



Treatment of Refractory Macrophage Activation Syndrome in Systemic Juvenile Idiopathic Arthritis with High Dose Anakinra

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Abstract

Objective: To describe a case of a patient with systemic juvenile idiopathic arthritis (sJIA) and Macrophage Activation Syndrome (MAS) requiring high dose anakinra (interleukin-1 receptor antagonist).

Case: An 8-year-old female diagnosed with sJIA was treated with pulse methylprednisolone (30mg/kg/day IV × 3 days), anakinra (3mg/kg/day SQ), followed by tocilizumab (monoclonal interleukin-6 receptor antibody) infusion. Symptoms resolved and inflammatory markers improved. Two weeks later, she developed unremitting fevers (105°F) and MAS was suspected.

Laboratory studies revealed significant hyperferritinemia, elevated D-dimers, transaminitis, and hypertriglyceridemia, with ESR in the normal range. A bone marrow biopsy revealed numerous hemophagocytic macrophages. She was diagnosed with MAS, and tocilizumab was discontinued. She received high dose methylprednisolone (30mg/kg/day IV × 6 days, then tapered over 7 months), cyclosporine, intravenous immunoglobulin, and anakinra. Anakinra was increased from 3mg/kg/day to 12mg/kg/day and disease control was achieved. Fever resolved in 4 days, and she was discharged home in 14 days with improvement. Medications were tapered over 12 months. She subsequently flared and was controlled on daily anakinra, four months after discontinuation. For convenience, she was switched to monthly canakinumab (anti-IL-1 beta monoclonal antibody), on which her disease continues to be in remission.

Discussion: We report a case of MAS occurring during the initial presentation of sJIA treated with high dose anakinra. Excess interleukin-1 can lead to the clinical and laboratory findings of sJIA and MAS, and the up regulation of interleukin-6. Uncontrolled production and activation of macrophages and T lymphocytes lead to MAS manifestations, including prolonged high fever, pancytopenia, coagulopathy, lymphadenopathy, hepatic insufficiency, and neurologic dysfunction. Anakinra is a recombinant interleukin-1 receptor antagonist with a short half-life (~ 4-6 hours). Our patient

responded to a nearly 6-fold increase in standard dosing (usual dosage: 1-2mg/kg/day), without adverse events. Our experience suggests that high dose anakinra is effective and safe in refractory MAS secondary to sJIA.

Keywords

Macrophage activation syndrome, Refractory, Anakinra, Interleukin-1 receptor antagonist, Systemic juvenile idiopathic arthritis

Abbreviations

MAS: Macrophage Activation Syndrome, sJIA: Systemic Juvenile Idiopathic Arthritis

Introduction

Macrophage Activation Syndrome (MAS), a potentially fatal complication of systemic juvenile idiopathic arthritis (sJIA), is characterized by high persistent fevers, hepatosplenomegaly, lymphadenopathy, pancytopenia, hyperferritinemia, hypertriglyceridemia and liver dysfunction. We describe a case of refractory MAS in a patient with recently diagnosed sJIA treated with high dose anakinra (interleukin-1 receptor antagonist).

Case Description

One week after an eight-year-old girl was discharged from the emergency department with a new diagnosis of sJIA, she presented again with symptoms including high fevers, cough, and rash.

The patient's past medical history was significant for her recently diagnosed sJIA and Henoch-Schonlein purpura three years prior, managed as an outpatient. She was up to date with her vaccinations. There was no family history of any autoimmune disorders, immunodeficiencies, or cancer. During her prior admission, she

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Table 1: Response after Increased Anakinra Dosing.

Labs	Hospital Day (HD) #1	HD #2	HD #3	HD #4	HD #5	HD #6
Aspartate Aminotransferase (AST)	468	2440	5234	3685	1891	684
Alanine Aminotransferase (ALT)	542	410	5480	5430	4345	2742
Erythrocyte Sedimentation Rate (ESR)	16	17	13	15	-	-
C – reactive Protein (CRP)	0.82	0.28	0.12	0.07	-	-
Ferritin	10,889	38,516	76,127	>100,000	99,648	58,023
D-dimer	25,062	8,657	7,095	6,653	12,356	-
Triglycerides	183	121	247	330	259	-
Treatment		Anakinra 3mg/kg/d SQ q 24 h	Anakinra 12mg/kg/d SQ ÷ q 6h	Anakinra 12mg/kg/d SQ ÷ q 6h	Anakinra 12mg/kg/d SQ ÷ q 6h	Anakinra 12mg/kg/d SQ ÷ q 6h
	Methylprednisolone 30mg/kg/d IV ÷ q 12h	Methylprednisolone 30mg/kg/d IV ÷ q 6h	Methylprednisolone 30mg/kg/d IV ÷ q 6h	Methylprednisolone 30mg/kg/d IV ÷ q 6h	Methylprednisolone 30mg/kg/d IV ÷ q 6h	Methylprednisolone 30mg/kg/d IV ÷ q 6h
	Cyclosporine 1mg/kg/d PO q24h	Cyclosporine 1mg/kg/d IV q24h	Cyclosporine 1mg/kg/d IV q24h	Cyclosporine 1mg/kg/d IV q24h	Cyclosporine 1mg/kg/d IV q24h	Cyclosporine 1mg/kg/d IV q24h
				IVIg 6% (1kg/kg) IV ×1		

presented with a thirteen-day history of intermittent high fevers, diffuse macular rash, joint pain involving multiple large and small joints, and diffuse lymphadenopathy. After investigations excluded infections, malignancies, and other rheumatic diseases, a diagnosis of sJIA was made. Her initial work up revealed elevated erythrocyte sedimentation rate (ESR) of 94mm/hr (reference 0-20mm/hr), C-reactive protein (CRP) of 20.7mg/L (reference 0.00-0.70mg/dL), elevated ferritin of 15,451ng/mL (reference 20-175ng/mL), elevated D-dimers of 1,716µg/mL D-DU (reference 0-243ng/mL D-DU), and elevated white blood cell count of 15,700 cells/uL (reference 4.8-10.7 Thousand/uL). An extensive infectious work-up was non-contributory and an oncologic work-up, including a bone marrow biopsy, was negative for malignancy. The bone marrow biopsy at this time demonstrated normocellular marrow with increased hemophagocytosis.

The patient was started on high dose intravenous methylprednisolone. Due to ongoing symptoms, she received one dose of anakinra (interleukin-1 receptor antagonist), followed by one dose of tocilizumab (humanized monoclonal antibody against the interleukin-6 receptor) because the patient experienced burning and discomfort with anakinra. She became afebrile with resolution of her symptoms and was discharged home on prednisone with a planned second dose of tocilizumab in two weeks. At her one-week follow up visit with her rheumatologist, she remained afebrile and asymptomatic.

Two days before her next scheduled tocilizumab infusion, she developed a fever of 40°C, fatigue, and erythema over her cheeks and palms, without complaints of joint pain. She again saw her rheumatologist in an outpatient clinic, who ordered further laboratory evaluation because of the new onset rash and fever. Laboratory studies revealed elevated ferritin at 10,880ng/mL, elevated D-dimers at 25,062µg/mL, elevated alanine and aspartate aminotransferases at 468 units/L and 542 units/L, respectively, and elevated triglycerides at 183mg/dL, but with a normal ESR at 16mm/hr and a CRP at 0.82mg/L. With these results, the leading differential diagnosis was considered to be MAS based on her predisposition due to her sJIA, her presentation, and her laboratory values. The rheumatologist immediately instructed the family to present to the emergency department for further evaluation.

On presentation to the emergency department, she complained of fevers of 40°C for two days, higher than during her previous hospitalization, which were temporarily relieved with antipyretics. She had associated symptoms of diffuse headache and erythema overlying her cheeks and hands since the morning. The patient denied any associated arthralgia, joint swelling, rhinorrhea, congestion, sore throat, dyspnea, chest pain, nausea, and vomiting, abdominal pain, changes in voiding or stooling, myalgia, weight loss, or change in mental status. She had no known sick contacts and had not yet returned to school since her last hospitalization. Her medications at

the time of admission included prednisone (30mg by mouth daily), a daily multivitamin, and acetaminophen and ibuprofen for fever.

Her physical examination at admission revealed a tired appearing child with erythema over her cheeks and palms. There were no other rashes or lesions, no conjunctival injection, discharge, and no sclera icterus on ocular examination. No cervical, axillary, supraclavicular, or inguinal lymphadenopathy was noted. Her respiratory, abdominal, cardiovascular, neurological and musculoskeletal examinations were benign.

Given the concern for MAS, the patient was empirically started on intravenous methylprednisolone (30mg/kg/day) and oral cyclosporine (1mg/kg/day). Except for her fever, she remained clinically stable while in the ER and was admitted to the general pediatric floor for further evaluation and care.

The next hospital day, she continued to be febrile (40.6°C) and was found to have increasing ferritin levels to 38,516 ng/mL, and increasing transaminases with alanine aminotransferase at 410 units/L and aspartate aminotransferase at 2,440 units/L. She was immediately transferred to the Pediatric Intensive Care Unit for closer monitoring. She was started on anakinra, an interleukin-1 receptor antagonist, with an initial dose of 100mg daily subcutaneously (approximately 3mg/kg/day) in addition to continuing the high dose intravenous steroids (total daily dose of 1000mg) and intravenous cyclosporine (initial dose at 100mg then second dose increased to 180mg). However, given persistent fever, the standard dose of anakinra was quickly titrated up to 100mg every 6 hours (nearly 12mg/kg/day) after the initial dose on the second hospital day. Intravenous immunoglobulin infusion of 36gm was added, on the third hospital day. Her ferritin continued to rise, peaking on hospital day 4 at greater than 100,000ng/mL. Finally, after 4 days of treatment with high dose intravenous steroids, continuous cyclosporine infusion at 3mg/hr, one intravenous immunoglobulin infusion, and high dose anakinra, her fevers resolved. On the fifth hospital day, a bone marrow biopsy was performed and revealed increased hemophagocytosis with no evidence of malignancy, confirming the diagnosis of MAS. On the sixth day, ferritin, transaminases, WBC, and triglycerides began to improve (Table 1).

Case Discussion

MAS falls within the spectrum of histiocytic disorders collectively known as hemophagocytic lymphohistiocytosis (HLH) [1]. Although there are many clinical similarities between MAS and HLH, the exact relationship between these conditions is not well understood.

MAS is seen most frequently in sJIA [2,3], and in its adult equivalent, Still disease. Others at risk for developing MAS include patients beginning certain drug therapies, and those with juvenile systemic lupus erythematosus, Kawasaki disease, certain periodic fever syndromes and immunodeficiencies, IgA nephropathy,

inflammatory bowel disease [4]. There is also accumulating evidence that heterozygous familial HLH associated genes are risk factors for MAS development, and that these mutants may act as dominant negatives [5,6].

The current hypothesis for the etiology of MAS is that there is a defect in the function of the natural killer cells and cytotoxic T-cells (CD8+ T cells) [1,2,7,8]. The failure of cytotoxic T cells to kill infected antigen presenting cells allows for continued antigenic stimulation and resultant cytokine storm [8,9]. This continuous stimulation of pro-inflammatory cytokines, especially interferon gamma, causes macrophages to become hemophagocytic. On bone marrow aspirate, the presence of numerous well-differentiated macrophages phagocytosing normal hematopoietic cells is commonly seen in MAS [4], but can be seen in almost any organ [1]. The cytokine storm leads to end organ toxicity and can ultimately be fatal.

An additional hypothesis for the etiology of MAS is based on multiple observations that Toll-like receptor and IL-1 signaling are upregulated in sJIA. Other rheumatic conditions like systemic lupus erythematosus have long been associated with hyperactive Toll-like receptor 9 (TLR9) function. EBV is perhaps the most common infectious trigger of secondary HLH, and EBV triggers TLR-9 [1,10]. In one study, mice subjected to repeated TLR9 stimulation and blocked IL-10 receptors developed many features of MAS including hemophagocytosis, suggesting IL-10 production may be a compensatory attempt to calm the cytokine storm [4,10]. Some studies have shown that patients with sJIA have decreased function of IL-10 [4,10]. In the setting of patients with underlying diseases, it has been suggested that severe IL-18/IL-18BP imbalance leads to Th-1 lymphocyte and macrophage activation which is not controlled by NK-cell cytotoxicity allowing for the development of secondary HLH [11,12].

The symptoms of MAS are acute in onset and can progress rapidly. MAS is characterized by a combination of symptoms, which can include non-remitting high fevers, pancytopenia, lymphadenopathy, liver dysfunction, hepatosplenomegaly, disseminated intravascular coagulation and hemorrhages, and neurologic dysfunction [3,4]. The hyperferritinemia found in MAS is striking, often greater than 10,000ng/dL [2]. The liver is commonly involved, manifesting with transaminitis [2] and hyperbilirubinemia, and sometimes jaundice. Serum ammonia levels are typically normal or only mildly elevated. Profound hypofibrinogenemia is a notable feature of MAS and is responsible for the lowered ESR [1]. Other laboratory values are leukopenia and thrombocytopenia, elevated CRP, moderate hypoalbuminemia and hypertriglyceridemia [2].

These physical and laboratory findings alone are not specific to MAS, but their overall constellation should heighten suspicion for MAS. Ravelli et al. [4] have outlined the proposed diagnostic criteria for MAS in the setting of sJIA [4]. In patients with underlying rheumatologic disease, a fall in the ESR, and/or blood counts in combination with increase in serum ferritin levels and D-dimers should immediately raise suspicion of impending MAS [13].

Therapy is focused on supportive care and suppressing the cytokine storm. The primary treatment for MAS includes glucocorticoids and cyclosporine A [14]. Other previously discussed therapies based on anecdotal experience include cyclophosphamide and TNF blockers [4]. Three medications that have been shown to augment the primary therapy are anakinra (an interleukin-1 receptor antagonist) [4], intravenous immunoglobulin (pooled, polyvalent IgG), and etoposide (a topoisomerase inhibitor). Anakinra has been discussed in prior studies as an effective therapy for MAS without the immunosuppressive effects of other conventional therapy [15,16]. When MAS occurs in the setting of inflammatory diseases such as sJIA, the pre-existing greater concentrations of IL-1 may necessitate a higher dose of IL-1 antagonist [17]. Several cases of anakinra use in sJIA-associated MAS after unsuccessful treatment with corticosteroids and cyclosporine have been reported [4]. In reported cases, dose escalation of anakinra was often necessary to obtain

control of MAS [4]. Treatment of refractory MAS with increased dose of anakinra has been previously discussed at 6.7mg/kg/day [17] in the case of an 11-year-old girl with medically refractory MAS. A 2011 case series also highlighted the use of abatacept, another biologic agent that selectively modulates CD80/CD86:CD28 costimulatory signal needed for T cell activation, in conjunction with high dose (up to 11mg/kg/day) anakinra for the use of treatment of MAS in the setting of sJIA [18]. A recent retrospective study discussed the case of a patient who was treated with high dose anakinra (up to 20mg/kg/day) with good response [19].

MAS is a serious, potentially life-threatening complication of rheumatic diseases, with an estimated mortality rate of 7 to 30% [1,2,3,15,16]. Complications include subsequent infection and multi-systemic organ failure. Patients with MAS require prolonged treatment, often over the course of a year after initial presentation. A subset of MAS patients suffers recurrent episodes; these patients require lifelong treatment and closer monitoring.

Our Patient

Our patient's MAS clinically resolved after two weeks of inpatient treatment with high dose glucocorticoids with an initial pulse and then taper, cyclosporine A, one dose of IVIG, and anakinra at nearly six times higher than the standard dose until she demonstrated marked improvement (a total of 10 days on high dose anakinra). After this episode, she was continued on oral glucocorticoids and anakinra 100mg daily. The medications were tapered over the course of twelve months. Four months following discontinuation of anakinra, the patient had a flare of her sJIA and was restarted on anakinra 100mg daily. The following month after improvement of her symptoms, canakinumab (anti-IL-1 beta monoclonal antibody) 180mg monthly (2.9mg/kg/dose) was started for ease of administration, and anakinra was discontinued [20]. On monthly canakinumab, she continues to remain clinically well.

This is an example of a case of a patient with newly diagnosed sJIA who developed MAS during her initial episode of sJIA that was treated with high dose anakinra. Although she was on many immune modulators, we believe that it was the higher dose of anakinra that helped reverse the MAS [17]. We were also able to avoid the associated morbidity and mortality of etoposide [2,16].

Conclusion

MAS can develop and progress very rapidly. If left untreated, MAS is associated with high morbidity and can rapidly progress to shock and death. It is important to have a low threshold for suspecting MAS in a child with an underlying rheumatologic disease. In suspicious cases, the key is to treat with immune suppression as early as possible in the disease process, covering all infectious etiologies and avoiding potential triggers. Treatment with high-dose anakinra can be effective in refractory cases of MAS [17].

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