiocytosis. At the initiative of Giulio D'Angio, MD, an International Histiocyte Society was formed in 1985. The Writing Group of this society recommended a classification of disorders associated with histiocytosis as follows: Class I - Langerhans cell histiocytosis; Class II - Non-Langerhans cell histiocytosis and Class III - Malignant histiocytosis (6). Subsequently this classification was modified (Table I) and these conditions were divided into the subgroups dendritic cell-related disorders, macrophage-related disorders, and malignant disorders of histiocytes (7).

Table I. Classification of histiocytic disorders (7).

Disorders of varied biological behaviour
Dendritic cell-related disorders
Langerhans cell histiocytosis
Secondary dendritic cellprocesses
Juvenile xanthogranuloma and related disorders
Solitary histiocytomas of various dendritic cell phenotypes
Macrophage-related disorders
Hemophagocytic syndromes
Primary hemophagocytic lymphohistiocytosis
Secondary hemophagocytic syndromes
Infection-related
Malignancy-related
Other
Roasi-Dorfman disease (sinus histiocytosis with massive lymphadenopathy)
Solitary histiocytoma with macrophage phenotype
Others including multicentric reticulohistiocytosis and generalized eruptive histiocytoma
Malignant Disorders
Monocyte related malignant disorders
Leukemia
Extramedullary monocyte tumor or sarcoma (monocyte counterpart of granulocytic sarcoma)
Dendritic cell-related histiocytic sarcoma (localized or disseminated)
Specific phenotype; follicular dendritic cell, interdigitating dendritic cell etc.
Macrophage related histiocytic sarcoma (localized or generalized)

Table II. Diagnostic guidelines for hemophagocytic lymphohistocytosis (HLH).

Clinical criteria
*Fever
*Splenomegaly

Laboratory criteria
*Cytopenias (affecting ≥ 2 of 3 lineages in the peripheral blood):
Hemoglobin (< 90 g/L)
Platelets (< 100 x 10^9/L)
Neutrophils (< 1.0 x 10^9/L)
*Hypertriglyceridemia and/or hypofibrinogenemia (fasting triglycerides ≥ 2.0 mmol/L or ≥ 3SD of the normal value for age, fibrinogen ≤ 1.5 g/L or ≤ 3 SD)

Histopathologic criteria
*Hemophagocytosis in bone marrow or spleen or lymph nodes. No evidence of malignancy

*All criteria required for the diagnosis of HLH. In addition, the diagnosis of FHL is justified by a positive family history, and parental consanguinity is suggestive.

Comments:
1. If hemophagocytic activity is not proven at the time of presentation, a further search for hemophagocytic activity is encouraged. If the bone marrow specimen is not conclusive, material maybe obtained from other organs,especially the lymph nodes or spleen (fine needle aspiration biopsy). Serial marrow aspirates over time may also be helpful.
2. The following findings may provide strong supportive evidence for the diagnosis: (a) Spinal fluid pleocytosis (mononuclear cells); (b) histologic picture in the liver resembling chronic persistent hepatitis (biopsy); (c) low natural killer cell activity.
3. Other abnormal clinical and laboratory findings consistent with the diagnosis are as follows:cerebromeningeal symptoms; lymph node enlargement; jaundice; edema; skin rash; hepatic enzyme abnormalities; hyperferritinemia; hypoproteinemia; hyponatremia; spinal fluid protein ≠; VLDL ≠; HDL ; circulating soluble IL-2 receptor ≠.

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Our interest is in the macrophage-related disorders. As can be seen in Table I, hemophagocytic syndromes form one of the subsets in this group. Among the secondary hemophagocytic syndromes (also called reactive hemophagocytic syndromes), the infection-associated (IAHS) and malignancy-associated (MAHS) forms are well known. The hemophagocytic syndrome associated with rheumatic disorders belongs to this subset and should be referred to as such – *viz.* rheumatic disease associated hemophagocytic syndrome (RAHS). The current terminology of MAS gives the impression that it is a unique syndrome with different characteristics.

The clinical, laboratory and pathological features of the primary variety, called Familial Hemophagocytic Lymphohistiocytosis (FHL, FHLH), and of the secondary varieties are almost identical. FHLH is an autosomal recessive condition which can be fatal (8, 9). The presentation is most often during the first year of life. It can be precipitated by an infection and therefore may be diagnosed as the secondary infection-associated hemophagocytic syndrome (IAHS or VAHS) during the first attack. Mortality is very high, with a median survival of 2 months from the time of diagnosis. Recently a defect in the gene for perforin has been found in some patients with this syndrome (10). Earlier treatments using corticosteroids, cyclosporine and ATG resulted in prolonged remissions, but allogenic bone marrow transplantation may lead to a cure (11).

Infection-associated (IAHP) hemophagocytic syndrome (histiocytosis) is seen in all age groups and has been reported mainly in association with herpes, adeno and Epstein-Barr viruses. It has also been reported in association with bacteria, rickettsia, parasites and fungi (5,12). In children it occurs most commonly before the age of 3 years. The mortality is high without treatment. Treatment approaches include IV gammaglobulin and etoposide.

Malignancy-related hemophagocytic lymphohistiocytic syndrome (MAHS) may be seen during the treatment of one of the malignancies or can occur as the initial manifestation, thus masking the features of the primary malignancy. Treatment depends on the type of malignancy involved (5).

Rheumatic disease-associated hemophagocytic syndrome has been seen most often with systemic onset JRA. This is the entity that has been named MAS. I have observed this syndrome in association with SLE as well and as the initial presentation of systemic JRA. Steroids, cyclosporine (13) and more recently anti-TNF agents (14), have been used with success in the treatment of this syndrome.

Signs and symptoms in the reactive or secondary form of hemophagocytic lymphohistiocytosis (IAHS, MAHS and RAHS) are almost identical to those seen in the familial variety. High fever, clouding of the consciousness and seizures may be dramatic. There is generalized lymphadenopathy and hepatosplenomegaly. There may be a rash which is different from the rash of JRA or petechiae and purpura due to thrombocytopenia. There may also be features of mild DIC. There is definitely thrombocytopenia. However, the presence of pancytopenia should alert the clinician, particularly in systemic JRA. Abnormal liver function studies include elevated aminotransferase and bilirubin levels and a prolonged prothrombin time. The most dramatic clues are a fall in the sedimentation rate in the face of a worsening clinical situation and the very high levels of ferritin. CSF pleocytosis may be seen. In one infant we were able to demonstrate phagocytosis in the CSF. Serum sodium may be low and some of the CNS changes may be related to the metabolic changes. The bone marrow or lymph node will show the accumulation of non-malignant histiocytes engulfing most often the red cells but sometimes also WBC and platelets (pac-man syndrome).

These features are the same in all three varieties. Therefore, what we in rheumatology call MAS should be placed under the major category of Macrophage-Related Disorders and be listed under Secondary or Reactive Hemophagocytic Syndromes. This would be helpful for the following reasons:

1. It would provide a common terminology for all the subspecialists (hematologists, neurologists, gastroenterologists, infectious disease experts and rheumatologists) who may be called on to care for these children.
2. We can start using the criteria developed by the Histiocyte Society (Table II), modifying these criteria instead of creating new ones.
3. The recognition of gene (s) involved in the familial variety may be of help in looking for related genes in the reactive types of lymphohistiocytic hemophagocytosis.
4. This in turn may help in the development of better treatment strategies to treat this potentially fatal syndrome.

It is interesting to note that the originators of the term MAS seem to agree with this idea, as shown in the title of an article published in November 2001 (15).

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