Macrophage Activation Syndrome Secondary to Adult Onset Still's Disease- An Important Sepsis Mimic

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Abstract

Adult Onset Still’s disease (AOSD) is a systemic inflammatory disorder of unknown aetiology. Rarely, it may be complicated by Macrophage Activation Syndrome (MAS), a multisystem inflammatory syndrome caused by massive cytokine release from activated lymphocytes and macrophages.

We report the case of a 31 year old female who presented with a 3 week history of arthralgia, myalgia, fever and sore throat. Adult Stills Disease (ASD) was diagnosed and the patient commenced on oral Prednisolone. The patient was readmitted 7 days later with significant deterioration in symptoms and was systemically unwell. Macrophage Activation Syndrome (MAS) was diagnosed. The patient was successfully treated with supportive therapy, IV Methylprednisolone, Cyclosporine and Anakinra. This case highlights the fact that active ASD and MAS can mimic sepsis. MAS is rare, and is most commonly seen secondary to underlying inflammatory disease. It is important that MAS is promptly recognised and treated, given its high mortality rate, despite treatment.

ABBREVIATIONS

AOSD: Adult Onset Still’s disease; MAS: Macrophage Activation Syndrome; ASD: Adult Stills Disease; SIRS: Systemic inflammatory response syndrome; MODS: Multiorgan dysfunction syndrome

INTRODUCTION

Adult Onset Still’s disease (AOSD) is a systemic inflammatory disorder of unknown aetiology. Rarely, it may be complicated by Macrophage Activation Syndrome (MAS), a multisystem inflammatory syndrome caused by massive cytokine release from activated lymphocytes and macrophages. We report the case of a 31 year old female who presented with a 3 week history of arthralgia, myalgia, fever and sore throat. Adult Stills Disease (ASD) was diagnosed and the patient commenced on oral Prednisolone. The patient was readmitted 7 days later with significant deterioration in symptoms and was systemically unwell. Macrophage Activation Syndrome (MAS) was diagnosed. The patient was successfully treated with supportive therapy, IV Methylprednisolone, Cyclosporine and Anakinra. This case highlights the fact that active ASD and MAS can mimic sepsis. MAS is rare, and is most commonly seen secondary to underlying inflammatory disease. It is important that MAS is promptly recognised and treated, given its high mortality rate, despite treatment.

CASE PRESENTATION

A 31-year-old female was admitted with a 3-week history of arthralgia, myalgia, fever and sore throat. She described a maculopapular rash, in the distribution of her abdomen and legs, at symptom-onset that resolved within 2 days. She attended the Accident and Emergency Department 1 week prior to admission and was given a short course of prednisolone with some benefit. She was 4 months post-partum following an uneventful caesarean section. There was no significant past medical history.

On examination, she was in discomfort and pyrexic (38.5°C). There was mild cervical lymphadenopathy and shoulder-girdle tenderness. No rash was present. Abdomen was soft and non-tender with a Pfannenstiel scar noted. Cardiovascular and respiratory examinations were unremarkable. Blood tests revealed a very high serum ferritin (>2000ug/L), ESR (55 mm/hr) and C reactive protein (205 mg/L). Blood cultures, Rheumatoid factor, ANA and ANCA were negative.

A diagnosis of Adult Stills Disease was made and she was commenced on Prednisolone 60mg daily. Her symptoms and...
pyrexia settled. She was discharged with outpatient review planned. She was readmitted 7 days later following an episode of significant diarrhoea and deterioration in symptoms. On examination she was tachycardic and hypotensive. Serum ferritin was elevated at 9000ug/L and liver function tests were significantly deranged (AST 1,048U/L, ALT 744U/L). The patient’s haemoglobin fell acutely to 5.7g/dL, her platelet count to 27 x10^9/L with associated hypo-fibrinogenaemia and coagulopathy. A bone marrow biopsy demonstrated haemophagocytosis.

The patient was commenced on IV Methylprednisolone on the ward however due to persistent hypotension despite fluid resuscitation she was transferred to the Intensive Care Unit. The patient received an IV immunoglobulin (2g per kg) infusion, along with blood transfusion, cryoprecipitate and fresh frozen plasma. She was continued on IV Methylprednisolone and commenced on Cyclosporine (150mg o. d). She stabilised on this therapy.

To treat the underlying problem of Adult Stills Disease, funding was secured for Anakinra (IL 1 inhibitor). She was commenced on Anakinra 100mg o. d. by subcutaneous injection. She improved markedly over the course of the next week. On the day of discharge her Haemoglobin was 10.5 g/dL, Platelets 178 x10^9/L, WBC 4.47 x10^9/L. Fibrinogen remained low at 1.2 g/L although her Thrombin Time had been normal for several days. Her CRP was 1 mg/L, ESR 2 mm/hr, ALT 55 U/L and GGT 175 U/L.

Medications on discharge: Anakinra 100mg o. d. SC, Cyclosporine oral 150mg daily, Prednisolone 90mg o. d (reducing dose), Folic Acid 5mg o. d., Lansoprazole 30mg o. d, Ondansetron 80mg b. d, Natacil D3 2 tablets daily, Ferrous Fumarate 305mg o. d.

**Patient outcome**

1 week later at her review appointment, the patient was doing well. Her haemoglobin had almost returned to the normal range at 11.2 g/dL, her Platelet count remained normal, although she had an on-going low Fibrinogen level at 1.2 g/L. Her CRP was <0.6 mg/L and ESR 2 mm/hr. ALT had returned to normal with GGT much improved at 119 U/L. Her dose of prednisolone was reduced weekly. After a month, her coagulation and Liver function tests were normal and her clinical improvement was maintained, although she had required 2 courses of antibiotic therapy for minor respiratory tract infections. When reviewed at 4 months after discharge, she remained well with no further infections and she was down to prednisolone 10mg o. d. Her FBC, LFTs, coagulation, ESR & CRP were normal and her Adult Still’s Disease was in remission.

**DISCUSSION**

Macrophage Activation Syndrome (MAS) is a life-threatening hyperinflammatory syndrome. It is a rare but major cause of morbidity and mortality in patients with autoimmune autoinflammatory diseases [1]. It is a multisystem inflammatory syndrome caused by massive cytokine release from activated lymphocytes and macrophages. The clinical picture may mimic sepsis and, as there are no validated diagnostic criteria, early diagnosis can be very difficult [2]. Clinical features include fever, hepatosplenomegaly, neurological abnormalities, skin rash, lymphadenopathy, jaundice and oedema. Laboratory findings include pancytopenia, hyperferritinaemia [3], hypertriglyceridaemia, hypo-fibrinogenaemia, coagulopathy, deranged liver function tests, hypoproteinaemia and hyponatraemia. Histopathological examination reveals accumulation of macrophages and lymphocytes in spleen, bone marrow, liver, lymph nodes and cerebrospinal fluid. Haemophagocytic activity may be observed. This describes aggressive proliferation of activated macrophages and histiocytes which phagocytose other cells including erythrocytes, leucocytes, platelets, and their precursors [4]. Treatment aims are two-fold. Firstly, suppression of the hyperinflammatory state by destruction of the activated macrophages and lymphocytes, and secondly treatment of any existing triggers. Treatment is with supportive therapy and Immunosuppressive drugs, initially IV Methylprednisolone. To achieve positive outcomes in MAS early diagnosis and prompt treatment are essential. When the patient was readmitted she was systemically unwell. Sepsis must be considered in a presentation such as this and a septic screen should be performed. Other differentials include Systemic inflammatory response syndrome (SIRS) and Multiorgan dysfunction syndrome (MODS). This patient’s underlying ASD, deterioration in symptoms and blood tests pointed to a diagnosis of macrophage activation syndrome. The development of MAS in this case is most likely related to the patient’s one week history of diarrhoea. This most likely prevented absorption of the oral Prednisolone and caused the ASD to flare, triggering the onset of MAS. The traditional treatment of MAS is based on the administration of high dose Intravenous steroids including Methylprednisolone [2]. There is good support in the literature for the use of Cyclosporine, an immunosuppressant drug most often associated with use in organ transplantation [5]. Both Methyl Prednisolone and Cyclosporine were used in this case. Failure of steroid and immunosuppressive therapy may require the addition of biologic therapy although there is no consensus on specific recommendations. The use of anti-TNF therapy has produced conflicting results [1].

The Interleukin-1- receptor antagonist Anakinra is an accepted treatment for Adult-onset Stills Disease which is refractory to conventional treatment. There is good evidence of benefit from case studies. Anakinra has also been used to successfully treat Macrophage Activation Syndrome in the context of severe paediatric rheumatic disease [6]. Tocilizumab is a humanized monoclonal antibody against the interleukin-6 receptor (IL-6R). Tocilizumab has been used to successfully treat Adult Onset Stills Disease. However, there have been reports of Macrophage Activation Syndrome occurring after treatment of Adult-onset Stills Disease with Tocilizumab [7,8].

Supportive therapy includes IV immunoglobulin, blood transfusion products including packed red cells, cryoprecipitate, platelets and Fresh Frozen Plasma. This was delivered in the ICU setting in this case.

MAS is part of a larger group of diseases referred to as haemophagocytic syndromes that may develop in patients who have lymphoma, organ transplantation, serious infection, and rheumatic diseases, most notably systemic lupus erythematosus and Adult Stills disease [9]. In this case the underlying pathology was Adult Stills Disease (ASD). MAS is well recognised in the literature as a complication of ASD [8,9]. This case highlights the fact that active AOSD and MAS can mimic sepsis. MAS is rare, and
is most commonly seen secondary to underlying inflammatory disease. It is important that MAS is promptly recognised and treated, given its high mortality rate, despite treatment [10].

REFERENCES