Macrophage Activation Syndrome

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KEYWORDS

- Macrophage activation syndrome • Systemic juvenile idiopathic arthritis
- Hemophagocytic lymphohistiocytosis • Hemophagocytic syndrome
- Proinflammatory cytokines • Interleukin-1 inhibitors

KEY POINTS

- Macrophage activation syndrome (MAS) is a potentially life-threatening complication of rheumatic disorders, particularly systemic juvenile idiopathic arthritis.
- Although the pathophysiology of MAS is unclear, it is characterized by a dysfunctional immune response that is similar to that seen in other forms of hemophagocytic lymphohistiocytosis.
- Because MAS may pursue a rapidly fatal course, prompt recognition of its clinical and laboratory features and immediate therapeutic intervention are imperative.
- Recently, a set of classification criteria for MAS complicating systemic juvenile idiopathic arthritis has been developed through a multinational collaborative effort.
- The role of cytokine inhibitors in the management of MAS deserves further studies, although recent data about interleukin-1 antagonists are promising.

INTRODUCTION

The term macrophage activation syndrome (MAS) refers to a potentially life-threatening complication of rheumatic disorders that is seen most commonly in systemic juvenile idiopathic arthritis (sJIA)[1,2] and in its adult equivalent, adult-onset Still

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disease,[3] although it is encountered with increasing frequency in systemic lupus erythematosus of either childhood or adult onset[4,5] and Kawasaki disease.[6] In spite of recent reports in periodic fever syndromes,[7,8] the occurrence of MAS in other autoinflammatory diseases is rare.

This article summarizes the characteristics of MAS occurring in the context of sJIA and discusses the recent advances in classification systems and management.

HISTORY, NOMENCLATURE, AND CLASSIFICATION

The first description of this condition dates back to 1985, when Hadchouel and colleagues[9] reported a clinical syndrome of acute hemorrhagic, hepatic, and neurologic abnormalities in patients with sJIA. The term MAS was proposed in 1993 by the same group of investigators, who found evidence of activation of the monocyte-macrophage system in patients with the syndrome and noticed that its clinical features were very similar to those observed in hemophagocytic lymphohistiocytosis (HLH).[10] The recognition that MAS belongs to the spectrum of HLH has subsequently led to a proposal to rename it according to the contemporary classifications of HLH[11] and to classify it among the secondary, or acquired, forms of HLH.[12,13]

EPIDEMIOLOGY

The incidence of MAS in sJIA is unknown. It is estimated that around 10% of children with this disease develop overt MAS, but recent data suggest that the syndrome may occur subclinically or in mild form in another 30% to 40% of cases.[14,15] In a recent multinational study of 362 patients, MAS occurred more frequently in girls, with a female/male ratio of 6:4.[16] This slight female predominance contrasts with the 1:1 sex ratio typical of sJIA. The median time interval between the onset of sJIA and the occurrence of MAS was 4 months, and MAS was diagnosed simultaneously with sJIA in 22% of the patients. The demographic, clinical, laboratory, and histopathologic features of MAS were overall comparable among patients seen in different geographic areas.[17]

PATHOGENESIS

An in-depth discussion of the pathogenesis of MAS is beyond the scope of this article, and has been covered recently elsewhere.[18–20] However, a few developments are worth noting. The starting point for most pathogenetic studies is the notion that MAS is characterized by a dysfunctional immune response that is similar to that seen in other forms of HLH. The prototype of these is familial HLH (FHLH), which is a constellation of rare autosomal recessive immune disorders resulting from homozygous deficiency in cytolytic pathway proteins.[12,13,21] In FHLH, the uncontrolled expansion of T cells and macrophages has been attributed to diminished natural killer (NK) cell and cytotoxic T cell function,[12,13,21,22] caused by mutations in particular genes whose products are involved in the perforin-mediated cytolytic pathway.[23–26] These mutations cause profound impairment of cytotoxic function, which, through mechanisms that have not yet been fully elucidated, leads to an exaggerated expansion and activation of cytotoxic cells with hypersecretion of proinflammatory cytokines, which ultimately results in hematologic alterations and organ damage.[27] Recent evidence suggests that defects in killing leads to prolonged interaction between the cluster of differentiation 8 (CD8) T cell or NK cell and the infected target cell, resulting in a proinflammatory cytokine storm.[28]

Although the pathophysiology of MAS is less clear, it probably involves related pathogenic pathways.[29,30] It has recently been shown that, as in FHLH, patients with MAS