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Macrophage Activation Syndrome After Initiation of Corticosteroid and Etanercept in a Patient with Adult Onset Still's Disease

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Abstract Macrophage activation syndrome is a life threatening complication of rheumatic diseases. We report a patient with adult onset Still's disease who developed macrophage activation syndrome and serious infections after starting high dose steroid and etanercept treatment.

Key words Adult onset Still's disease; Etanercept; Macrophage activation syndrome

Case Report

A 17-year-old Japanese boy was referred to us on day 39 of his adult onset Still's disease (AOSD) for further management. He first presented with flu-like symptoms, sore throat and fever to his family doctor in November 2003, and oral cefuroxime was given as the treatment of pharyngitis. His fever persisted and he experienced polyarthritis, myaglia and maculopapular rash one week later. He was admitted to a private hospital for suspected sepsis in view of persistent fever for two weeks. Polyarthritis and skin rash were associated with spikes of fever. There was multiple cervical lymphadenopathy but no hepatosplenomegaly detected initially. He was treated empirically with broad spectrum antibiotics including penicillin, clindamycin and levofloxacin.

He was then seen by a rheumatologist for the persistent fever and polyarthritis of three weeks duration. The affected joints included the small hands joints and wrist joints. The evanescent maculopapular rash was associated with spikes of fever. There was elevated white cell count and erythrocyte sedimentation rate (ESR) was 55 mm/hr. Ferritin level was 7592 pmol/L. Anti-nuclear antibody (ANA) and rheumatoid factor (RF) were negative. Extensive work up for infectious diseases including blood culture, urine for bacterial culture and viral studies including human immunodeficiency virus were all negative. Tuberculin test was negative. Bone marrow aspirate culture was negative. There was hyperplastic reactive marrow with megaloblastoid changes, and no blast cells found. Lymph node biopsy showed reactive lymphadenopathy with evidence of focal erthyrophagocytosis. Positron emission tomography (PET) scan showed generalised lymphadenopathy and hepatosplenomegaly.

Clinical diagnosis of adult onset Still's disease was made. He was put on oral prednisolone 15 mg twice per day and oral diclofenac. Pulse methylprednisolone 1000 mg daily for three days was started because of persistent quotidian fever two days later. Joint pain and skin rash were improved but fever spikes persisted at more than 39°C. Etanercept 25 mg twice per week subcutaneously was started as the second line treatment four weeks after onset of illness.

There was liver impairment noticed one week after starting etanercept. The alanine transaminase (ALT) was

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201 IU/L and aspartate aminotransferase (AST) was 82 IU/L. Serology for hepatitis A, B, C virus, cytomegalovirus (CMV), Epstein-Barr virus (EBV) and parvovirus B19 were all negative. Liver biopsy was done and only showed non-specific reactive changes.

He complained of generalised abdominal pain, vomiting, diarrhoea two days after liver biopsy. Liver function was further deranged. Stool cultures were negative but stool for white blood cell and occult blood were present. Ultrasound abdomen showed no dilated bile duct, no ascites but splenomegaly noticed.

He was then transferred to our unit for further management on day 39 of his illness. Colonoscopy showed severe colitis and histology was positive for CMV inclusion body. Blood test for CMV PCR was positive and the CMV-pp65 antigenemia was 15 positive cells/2 $x10^5$ white blood cell. Gancyclovir was therefore started. His fever persisted and was up to 39°C. Pancytopenia was already noted upon transferal to our unit. The white cell count dropped to 3.9 x 10^9/L with neutropenia at 0.4 x 10^9/L. Platelet count dropped to 75 x 10^9/L and the lowest haemoglobin was 7.5 g/dL. Ferritin level elevated to >3000 pmol/L, and C-reactive protein 4.94 mg/dL (normal <0.75 mg/dL). Paradoxically, ESR dropped to 13 mm/hr. Clotting profile was slightly impaired with elevated prothrombin time 20.1 seconds but fibrinogen was normal. Liver function further deteriorated, with ALT at 647 IU/L, AST 1193 IU/L and LDH 7348 IU/L.

Macrophage activation syndrome (MAS) was suspected because of non-remitting fever, hepatosplenomegaly and persistent lymphadenopathy. It was supported by the laboratory results including pancytopenia, low ESR, high ferritin, deranged liver function and mild derangement in clotting profile. Lymph node biopsy showed reactive lymphadenopathy with evidence of erthyrophagocytosis. Pulse methylprednisolone 1000 mg daily for three days, cyclosporine A 60 mg twice per day and intravenous immunoglobulin 54 g were given for the MAS.

Early morning urine saved on admission grew *Mycobacterium tuberculosis*. The patient did not have clinical symptoms of tuberculosis (TB). There was no pulmonary changes. The computerised tomography (CT) abdomen did not show any abscess, miliary TB or enlarged lymph nodes but there was a one centimeter splenic lesion at the anterior tip. Gallium scan did not show increased uptake over spleen. Ethambutol, levofloxacin and amikacin were started for the treatment of extra-pulmonary tuberculosis instead of the usual first line medications because of the impaired liver function.

He was in remission after completion of the treatment and remained well with no symptoms and normal blood counts and immunoglobulin levels at the time of reporting. Table 1 summarises the chronology of the clinical features.

Discussion

We report a young man with complicated AOSD. He was complicated with MAS, CMV colitis and tuberculosis after the treatment of high dose methylprednisolone and etanercept. This case illustrated the difficulty in the diagnosis of MAS with AOSD. It also implicated the treatment of AOSD could be the triggering factor of MAS. The use of biologics should be cautious in AOSD as it may trigger both infections and MAS. Evaluation of infectious disease as latent tuberculosis should be done before initiating the drug treatment. In the following, we would like to discuss on the presentation of MAS and AOSD and compare the clinical features of these two diseases.

AOSD is an uncommon systemic inflammatory disorder. The aetiology is not known but infection may be the triggering factor from observational case series.[1] Patients with AOSD mostly have alteration of cytokine production, including increased production of interleukin, tumor necrosis factor and interferon. Diagnosis is usually made clinically. Our patient was diagnosed adult onset Still's disease (AOSD) according to the Yamaguchi diagnostic criteria.[2] Presentations include fever, arthritis and skin rash. Sore throat is a common prodromal presentation observed in case series.[1] Other presentations are myaglia, liver function derangement, lymphadenopathy, hepatosplenomegaly and serositis. Rarely, patients with AOSD can have renal involvement and neurological complications.[1,3]

There is no autoimmune marker for AOSD, neither rheumatoid factor nor anti-nuclear antibody is associated. The erythrocyte sedimentation rate (ESR) is elevated in most patients.[1,3] During the active phase of disease, complete blood pictures show anaemia, leucocytosis or thrombocytosis. Serum ferritin is high in patients with AOSD and it reflects the disease activity.[1]

MAS is also known as secondary haemophagocytic syndrome or reactive haemophagocytic lympho-histiocytosis. The term MAS is used when this potential fatal condition complicates existing rheumatic disease.[4] MAS may be difficult to recognise because it can occur as part of the early presentation, flare up of the AOSD, and it also mimics severe sepsis.[4]

Table 1 Summary of clinical features and investigation results

Presentation	Investigations	Treatment
Day 1: ◆ Flu-like symptoms ◆ Low grade fever ◆ Sore throat		◆ Oral cefuroxime
Day 7: ◆ Myalgia ◆ Polyarthritis ◆ High fever ◆ Maculopapular rash ◆ Cervical lymphadenopathy	◆ Neutrophilia with toxic granules ◆ ESR 55mmHg ◆ Infection screening: negative	◆ Intravenous antibiotics
Day 21: ◆ Persistent fever with rash ◆ Polyarthritis >3 weeks ◆ Lymphadenopathy ◆ Clinical diagnosis of AOSD made	◆ ANA/RF/ANCA: negative ◆ Lymph node biopsy: focal erythrophagocytosis ◆ Bone marrow biopsy: reactive marrow with megaloblastoid change	◆ Oral prednisolone ◆ Diclofenac ◆ Pulse methylprednisolone ◆ Etanercept
Day 36: ◆ Impaired liver function	◆ Hepatitis A,B,C, HIV, CMV, parovirus B19, EBV: negative ◆ Liver biopsy: non specific reactive changes	
Day 37: ◆ Abdominal pain ◆ Diarrhoea ◆ Vomiting	◆ Faecal occult blood: positive ◆ Stool for parasite / ova / amoba / bacterial culture: negative ◆ Clostridium difficile: negative	
Day 39: ◆ Bloody diarrhoea	◆ CT abdomen: distal small bowel and large bowel filled with fluid	◆ Transferred to our unit for management
Day 41: ◆ Persistent fever ◆ Bloody diarrhoea ◆ Impaired liver function	◆ Low white cell count, thrombocytopenia and deranged clotting profile ◆ ESR 13 mmHg ◆ Elevated ferritin ◆ Repeated hepatitis screening: CMV PCR: positive ◆ CMV-pp65 elevated ◆ Early morning urine for TB ◆ Colonoscopy: severe colitis and histology showed CMV inclusion body	◆ Pulse methlyprednisolone ◆ Gancyclovir ◆ Cyclosporine A ◆ IVIG
Day 82: ◆ Mild liver derangement	◆ CMV-pp65: negative ◆ Early morning urine: postivie for Mycobaterium tuberculosis	◆ Anti-TB treatment

ESR, erythrocyte sedimentation rate; IVIG, intravenous immunoglobin; CMV, cytomegalovirus; TB, tuberculosis; AOSD, adult onset Still's disease; HIV, human immunodeficiency virus; ANA, antinuclear antibodies; ANCA, Anti-neutrophil cytoplasmic antibodies; RF, rheumatoid factor.

The pathogenesis of MAS is similar to AOSD in terms of deregulation of T lymphocyte and cytokine production.[5] There is abnormal activation of macrophage and NK cell dysfunction caused by excessive production of cytokines. It results in phagocytosis of haemopoietic cells by the activated macrophage in various organs.[6,7]

The prevalence of MAS in patients with AOSD is 12% in one report.[5] Although MAS is a rare condition, it is not uncommon in AOSD. It is important to recognise this condition as MAS can occur at anytime during AOSD.[5] Infections, drugs, and flare up of rheumatic disease can be the triggering factors of MAS.[5,8-10] The presentations include high fever, lymphadenopathy, hepatosplenomegaly, pancytopenia, elevated serum ferritin, impaired liver function and paradoxically low ESR but these may also be present in flare up of AOSD.[5-9]

Patients with non-remitted high fever and pancytopenia should alert one of MAS.[7,9,10] Leucopenia and thrombocytopenia is not common in acute AOSD. A raised serum triglyceride is present in all patients with MAS in a series but it is not a marker for AOSD.[5] We should look for any hypertriglyceridemia in AOSD patient suspected to have MAS. Coagulopathy is characteristic in MAS, which is sometimes present in AOSD. Table 2 summarises the comparison of features in MAS and AOSD.

There are no diagnostic criteria of MAS in patients with AOSD. A preliminary diagnostic guideline for MAS complicating SOJIA was published based on laboratory and clinical criteria.[10] Bone marrow aspiration showing haemophagocytosis is only required in doubtful case. There are false negative results or occult changes in bone marrow or other tissue biopsy.[9-11] The laboratory criteria include low platelet and white cell count, hypofibrogenemia and elevated AST. The clinical criteria include central nervous system dysfunction, haemorrhages and hepatomegaly. The presence of any two or more of the laboratory or clinical criteria is highly suggestive of MAS in patients with SOJIA.[10] Our patient also fulfilled these criteria of MAS by this diagnostic guideline.

The management of MAS in AOSD is empirical and high dose corticosteroid is used as first line treatment in most case series.[5,8,9,12] Cyclosporin A, intravenous immunoglobin (IVIG), etoposide are second line treatment.[7,8] In our patient, pulse methylprednisolone was the initial treatment followed by IVIG and cyclosporin A.

There are only few case reports of MAS following the use of etanercept in both patients with AOSD and systemic onset juvenile idiopathic arthritis (Table 3).[13,14] Case 2 received etanercept after MAS has already complicated her AOSD, and her MAS worsened after initiation of etanercept. The drops in ESR and white cell count after etanercept may be misinterpreted as a treatment response. But it may actually reflect the early phase of MAS. MAS should be a differential diagnosis in these patients once the white cell

Table 2 Comparison of clinical and laboratory features of adult onset Still's disease and macrophage activation syndrome

	AOSD	MAS
Fever pattern	Quotidian	Non-remitting
Skin rash	Evanescent macuolopapular rash	Urticaria
Lymphadenopathy	+	++
Hepatosplenomegaly	+	++
Arthritis	+	-
Serositis	+	-
Encephalopathy	Rarely	+
White cell count	High	Low or normal
Platelet	Normal or high	Low or normal
ESR	High	Low
Ferritin	High	High or very high
AST/ALT	Normal or deranged	Deranged or normal
PT/APTT	Normal	Deranged or normal
Fibrinogen	Normal	Low or normal
Triglyceride	Normal	High

ALT, alanine aminotransferase; AST, aspartate aminotransferase; ESR, erythrocyte sedimentation rate; PT, prothrombin time; APTT, activated partial thromboplastin time, AOSD, adult onset Still's disease; MAS, macrophage activation syndrome.

Table 3 Clinical features and laboratory findings of patient with MAS

	Case 1 (Our patient)	**Case 2 (Ref 12)**	**Case 3 (Ref 14)**	**Case 4 (ref 13)**
Age/Sex	M/17	F/22	F/50	F/4.5
Disease	AOSD	AOSD	AOSD	SOJIA
Disease duration before MAS	5 weeks	8 weeks	5 weeks	3.5 years
Treatment received	Prednisolone Etanercept	Prednisolone Etanercept	Prednisolone Hydroxychloroquine	Prednisolone Etanercept
Clinical features				
Persistent fever	+	+	+	+
Myaglia	+	+	+	+
Urticaria rash	+	+	-	+
Lymphadenopathy	+	n	n	-
Hepatomegaly	+	+	n	-
Splenomegaly	+	-	n	-
Encephalopathy	-	-	+	-
Laboratory findings				
White cell count (10^9/L)	3.9	2.5	6	6.5
Platelet (10^9/L)	78	53	354	122
ESR (mm/hr)	13	-	130	2
Ferritin (pmol/l)	>33000	-	>3370	2166
ALT (IU/l)	647	95	84	-
AST (IU/l)	1193	249	-	95
Fibrinogen (g/l)	2.36	0.6	6.79	1.96
Infection screen	CMV/ TB	EBV	Negative	Negative
Treatment	IVIG Pulse methylprednisolone Cyclosporin A	IVIG Pulse methylprednisolone Cyclosporin A	Pulse methylprednisolone Cyclosporin A	Two pulses of methylprednisolone

AOSD, adult onset Still's disease; SOJIA, systemic onset juvenile idiopathic arthritis; MAS, macrophage activation syndrome; n, not mentioned

and platelet count drop without obvious clinical improvement.[6,7,9,10] Recently, tocilizumab, an anti-interleukin-6-receptor monoclonal antibody has been reported to be effective in the treatment of SOJIA, and the authors have expressed an opinion that the complication of MAS could develop during tocilizumab treatment.[15]

In summary, we report a case of patient with AOSD who developed MAS and severe infectious complications after initiation of steroid and etanercept. Therefore, close monitoring for MAS is necessary after starting treatment for AOSD or SOJIA.

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