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REVIEW ARTICLE

Macrophage Activation Syndrome

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Abstract Macrophage activation syndrome (MAS) is a potentially life-threatening complication of rheumatic diseases such as systemic juvenile idiopathic arthritis (sJIA) and systemic lupus erythematosus. It is often considered a type of secondary hemophagocytic lymphohistiocytosis (HLH) and results from over-activation of T lymphocytes and macrophages leading to a "cytokine storm". Characteristic features are persistent fever, lymphadenopathy, hepatosplenomegaly, cytopenias (anemia, leucopenia, thrombocytopenia), raised C-reactive protein, falling erythrocyte sedimentation rate, hypofibrinogenemia, transaminitis, hypertriglyceridemia and extreme hyperferritinemia often associated with multi-organ impairment. Key to its management is early recognition of MAS which may be difficult due to similarity to systemic sepsis or flares of the underlying rheumatic disease. To aid with this process, criteria for the diagnosis of MAS in patients with sJIA derived by international consensus have been published. Although bone marrow biopsy showing hemophagocytosis is strongly supportive it is not essential for diagnosis. Together with appropriate supportive care, first-line treatment is high-dose intravenous corticosteroids with cyclosporin or intravenous immunoglobulin (IVIg) added if there is not initial response. Although etoposide is used by hematologists in treatment of HLH, there are concerns regarding organ toxicity and bone marrow suppression which weigh against its use in initial management of MAS. With increasing understanding of the pathogenesis of MAS, use of drugs targeting specific cytokines has been reported in case series. The relatively rapid effectiveness of anakinra, a recombinant IL-1 receptor antagonist, has been documented. Further studies of this and other biologic agents are required to identify the most effective and safest treatment option for refractory MAS.

Keywords Macrophage activation syndrome · Hemophagocytic lymphohistiocytosis · Systemic juvenile idiopathic arthritis · Hyperferritinemia · Interleukin-1

Introduction

Macrophage activation syndrome (MAS) is a serious complication of rheumatic diseases, with mortality rates reported to be as high as 8–22 % [1, 2]. Excessive T cell and macrophage activation and proliferation leads to hypercytokinemia and hemophagocytosis. This activation cascade can lead to an overwhelming, and potentially fatal, multisystem inflammatory response.

MAS belongs to a group of disorders known as hemophagocytic lymphohistiocytosis (HLH). Primary, or familial, HLH includes patients with a variety of rare, autosomal recessive immune defects. These patients present early in life and are unlikely to survive without hematopoietic stem cell transplantation. Secondary HLH includes patients, usually older children, in whom the condition is associated with a trigger such as an identifiable infectious episode or malignancy. MAS has close similarity with secondary HLH and is classified by some as a type of secondary HLH occurring specifically in the context of rheumatic disease [3].

The purpose of this article is to highlight the clinical features of MAS which should increase the index of suspicion for

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the condition, the laboratory tests which help support a diagnosis and an approach to managing patients with MAS.

Epidemiology

MAS is seen in a variety of different rheumatic diseases in adults and children, but is most commonly reported in systemic juvenile idiopathic arthritis (sJIA) and its adult equivalent, adult-onset Still's disease. Overt MAS is seen in approximately 7–13 % of patients with sJIA [2, 4, 5] and a more occult/subclinical phenotype is seen in up to a third of patients with active sJIA [4, 6]. After sJIA, MAS is most frequently encountered in systemic lupus erythematosus (SLE) [7, 8] and Kawasaki disease [8–10] but it has also been reported in the context of polyarticular JIA [1, 11, 12], juvenile dermatomyositis [13], antiphospholipid syndrome [14] and mixed connective tissue disease [14].

Etiology

Whilst the precise etiology of MAS is unknown, the condition is thought to be due to abnormal immune regulation giving rise to an exaggerated inflammatory response. MAS can be triggered by a flare of an existing rheumatic disease or can be the presenting feature of the new rheumatic diagnosis. Avcin et al. reported three patients who presented with MAS as the initial presentation of SLE, sJIA and Kawasaki disease [8].

In common with other HLH conditions, infections and medications have been identified as triggers for MAS. Infection is thought to be the trigger for MAS in approximately half of the patients; these include both viral infections [typically Epstein-Barr virus (EBV), cytomegalovirus and herpes viruses] and bacterial infections [12, 15]. Recently, reactive HLH has been described in association with Dengue and Ebola virus infections [16, 17]. A systematic review of reported cases of HLH in India found that in 44 % of 93 children infection was the trigger while connective tissue disease was the cause in 18 % [18]. Amongst the 41 patients with infectious etiology, viruses (such as EBV and Dengue) were the cause in 56 % and tropical infectious agents in 32 %. In addition, a diverse range of drugs have been implicated in the development of MAS, including biological therapies [19, 20].

Clinical Features

MAS can affect many organ systems (Table 1). Clinical findings can evolve rapidly causing patients to become acutely, significantly unwell. Typical features of MAS include unremitting high fevers, altered mental state, lymphadenopathy and hepatosplenomegaly. Patients develop a hemorrhagic, disseminated intravascular coagulation (DIC)-like syndrome causing skin rashes ranging from mild petechiae to purpura and extensive ecchymoses [21]. As the disease progresses patients may also bleed from other sites (*e.g.*, respiratory and gastrointestinal tract). Patients become encephalopathic with a number of CNS abnormalities. Renal involvement has been reported in a number of series [2, 22] and patients with renal dysfunction have a substantially higher risk of mortality [2]. Respiratory manifestations of MAS include pulmonary infiltrates and acute respiratory distress syndrome [11, 12].

Laboratory Features

There are a number of features, highly suggestive of MAS, which are found on laboratory tests. One of the earliest features is a fall in two of the three blood cell lines (leucocytes, erythrocytes and platelets), with the drop in platelets tending to occur first [21]. This drop in cell counts is thought to be due to increased cell destruction by phagocytosis and consumption due to inflammation, rather than bone marrow suppression; bone marrow aspirates from MAS patients show significant hypercellularity and normal megakaryocytes [23]. Changes in inflammatory parameters are also typical in

Table 1 Clinical and laboratory features of MAS

System	Clinical features	Laboratory features
General	Fever	Fall in ESR Raised CRP Elevated sIL-2Ra
Hematological	Coagulopathy Petechiae, purpura, ecchymoses Epistaxis	Extreme hyperferritinemia Leucopenia Anemia Thrombocytopenia Hemophagocytosis and hypercellularity on bone marrow aspiration
Central nervous system	Altered mental state Seizures Encephalopathy Coma	CSF pleiocytosis
Gastrointestinal	Hematemesis Rectal bleeding Liver dysfunction	Transaminitis Mildly elevated bilirubin Hypoalbuminemia Normal or mildly raised ammonia Elevated triglycerides
Renal	–	Abnormal renal function
Respiratory	ARD Pulmonary infiltrates	–

ARD Acute respiratory distress; *CRP* C-reactive protein; *CSF* Cerebrospinal fluid; *ESR* Erythrocyte sedimentation rate; *sIL-2Ra* Soluble interleukin-2 receptor alpha chain (also known as sCD25)

MAS. C-reactive protein (CRP) remains high whereas paradoxically erythrocyte sedimentation rate (ESR) drops considerably (possibly due to reduced fibrinogen). Ferritin is seen at extremely high levels in MAS patients and is a distinctive feature; a ferritin value of >10,000 ng/ml has been shown to be highly sensitive and specific for a diagnosis of HLH in children [24]. Extreme hyperferritinemia is thought to be secondary to excessive erythrophagocytosis and sequestration of resultant free iron.

Diagnosis

Early diagnosis and initiation of treatment is paramount in MAS given the severity of the condition. However, clinical features of MAS show considerable overlap with the underlying rheumatic condition, making early diagnosis difficult. Thus, it is the results of laboratory tests which heavily support the diagnosis of MAS in patients with clinical features suggestive of the condition. For *example*, in juvenile SLE patients, hyperferritinemia is a key discriminator between a SLE flare and SLE-induced MAS as features such as fever, cytopenias and liver dysfunction are common to both. Similarly, in patients with sJIA, an absence of arthritis and serositis, a haemorrhagic rather than maculopapular rash and a sudden drop in ESR are highly suggestive of MAS (Table 2).

Whilst diagnostic and therapeutic guidelines exist for HLH [25], there are no such consensus diagnostic criteria for MAS, thus clinical vigilance with attention to the features above is paramount, particularly in rheumatology patients who are at an increased risk of MAS. Whilst MAS is considered by some to be a form of secondary HLH, when the HLH criteria are applied to patients with MAS and sJIA they are highly specific but have low sensitivity [26]. In addition, the overlap in clinical features between HLH diagnostic guidelines and those seen in the rheumatic conditions underlying MAS limit their usefulness in the pediatric rheumatology population. As a result, preliminary guidelines for diagnosing MAS in sJIA patients were drafted [27] which showed improved sensitivity for diagnosing MAS in these patients [26]. Work is ongoing to optimise the diagnostic criteria for MAS to produce consensus guidelines for use in patients with rheumatic disease [28]. The key features of MAS identified from this work are:

1. Falling platelet count
2. Hyperferritinemia
3. Hemophagocytosis on bone marrow biopsy
4. Raised liver enzymes
5. Falling leucocyte count
6. Persistent, continuous fever of ≥38 °C
7. Falling ESR
8. Hypofibrinogenemia
9. Hypertriglyceridemia

After a consensus conference of international experts on MAS, the following definition was agreed upon: "A febrile patient with known or suspected sJIA is classified as having MAS if the patient has: ferritin >684 ng/ml and at least 2 of the following 4 laboratory abnormalities: platelets ≤ 181×10^9 /L, aspartate aminotransferase (AST) > 48 U/L, triglycerides > 156 mg/dl, and fibrinogen ≤ 360 mg/dl" [29].

A diagnosis of MAS can be confirmed by the presence of hemophagocytosis on bone marrow biopsy but hemophagocytosis can be variable, particularly early in the disease and is subject to sampling error. A multinational study of 362 patients with MAS complicating sJIA reported that only 60.7 % of patients whose bone marrow was examined showed hemophagocytosis [30]. In the negative cases, serial bone marrow biopsies may be required to demonstrate hemophagocytosis although this is not essential for a diagnosis of MAS to be made. Recent work has shown that staining bone marrow samples with anti-CD163 antibody demonstrates a massive expansion of highly activated histiocytes in MAS patients and has led to the demonstration of

Table 2 Comparison of clinical and laboratory features of systemic juvenile idiopathic arthritis (sJIA) and macrophage activation syndrome (MAS), reproduced from [21] with publisher's permission

	sJIA	MAS
Fever pattern	Quotidian	Unremitting
Rash	Evanescent, maculopapular	Petechial or purpuric
Hepatosplenomegaly	+	+
Lymphadenopathy	+	+
Arthritis	+	–
Serositis	+	–
Encephalopathy	±	+
WCC and neutrophil count	↑↑	↓
Hemoglobin	Normal or ↓	↓
Platelets	↑↑	↓
ESR	↑↑	Normal or sudden ↓
Bilirubin	Normal	Normal or ↑
ALT/AST	Normal or ↑	↑↑
PT	Normal	↑
PTT	Normal	↑
D-dimers	↑	↑↑
Fibrinogen	↑	↓
Ferritin	Normal or ↑	↑↑
sIL-2Ra	Normal or ↑	↑↑
CD163	Normal or ↑	↑↑

ALT Alanine aminotransferase; *AST* Aspartate aminotransferase; *ESR* Erythrocyte sedimentation rate; *MAS* Macrophage activation syndrome; *PT* Prothrombin time; *PTT* Partial thromboplastin time; *sIL-2Ra* Soluble interleukin-2 receptor alpha chain (also known as sCD25); *sJIA* Systemic juvenile idiopathic arthritis; *WCC* White cell count

hemophagocytosis in bone marrow samples reported to be normal using standard staining techniques. Thus anti-CD163 antibody can add to the diagnostic yield [4], particularly in patients early in the disease course where hemophagocytosis is more limited or with occult/subclinical disease.

Soluble IL2-Ra and soluble CD163 in serum have also been suggested as diagnostic markers as they are thought to reflect T cell and macrophage activation [6], however, at the current time these tests are only available in specialist laboratories.

Management

Central to the management of MAS is its early recognition, which requires increased awareness of the condition amongst the medical community, followed by prompt treatment. In its early stages, it may mimic infection or flares of the underlying rheumatic disease, such as sJIA or SLE. The clinical features and investigations described above assist in the differential diagnosis.

MAS is a potentially life-threatening disease and in all cases appropriate resuscitation and supportive care is required. A multicentre study of MAS in sJIA reported that 35 % of 235 patients required admission to the intensive care unit (ICU) [30]. No randomised controlled trials (RCTs) of targeted treatment of MAS have been performed; therefore, evidence derives from case series and individual case reports. The commonest initial treatment is corticosteroids commencing with high-dose intravenous (IV) methylprednisolone (30 mg/kg, maximum 1000 mg, daily for 3 d) followed by oral prednisolone 2–3 mg/kg/d in divided doses [31]. This controls disease in almost half of patients [21]. If not immediately effective, cyclosporin (2–7 mg/kg/d IV) is often used as a second line agent with reports of its effectiveness from several case series [11, 32]. Intravenous immunoglobulin (IVIg, 2 g/kg in a single dose) can be considered, particularly if the exclusion of sepsis is difficult in a ill child with MAS [33].

If MAS remains active despite the above treatments, etoposide may be considered as part of the HLH-2004 treatment protocol [25]. It is used more frequently as first-line treatment by hematologists/oncologists for other forms of secondary HLH, however is felt by rheumatologists to be too aggressive for initial treatment of sJIA-associated MAS [34]. Particular concern surrounds toxicity of etoposide which is metabolised by the liver and excreted by the kidneys, both organ systems which may be impaired in severe MAS. Side effects such as bone marrow suppression and overwhelming sepsis may be reduced by using fewer, lower doses of etoposide than the HLH-2004 protocol suggests but there are no studies examining this. An alternative to etoposide, particularly in cases of MAS with renal or hepatic involvement, is anti-thymocyte globulin (ATG) [35]. Although well-tolerated in case reports, it frequently causes infusion reactions in the context of hematopoietic stem cell transplantation.

During the past decade, biologic agents have been given to treat steroid- and cyclosporin-refractory MAS and were used in 15.2 % of 341 patients in a retrospective multicentre study [30]. Tumour necrosis factor (TNF) inhibitors have shown efficacy in some cases, however there have been reports of MAS developing in patients while on these drugs [20, 21]. Key cytokines in the pathogenesis of sJIA are IL-1 and IL-6 [31]. Since MAS often coincides with flares of sJIA, drugs targeting these cytokines have been employed in treatment. Several case reports and series have shown clear and rapid benefit from anakinra, a recombinant IL-1 receptor antagonist, when used in addition to steroids, cyclosporin or IVIg [36, 37]. A series of 12 patients with MAS who had not been controlled by corticosteroids and other immunosuppressants [IVIg (n=9), cyclosporin (n=10), etoposide (n=2), etanercept (n=1)] were given subcutaneous anakinra (2 mg/kg/d, maximum 100 mg) [37]. All patients achieved remission of MAS within a median of 13 d (range 2–19) after starting anakinra and remained in remission at median of 22 mo follow-up. This study reported that no side effects of anakinra were noted. However, other studies have documented new-onset MAS in sJIA patients while being treated with anakinra [38, 39]. Canakinumab, an anti-IL-1β monoclonal antibody, has not been shown to prevent MAS despite maintaining control of sJIA [40].

Tocilizumab, a monoclonal antibody against the IL-6 receptor, has shown efficacy in treatment of sJIA in RCTs [41, 42]. There is one report of its use for treatment of MAS in adult-onset Still's disease [43]. However, of concern, one RCT of tocilizumab in sJIA reported 1.5 new MAS cases per 100 patient-years of treatment [41]. Another study highlighted that tocilizumab may mask changes in laboratory values in sJIA patients who developed MAS: the CRP remained normal and rise in ferritin was moderate [44]. Therefore, caution must be used when reviewing sJIA patients treated with tocilizumab to ensure that the diagnosis of MAS is not missed.

In cases of MAS triggered by Epstein-Barr virus (EBV) infection, depletion of B lymphocytes using rituximab, a monoclonal antibody against CD20 has been shown to be effective [45]. The body of evidence supporting use of biologics for MAS after failure of other immunomodulatory treatment is growing: Minoia et al. reported 52 patients receiving these agents, of whom 33 were given anakinra [30].

Future therapies for MAS will need to focus on pathways involved in triggering the "cytokine storm". One potential target is interferon-gamma (IFNγ), which is thought to be involved in pathogenesis of both familial and secondary forms of HLH, and clinical trials of drugs blocking IFNγ are in progress [31].

Conclusions

Macrophage activation syndrome is a potentially life-threatening complication of a range of rheumatic conditions in children. Key features are unremitting fever, lymphadenopathy, hepatosplenomegaly, cytopenias and marked hyperferritinemia. Central to its management is early recognition and rapid treatment. Consensus criteria for diagnosis of MAS in the context of sJIA will assist with this process. First-line treatment involves multi-system supportive care and high-dose corticosteroids with addition of cyclosporin if there is not a rapid response to initial therapy. For refractory cases, etoposide or anti-thymocyte globulin have been used, although the biologic agent anakinra is increasingly being reported as the next step after steroids and cyclosporin.

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