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The role of infective trigger for macrophage activation syndrome in rheumatic diseases. A retrospective analysis in a tertiary pediatric care centre and review of the literature

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Background: The role of infection in Macrophage Activation Syndrome (MAS) is controversial. In order to evaluate the prevalence of infections preceding the onset of MAS, we retrospectively analysed the cases of MAS complicating rheumatic diseases recorded in our tertiary hospital between 2005 and 2015.

Methods: The clinical records of patients diagnosed with MAS and hospitalised between January 2005 and December 2015 were reviewed in order to identify their demographic characteristics, underlying rheumatological diseases, clinical and laboratory data, treatments, and complications. There was considered if an infection was documented during the 15 days preceding the onset of MAS. The presence of specific immunoglobulin M was considered separately as a possible indirect sign of recent infection

Findings: Twelve children (eight females and four males) with underlying rheumatic disorders developed MAS during the study period: six were affected by systemic-onset juvenile idiopathic arthritis, three by systemic lupus erythematosus, two by dermatomyositis, and one by undifferentiated arthritis. There were 14 MAS-related events (one patient experienced three episodes). MAS occurred within 30 days of the onset of rheumatic disease in five cases, and during disease relapses in nine. In two cases, it followed the start of treatment with a new drug. Twelve of the 14 MAS episodes were suspected to be preceded by infections due to various pathogens, including *Clostridium difficile*, group A *Streptococcus*, *Staphylococcus hominis*, *Escherichia coli*, *Entamoeba histolytica*, *Endolimax nana*, *Pseudomonas aeruginosa*, *Borrelia burgdorferi*, *Adenovirus, Coxsackie virus, Epstein-Barr virus,* and *Cytomegalovirus.*

Conclusions: The prevalence of infections in patients developing MAS may be underestimated, and their pathogenetic role should be considered also in patients with underlining rheumatic diseases.

Keywords: MAS ● rheumatic diseases ● infection trigger

Introduction

Macrophage Activation Syndrome (MAS) is a rare, serious and potentially life-threatening complication of rheumatic diseases due to the activation of the monocyte-macrophage system. It was first described in patients with systemic-onset Juvenile Idiopathic Arthritis (soJIA), but has also been reported in patients with juvenile Systemic Lupus Erythematosus (SLE), Dermatomyositis (DM), and Kawasaki Disease [1]. The preliminary diagnostic criteria for MAS complicating soJIA were published by Ravelli *et al*. in 2005 [2], and have recently been revised [3] (**Tables 1 and 2**).

The clinical presentation of MAS is characterised by uncontrolled inflammation manifesting as unremitting fever, lymphadenopathy, hepatosplenomegaly, liver dysfunction, Central Nervous System (CNS) dysfunction, coagulopathy, multi-

Table 1. Preliminary diagnostic guidelines for MAS complicating soJIA (2005).			
Laboratory criteria	**Clinical criteria**	**Histopathological criterion**	**Diagnostic rule**
Decreased platelet count (£262 x 10^9/L)	Central nervous system dysfunction (irritability, disorientation, lethargy, headache, seizures and coma)	Evidence of macrophage hemophagocytosis in bone marrow aspirate	The diagnosis of MAS requires the presence of any two or more laboratory criteria or any two or three or more clinical and/or laboratory criteria. A bone marrow aspirate is only required in doubtful cases.
Elevated levels of aspartate aminotransferase (>59 U/L)	Hemorrhages (purpura, easy bruising, mucosal bleeding)		
Decreased white blood cell count (£4.0 x 10^9/L)	Hepatomegaly (3^3 cm below costal arch)		
Hypofibrinogenemia (£2.5 g/L)			

Table 2. Classification of Macrophage Activation Syndrome in systemic juvenile idiopatic arthritis (2016).
Ferritin >684 ng/mL
Platelet count £181 x 10^9/l
Aspartate aminotrasferase >48 U/L
Triglycerides >156 mg/dL
Fibrinogen £360 mg/dL

system organ failure and, in its most severe form, death. [4] The characteristic laboratory abnormalities include pancytopenia and high serum levels of liver enzymes, triglycerides, lactate dehydrogenase, ferritin and C-reactive protein, accompanied by a declining Erythrocyte Sedimentation Rate (ESR) due to low levels of fibrinogen [5-6]. A bone marrow examination often reveals macrophage hemophagocytosis, but this may be absent, especially in the initial stages of the syndrome.

In 2014 Minoia et al. published the study on largest population of patients with systemic JIA with MAS reported to date. [4] MAS was reported to occur most frequently (51.7%) in the setting of active systemic JIA or during a systemic JIA flare. An infectious trigger was detected in 34.1% of the patients. Epstein-Barr virus was the most common causative agent (in 25% of patients) among the 24 patients in whom the specific etiology or the type of infection was established or reported. Unfortunately, for the majority of patients, the causative agent was not mentioned by the investigator who entered the information.

Other infectious agents most frequently associated with the development of acquired forms of HLH were Cytomegalovirus [CMV] with other herpes viruses [7]; bacterial, parasitic and fungal infections have also been described [8].

There have also been reports of MAS occurring at the time of changes in drug therapy, although these reports should be interpreted cautiously because many of the described patients had very active underlying rheumatic disease and the association may have been coincidental as many cases of MAS seem to have been triggered by disease flares [9-11].

In order to evaluate the prevalence of infections preceding the onset of MAS and to evaluate the causative agents in our population, we retrospectively analysed the cases of MAS complicating rheumatic disorders occurring over a period of 10 years at our tertiary pediatric care unit.

Materials and Methods

We reviewed the clinical records of all of the patients with rheumatic diseases complicated by MAS observed in our Centre between 2005 and 2015. The MAS events were originally diagnosed using the 2005 preliminary diagnostic criteria for the diagnosis of MAS in JIA [2], and retrospectively confirmed on the basis of the 2016 criteria [3]. In patients with Systemic Lupus Erithematosus (SLE), the diagnosis of MAS was compared with the Preliminary diagnostic guidelines for macrophage activation syndrome as a complication of juvenile SLE [12].

The information extracted from the clinical records included the patients' demographic characteristics, underlying rheumatological diseases, clinical and laboratory data, treatments, and complications. The clinical and laboratory data were also used to make a retrospective evaluation of possible causes triggering MAS. Any evidence of an infection was considered if it had been documented microbiologically or was suspected on the basis of pathognomonic signs during the 15 days preceding the onset of MAS. The presence of specific Immunoglobulin M was recorded separately as a possible indirect sign of recent infection.

Results

Between January 2005 and 31 December 2015, twelve children with underlying rheumatic disorders (eight females and four males) developed a total of 14 MAS episodes: six were affected by soJIA, three by Systemic Lupus Erythematosus (SLE), two by dermatomyositis

(DM), and one by undifferentiated arthritis (UA) (case #1, who experienced three episodes of MAS [13]. Median age at the time of the diagnosis of MAS was 11.75 years (range 2.75-18.8). Diagnosis of underlying rheumatic diseases was confirmed on the bases of the current classification criteria. [14-16].

MAS occurred within 30 days of the onset of the underlying rheumatic disease in five cases, and during disease relapses in nine. Infections were identified by means of microbiological tests carried out during hospitalisation before the onset of MAS in six cases, and on the basis of clinical signs in four. Specific IgM was retrieved in three cases (#1b, #7, #8). Two of the patients presented MAS within seven days of beginning a new drug. No trigger was identified in case #12 (**Table 3**).

The cultures or microbiological investigations used to diagnose and differentiate the infections were a fecal test positive for *Clostridium difficile* toxin (case #1a), a throat swab positive for group A *Streptococcus* (case #2), blood cultures positive for *Staphylococcus hominis* (case #4), parasitological search of feces positive for *Entamoeba dispar/hystolitica* and *Endolimax nana* (case #5), a cutaneous swab of bullous lesions positive for *Pseudomonas aeruginosa* (case #10), and blood polymerase chain reaction positive for adenovirus (case #11). Specific IgM was found in case #1b (Coxsackie virus) and case #8 (adenovirus).

Case #6 had the clinical features of varicella, and case

Table 3. Demographic characteristics of the patients, pathogens identified during hospitalisation, and new drugs introduced in the seven days preceding the onset of MAS.

Patient	Gender	Rheumatic disease	Age at time of onset of rheumatic disease (years)	Age at time of onset of MAS (years)	Suspected triggers
1	F	UA	10.75	1a) 10.8;	*Clostridium Difficile*;
				1b) 13.5;	Coxsackie Virus*;
				1c) 17	UTI
2	F	DM	4.3	4.4	Group A *Streptococcus*
3	F	soJIA	3	14.5	Sulphasalazine
4	M	soJIA	7.3	10.2	*Staphylococcus Hominis*
5	F	soJIA	14.25	17	*Entamoeba dispar/histolytica* and *Endolimax nana*
6	M	soJIA	3	3.5	VZV
7	F	DM	13.2	14	EBV
8	F	SLE	12.25	12.3	*Adenovirus**
9	M	soJIA	2.5	2.75	Gastroenteritis
10	F	SLE	16.6	18.8	*Pseudomonas Aeruginosa*
11	M	SLE	10.2	10.25	Adenovirus; Mycophenolate Mofetil
12	F	soJIA	10	10	Not identified

UA: Undifferentiated Arthritis; soJIA: Systemic-Onset Juvenile Idiopathic Arthritis; DM: Dermatomyositis; SLE: Systemic Lupus Erythematosus; UTI: Urinary Tract Infection; VZV: Varicella Zoster Virus; EBV: Epstein-Barr Virus.
*Presence of infection demonstrated by specific IgM

Table 4. Principal clinical features observed during the course of MAS.

	No. of cases	Specification	No.	Cases
Persistent fever ≥ 38°C	13/14			1a, 1b, 1c, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11
Hepatomegaly	Oct-14			1a, 2, 4, 5, 6, 7, 8, 9, 10,
Splenomegaly	Sep-14			1b, 2, 3, 6, 7, 8, 9,12
Lymphadenopathy	Apr-14			4, 6, 7, 9,
Hemorrhaging	Feb-14	Petechiae	1	3
		Brain hemorrhage	1	4
Nervous system involvement	Mar-14	Motor polyneuropathy	1	1a
		Spastic tetraplegia	1	2
		Brain hemorrhage	1	4
Cardiac involvement	Aug-14	Pericardial effusion	7	1a, 1b, 1c, 4, 5, 7, 11
		Cardiac arrest	1	2
Pulmonary involvement	Jul-14	Pleural effusion	5	1a, 1c, 2, 7, 11
		Interstitial lung disease	4	2, 4, 6, 7
Acute renal failure	Apr-14			1a, 1c, 2, 3
Cholecystitis	Feb-14			4, 5

#7 the clinical features of mononucleosis, which was confirmed by the presence of specific IgM for EBV.

The infections suspected on the basis of clinical signs were acute gastroenteritis (vomiting and diarrhea in case #9) and urinary tract infection (case #1c: strangury with a urine test positive for hematuria, proteinuria and leukocyturia; a urine culture was not reliable because the patient was receiving antibiotic therapy).

A bone marrow aspirate was performed in nine cases: five were positive for hemophagocytosis and four were negative.

Table 4 summarises the clinical features of the patients during the course of MAS.

Discussion

We describe 12 patients with an active underlying rheumatic disease who experienced a total of 14 episodes of MAS in our unit between 2005 and 2015, most of which were preceded by an infection.

The infections were documented by culture or microbiological investigations in six of the 14 cases, and were suspected on the basis of clinical signs of infection in another four.

MAS develops in patients with soJIA during disease flares [17], and the association between MAS and infections has been previously reported. The authors of the first description of MAS in a patient with soJIA underlined a possible relationship with infection in 1985 [18] and, in 2001, Sawhney published a 20-year retrospective review of nine cases of MAS in children with rheumatic diseases, eight of whom had had infections 4 weeks to 8 weeks before developing MAS [19], although a specific infection was identified only in four cases and the others were not thoroughly documented.

The clinical features of MAS are shared by other cytokine storm syndromes, and are believed to represent the same end-stage pathophysiological state reached by disparate initiating triggers of uncontrolled inflammation [20]. These are classified on the basis of known underlying defects: genetic defects in cytotoxicity leading to familial hemophagocytic lymphohistiocytosis (FHL); deficient immune responses leading to Immunodeficiency-Associated Hyperinflammatory Syndrome (IDAHS); and pathogenic microbial triggers leading to infection-associated hyperinflammatory syndrome (IAHS) including severe sepsis. However, the cellular and molecular mechanisms underlying their pathogenesis are not fully understood, although a growing body of evidence suggests that cytolytic dysfunction plays a central role [21].

Natural killer (NK) cells are major players in the body's defences against tumours and viral infections. [22] A transient defect in their cytotoxic activity and a transient reduction in perforin expression have been observed in patients with soJIA, particularly during MAS. [23, 24] Although patients with an underlying rheumatic disease are prone to recurrences, the disease can be offset for years in the absence of a trigger which, depending on the patient's genotype, may need to be more or less powerful before the clinical picture of HLH appears [8]. One emerging theory is the two-hit hypothesis that MAS develops when a genetically susceptible subject with immunoregulatory defects (including NK cell dysfunction and/or impaired perforin pathways) experiences a hyper-inflammatory state due to infection or rheumatic disease [21].

In patients with primary NK cell dysfunction, it is possible that the cytolytic activity already stressed during the course of a rheumatic disorder becomes critically compromised as a result of a second trigger such as an infection. It is therefore possible that the presence of infection may be a necessary condition for the development of MAS even in patients with underlying rheumatic diseases.

The limitations of this study include its retrospective nature as the evidence of infection is based on clinical records and the laboratory findings (particularly those of serological tests) may have been affected false positive or negative results. In an attempt to compensate for this, we tried to distinguish infections supported by positive cultural examinations or clear clinical signs from those suspected on the basis of serological tests. Secondly, the criteria used diagnose MAS have only been validated in patients with soJIA, whereas we also used them when evaluating patients with other rheumatic diseases.

However, despite these limitations and even if the role of infection in the pathogenesis of MAS still needs to be clarified, our findings suggest that the prevalence of infectious events preceding MAS may be underestimated.

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Conflict of interest

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