

## ORIGINAL ARTICLE-CASE REPORT

**Macrophage activation syndrome (MAS) during anti-IL1 receptor therapy (anakinra) in a patient affected by systemic onset idiopathic juvenile arthritis (soJIA): A report and review of the literature.**

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### Introduction

Systemic JIA, a subtype of juvenile idiopathic arthritis, requires the presence of arthritis in one or more joints associated with systemic involvement. The systemic features consist of daily fevers above 39 degrees centigrade for a minimum period of 15 days with the presence of at least one of the following manifestations: classic soJIA rash, generalized lymphadenopathy, pericarditis, pleuritis, hepatomegaly and/or splenomegaly. [1]

Macrophage activation syndrome (MAS) is a life threatening complication of systemic onset juvenile idiopathic arthritis first described by Hadchouel et al. in 1985. [2] The etiology remains unknown. [2-4] MAS is reported in the literature also as: reactive hemophagocytic syndrome,

hemophagocytic lymphohistiocytosis, or disseminated intravascular coagulation (DIC) with liver failure. [5-6] Many factors have been described as triggers for MAS: viral agents such as varicella-zoster, hepatitis A, Epstein-Barr and coxsackie B [7-9], therapies with acetylsalicylic acid and NSAIDs [10-11], DMARDs as gold salts, methotrexate sulfasalazine and penicillamine [12-13], and biologic drugs [14-15].

Clinically, MAS is characterized by a prolonged and often continuous high fever, hepatosplenomegaly, generalized lymphadenopathy, rash, intravascular disseminated coagulation (DIC) anemia, leukopenia, thrombocytopenia, hypofibrinogenemia, elevated liver enzyme levels, a sudden fall in erythrocyte sedimentation rate (ESR) and prolonged coagulation times. The diagnosis can be confirmed by a bone marrow aspiration and biopsy that demonstrates numerous macrophages that are phagocytosing blood cells (hemophagocytosis). [16-18] In this paper, we describe the case of an adolescent with soJIA who developed MAS during treatment with recombinant IL-1 receptor antagonist (rIL-Ra) therapy.

### **Case report**

The patient is an 18 year old female with soJIA who had a polyarticular course since the age of 7. During the course of her illness, she was previously treated with DMARDs (cyclosporine, methotrexate) and other biological drugs (etanercept, infliximab) without a significant clinical response. In February 2003, recombinant IL1 receptor antagonist (anakinra) therapy was started at the standard dose of 100 mg/day via subcutaneous injection. During this treatment, she developed the MAS syndrome without another evident trigger.

Laboratory tests revealed a hemoglobin of 11g/dl, white blood cell count of 6000, platelets  $250,000/\text{mm}^3$ , ESR 60 mm/hour (normal value  $<12$  mm/h), ferritin 670 (normal values 8-120 ng/ml). With the first few doses, the patient showed clinical improvement in articular involvement of the underlying disease. After the first week of therapy, a persistent fever began and cutaneous lesions appeared that were compatible with Weber Christian panniculitis. The rIL-1-Ra therapy was continued.

After the 10th dose of anakinra, the laboratory tests revealed a low white blood cell count of  $3400$  cells/ $\text{mm}^3$ , low platelets ( $110,000$  cells/ $\text{mm}^3$ ), increased level of serum ferritin ( $>1500$ ), high liver enzyme level (aspartate aminotransferase 120, normal values 10-34 IU/L) and alanine aminotransferase 150 (normal values 10-40 UI/L). The adolescent now had new findings of hypertriglyceridemia (350 mg/dl, normal values  $<160$  mg/dl), and the presence of fibrin degradation products.

These laboratory findings were accompanied clinically by a high continuous fever ( $>39.5$  C) and a progressively falling ESR, decreasing to 30 mm/h. No microbiological or serological evidence of viral infection was found, including EBV, CMV, and HBV. Multiple blood cultures for aerobic and anaerobic species were negative. No immature cells were present in the peripheral

blood. The clinical and laboratory features were consistent with MAS. The clinical picture, supported by the biochemical and hematologic lab results, was considered so typical for MAS that confirmation of the diagnosis by a bone marrow aspirate was considered unnecessary.

The rIL1-Ra therapy was suspended and the patient was treated with high doses of intravenous corticosteroids (methylprednisolone at 16.6mg/kg/day) as well as oral cyclosporine (4mg/kg/day). She experienced a prompt clinical improvement associated with resolution of the fever, and normalization of the liver enzymes, triglycerides and coagulation abnormalities. The adolescent was discharged on 8 mg of prednisone per day and cyclosporine (3.5mg/kg). The disease activity of her soJIA has been minimal on this treatment regimen.

## **Discussion**

MAS is a descriptive term to designate the clinicopathologic entity that can occur in a varied group of diseases. MAS is now classified among the histiocytic disorders as the hemophagocytic syndromes (HSs). [19] Primary or familial hemophagocytic lymphohistiocytosis (primary HLH or FHL) is regarded as the prototype of HS and has a genetic basis, resulting in the inability of cytotoxic T lymphocytes (CTLs) or natural killer (NK) cells (or both) to efficiently kill target cells. Mutations in the perforin gene are found in 20% to 40% of patients with primary HLH. Secondary HS (also referred to as secondary HLH) includes the entity MAS that complicates infections, malignancies, or inflammatory diseases such as juvenile idiopathic arthritis (JIA). [20-21]

Remarkably, a reduced expression of perforin (a key protein in the lysis of CD3+CD8+ targeted cells) is described by Wulffraat et al. and Normand et al. in patients affected by soJIA. [22-23] Evidence is emerging indicating that in patients with systemic-onset JIA, preexisting impaired NK cell function may predispose to MAS. Villanueva et al [24] suggest that the distinguishing feature that separates systemic JIA from other subtypes of JIA, and is common to the major hemophagocytic syndromes, is NK cell dysfunction. [25]

The exact mechanisms that would link deficient NK cell function and, in some cases, depressed perforin expression, with the expansion of activated macrophages are not clear. [26] One possible explanation is that decreased NK function might be responsible for a diminished ability to clear the infecting pathogen and remove the source of antigenic stimulation at early stages of infection. [27] This would lead to persistent antigen-driven T cell activation associated with an increased production of cytokines, such as IFN- $\gamma$  and granulocyte/macrophage colony-stimulating factor, that stimulate macrophages. Subsequently, the sustained macrophage activation would result in tissue infiltration and in the production of high levels of TNF- $\alpha$ , interleukin-1, and interleukin-6, cytokines that have a major role in the various clinical symptoms and tissue damage. The various MAS triggers such as viruses, autoimmune diseases, and drugs may produce inflammation. These abnormal cytotoxic and NK cells might fail to provide appropriate apoptotic signals for the removal of activated macrophages and T-cells during this inflammatory process,

leading to the T cell activation. Yet the exact pathways that would link the decreased NK and cytotoxic T cell function with macrophage expansion have not been confirmed. [28]

No diagnostic criteria for MAS are yet available. Ravelli et al. performed a retrospective study of 88 patients with JIA (72 reported in published literature and 16 new Italian cases) and the variables that offered greatest sensitivity and specificity (both above 0.75) were : ferritin >10,000 ng/ml (1.0; 1.0), triglycerides > 160 mg/dl (0.9; 1.0), AST > 40 U/ml (0.93; 0.97), fibrinogen < 250 mg/dl (0.85; 1.0), ALT > 40 U/ml (0.87; 0.93), thrombocytopenia < 150,000/mm<sup>3</sup> (0.76; 1.0), bone marrow with macrophage proliferation and hemophagocytosis (0.75; 1.0), hepatomegaly (0.76; 0.86) and splenomegaly (0.77; 0.82). [30] As prompt recognition and treatment are imperative because of the risk of a fatal outcome, MAS must be differentiated from a soJIA flare. There are several criteria that are useful in this differentiation:

- 1) Fever is persistent and often continuous in MAS, in contrast with systemic soJIA where it occurs once or twice a day (spiking fevers),
- 2) In soJIA the fever is accompanied commonly by the typical diffuse, evanescent, rash (Still's rash).
- 3) The characteristic blood test results indicating systemic JIA activity will show leukocytosis in 80% and thrombocytosis in 70% of cases. In contrast, MAS typically is associated with leukopenia and thrombocytopenia.
- 4) In relapsing soJIA, there is often a progressive increase in the ESR, while in MAS typically there is a progressive decrease in the ESR.[5,13]

Histological findings of involved organs are pathognomic and typically show infiltration by histiocytes and lymphocytes with hemophagocytosis. Spleen biopsy may also provide evidence of hemophagocytosis, but because of possible complications spleen biopsies are usually avoided. Bone marrow aspirations appear to be the best approach for the documentation of hemophagocytosis. [5]

Although MAS may occur without any identifiable precipitating factor, it has been related to a number of triggers, including drugs. [7-14] This issue is particularly relevant in the age of biologic treatments for JIA. Our patient developed MAS shortly after the start of anakinra therapy in the absence of any triggering event, suggesting that MAS could have been a direct result of anakinra therapy. As of now, only two cases of MAS during biologic therapy have been reported. One case of MAS occurred in a soJIA patient during etanercept therapy. [14] The second case occurred when a child with soJIA on infliximab therapy experienced a disease flare. [15]

The risk of developing MAS while on biologic therapy such as anakinra is unclear. It is made even more unclear by the reports that a child with soJIA and MAS was successfully treated

with etanercept and that a patient with soJIA and MAS was treated successfully with anakinra. [15-16] It is interesting that a class of drugs may be simultaneously a likely trigger for MAS and the therapy for a clinical challenge such as MAS. It is even more interesting that anakinra is now being tested as a treatment for soJIA.

### **Summary**

Systemic JIA is classified as a form of JIA because of the presence of chronic arthritis typical for these illnesses. Yet there is evidence that soJIA may be very different from the other subtypes of JIA. [1] The pathogenesis of systemic JIA could be different from the other onset forms, which is underlined not only by the characteristic clinical presentation and course of the disease but also by common immunological alterations (low levels of perforin in CD8+ cells, defective NK cells function) and the occurrence of the MAS. [19-20]

It has been proposed that in MAS the natural killer and cytotoxic cell dysfunction may lead to inadequate control of cellular immune responses. Yet the exact nature of such dysregulation is still unknown. [21-22] The mechanism whereby anakinra can trigger MAS is therefore unclear, but the development of MAS after few days of anakinra therapy does strongly suggest that the rIL-1ra treatment may have played a role in the cause of this child's MAS. This association of biologics with MAS as well as the successful use of biologics to treat MAS should give clinicians pause. Each child on anakinra should be closely monitored for the evolution of this serious and potentially life-threatening complication. Systemic JIA, MAS and the underlying immunological status of these children, including the cytokine milieu, are poorly understood and the role of therapies targeting cytokine modulation needs to be further investigated.

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