Weathering a Macrophage Storm

In rheumatology circles, macrophage activation syndrome (MAS) describes a potentially life-threatening complication of systemic inflammatory disorders, frequently making matters worse for those with systemic juvenile idiopathic arthritis (sJIA) and its adult counterpart, adult-onset Still disease (AOSD). A dysfunctional immune response results in continuous activation and expansion of T lymphocytes and macrophages, leading to an overproduction of proinflammatory cytokines (a cytokine storm) and resulting in multiorgan dysfunction. Like the related disorder, secondary hemophagocytic lymphohistiocytosis (HLH), MAS features include high, unremitting fever, hyperferritinemia, hepatosplenomegaly, lymphadenopathy, pancytopenia, and hypofibrinogenemia. Other laboratory abnormalities include elevated liver enzymes, D-dimers, lactate dehydrogenase, and triglycerides (TGC). Soluble interleukin 2 receptor α (sCD25) may be elevated, but testing is often not available at an on-site laboratory and therefore is not routinely done at the time of diagnosis[1,2,3,4]. Histopathology often reveals characteristic increased hemophagocytic activity in the bone marrow (and other tissues), with positive CD163 (histiocyte) staining, although this feature is often not present in initial stages and is neither highly sensitive nor specific for MAS[5,6].

Most commonly studied as a complication of sJIA, the reported prevalence of MAS is estimated to be about 10%; however, reports suggest subclinical MAS may be present in 30%–40% of patients with sJIA[7,8]. There are several diagnostic challenges in the early recognition of MAS, particularly in distinguishing it from a flare of sJIA or AOSD. Moreover, there is no single pathognomonic feature of MAS, and many clinical features and laboratory abnormalities overlap with those of systemic inflammatory disorders, making it difficult to distinguish the underlying disease from the life-threatening comorbidity[1,2,3,4]. Further, until very recently, there were no universal validated criteria to aid in diagnosis. However, patient data–based classification criteria for MAS in patients with sJIA were recently reported[1,9]. The criteria were developed in an iterative process over several years and relied on real patient data and controls (> 1100 subjects from 33 countries). The final criteria were chosen by MAS experts selecting from nearly 1000 computer-generated combinations of clinical and laboratory findings. The final MAS criteria for children with sJIA proved to be both sensitive (0.73) and specific (0.99). The diagnosis of MAS can be made in a febrile patient with sJIA or suspected sJIA who has a serum ferritin level > 684 ng/ml plus any 2 of the following: platelet count ≤ 181 × 10^9/l, aspartate aminotransferase > 48 units/l, TGC > 156 mg/dl, or fibrinogen ≤ 360 mg/dl (Table 1)[1,9]. These relatively few total criteria are routinely readily available and timely.

The clinical overlap of MAS and secondary HLH has led some practitioners to use the longer-standing HLH-2004 diagnostic guidelines, which require 5 of the following 8 criteria to be met for diagnosis: fever, splenomegaly, cytopenias (affecting ≥ 2 of 3: hemoglobin < 90 g/l, platelets < 100 × 10^9/l, neutrophils < 1.0 × 10^9/l), hypertriglyceridemia (≥ 265 mg/dl) and/or hypofibrinogenemia (≤ 1.5 g/l), hemophagocytosis in bone marrow or spleen or lymph nodes, low or absent natural killer cell activity, ferritin ≥ 500 µg/l, and sCD25 ≥ 2400 units/ml[10,11]. Using this strict set of criteria may delay diagnosis in patients with a less severe initial presentation, putting them at risk for rapid clinical decline and potential death from delayed treatment. To improve upon this, Fardet, et al developed a modified scoring system (HScore)[12], based on the HLH-2004 criteria, to estimate a patient's risk of having secondary HLH; however, this has not been validated in patients with an underlying rheumatic systemic inflammatory condition such as sJIA or AOSD. In fact, a majority of patients included in this study had HLH secondary to an underlying malignancy or infection[12]. Nevertheless, the HScore is being explored in other clinical settings of children and adults with secondary HLH[13,14].

In this issue of *The Journal*, Ahn, et al[15] present an

Table 1. Classification criteria for macrophage activation syndrome in known or suspected systemic juvenile idiopathic arthritis. From Ravelli, et al. Ann Rheum Dis 2016;75:481-9; and Ravelli, et al. Arthritis Rheumatol 2016;68:566-76; adapted with permission[1,9].

Classification Criteria for MAS

- Fever AND ferritin > 684 ng/ml

Plus any 2 of the following 4 criteria:
- Platelet count ≤ 181 × 10⁹/l
- AST > 48 units/l
- Triglycerides > 156 mg/dl
- Fibrinogen ≤ 360 mg/dl

MAS: macrophage activation syndrome; AST: aspartate aminotransferase.

expansion of the 2016 European League Against Rheumatism/American College of Rheumatology/Pediatric Rheumatology International Trials Organization (EULAR/ACR/PRINTO) classification criteria for MAS in patients with sJIA to include the related disorder of AOSD. They retrospectively analyzed 64 hospitalized patients with AOSD and fever and classified them as having MAS based on the 2016 sJIA MAS criteria[1,9,15]. They further divided the patients into 2 categories: those with MAS prior to admission, and those who developed MAS after admission. Ahn, *et al* also calculated the HScore to estimate a patient's risk of having MAS/secondary HLH and compared it to those with MAS and those without MAS based on the 2016 pediatric sJIA MAS criteria. They found that 56.2% of hospitalized patients with AOSD met criteria for sJIA associated MAS. Of the 36 patients with MAS, 61.1% had MAS at the time of admission, and the remaining 38.8% developed MAS during the hospitalization[15]. Clinical manifestations were similar between the groups; however, the erythrocyte sedimentation rate and platelet counts were lower, and lactate dehydrogenase and TGC levels were higher, in patients with MAS at the time of admission, similar to what others have seen in AOSD[16].

Survival rates were lower in AOSD patients with MAS (66.6%) compared to those without MAS (100%). Mortality was higher in patients with MAS at the time of admission, with a majority of these resulting from multiorgan failure as opposed to secondary infection. A higher-fold increase in ferritin, defined as the maximum ferritin value divided by baseline ferritin level, was also associated with lower survival rates. Similarly, AOSD MAS patients with an Hscore ≥ 80% had a higher mortality rate than those with scores < 80%. Treatment was more aggressive in AOSD patients with MAS compared to those without, and included higher glucocorticoid dosage and more frequent use of cyclosporine, etoposide, and intravenous immunoglobulin[15].

Only 26 (18 with MAS and 8 without MAS) of the 64 AOSD patients had a bone marrow biopsy performed. Hemophagocytosis was found in 9 of the 18 AOSD patients with MAS (50%) and in 0 patients without MAS[15]. These findings are consistent with literature suggesting that bone marrow hemophagocytosis is not highly sensitive in confirming MAS (~60%) and may delay diagnosis and ultimately, treatment[5,6]. Additionally, strict application of the HLH-2004 criteria classified only 7 patients as having MAS, meaning MAS would have gone unrecognized in 29 patients. Thus, the HLH-2004 criteria are likely insensitive for diagnosing MAS in the setting of AOSD, and at a minimum, may cause a delay in treatment, thereby potentially increasing mortality rates[15].

The study by Ahn, *et al* explores the clinical crossover of sJIA and AOSD and attempts to expand the 2016 classification criteria for MAS, which have been validated only in pediatric patients with sJIA[1], to include adult patients with AOSD[15]. Based on these results, the 2016 EULAR/ACR/PRINTO MAS criteria may be clinically useful in patients with AOSD. These criteria may thus aid in a prompt diagnosis and subsequent aggressive and targeted treatment of MAS to better improve longterm morbidity and mortality in those with AOSD. The 2016 MAS criteria are based largely on laboratory values, with fever being the only clinical manifestation[1]. Some of these laboratory abnormalities can be seen in other systemic inflammatory conditions, such as systemic lupus erythematosus (SLE) and Kawasaki disease, making it difficult to generalize the criteria to include all rheumatologic conditions. It is therefore important to have additional validation studies to determine the clinical relevance of these criteria with respect to other specific inflammatory conditions.

Validated MAS criteria for rheumatic conditions will allow for more controlled treatment studies. To date, there is no standardized treatment protocol, and management remains largely anecdotal. Traditionally, high-dose corticosteroids have been the mainstay of treatment. Addition of cyclosporine has also been used and may be beneficial in patients refractory to steroids[1,2,3,4]. Etoposide has been included as standard treatment per HLH-1994 and HLH-2004 protocols; however, there are significant risks associated with cytotoxic chemotherapy, and it may not be the best choice for MAS patients with underlying rheumatologic disorders[10,11]. By comparison, several recent case series have suggested targeted interleukin 1 inhibition with anakinra may be a safe and effective first-line therapy for controlling MAS[17,18,19]. To better study safety and efficacy of treatments, it is crucial to validate classification criteria for various inflammatory disorders to be used in clinical trials.

With a mortality rate of 8% among patients with sJIA, and likely a notably higher one for those with AOSD, it is important for practitioners to recognize MAS early and to treat it aggressively in hopes of improving patient survival[20]. While this current AOSD study has several limitations, including a small patient sample, restriction to hospitalized patients, and lack of treatment outcomes, it serves as an initial study to explore the clinical relevance of the 2016 sJIA MAS

criteria in patients with AOSD, a related systemic inflammatory condition[15]. With additional studies, it may be possible to apply modified MAS criteria for sJIA patients to those with pediatric and adult SLE, Kawasaki disease, spondyloarthritis, etc., with the potential for earlier recognition and treatment, in hopes of reducing overall mortality for patients with rheumatic disorders.

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