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Macrophage Activation Syndrome in Juvenile Idiopathic Arthritis

Yackov Berkun and Shai Padeh

Abstract Macrophage activation syndrome (MAS), life-threatening syndrome of overwhelming inflammation caused by uncontrolled hyperactivation of macrophages, is a rare complication of childhood systemic inflammatory disorders, affecting most often patients with systemic onset juvenile idiopathic arthritis (soJIA). The diagnosis of MAS in soJIA is challenging due to overlapping manifestations of the two diseases. Because MAS is often a fatal condition, prompt diagnosis and immediate therapeutic intervention are important.

Keywords Hemophagocytic lymphohistiocytosis (HLH) · macrophage activation syndrome (MAS) · juvenile idiopathic arthritis (JIA) · diagnosis · criteria

Introduction

Macrophage activation syndrome (MAS) is a term coined in the past decade to describe a rare, life-threatening syndrome of overwhelming inflammation caused by proliferation and uncontrolled activation of well differentiated macrophages secreting large amounts of inflammatory cytokines. MAS has been reported as a severe complication of childhood systemic inflammatory disorders, affecting most often patients with systemic juvenile idiopathic arthritis (soJIA), but also rarely associated with systemic lupus erythematosus and other rheumatic diseases in children (1). Hyperactivation of macrophages probably driven by T and natural killer (NK) lymphocytes is the cause of the disease. It is characterized by prolonged non remitting fever, pancytopenia, liver disease and hepatosplenomegaly, hemorrhagic diathesis, and neurologic involvement (2). Characteristic biochemical markers include elevated triglycerides, very high serum ferritin and low fibrinogen levels. Low NK cell activity and elevated serum soluble interleukin-2 receptor (sCD25) levels have been recently described (3).

Hemophagocytosis is found in bone marrow, liver, spleen and lymph nodes. MAS usually occurs without any evident trigger, or may follow infection or change in medication regimen in patients with long standing rheumatic diseases, or in some cases, it may herald the rheumatic disease (4). MAS is one of macrophage related disorders, and belongs to a group of acquired, secondary hemophagocytic lymphohistiocytosis (HLH), seen in hematological diseases and different malignancies, viral infections, and autoimmune disorders. It has been suggested to change the term of the disorder to rheumatic disease associated hemophagocytic syndrome, similar to other secondary hemophagocytic syndromes for better uniformity in terminology and medical communication (5). The diagnosis of MAS in soJIA is challenging due to overlapping manifestations of the two diseases. Because MAS is often a fatal condition, prompt diagnosis and immediate therapeutic intervention are important.

Epidemiology

MAS is reported to occur in 7–13% of patients with soJIA (6, 7). Subclinical MAS in soJIA patients is even more common, and it has been suggested that they may be 2 ends of the spectrum of one disease (7, 8). Mortality of 8–22% in MAS has been reported (6, 9), and MAS is responsible significantly to the morbidity and mortality in JIA.

Pathogenesis

Extensive lymphocytes and macrophages activation with overproduction of inflammatory cytokines such as tumor necrosis factor-α, interleukin (IL)-1, and IL-6, account for the clinical and laboratory manifestations. Defective NK cell function has been demonstrated in patients with

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MAS, often with a pattern indistinguishable from other HLH (3, 10). Interestingly, similar NK dysfunction has been demonstrated in soJIA patients, distinguishing it from other JIA subtypes by lower NK cell number and function, and perforin expression (3). The exact mechanism by which deficient NK and cytotoxic T-lymphocyte functions cause the clinical disorder, is unknown. Perforin, antiviral cytotoxic protein secreted by lymphocytes, downregulates cellular immune response. The deficient NK activity may lead to lymphocyte hyperactivity with secretion of potent macrophage activators. One suggested explanation is that diminished cytotoxic function in MAS patients lead to defective control of infection, persistent antigen stimulation with following escalation of inflammatory process and macrophage overstimulation. Alternative explanation is that deficient cytotoxic function may lead to inefficient apoptosis and removal of overactivated macrophages and lymphocytes (11). These pathogenic findings, common to MAS, HLH and soJIA patients, support the hypothesis that these diseases are different ends of the same spectrum (12).

Clinical and Laboratory Manifestations

The clinical picture of MAS is of acute episode consists of non remitting fever, hepatosplenomegaly, lymphadenopathy, cytopenia, coagulopathy, and central nervous system (CNS) manifestations (headache, disorientation, irritability or lethargy, seizures, coma), (Table 4.1). Other symptoms may include rash (usually fixed), serositis, cardiac and renal involvement. It is often life-threatening, and occasionally fatal (13, 14). Characteristic laboratory findings include a very high serum ferritin, elevated levels of triglycerides, liver enzymes and bilirubin, D-dimers, prolonged prothrombin time with decreased blood cell counts, ESR, fibrinogen and sodium (Table 4.2). Additional markers are low NK cell activity and elevated serum sCD25 levels (3).

A sharp increase in ferritin and decreasing ESR and fibrinogen in face of deteriorating clinical condition of a JIA patient are clues, and should point to the diagnosis of MAS. The pathognomonic histopathological finding is activated macrophages phagocytosing hematopoietic cells in bone marrow, spleen, or liver.

TABLE 4.1. Symptoms and signs of MAS (2, 13).

	Prevalence (%)
High fever	78–94
Hepatomegaly	61–88
Splenomegaly	45–59
Central nervous system dysfunction	38–53
Hemorrhages	39–44
Lymphoadenopathy	28–41

TABLE 4.2. Laboratory features of MAS (2, 13).

	Prevalence (%)
Hyperferritinemia	87–100
Hypertriglyceridemia	77–100
Abnormal liver function tests	94
Decreased ESR	79–92
Thrombocytopenia	89
Decreased fibrinogen	78–89
Anemia	67–82
Macrophage hemophagocytosis BM	81
Hyponatremia	67–78
Leukopenia	39–56
Hypoalbuminemia	35–54

Diagnostic Criteria

The diagnosis of MAS in soJIA is challenging due to multiple similar manifestations of these diseases, such as fever, hepatosplenomegaly and lymphadenopathy, rash. MAS may be confused with exacerbation of soJIA, a disease with flares and remissions; with infections, which are more common in these patients who are immunosuppressed by their treatment. There is a need for specific diagnostic criteria of the disorder which will take into consideration the similarity to SoJIA.

Previous diagnostic criteria for HLH from 1991 have been used for the diagnosis of MAS (15). They included clinical (fever, splenomegaly), laboratory (cytopenia of two lineages, hypertriglyceridemia and/or hypofibrinogenemia) and histopathological criteria (demonstration of hemophagocytosis in bone marrow or spleen or lymph nodes) (15). For the diagnosis of HLH all criteria are required. In a large series of patients with secondary HLH, elevated levels of ferritin and lactate dehydrogenase were found to be significantly more sensitive than the diagnostic criteria of hypertriglyceridemia and hypofibrogenemia, that were found in only half of patients (16). Another shortcoming of these criteria was the need for tissue confirmation of hemophagocytosis, since biopsy is problematic due to the coagulopathy, and bone marrow aspiration may not always show hemophagocytosis, which may appear later (14). The recent 2004 Revised Diagnostic Guidelines for HLH, includes these five old criteria, and three additional criteria – low or absent NK-cell activity, hyperferritinemia, and high levels of sCD25 (17). For secondary HLH, five of the eight criteria must be fulfilled. In a cohort of familial HLH, the sensitivity of elevated serum ferritin was 0.84, and of high levels of sCD25–0.93 (17). These HLH criteria are been currently used for MAS diagnosis, but are not sufficient to distinguish MAS from SoJIA. As soJIA is characterized by leukocytosis,

thrombocytosis, elevated ESR, fibrinogen, ferritin, these tests should be taken into consideration when using criteria for MAS diagnosis.

Recently, Ravelli et al. suggested preliminary diagnostic guidelines for MAS complicating soJIA (13). They compared the frequency of clinical, laboratory, and histopathological features in soJIA patients with MAS to patients with active soJIA. The clinical features analyzed were fever, rash, hepatomegaly, splenomegaly, lymphoadenopathy, hemorrhages, and CNS dysfunction. Laboratory findings included leucopenia, anemia, thrombocytopenia, high ferritin, elevated aspartate and alanine aminotransferase, bilirubin, lactate dehydrogenase, triglycerides, low ESR, albumin, fibrinogen, serum sodium, and bone marrow hemophagocytosis. The ability of each feature to discriminate the episodes of MAS from JIA was evaluated by calculating the sensitivity rate, specificity rate, area under receiver operating characteristic and diagnostic odds ratio (DOR) (Table 4.3). Laboratory and histopathological features, as compared with clinical manifestations, had better discriminating values. Almost all clinical manifestations had higher specificity than sensitivity rate. Hemorrhages and CNS disease, that were present in MAS patients only, had maximal specificity rate and were best clinical discriminators. The strongest laboratory discriminators were decreased platelet count, elevated aspartate aminotransferase, leukopenia, and hypofibrinogenemia, followed by hyponatremia, hyperferritinemia, hypertriglyceridemia, and decreased white blood cell count (13). The combinations of variables that led to best separation between patients and control subjects were identified through "the number of criteria present" method. Only variables available for sufficient number of patients that provided strong discriminating properties and were not duplicative were used.

The best separation between patients and control subjects occurred when any two or more laboratory criteria (DOR = 1309) were simultaneously present; the second best performance was provided by the presence of any 2, 3, or more clinical and/or laboratory criteria (DOR = 765 and 743, respectively). Preliminary diagnostic guidelines for MAS in soJIA, which included 3 clinical and 4 laboratory criteria, were suggested (Table 4.4). Bone marrow examination for demonstration of macrophage hemophagocytosis was suggested only in cases with doubtful diagnosis (13).

TABLE 4.3. Sensitivity, specificity, diagnostic odds ratio (DOR) of clinical features in MAS patients (13).

	Sensitivity	Specificity	DOR
Fever	0.81	0.04	0.2
Rash	0.45	0.53	0.9
Hepatomegaly	0.61	0.80	6.4
Splenomegaly	0.45	0.71	1.9
Lymphoadenopathy	0.28	0.67	0.8
Hemorrhages	0.39	1	66.8
Central nervous system dysfunction	0.38	1	63.1

TABLE 4.4. Sensitivity, specificity, diagnostic odds ratio (DOR) of laboratory features in MAS patients (13).

	Sensitivity	Specificity	DOR
WBC count < 9.0	0.78	0.88	25.3
Anemia < 10.1	0.94	0.44	13.4
Thrombocytopenia < 262	1.00	0.92	1092
AST > 59	0.92	0.96	248
Fibrinogen < 2.5	0.81	0.97	165
Decreased ESR < 57	0.87	0.76	19.4
Hypertriglyceridemia > 181	0.94	0.88	115
Hyponatremia < 130	0.67	1.00	157
Hypoalbuminemia < 3.2	0.81	0.57	5.6
Hyperferritinemia > 3410	0.88	1.00	115
Macrophage hemophagocytosis in BM	0.81	1.00	45.0

Problems in Current Diagnostics Criteria

Ravelli's guidelines have not been prospectively evaluated. Furthermore, biomarkers such as NK cell activity and sCD25 levels should be considered for incorporation in the criteria. Several new markers, specific for MAS found recently, have not been included in proposed diagnostic criteria. In a recent report of 5 soJIA patients with 9 MAS events, additional laboratory markers, $\beta_2$microglobulin and soluble interleukin-2 receptor were found to be a sensitive indicator of MAS, even when other laboratory markers had not obviously changed, while hypertriglyceridemia, hypoalbuminemia and hyponatremia appeared in 2 patients only (18). The hemoglobin scavenger receptor (CD163), a recently described macrophage differentiation antigen, was found to be useful clinical marker of disorders of macrophages, including HLH (19). Extensive expression of CD163 on hemophagocytic macrophages has been found in MAS patient, suggesting a possible role for CD163 as a specific marker of MAS associated with rheumatic diseases (4). The ability of all these new macrophage specific markers in discriminating between active soJIA and MAS should be further evaluated and incorporated into the criteria.

Treatment

The immediate aim in the treatment of patient with MAS is early and effective suppression of severe hyperinflammation. Intravenous corticosteroids as a first line medication in doses ranging from conventional to pulse methylprednisolone had been proven successful in more than two thirds of MAS patients (9). Cyclosporin A, calcineurin

inhibitor of early T-lymphocytes activation, is a preferred second line medication (9). Other second line medications are etoposide and intravenous γ immunoglobulin. Recent HLH 2004 new treatment protocol recommends treating patients with HLH by combination therapy with dexamethasone, etoposide and cyclosporine A (20). In cases of CNS disease, methotrexate is given intrathecally. Serum ferritin level has been recommended for follow up of the treatment response. In patients with severe HLH hematopoietic stem cell transplantation should be considered (20). Considering MAS patients, there are only a few reports of cases treated with etoposide and etanercept.

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