Diagnosis of MAS Hinges on Lab Findings

BY BRUCE JANCIN

FROM A SYMPOSIUM SPONSORED BY THE AMERICAN COLLEGE OF RHEUMATOLOGY

SNOWMASS, COLO. – Macrophage activation syndrome is a challenging diagnosis whose most useful clues are to be found in the laboratory report.

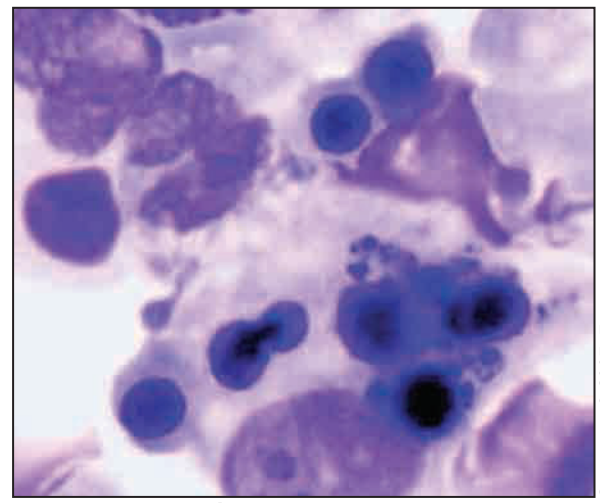
Suspect the life-threatening diagnosis of macrophage activation syndrome (MAS) in a patient with virtually any form of active rheumatologic disease who becomes acutely ill with a sharp drop in both erythrocyte sedimentation rate and platelet count in the presence of a persistently high C-reactive protein and escalating levels of serum D-dimers, urged Dr. Alexei A. Grom.

Another suggestive laboratory feature is marked hyperferritinemia. Patients with MAS often have a serum ferritin level in excess of 10,000 ng/mL, Dr. Grom said at the meeting.

Moreover, while normally 60%-80% of serum ferritin is glycosylated, in MAS it's typically less than 20%. This makes measurement of serum glycosylated ferritin a useful diagnostic tool, noted Dr. Grom, a pediatric rheumatologist at Cincinnati Children's Hospital Medical Center.

Assessment of serum levels of soluble CD163 and soluble interleukin-2-receptor-alpha chains can also help pin down the diagnosis. They are strikingly elevated in MAS, and not in many other conditions. Extreme hypertriglyceridemia is another characteristic feature of the syndrome.

The central feature of MAS, he continued, is uncontrolled expansion of cytotoxic CD8 cells secreting cytokines that stimulate macrophages to exhibit hemophagocytic activity.



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Bone marrow specimen shows macrophage hemophagocytosis in a patient with systemic juvenile idiopathic arthritis and MAS.

Indeed, hemophagocytic activity on the part of highly activated macrophages is the hallmark of MAS. Identification of hemophagocytic macrophages in the bone marrow confirms the diagnosis. Unfortunately, often this finding is not present early in the course of the disease.

This macrophage hemophagocytosis explains the extreme hyperferritinemia seen in MAS. Free hemoglobin is released as erythrocytes are phagocytized. This creates a need to boost ferritin production in order to sequestrate the free iron, he explained.

Three cardinal features of the massive systemic inflammatory response that defines MAS are liver dysfunction, cytopenias, and coagulopathy consistent with disseminated intravascular coagulation. However, like hemophagocytic macrophages in the bone marrow, these features often are not of much help in making an early diagnosis. Overt cytopenia is seen only in the late stages of MAS.

Abnormal liver function tests and laboratory evidence of coagulopathy can also occur in a flare of systemic juvenile idiopathic arthritis – and since 80% of pediatric MAS occurs in patients with SJIA, hepatic dysfunction and coagulopathy are not useful in making the distinction.

The clinical presentation of MAS includes persistent fever, impressively enlarged lymph nodes, prominent hepatosplenomegaly, and a hemorrhagic rash featuring bruising, then purpura, followed by mucosal bleeding. Many patients also develop mental status changes and/or seizures.

These clinical features can be viewed as largely a consequence of a cytokine storm involving increased interferon-gamma, granulocyte macrophage colony–stimulating factor, tumor necrosis factor-alpha, and interleukin-1, -6, and -18.

No trigger is identifiable in the majority of cases of MAS. When a trigger is found, it is most commonly an infection with Epstein-Barr virus or cytomegalovirus.

MAS has a 10%-20% mortality. The death rate is declining in pediatric patients because of increasing aware-

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MAS Treatment Failures Stir Controversy

BY BRUCE JANCIN

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SNOWMASS, COLO. – Treatment of macrophage activation syndrome with a combination of high-dose corticosteroids and cyclosporine is quite effective in the majority of cases if started sufficiently early; it's what to do for the others where the controversy arises, according to Dr. Alexei A. Grom.

One reasonable option is to use the International Histiocyte Society treatment protocol for hemophagocytic lymphohistiocytosis, a hematology/oncology disorder bearing clinical similarities to macrophage activation syndrome (MAS). This protocol entails supplementing corticosteroids and cyclosporine with etoposide (VP-16), a mitotic inhibitor and antineoplastic agent used in treating a variety of cancers. Etoposide is employed to induce apoptosis of activated phagocytic macrophages and other immune cells, he said at the symposium.

But while etoposide is a reasonable next step, the drug's numerous short- and long-term side effects – including severe myelosuppression leading to fatal sepsis – have caused many physicians to look for alternatives. Among the more promising are antithymocyte globulin and rituximab, said Dr. Grom, a pediatric rheumatologist at Cincinnati Children's Hospital Medical Center.

Antithymocyte globulin depletes T cells, including CD8 cells, and monocytes. Numerous case reports describe successful use of this agent in treating MAS.

The rationale for using rituximab, a potent depleter of B cells, applies to patients with Epstein-Barr virus–induced MAS. Because of the immune dysfunction present in MAS, these patients develop persistent viral infection harbored chiefly by B cells. Dr. Grom has used rituximab successfully in patients with Epstein-Barr virus–triggered MAS, and he suspects that this approach may also be very effective in the setting of MAS associated with systemic lupus erythematosus.

The increased level of tumor necrosis factor present in MAS has prompted numerous attempts to use etanercept and other anti–tumor necrosis factor biologics. Results have been largely disappointing.

"Personally, I think we should stay away from TNF-alpha antagonists in MAS," the pediatric rheumatologist said.

The efficacy of interleukin-1 and -6 inhibiting agents in systemic juvenile idiopathic arthritis (SJIA) makes them appealing agents for the treatment of MAS, because MAS episodes are often triggered by flares of SJIA. However, case reports involving the interleukin-1 inhibitor anakinra have yielded mixed results, and to date there is very little experience with interleukin-6 inhibition in MAS.

First-line treatment of MAS by Dr. Grom and his Cincinnati colleagues begins with high-dose steroids, typically 3-5 days of intravenous methylprednisolone pulses at 30 mg/kg per day before dropping down to 2-3 mg/kg in two or three divided doses. Cyclosporine is dosed at 2-5 mg/kg in two divided doses, usually given intravenously.

Dr. Grom said he had no relevant financial disclosures. ■

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ness of the syndrome and consequent earlier diagnosis and initiation of treatment.

"I think that in adult rheumatology this condition is still relatively unrecognized. My adult rheumatology colleagues in Cincinnati believe that many of these patients end up with a diagnosis of culture-negative sepsis," he said.

It is crucial to understand that roughly one-third of patients with MAS will experience recurrent episodes.

For this reason, Dr. Grom provides patients with a letter explaining their condition in the event they should have a recurrence while out of town, necessitating a visit to an emergency department where physicians may be MAS inexperienced.

Dr. Grom declared having no relevant financial interests. ■