Macrophage activation syndrome (MAS) is a serious complication of childhood systemic inflammatory disorders that is thought to be caused by excessive activation and proliferation of T lymphocytes and macrophages. Recent findings in hemophagocytic lymphohistiocytosis, a disease that is clinically similar to MAS, highlight the possible pathogenetic role of a defective function of perforin, a protein involved in the cytolytic processes and control of lymphocyte proliferation. Although the clinical features of MAS have been well documented, early diagnosis can be difficult. Measurement of the serum ferritin level may assist in the diagnosis and may be a useful indicator of disease activity, therapy response, and prognosis. The recognition that MAS belongs to the secondary or reactive hemophagocytic syndromes has led to the proposal to rename it according to the contemporary classification of histiocytic disorders. Cyclosporin A has been found effective in patients with corticosteroid-resistant MAS. A recent report has suggested that etanercept may be a useful adjunctive therapeutic agent.

Clinical features
The clinical presentation of MAS is generally acute and can be dramatic. Typically, patients become acutely ill with the sudden onset of nonremitting high fever, hepatosplenomegaly, lymphoadenopathy, profound depression of all three blood cell lines (leukopenia, anemia, and thrombocytopenia), and elevated serum liver enzymes. High concentrations of triglycerides and lactate dehydrogenase and low sodium levels are observed consistently. There is usually an abnormal coagulation profile, with prolonged prothrombin activity and partial thromboplastin time, hypofibrinogenemia, and the presence of fibrin degradation products. As a result, a patient may have purpura, easy bruising, and mucosal bleeding. Central nervous system dysfunction occurs frequently and may cause lethargy, irritability, disorientation, headache, seizures, or coma. Occasionally, renal, pulmonary, and cardiac involvement has been reported. In children with systemic JIA, the clinical picture may mimic sepsis or a flare-up of the underlying disease. However, the pattern of nonremitting fever is different from the remitting high-spiking fever seen in systemic JIA. Moreover, patients may show a paradoxical improvement in the underlying inflammatory disease at the onset of MAS, with the disappearance of the signs and symptoms of arthritis and a decrease in the erythrocyte sedimentation rate. The pathognomonic feature of the syndrome is seen on bone marrow examination, which reveals numerous well-differentiated macrophages actively phagocytosing hematopoietic cells. Such cells may be found in various organs and may account for many of the systemic manifestations.

Hyperferritinemia is an important laboratory hallmark of MAS that has received little attention to date. Phagocytic macrophages are thought to be an important source of serum ferritin [3]. In vitro studies have shown that intracellular ferritin accumulates markedly during the maturation of monocytes into macrophages and that cultured monocytes in iron-containing medium or in the phago...
Epidemiology
The exact incidence of MAS in childhood systemic inflammatory disorders is unknown. Although it is considered a rare complication, it is probably more common than previously thought. To date, approximately 100 cases have been reported in the literature [1,10•, 11•,12•]. MAS affects most commonly children with systemic JIA but has been observed in different subtypes of JIA or in other systemic diseases such as systemic lupus erythematosus (SLE). It generally develops in the earlier phases of the underlying disease and may occasionally be the presenting manifestation, but occurrence as late as 14 years after diagnosis has been reported. In most patients, the primary disease is clinically active at the onset of MAS, but the syndrome may also develop during quiescent phases.

Although MAS may occur without any identifiable precipitating factor, it has been related to a number of triggers, including a flare-up of the underlying disease, aspirin or other nonsteroidal anti-inflammatory drug toxicity, viral infections, a second injection of gold salts, and sulfasalazine therapy. A young girl with systemic JIA was described who developed MAS shortly after the first methotrexate (MTX) dose in the apparent absence of any triggering event, suggesting that MAS could have been a direct consequence of MTX toxicity [7]. The short time interval (24 hours) between MTX dosing and the onset of MAS and the characteristics of clinical symptoms, particularly the occurrence of intense and generalized pruritus, argued for a hypersensitivity or idiosyncratic reaction, a mechanism similar to that hypothesized in the pathogenesis of MAS associated with gold salt injections. This report reinforces a previous observation of a possible relationship between MTX toxicity and MAS [13] and suggests that MTX may act as an inciting factor of MAS in children with systemic JIA.

Pathogenesis
The exact cause of MAS is poorly understood. Most of the hypotheses on its pathogenesis are derived from data obtained in primary hemophagocytic lymphohistiocytosis (HLH) [14••], a disease that is clinically similar to MAS. In general, most clinical features and laboratory findings, including pancytopenia with phagocytosis of bone marrow-derived elements, liver abnormalities, and coagulopathy, could be explained by the widespread dissemination of hyperactivated lymphocytes and macrophages and are compatible with the biologic effects of several T lymphocyte- and macrophage-derived proinflammatory cytokines such as tumor necrosis factor-α (TNF-α), interleukin (IL)-1, IL-6, and interferon-γ [15]. Increased serum levels of TNF-α have been documented in patients with MAS [16,17]. Furthermore, the importance of TNF-α in the development of coagulation abnormalities in systemic JIA has been demonstrated by De Benedetti et al. [18], who found a strong correlation between the serum levels of soluble TNF receptors and prolongation of partial thromboplastin time and a decrease in prothrombin activity.

It was recently shown that primary HLH, as well as other related conditions such as Chédiak-Higashi and Griscelli syndromes, may be the result of a mutation in the perforin gene leading to decreased expression of perforin [19]. Perforin is a protein that is expressed in lymphocytes, macrophages, and other bone marrow precursors. Its main role in the cytolytic process is to form pores in the cell membrane, leading to osmotic lysis of the target cells. Evidence obtained in animal models showed that perforin-deficient mice cannot lyse target cells [20] and have impaired defense against cancer and intracellular pathogens [20,21]. It has been suggested that perforin may also control lymphocyte proliferation [19,22]. Perforin deficiency may therefore lead to persistent lymphocyte activation associated with production of large amounts of interferon-γ and granulocyte-macrophage colony-stimulating factor, which are important macrophage activation syndrome features.

Table 1. Main features of the macrophage activation syndrome

<table>
<thead>
<tr>
<th>Clinical features</th>
<th>Laboratory features</th>
<th>Pathological features</th>
</tr>
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<tbody>
<tr>
<td>Nonremitting high fever</td>
<td>Cytopenia</td>
<td>Macrophage hemophagocytosis in the bone marrow</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>Abnormal liver function tests</td>
<td></td>
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<tr>
<td>Splenomegaly</td>
<td>Coagulopathy</td>
<td></td>
</tr>
<tr>
<td>Lymphoadenopathy</td>
<td>Decreased erythrocyte sedimentation rate</td>
<td></td>
</tr>
<tr>
<td>Hemorrhages</td>
<td>Hyperglycemia</td>
<td></td>
</tr>
<tr>
<td>Central nervous system dysfunction</td>
<td>Hypernatremia</td>
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<td></td>
<td>Hypoalbuminemia</td>
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<td></td>
<td>Hyperferritemia</td>
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pabilities. Histiocytic disorders are conditions characterized by the proliferation and accumulation of macrophages and dendritic cells. In the most recent classification, these conditions are grouped under three categories: dendritic cell-related disorders, macrophage-related disorders, and malignant disorders of histiocytes [28]. As shown in Table 2, the secondary hemophagocytic syndromes, of which MAS is one, constitute one subset in the group of macrophage-related disorders. To use uniform terminology and incorporate MAS in the classification of histiocytic disorders, a suitable name could be, as suggested by Athreya [26••], rheumatic disease-associated hemophagocytic syndrome.

Diagnostic guidelines

Macrophage activation syndrome is a serious complication of childhood systemic inflammatory disorders that is associated with considerable morbidity and death. Early recognition of its clinical features and immediate therapeutic intervention to produce a rapid clinical response are therefore critical. However, the diagnosis of MAS, particularly in its early phase, can be difficult. In patients with systemic JIA, a condition characterized by repetitive flares, the onset of MAS may be confused with a disease exacerbation; other important differential diagnoses include intercurrent infections and side effects of medications. The recognition of MAS can be problematic in patients with SLE because it may mimic the clinical features of the underlying disease. In a young patient reported recently, this complication presented as unexplained fever and cytopenia, thus suggesting a SLE flare. The diagnosis was facilitated by the absence of other

Table 2. Contemporary classification of histiocytic disorders with the inclusion of the macrophage activation syndrome

<table>
<thead>
<tr>
<th>Disorders of varied biological behavior</th>
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<tbody>
<tr>
<td>Dendritic-cell related</td>
</tr>
<tr>
<td>Langerhans cell histiocytosis</td>
</tr>
<tr>
<td>Secondary dendritic cell processes</td>
</tr>
<tr>
<td>Juvenile xanthogranuloma and related disorders</td>
</tr>
<tr>
<td>Solitary histiocytomas of various dendritic cell phenotypes</td>
</tr>
<tr>
<td>Macrophage-related</td>
</tr>
<tr>
<td>Hemophagocytic syndromes</td>
</tr>
<tr>
<td>Primary hemophagocytic lymphohistiocytosis</td>
</tr>
<tr>
<td>Secondary hemophagocytic syndromes</td>
</tr>
<tr>
<td>Infection-associated</td>
</tr>
<tr>
<td>Malignancy associated</td>
</tr>
<tr>
<td>Rheumatic-disease associated</td>
</tr>
<tr>
<td>Other</td>
</tr>
<tr>
<td>Rosai-Dorfman disease</td>
</tr>
<tr>
<td>Solitary histiocytoma with macrophage phenotype</td>
</tr>
<tr>
<td>Malignant disorders</td>
</tr>
<tr>
<td>Monocyte-related</td>
</tr>
<tr>
<td>Leukemias</td>
</tr>
<tr>
<td>Monocytic leukemia M5A and B</td>
</tr>
<tr>
<td>Acute myelomonocytic leukemia M4</td>
</tr>
<tr>
<td>Chronic myelomonocytic leukemia</td>
</tr>
<tr>
<td>Extramedullary monocytic tumor or sarcoma</td>
</tr>
<tr>
<td>Dendritic cell-related histiocytic sarcoma</td>
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<tr>
<td>Macrophage-related histiocytic sarcoma</td>
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The term histiocytes refers to a group of immune cells that includes macrophages, which have predominantly antigen-processing functions, and dendritic cells, which possess primarily accessory cell or antigen-presenting ca-
clonal or serologic indicators of SLE exacerbation or signs of infection [29].

The difficulties in making the diagnosis and the recent therapeutic advances (see below) emphasize the need for diagnostic tools and well-established diagnostic guidelines. Diagnostic criteria would be also important for research purposes and use in publications. To identify potential criteria for MAS complicating systemic JIA, the diagnostic sensitivity and specificity of the main components of the clinical and laboratory picture of MAS were recently evaluated [12•]. The features of 109 cases of MAS seen in 88 patients reported in the literature or observed by the authors were compared with those of a cohort of control patients with a confusable condition, which included 35 patients with systemic JIA assessed at the time of their first disease flare. The variables that showed the highest (≥0.75) sensitivity and specificity for MAS were ferritin (≥10,000 ng/mL), triglycerides (≥160 mg/dL), aspartate aminotransferase (≥40 IU/mL), fibrinogen (≥250 mg/dL), alanine aminotransferase (≥40 IU/mL), γ-glutamyl transferase (≥40 IU/mL), platelet count (≤150,000/mm³), and bone marrow aspirate showing hemophagocytosis, hepatomegaly, and splenomegaly. Variables that did not prove sufficiently sensitive and specific included fever (≥38°C), lymphoadenopathy, neurologic manifestations, arthritis, rash, hemorrhages, leukocyte count (≥4,000/mm³), erythrocyte sedimentation rate (≤50 mm/h), lactate dehydrogenase (≥900 IU/mL), bilirubin (≥1.2 mg/dL), and serum sodium (≤130 mEq/L).

Management

The treatment strategy for MAS is usually based on the parenteral administration of high doses of corticosteroids. However, there have been some fatalities in reported series, even among patients treated with massive doses of corticosteroids [1,10•,11•]. The administration of high-dose intravenous immune globulins, cyclophosphamide, plasma exchange, and etoposide has provided conflicting results. The use of cyclosporin A was recently advocated based on its proven benefit in the management of other disorders affecting macrophages such as primary HLH [16]. Cyclosporin A proved effective in treating severe or corticosteroid-resistant MAS [7,29,30]. In some patients, the introduction of this drug exerted a “switch-off” effect on the disease process, leading to resolution of fever and improvement of laboratory abnormalities within 12 to 24 hours [29]. Although the exact mechanism by which cyclosporin A achieves immunosuppression is unknown, it is believed to exert its major effects by the suppression of the early steps in T-cell activation, leading to failure to activate the transcription of early genes such as those encoding for cytokines [31]. Cyclosporin A has also been shown to affect macrophage production of IL-6, IL-1, and TNF-α and to inhibit the expression of inducible nitric oxide synthetase and cyto-

Based on the observation of increased serum levels of TNF-α in patients with MAS [16,17] and the notion that this cytokine may play a central role in its pathogenesis, it has been hypothesized that rapid blocking of TNF-α activity may provide another efficient way to reduce the consequences of excessive activation of macrophages. Prahalad et al. [8] evaluated the use of the anti–TNF-α agent etanercept in a boy with probable systemic JIA who developed MAS that required large doses of corticosteroids to control symptoms. The addition of etanercept (0.4 mg twice weekly) 4 weeks after the onset of MAS was followed by dramatic improvement of symptoms within 24 hours after the first dose, which was paralleled by normalization of the erythrocyte sedimentation rate after four doses of etanercept. Over the next 5 weeks, prednisone was tapered completely without recurrence of symptoms. The outcome in this patient suggests that etanercept might be an effective adjunctive therapeutic agent in MAS.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

• Of special interest
•• Of outstanding interest

3 Finch CA, Huebers HA, Cazzola M, et al.: Storage iron. In Ferritins and iso-
ferritins as biochemical markers. (Symposia of the Giovanni Lorenzini Foun-
8 Prahalad S, Bove KE, Dickens D, et al.: Etanercept in the treatment of mac-
10 Sawhney S, Woo P, Murray KJ: Macrophage activation syndrome: a poten-
This study retrospectively reviews the precipitating events, clinical manifestations, treatment, and outcome of nine children with MAS seen in a single institution over a 20-year period. The unique features of MAS in systemic rheumatic diseases compared with other hemophagocytic syndromes are discussed.


This study retrospectively reviews the clinical and biologic features and treatment of 24 children with MAS identified over a 10-year period in French pediatric units. Eighteen patients had systemic JIA, two had polyarticular JIA, two had SLE, and two had unclassifiable systemic inflammatory disorders.


26 Athreya BH: Is macrophage activation syndrome a new entity? [editorial]. Clin Exp Rheumatol 2002 (in press). This editorial analyzes the issues related to the nosology and classification of MAS. The relationship of MAS with the other secondary or reactive hemophagocytic syndromes and its proper allocation within the contemporary classification of histiocytic disorders are discussed.


