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A Case of Adult-Onset Still's Disease Complicated With Macrophage Activation Syndrome

KEYWORDS: Adult-onset still's disease, Macrophage activation syndrome, Hemophagocytic syndrome

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ABSTRACT *Adult-onset still's disease (AOSD) is a rare systemic inflammatory disorder of unknown etiology and pathogenesis. ASOD is characterized by high spiking fever, rash, arthritis and multi-organ involvement. Macrophage activation syndrome (MAS) is a rare but life threatening complication of AOSD. Here, we describe a case of female patient with MAS as a complication of ASOD with highest serum ferritin level. Her manifestations responded well to high dose steroid therapy and disease modifying antirheumatic drugs (DMARDs).*

Introduction
Adult-onset still's disease (AOSD) is a rare systemic inflammatory disorder characterized by high spiking fever, rash, arthritis and multi-organ involvement[1]. Etiology and pathogenesis of AOSD is not fully understood[2]. Macrophage activation syndrome (MAS), a hemophagocytic syndrome, is a rare but life threatening complication of AOSD.MAS is suspected in AOSD when presented with acute febrile illness, hepatosplenomegaly and increased serum liver enzymes with increased serum ferritin level [2]. Here, we described a case of female patient with MAS as a complication of ASOD. Her manifestations respond well to high dose steroid therapy and disease modifying antirheumatic drugs (DMARDs).

Case report
A 40-year-old female was admitted with 10-days history of high-grade fever with chills, generalized body ache and rash all over the body. She had history of loose stools prior to hospitalization.

On examination, the patient was febrile (102^{0}F), but hemodynamically stable. She had a red, evanescent, non-pruritic macular rash on the extensor aspect of both forearms. Rash was more prominent whenever she had a fever. Polyarthritis was found in the form of swelling and tenderness at first metacarpophalangeal and proximal interphalangeal joints on the left hand. Abdominal examination showed mild hepatosplenomegaly. Rest of systemic examination revealed no significant abnormality.

Laboratory investigations revealed leukocytosis (Total leukocyte count 12700/mm^3, normal range : 4,500-10,000/mm^3) (Table 1).ECG was suggestive of sinus tachycardia. Chest radiograph was normal. Blood culture was sterile. Ultrasonography of an abdomen showed mild hepatomegaly with mild splenomegaly.

Rheumatoid factor (RA) and anti-nuclear antibody (ANA: 0.90) were negative. However, serum lactate dehydrogenase (LDH) was 3650 IU/L (normal range: 105-333 IU/L) and serum triglyceride was 185 mg/dl (normal range: less than 150 mg/dl). Serum ferritin was extremely elevated to 76594.3 ng/ml (normal range: 12-150 ng/ml) (Table 2) . In view of persistent diarrhea, colonoscopy was done which was normal and gastroscopy revealed mild antral gastritis. Bone marrow aspiration revealed evidence of haemophagocytosis with erythroid suppression, hence diagnosis of MAS was confirmed.

Treatment with high-dose corticosteroids in the form of intravenous methylprednisolone 500 mg for three days was started followed by oral administration of prednisolone and hydroxychloroquine 200mg daily at night. Patient improved dramatically over five days and was discharged with all parameters almost returning to normal. Evidence of hemophagocytosis in bone marrow examination and extremely high serum ferritin levels clinched the diagnosis of AOSD complicated with MAS.

Discussion
Adult-onset still's disease (AOSD) is a systemic inflammatory disorder characterized by high spiking fever, rash, arthritis and multi-organ involvement[1]. Etiology as well as pathogenesis of AOSD is largely obscure[2]. Firstly, Still disease in adult was described by Eric Bywaters in 1971who called it as 'ASOD' due to similarity with pediatrics cases described by Dr. George Still in 1899[1,2,3,4]. AOSD is extremely uncommon but occur worldwide, with an estimated prevalence of 1.5 cases per 100,000-1000, 000 people[2]. The disease specifically affects young people between 16 to 35 years of age and more commonly noted among women as compared to men[4, 5,6]. However, cases are also reported in older patients[6].

The pathogenesis of AOSD is not fully understood and cytokines like TNF-α, IL-1β, IL-6, IL-8, and IL-18 are variably implicated[2, 3,5,6,7]. The common manifestations of AOSD are fever, arthralgia, rash and sore throat[6]. Fever is often cyclical, with temperature spikes of 39^{0}C, frequently in the evening and associated with chills[2, 6.] Joint pain is severe during fever spikes. The commonly involved joints are knees, wrists, ankles and elbows [2, 6]. Bilateral ankylosing carpal arthritis is a classical feature[2]. The typical rash of AOSD is small, discrete, non-pruritic, salmon-pink macule, which is evanescent and often coincides with the fever spike[2, 6](as shown in photos).

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Photos 1-5: Small, discrete, non-pruritic, salmon-pink macule like rash of AOSD

Clinically, AOSD is reported in three forms[6]. A self-limited form may exist with a long period of remission. Intermittent or polycyclic systemic pattern is present with one or more relapses. A chronic articular pattern may associate with increased severity and joint destruction[6, 8]

Hyperferritinaemia is a powerful marker of AOSD and hence always used for screening[4]. Elevated serum ferritin level was noted in 89% of patients and act as an indicator of disease activity due to macrophage activation[6, 9]. Ferritin level in AOSD is usually higher than those found in other autoimmune disease[2, 4]. A decreased in glycosylated ferritin, an isoform of ferritin, have been observed in AOSD compared with other inflammatory diseases[2, 4, 6.] Hence, glycosylated ferritin has been said to be more useful in AOSD.

As there is no definitive diagnostic test for AODS, diagnosis is totally clinical based on set of criteria[2, 3, 6]. Fautrel proposed a new set of criteria for diagnosis that included the use of glycosylated ferritin[8]. However, as glycosylated ferritin is not widely available so these criteria are still not commonly used.

Numerous other criteria have been proposed, but the Yamaguchi criteria (Table 3) remain the most sensitive [2, 6, 8]. The classification of AOSD requires the presence of five or more criteria, of which two must be major criteria. Our patient had all four major and three minor criteria.

Macrophage activation syndrome (MAS), a hemophagocytic syndrome, is a rare but life threatening complication of AOSD.MAS is suspected in AOSD when presented with acute febrile illness, hepatosplenomegaly and increased serum liver enzymes[2]. Our patient had history of high spiking fever, mild hepatosplenomegaly and serum lactate dehydrogenase was 3650 IU/l suspecting the diagnosis of MAS. In India, Singh S et al in 2008 have reported macrophage activation syndrome in a patient with AOSD, however one of their patient succumbed to death[10].

It is a result of increased activation of benign macrophages, leading to persistent immune stimulation and cytokine from storm[9].Neurological manifestations like coma, seizures, meningism, mood disorders, delirium, and psychosis are seen more commonly in macrophage activation syndrome compared to AOSD.MAS has also been reported with other autoimmune disease[11]. Hence exclusion of such disorders is necessary while diagnosing case of AOSD. Bode SF et al in 2012 mentioned that hemophagocytosis in bone marrow aspiration establishes the diagnosis of MAS as seen in our case[12]. Hemophagocytosis can also be seen in biopsies from

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liver, lymph node and spleen. Allen et al found that serum ferritin > 10000ng/ml 90% sensitive and 96% specific for the diagnosis of Macrophage activation syndrome[13]. Our patient had serum ferritin level of 76594 ng/ml. Clinical manifestations are due to infiltration of activated macrophages and T cells into various organs causing organ damage.

Treatment of AOSD focused on use of Non-steroidal anti-inflammatory drugs (NSAIDs), steroid and DMARDs[6]. Earlier studies showed NSAID monotherapy is beneficial in 7-15 % patients[6]. NSAID particularly indomethacin and naproxen have been shown to be effective. Now a day corticosteroids form the crux of AOSD therapy[3,5]. Corticosteroids are usually required to induce remission.

For steroid-resistant cases or those requiring reduced steroid dose DMARDs like methotrexate, azathioprine, hydroxychloroquine, cyclophosphomide, cyclosporine have been used as steroid sparing agents[5,6].

Methotrexate is especially effective to induce remission in refractory cases and control of arthritis, ankylosis and disability[3].IL-1 acts as a trigger for events in the inflammatory cascade and hence IL-1 receptor antagonist like anakinra play a key role in control of AOSD manifestations[3,5]. Other agents which have been used to varying degrees of efficacy include TNF-α blockers such as etanercept[5,6].

Use of corticosteroid to induced immunosupression is demonstrated as effective therapy for MAS[12]. Cyclosporine A is also proved to beneficial in management of MAS and reduces the need of steroid[14].

Conclusion

MAS is a rare but life-threatening complication of AOSD.As MAS can be a presenting feature of other autoimmune diseases it is necessary to exclude these diseases. Judicious use of corticosteroids and DMRDs act as an effective management strategy.

Investigations	On admission	On discharge
Hb (gm/dl)	11.2	11.2
TLC(/mm^3)	12700	5200
Platelet count (/mm^3)	2.4 lakh	1.26 lakh
Blood urea (mg/dl)	26	100
Serum creatinine (mg/dl)	0.97	1.8
S.Bilirubin (Total) (mg/dl)	0.14	0.21
S.Bilirubin (Direct) (mg/dl)	0.1	0.13
SGOT (IU/L)	46	104
SGPT (IU/L)	20	59
S.Alkaline phosphatase (IU/L)	69	71

Table 1.Patient laboratory data on admission and on discharge

Other investigations	Values in patient
ESR	89 mm/hr
S.ferritin	76594ng/ml
RA	Negative
ANA	Negative
S.LDH	3650IU/L
S.Triglycerides	185 mg/dl
Dengue (IgG,IgM,Ns1)	Negative
Rapid malaria test	Negative
Stool for occult blood	Present
HIV,HBsAG	Negative

Table 2.Patient laboratory data during hospital stay

Major criteria	Minor criteria	Exclusion criteria
• Arthralgia > 2 weeks • Fever > 39^{0}C,intermittent > 1 week • Typical rash (maculopapular,non-pruritic) • WBC > 10,000 (> 80% granulocytes)	• Sore throat • Lymphadenopathy and /or splenomegaly • Abnormal liver function test • Rhematoid factor and ANA negative	• Infection,especially sepsis • Epstein-Barr infection • Malignancy • Inflammatory disease

Table 3. Yamaguchi Criteria (Source: Ann Rheum Dis 2006; 65:564-72)

REFERENCE

1. Bywaters EG.Still's disease in the adults.Ann Rheum Dis 1971; 30:121 | 2. Owlia MB, Mehrpoor G. Adult-onset Still's disease: a review. Indian J Med Sci 2009; 63:207-21 | 3.Efthimiou P,Moorthy LN,Mavragani CP,Skokos D,Fautrel B.Adult-onset still's disease and autoinflammation.Int J Inflam 2012;2012 | 4. Mehata B,Efthimiou P. Ferritin in adult-onset Still's disease : just a useful innocent bystander? Int J Inflam 2012; 2012 | 5. Mavragani CP,Spyridakis EG,Koutsilieris M. Adult-onset Still's disease: From pathophysiology to targeted therapies. Int J Inflam 2012; 2012 | 6. Efthimiou P,Paik PK,Bielory L.Diagnosis and management of adult-onset Still's disease.Ann Rheum Dis 2006;65:564-72 | 7.Chen DY,Chuang HC,Lan JL,Chen YM,Hung WT,Lai KL, et al .Germinal center kinase-like kinase (GLK/MAP4K3) expression is increased in adult-onset Still's disease and may act as an activity marker.BMC Med 2012;10:84 | 8. Fautrel B. Adult-onset Still disease. Best Pract Res Clin Rheumatol 2008;22:773-92 | 9.Rosario C,Zandman-Goddard G,Meyron-Holtz EG,D'Gruz DP,Shoenfeld Y.The hyperferritinemic syndrome:macrophage activation syndrome,still's disease,septic shock and catastrophic antiphospholipid syndrome.BMC Med 2013;11:185 | 10. Singh S,Samant R,Joshi VR.Adult-onset Still's disease : a study of 14 cases. Clin Rheumatol 2008; 27:35-9 | 11.Deane S,Selmi C,Teuber SS,Gershwin ME. Macrophage activation syndrome in autoimmune disease.Int Arch Allergy Immunol 2010;153:109-20 | 12.Bode SF,Lehmberg K,Maul-Pavicic A,Vraetz T,Janka G,Stadt UZ, et al.Recent advances in the diagnosis and treatment of hemophagocytic lymphohistiocytosis.Arthritis Res Ther.2012;14:213 | 13.Allen CE,Yu X,Kozinetz CA,McClain KL. Highly evevated ferritin levels and the diagnosis of hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer 2008;50:1227-35 | 14.Mouy R,Stephan JL,Pillet P,Haddad E,Hubert P,Prieur AM. Efficacy of cyclosporine A in the treatment of macrophage activation syndrome in juvenile arthritis: report of five cases.J Pediatr 1996; 129:750-4 |