Editorial

Macrophage Activation Syndrome — What's in a Name!


What's in a name? That which we call a rose
By any other name would smell as sweet
— William Shakespeare: *Romeo and Juliet*

Macrophage activation syndrome (MAS) is a severe, potentially life-threatening complication of chronic rheumatic diseases in childhood. It is characterized by the excessive activation of well differentiated macrophages, resulting in fever, hepatosplenomegaly, lymphadenopathy, severe cytopenia, serious liver disease, intravascular coagulation, and neurological involvement.

The term MAS has been used almost exclusively to describe this condition in association with rheumatic diseases. It is seen most commonly with systemic onset juvenile rheumatoid arthritis (JRA) and has also been reported with systemic lupus erythematosus, juvenile dermatomyositis, and Kawasaki disease[1-6]. The report of deaths from hepatic failure in patients with systemic onset JRA described by Boone in 1976 at the first American Rheumatism Association conference on the rheumatic diseases of childhood in Park City, Utah, may represent the earliest descriptions of MAS in pediatric rheumatic diseases[7]. The term MAS was coined by Hadchouel, *et al* in 1985 in their description of 7 patients with systemic onset JRA who developed this complication during the course of their disease[6]. There are no true estimates of the incidence of MAS in systemic onset JRA. MAS accounts for a significant proportion of the morbidity and mortality seen with systemic onset JRA. Two recent case series reported a mortality of 8 to 22%[8,9]. The risk of recurrence with MAS is not known but the relapse rate in the recent French series was 16% (4/24), with one patient having 2 relapses[9].

NOMENCLATURE

It is now increasingly recognized that MAS bears close resemblance to a histiocytic disorder, secondary hemophagocytic lymphohistiocytosis (HLH), which is seen in a heterogeneous group of diseases, including infections, neoplasms, hematological conditions, and autoimmune disorders[10,11].

The term histiocytosis identifies a group of disorders that have in common the proliferation and accumulation of macrophages and dendritic cells. In 1987, the writing group of the Histiocyte Society recommended a division of the histiocyte disorders into 3 classes: Langerhans cell histiocytosis (LCH) (Class I); non-Langerhans cell histiocytosis (Class II), to which belongs HLH; and malignant histiocyte disorders (Class III)[12]. A further revision of this classification[13] has now termed the 3 major groups as (1) the dendritic cell related disorders; (2) the macrophage related disorders; and (3) the malignant disorders.

HLH falls into the category of macrophage related disorders and accounts for most of the patients in this category (Class II histiocytosis). There are 2 distinct types of HLH:

1. Primary HLH — familial and sporadic; commonly precipitated by viral infections. Familial HLH is an autosomal recessive disorder recently shown to be due to a number of different genetic mutations[14].

2. Secondary HLH — this has also been termed virus associated hemophagocytic syndrome (VAHS) and malignancy associated hemophagocytic syndrome (MAHS) in the literature[15].

Currently, diagnosis of familial HLH requires a positive family history of HLH, or presence of genetic mutations, such as perforin gene mutations, can confirm the diagnosis[16,17]. Secondary HLH occurs in association with a variety of infectious agents including viruses (especially the herpes group), bacteria, fungi, rickettsia, and protozoae[15]. It is also seen with malignancies, particularly with acute lymphoblastic leukemia, germ cell tumors, and non-Hodgkin's lymphoma[15]. It is rarely seen with prolonged intravenous administration of soluble lipids (fat overload syndrome)[18].

DIAGNOSTIC CRITERIA

Diagnostic criteria for HLH were established in 1991 by members of the Histiocyte Society[16] (Table 1). Although there are no formal and universally accepted criteria for the diagnosis of MAS, many clinicians in practice use the HLH criteria. One of the problems with the diagnostic criteria for HLH is the need for tissue confirmation of hemophagocytosis. It is now recognized that bone marrow aspirate or biopsy may not always show hemophagocytosis, and further, hemophagocytosis is not always demonstrable at onset[19]. Although hemophagocytosis may be seen more frequently in liver, lymph node, or splenic biopsies than in

Table 1. Diagnostic guidelines for hemophagocytic lymphohistiocytosis (HLH)[16].

Clinical criteria
- Fever
- Splenomegaly

Laboratory criteria
- Cytopenia (affecting > 2 of 3 lineages in the peripheral blood)
  - Hemoglobin < 90 g/l
  - Platelets < 100×10^9/l
  - Neutrophils < 1.0×10^9/l
- Hypertriglyceridemia and/or hypofibrinogenemia (fasting triglycerides ≥ 2.0 mmol/l or ≥ 3 SD 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 may be 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; rash; hepatic enzyme abnormalities; hyperferritinemia; hypoproteinemia; spinal fluid protein ↑; VLDL ↑; HDL ↓; circulating soluble IL-2 receptor ↑.

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the bone marrow, these biopsies are often difficult in children with disseminated intravascular coagulation. It is important to realize that failure to demonstrate hemophagocytosis does not negate the diagnosis of HLH.

Additional laboratory measures, such as serum concentrations of ferritin and lactate dehydrogenase, which are not currently part of the diagnostic criteria, may require consideration. In a large series of patients with secondary HLH, hyperferritinemia (> 1000 µg/l) and elevated blood levels of lactate dehydrogenase (> 1000 IU/l) were observed in 90% and 89.7% of patients, respectively[20]. In contrast, hypertriglyceridemia (> 2 mmol/l) and hypofibrogenemia (< 1.5 g/l), which are part of the diagnostic criteria, were seen in only 50% and 57.4% of patients, respectively. Serum ferritin and lactate dehydrogenase levels may be more sensitive measures for HLH even though they lack specificity. The measurement of natural killer (NK) cell activity has also been shown to be useful in distinguishing primary from secondary HLH. Children with confirmed familial disease have been reported to have persistently low or absent NK cell activity. Those with secondary HLH may have low NK cell activity at presentation, but this typically normalizes with remission of illness[21-23]. Any attempt to define new diagnostic criteria for HLH/MAS should include an evaluation of the sensitivity and specificity of these laboratory markers, which could potentially obviate the need for tissue diagnosis[24,25].

The difficulty in diagnosing MAS in systemic onset JRA is compounded because some of the typical features such as fever, splenomegaly, and anemia are also seen in active systemic onset JRA. For MAS to be diagnosed and therapy instituted early, certain criteria may need to be modified in patients with systemic onset JRA. The occurrence of relative cytopenia (reduction in hemoglobin, white blood cell count, and platelets by a certain fraction) rather than the absolute cytopenia required by the HLH criteria may be important in making an early diagnosis.

ETIOPATHOGENESIS

It is still unclear why some individuals with chronic rheumatic diseases (particularly systemic onset JRA) get MAS. The perforin gene defects are now thought to account for 30–40% of the primary HLH cases[26,27].

Defects in genes at chromosome 9 and 10 have recently been shown to be associated with FHL[28,29].

It has been suggested that perforin deficiency (as well as the other genetic mutations identified in familial HLH) results in impaired lymphocyte mediated cytotoxicity and defective triggering of apoptosis of target cells[17]. This in turn may result in lymphocyte proliferation associated with production of increased quantities of macrophage-activating cytokines such as interferon-γ and granulocyte macrophage-colony stimulating factor. Sustained lymphocyte and macrophage activation and multivisceral infiltration, plus

the production of additional cytokines such as tumor necrosis factor-α, interleukin 1 (IL-1), and IL-6, may explain the clinical syndrome.

There are recent reports of defective perforin function in patients with systemic onset JRA[30-32]. A study of 7 patients with MAS described decreased NK cell function in all 7 and decreased perforin expression in 2/7, despite normal PRF1 gene sequences. Perforin function in MAS, however, remains to be fully evaluated. A better understanding of the genetic defects seen in HLH may help to unravel the pathogenesis of MAS seen in chronic rheumatic diseases.

TREATMENT OF HLH

The treatment of secondary HLH has included a variety of chemotherapeutic and immunosuppressive agents including corticosteroids, cyclosporine, and intravenous gammaglobulin[14,17]. The most frequently used regimen is etoposide with prednisolone with or without cyclosporin A. The treatment protocol for primary HLH has now been standardized by a consensus treatment protocol (HLH 94 protocol) by the HLH international study group[33,34]. MAS, on the other hand, has been reported to respond to corticosteroids alone along with appropriate supportive management. In a recent case series, remission was induced in 15 of the 21 episodes of MAS by steroids alone[9]. Patients with a suboptimal response to corticosteroids have been reported to do well with the addition of cyclosporin A[8,9,35]. There are only a few reports of patients with MAS who have been treated with other agents including etoposide[8,9].

Is the nomenclature really important? We believe so. First, as pediatric rheumatologists we may fail to take into account the reports of patients published with the diagnosis of HLH. It is notable that the medical subject headings (MeSH) for most of the HLH articles published in hematology journals do not include MAS, and the MAS publications in rheumatology journals do not include HLH. Hemophagocytosis is seen as a secondary phenomenon in a number of conditions, and studying all of them in conjunction with systemic JRA may lead to better understanding of this potentially fatal complication.

There is a need to develop consensus guidelines for diagnosis of MAS, which should then be validated. This will enable timely diagnosis and will assist in the evaluation of different therapeutic approaches. In summary, MAS is a secondary HLH disorder and needs to be recognized as such. The diagnostic and therapeutic challenges posed by this major life-threatening complication of systemic onset JRA need urgently to be addressed.

ATHIMALAIPET V. RAMANAN, MRCP(UK), MRCPCH(UK); **RAYFEL SCHNEIDER,** MBBCh, FRCPC,
Division of Pediatric Rheumatology,
The Hospital for Sick Children,
Department of Pediatrics, University of Toronto,
Toronto, Ontario, Canada.

Address reprint requests to Dr. R. Schneider, Division of Pediatric Rheumatology, Hospital for Sick Children, 555 University Avenue, Toronto, Ontario M5G 1X8.

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