Case Report

Adult Onset Stills Disease- "A Need for Early Diagnosis and Detection of Systemic Score"

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ABSTRACT

AOSD (adult onset stills disease) is a rare systemic inflammatory disorder of unknown etiology, which is typically characterized by a clinical triad (a high spiking fever, {an evanescent, nonpruritic, macular and salmon coloured rash} and arthritis) and a biological triad (hyperferritinemia, hyperleucocytosis with neutrophilia and abnormal liver function test). We present a case of an adult onset stills disease in a 47 years male patient with presenting complaints of fever, polyarthralgias, cough, pus discharge from nails and lab abnormalities (including anemia, hyperferritinemia and abnormal liver function test). The patient was also complicated with pneumonia. The patient had a past history of herpes oral ulcer and colitis (caused by cytomegalovirus) which was excluded during the diagnosis (made based on yamaguchi criteria) as the patient had the complaints for a long period. The systemic score in our patient was found to be 8, therefore a systemic score of greater than 7 indicates a high risk of mortality. Early detection of systemic score and understanding the clinical presentation of AOSD could be helpful in deciding the therapy and may help to reduce the risk of mortality by improving patient condition. Here we present a case in which the patient was exhibiting clinical presentations of AOSD from a long period of time but was not evaluated, when the condition got worsened the disease was ruled out and started with glucocorticoids but the patient did not respond to the therapy despite of adding 2 corticosteroids and also the TOCILIZUMAB, it was too late as the patient developed complications associated with AOSD such as, the patient complicated with pneumonia and hypotension, contributing to AKI and refractory shock. Development of refractory shock and multiorgan dysfunction led to death.

Key words: Adult onset stills disease, Yamaguchi criteria, Hyperferritinemia, Systemic score, Pneumonia, Corticosteroid, Tocilizumab.

INTRODUCTION

AOSD (adult onset stills disease) is a rare systemic inflammatory disorder of unknown etiology, which is typically characterized by a clinical triad (a high spiking fever, {an evanescent, nonpruritic, macular and salmon coloured rash} and arthritis) and a biological triad (hyperferritinemia, hyperleucocytosis with neutrophilia and abnormal liver function test- includes high level of aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, gamma- glutamyltransferase, lactate dehydrogenase and bilirubin).[1]

Other laboratory findings includes inflammatory markers (such as high CRP and ESR), low glycosylated fraction of ferritin (more specific marker than ferritin itself), anemia, thrombocytosis, immune markers (such as high IL-6, IL-8, TNF-alpha), coagulation abnormalities are rare if it is present it shows prolongation of partial thromboplastin time, cases of disseminated intravascular coagulation have been described that have led to death, high level of germinal center kinase- like kinase (GLK)- expressing T-cells in sera of AOSD patient (showed in recent study).[2,3] Other diagnostic test performed includes- liver biopsy, bone marrow biopsy, serology (showing negative rheumatoid factor and antinuclear antibody).[2,3]

Yamaguchi criteria is the most sensitive (96%) and highly specific (92%), among the different criteria available for the classification of AOSD.[4]

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The AOSD has a heterogenous clinical presentation and a wide spectrum of differential diagnosis which includes infectious, neoplastic and autoimmune disorders whose clinical presentations mimics the AOSD, so before diagnosing AOSD these should be ruled out and excluded.[2]

Viral syndrome (for example- rubella, cytomegalovirus, Epsteinbarr virus, mumps, coxsackievirus, adenovirus) can be excluded if the symptoms persist beyond 3 months.[2]

Sir George Frederick Still described 22 cases of chronic polyarthritis (in children) in 1897 and referred it as juvenile rheumatoid arthritis, for more than 20 years question where raised based on their nomenclature and disease condition, later in 1971, Dr. Bywaters described 14 cases in adults and made it clear that it was different from juvenile rheumatoid arthritis and also noted that the patient with stills disease where sero negative (negative rheumatoid factor and negative antinuclear antibody- considered as one of the main diagnostic criteria for AOSD) and referred it as adult onset stills disease.[1,2]

The distribution of age in stills disease is not unimodal as it occurs in young adults (15-25 years) and also in patients older than 60 years of age.[5]

Its prevalence rate has been estimated to be 0.22 in japan, 0.16 per 1,00,000 persons in France and 0.4 in Norway. 1 to 34 cases per million persons is been reported in European and Japanese population.[6]

The etiology of AOSD remains unknown but an infectious etiology has been suspected because AOSD and established infectious syndrome (e.g., abrupt onset, high fever, generalized adenopathy, spleenomegaly and leukocytosis) shows similar clinical presentation. A number of viruses (such as rubella, measles, Echovirus 7, Coxsackievirus B4, Cytomegalovirus, Epstein–Barr virus, Human herpesvirus 6, Parainfluenza, influenza A, Adenovirus, Hepatitis B and C and Parvovirus B19) and bacteria (Mycoplasma pneumonia, Chlamydia pneumonia, Yersinia enterocolitica, Brucella abortus and Borrelia burgdorferi) where isolated in patients with AOSD but did not clearly established it to be responsible. It is proposed that an infection can be triggering factor for an interplay between host genetic factors, autoimmunity mechanism and pathogenic antigens, which can ultimately lead to AOSD pathogenesis.[6] Malignancies including solid cancer (mainly breast and lung) and hematological malignancies (mainly malignant lymphoma) may also trigger the onset of AOSD.[6]

Cytokines (such as IL-1beta, IL-18, IL-6, TNF-alpha) plays a major role in pathogenesis of AOSD.[7]

The drug of choice for the treatment of AOSD includes- NSAIDS, corticosteroids (such as prednisolone- as a first line treatment regardless of clinical presentation), DMARDs (in severe complications-cyclosporine A, leflunomide, azathioprine, hydroxycholoroquine, D- penicillamine and tacrolimus, in first line steroid sparing treatment in AOSD methotrexate has beneficial effect), biological therapies (such as ANAKINRA{ IL-1 antagonist}, TOCILIZUMAB {IL- 6 antagonist} and TNF-alpha- such as infliximab, etanercept, adalimumab- {for refractory AOSD}).[7]

Lifethreatening complication of AOSD includes- reactive hemophagocytic lymphohistiocytosis, disseminated intravascular coagulopathy, myocarditis, thrombocytopenia purpura, diffuse alveolar hemorrhage.[7]

CASE REPORT

A 47 years male patient presented with complaints of fever, multiple joint pains, cough and pus discharge from nail end. In 2017, at first presentation outside he was evaluated for complaints of generalized lymphadenopathy, pneumonia, anemia, pyoderma, hepatosplenomegaly, biopsy of lymph node was reactive and the patient was treated with steroids and iron supplements. Later he developed herpes oral ulcer and HSV1 was positive. Later he was diagnosed with CMV colitis, colonoscopy showed inflamed right colon, biopsy showed CMV (cytomegalovirus) was positive, antinuclear antibody was positive, PET (positron emission tomography) was done it showed loculated pleural effusion, circumferative mural thickening, enlarged multiple lymph nodes and was treated with tablet valganciclovir.

At present the patient presents with complaints of fever (temperature- 101.1°F), polyarthralgia, cough and pus discharge from nails. He was evaluated and on percussion and auscultation it revealed hepatosplenomegaly, on general physical examination the joints were swollen and tender, on chest examination it showed left infrascapular and infraaxillary crepts. The vitals were abnormal- revealing the patient was hypotensive (blood pressure- 100/80mmHg), tachycardiac (pulse rate- 115 beats per min. The patient was further evaluated and the laboratory investigation revealed- anemia, leukocytosis with neutrophilia and lypmphocytopenia, hyperferritinemia (serum ferritin- 1551.6 increased ten folds), abnormal liver function test (hypoalbuminemia- 1.2 g/dl; decreased albumin globulin ratio- 0.16, increased level of SGOT [serum glutamate oxaloacetate transaminase- 51 U/L] and high level of ALP [alkaline phosphatase- 270 U/L], high levels of gamma glutamyl transferase [GGT- 107 U/L]), proteinuria, a high CRP level (115mg/L) and a

high ESR level (120mm/hr). The patient started with methylprednisolone.

Considering clinical triad (fever, polyarthralgia, pyoderma) and biological triad (hyperferritinemia, hyperleucocytosis with neutrophilia and abnormal liver function test) seen in patient, it was suspected AOSD, it was further evaluated to rule out infectious and autoimmune etiology. Serology was performed first day its showed HBsAg and HIV-chemiluminescence was non-reactive.

The patient had persistent cough and codeine syrup was added and advice to take pulmonology opinion. The chest X ray revealed left sided lower zone opacity suggestive of pneumonia, culture (sputum gram stain) showed few inflammatory cells, gram positive cocci in short chain, gram positive cocci in budding yeast cells with pseudohyphae and gram-negative bacilli. The infectious disease (pneumonia) was confirmed (INJ. PIPERACILLIN/ TAZOBACTAM was started).

Though the patient had pneumonia which are to be excluded in stills disease diagnosis according to yamaguchi criteria it was classified and confirmed as stills disease.

On 3rd day the patient had one episode of PLE (protein loosing enteropathy), mild to moderate in amount, bright red in colour, advice to take gastrology opinion. Sigmoidoscopy was done it revealed diminutive rectal polyps, type I hemorrhoids and advice to start on ANOVATE (beclomethasone+ lidocaine+ phenylephrine) ointment and fibril powder.

As the patient was feeling better on 4th day the INJ. Methylprednisolone was changed to TAB. Prednisolone, but the next day the patient experienced lot of pain (multiple joint pain), so again they added methylprednisolone and INJ. TOCILIZUMAB was also added, later both prednisolone and methylprednisolone was continued.

The patient had lot of pain in legs and thigh, severe dyselectrolytemia also occurred (hypokalemia), it was aggressively managed with syrup potassium chloride, he had an episode of coughing up of blood. Sputum gram stain was performed it showed few inflammatory cells, moderate epithelial cells, plenty of gram-negative bacilli, yeast cells with pseudphyphae and few gram-positive cocci seen. Sputum was checked for AFB (acid fast bacilli) no acid fast bacilli was seen, KOH preparation fungus noted it showed budding yeast cells with pseudohyphae. In view of multiple abscess of skin, staphylococcus infection was considered and INJ. VANCOMYCIN was added.

CT (computed tomography) chest with intravenous contrast was performed the result showed areas of well-defined soft tissues densities in lingular segments, left lower lobe segments and posterior segment of right upper lobe with 'air bronchogram'- suggestive of infective etiology; it also showed areas of cavitation with heterogenous enhancement in left lower lobe consolidation, concern for nectrotizing pneumonia and noted Diffuse interlobular septal thickening in both lungs, predominantly involving bilateral upper lobes – it could be due to contiguous inflammation; few enlarged mediastinal lymph nodes was also noted; and presented old fracture along anterior aspect of right 4th rib. The patient also exhibited hepatosplenomegaly and mild ascites.

The blood urea nitrogen BUN and uric acid level was also high, considering this and ascites it was confirmed that patient had acute kidney injury. This may be due to hypotension, as the patient was hypotensive there may be no proper blood supply to the kidney which may have led to acute kidney injury.

The patient developed severe hypotension which led to inadequate blood supply to various organ and the patient had multiple organ dysfunction. He was shifted to MICU and was intubated, put on ventilator support, there he continued to worsen, he developed cardiac arrest (refractory shock which is lethal manifestation of cardiovascular failure, which occurs when a high dose of vasopressor fails to show adequate hemodynamic response), CPR (cardio pulmonary resuscitation) was initiated as per ACLS protocol (advanced cardiac life support) but could not be revived and death was declared.

DISCUSSION

AOSD is a rare systemic inflammatory disorder which has been recently classified as an autoinflammatory condition.[1,7] Its prevalence rate has been estimated to be 0.22 in japan, 0.16 per 1,00,000 persons in France and 0.4 in Norway. 1 to 34 cases per million persons is been reported in European and Japanese population.6

The etiology and pathogenesis of AOSD is unknown, but it is suspected that an infection can trigger the pathogenesis of the disease.[6] In our patient the possible cause or triggering factor was found to be herpes simplex virus and cytomegalovirus, as the patient had history of herpes oral (caused by herpes simplex) and colitis (caused due to cytomegalovirus).

The Severe AOSD often mimics the infection and hence the differential diagnosis must be considered and

Table 1: Adult onset stills disease diagnostic criteria.[4,10-12]

Yamaguchi criteria[4,10]	Fautrel's criteria[11]	Cush criteria[12]
Major: • Fever > 39°, intermittent, ≥ 1 week • Arthralgia lasting 2 weeks or longer • Typical rash • Leukocytosis (WBC > 10,000/cmm) including > 80% granulocytes Minor: • Sore throat • Lymphadenopathy and / or splenomegaly • Liver dysfunction • Negative antinuclear antibody (ANA) and rheumatoid factor (RF) Exclusion Criteria: • Infections, malignancies, rheumatoid diseases. Diagnosis: • Diagnosis is made when there are 5 or more criteria which include atleast 2 major criteria.	Major: • Spiking fever ≥ 39°C • Arthralgia • Transient erythema • Pharyngitis • Polymorphonuclear cells (PMN) ≥ 80% • Glycosylated ferritin ≤ 20% Minor: • Maculopapular rash • Leukocytes ≥ 10,000/mm^3 Diagnosis: 4 or more major criteria are required [OR] 3 major criteria + 2 minor criteria are required	Requires all of the following: • Fever > 39° • Arthralgia or arthritis • Rheumatoid factor < 1:80 • Antinuclear antibody < 1:100 In addition to any 2 of the following: (MAJOR) • WBC count > 15,000 + ESR > 40 mm /1st h • Stills (evanescent) rash • Negative ANA and RF • Pleuritis or pericarditis • Carpal ankylosis • Hepatomegaly, splenomegaly, or lymphadenopathy Minor: • Arthritis • Prodromal sore throat • RES (reticuloendothelial system) involvement or abnormal LFTs • Serositis • Cervical or tarsal ankylosis Diagnosis: • Probable AOSD: 10 points with 12 weeks' observation • Definite AOSD: 10 points with 6 months' observation

excluded before diagnosing it as AOSD and must not be treated as a sepsis case.[8]

In AOSD patients frequently pulmonary manifestation is seen and hence AOSD can be complicated with pneumonia.[9] We present a similar case, the patient had persistent cough which was not releaved after adding codeine syrup, when pulmonology consult taken, the chest X ray revealed left sided lower zone opacity suggestive of pneumonia, culture was also positive for gram positive cocci in short chain, gram positive cocci in budding yeast cells with pseudohyphae and gram negative bacilli was also seen.

Viral syndrome (for example- rubella, cytomegalovirus, Epsteinbarr virus, mumps, coxsackievirus, adenovirus) can be excluded if the symptoms persist beyond 3 months.[2] The patient had a past history of colitis which was caused due to cytomegalovirus, this was excluded in the diagnosis as the patient had AOSD symptoms (fever, multiple joint pains, pyoderma) from a long period of time.

Both colitis (due to cytomegalovirus) and pneumonia was excluded and the diagnosis of AOSD was confirmed according to the Yamaguchi criteria.

Most frequently used diagnostic criteria for AOSD are Yamaguchi criteria (most sensitive- 93.5%) and Fautrel's criteria (80.6% sensitive) (shown in Table 1) there are other criteria for diagnosis of AOSD such as Cush's criteria (Table 1) and Calare's criteria.[6]

In our case the patients presented with complaints of fever, multiple joint pains (polyarthralgia), on evaluation the laboratory findings showed leukocytosis (WBC > 34,500) and neutrophilia (neutrophils >85.6%) which meets with the 3 major diagnostic criteria for AOSD (according to Yamaguchi criteria Table 8), the patient also had lymphadenopathy and abnormal liver function test (high SGOT levels- 51 IU/L, high ALP levels- 270 IU/L, low serum albumin- 1.2g/dl, high serum globulin level- 7.6g/dl, high gamma glutaryl transferase level- 107 U/L) (Table 2) which are 2 minor Yamaguchi criteria for AOSD.

The serum ferritin levels are much higher (threshold- five times the normal value, i.e. 1000µg/l) in AOSD, than any other autoimmune or inflammatory diseases.[13] In our case the patient's serum ferritin level was 1551.6 µg/l which is greater than 5 times the normal value (Table 2) (23-110 µg/l). Hyperferritinemia occurs in AOSD due to increased levels of IL-6 (involved in pathogenesis of AOSD), as IL-6 is responsible for liver synthesis and fast

release of ferritin.[6] Cytokines (such as IL-1beta, IL-18, IL-6, TNF-alpha) plays a major role in pathogenesis of AOSD.[7]

The glycosylated fraction of ferritin is more specific marker for the diagnosis of AOSD than the ferritin levels, glycosylated ferritin are formed by glycosylation which is a process by which glucose molecule are attached at the surface of the ferritin molecule by which they are protected from proteolysis enzymes.[2,14] In AOSD due to hyperferritinemia there is saturation of glycosylation which leads to drop in glycosylated ferritin levels and in addition there might be decreased clearance of non-glycosylated protein by histiocyte macrophage system.[2] The glycosylated ferritin levels remain low for many months even after AOSD remission, so they cannot be used to monitor disease activity or response to the treatment and low glycosylated ferritin levels can be seen in other conditions such as in other inflammatory disorder or in infectious disease.[2,14] Hence glycosylated ferritin are less sensitive (<43%), but are more specific (specificity- >93%) than the ferritin. So glycosylated ferritin is checked whenever it is available.[2] In our case the glycosylated ferritin levels were not checked.

Other laboratory findings used in diagnosis of stills disease includes inflammatory markers (such as high CRP and ESR), low glycosylated fraction of ferritin (more specific marker than ferritin itself), anemia, thrombocytosis, immune markers (such as high IL-6, IL-8, TNF- alpha).[2] In our case patient had high ESR (120mm/hr), high CRP (115) levels and the patient was anemic (low hemoglobin- 4.4 g/dl, low RBC- 2.02) (Table 2).

The drug of choice for the treatment of AOSD includes- NSAIDS, corticosteroids (such as prednisolone- as a first line treatment regardless of clinical presentation) and DMARDs. DMARDs are considered when there is failure of corticosteroid treatment or when there is corticosteroid dependency. The examples of DMARDS which showed greater efficacy in AOSD patient includes cyclosporine A, leflunomide, azathioprine, hydroxycholoroquine, D- penicillamine, methotrexate and tacrolimus. The first line steroid sparing treatment in AOSD patients include methotrexate (which has beneficial effect) and targeted biological therapies such as ANAKINRA (IL-1 antagonist), TOCILIZUMAB (IL- 6 antagonist) which can be used as an alternative. The biological therapies such as ANAKINRA (IL-1 antagonist), TOCILIZUMAB (IL- 6 antagonist) and TNF-alpha- such as infliximab, etanercept, adalimumab is actually reserved for refractory AOSD (which occurs when there is resistance to 1st line corticosteroid treatment and 2nd line DMARDs.[7]

Articular involvement is common and is one of the major criteria for the diagnosis in stills disease.[15] In our case the patient had multiple joint pains, joints were swollen and tender indicating stills disease. The patient was treated with corticosteroids, first methylprednisolone was added and was given for 3 days later it was discontinued and prednisolone was started, but the patient experienced aggravated pain so again methylprednisolone was added and then both were continued.

Corticosteroids have benefited about 60% of patients and have shown greater efficacy with regard to systemic symptoms than articular ones and hence it is considered as 1st line treatment for AOSD, regardless of the clinical presentation.[7]

Other medication prescribed were INJ. Ceftriaxone (empirical treatment- for infection) TAB. Alprazolam (to reduce stress and anxiety), powder ALBUMEN RRT (for hypoalbuminemia), CAP. FEFOL-Z (elemental iron+ elemental zinc+ folic acid- for anemia), anovate ointment (beclomethasone+ lidocaine+ phenylephrine) and fibril powder was added to treat hemorrhoids (type 1, diminutive rectal polyp observed in sigmoidoscopy), syrup potassium chloride (to aggressively manage hypokalemia- potassium levels was- 2.6 mEq/L), codeine syrup (for cough) and many antibiotics (such as TAB. Doxycycline, INJ. Piperacillin and tazobactam, INJ. VANCOMYCIN) were added to treat pneumonia.

In AOSD patients due to hyperferritinemia, the iron is sequestered in ferritin contained inside the macrophages, which leads to decrease in serum iron levels. This is an artificial iron deficiency, which in reality is due to scarcity in serum iron levels as all the iron is being stored in the ferritin and there is defect in its release. One study has suggested that when a low dose intravenous iron supplementation is given in AOSD patients the IV iron could bypass macrophage trapping and become directly available for erythropoiesis and hence could be effective in treating anemia in AOSD patients.[14] In our case the patient had anemia (low hemoglobin- 4.4 g/dl, low RBC- 2.02) which was treated by giving FEFOL-Z (which contains elemental iron+ elemental zinc+ folic acid).

Recent studies showed that monocytes - macrophage activation is central for the pathogenesis of AOSD. In active AOSD patients, activated monocytes macrophages can produce large amounts of cytokines such as TNF-α, IL-6, IL-1 and IL-18, IL-4, IL-2; proinflammatory cytokines such as IL-1beta; IFN-gamma and chemokines such as CXCL8, CX3CL1 and so on.[6,16] The IL-6 is

Table 2: Laboratory Investigation.

Parameter	Normal Value	Observed Value	Remarks
Hemoglobin	13-17 g/dl	4.4 g/dl 5.3 g/dl 5.7 g/dl 6.6 g/dl 5.9 g/dl 7.0 g/dl	The patient was anemic due to iron deficiency anemia
Red Blood Cell	4.5-5.5 million cells per microliter	2.02 2.41 2.54 2.60 3.04	low levels of RBC anemia due to iron deficiency (resulting due to stills disease)
Packed Cell Volume	40-50%	14 % 17 % 18.3 % 21.1 % 19.2 % 23.1 %	Decreased packed cell volume due to anemia
Mean Cell Volume	83-101 femtoliter/ red cell	69.1 fL 70.6 fL 72.0 fL 74.0 fL 76.0 fL	Low mean cell volume (iron deficiency anemia)
Mean Corpuscular Hemoglobin	27-32 picograms/cell	21.5 pg/c 22.1 pg/c 22.3 pg/c 22.8 pg/c 23.0 pg/c	Low MCH due to anemia
Mean Corpuscular Hemoglobin Concentration	31.5-34.5 g/dl	31.1 g/dl 31.3 g/dl 31.0 g/dl 30.8 g/dl 30.3 g/dl	Low MCHC due to anemia
RBC Distribution WIDTH	11.6-14.0%	26.6 % 23.9 % 23.6 % 22.6 % 20.5 %	High RBC distribution width due to stills disease
Total Leukocyte Count	4.5-11.0 × 10^9/L	34,500 26,400 27,500 53,400	Leukocytosis- it occurs in AOSD patients because it involves inflammatory pathogenesis
Neutrophils	40-70%	85.6 % 93.8 % 96.1 %	neutrophilia- it occurs in AOSD patients because it involves inflammatory pathogenesis
Lymphocytes	20-40%	10.5 % 4.4 % 1.9 %	Lymphocytopenia- due to inflammatory pathogenesis of AOSD
Serum Ferritin	22-322 ng/ml	1551.6 ng/ml	Hyperferritinemia
Serum Creatinine	0.6-1.2 mg/dl	1.7 mg/dl	High creatinine level indicating kidney damage
GFR (glomerular filtration rate)	>60%	43.42 % 59.17 %	Low GFR indicating kidney damage
		64.9 %	Maintained to normal with furosemide
LFT			
Total Protein	6.4-8.2 g/dl	8.8 g/dl 8.2 g/dl 7.2 g/dl	Normal

Serum Albumin	3.4-5.0 g/dl	1.2 g/dl 1.2 g/dl 1.2 g/dl 1.4 g/dl 1.3 g/dl	Hypoalbuminemia Due to liver dysfunction associated with stills disease.
Serum Globulin	2-3.5 g/dl	7.6 g/dl 7.0 g/dl 7.0 g/dl 5.2 g/dl	High globulin levels due to inflammatory pathogenesis of stills disease.
A/G Ratio (albumin/globulin ratio)	1.0-2.1	0.16 0.17 0.17	Low A/G ratio- indicating inflammatory and immune disorder
SGPT (serum glutamic pyruvic transaminase)	16-63 U/L	10 U/L 9 U/L 38 U/L	Low levels are usually normal the levels are increasing due to liver damage.
SGOT (serum glutamic oxaloacetic transaminase)	15-37 U/L	51 U/L	High SGOT due to liver damage associated with AOSD
ALP (alkaline phosphatase)	46-116 IU/L	270 IU/L 193 IU/L 201 IU/L 380 IU/L	High ALP levels due to liver damage associated with AOSD
GGT (gamma glutaryl transferase)	5-55 Units/ liter	107 U/L 271 U/L 297 U/L	High GGT levels due to liver damage associated with AOSD
CRP (C- Reactive protein)	0-6 mg/L	115 mg/L	High CRP levels due to inflammatory pathogenesis of AOSD
ESR (erythrocyte sedimentation rate)	0-10mm/ hr	120 mm/ hr 119 mm/hr 128 mm/hr 83 mm/hr	High ESR value due to inflammatory pathogenesis of AOSD
Potassium	3.5-5.0 mEq/L	2.6 mEq/L 2.2 mEq/L 2.6 mEq/L 3.1 mEq/L	HYPOKALEMIA – due to administration of loop diuretic (FUROSEMIDE)
Calcium	8.5-10.1 mg/dl	7.7 mg/dl	HYPOCALCAEMIA- due to kidney damage
Chloride	95-106 mEq/L	107 mEq/L	NORMAL
BUN	7-20 mg/dl	26 mg/dl 40 mg/dl	High levels of BUN indicating kidney damage
Uric Acid	3.4-7 mg/dl	7.5 mg/dl	High uric acid level indicating kidney damage.
Urine Routine			
Proteins	0-20 mg/dl	Traces	NORMAL
Epithelial Cells	2-3	1-2	NORMAL
PUS Cells	0-2	2-4	Inflammation and infection

associated with symptoms including fever, rash, elevated inflammatory markers, leukocyte hyperplasia and liver dysfunction in patients with AOSD. In recent years, it has been reported that many groups were successfully treated AOSD with biologic therapies targeting at cytokines.[16]

Tocilizumab which is an IL-6 receptor antagonists is found to alleviate the clinical manifestations of refractory AOSD rapidly and efficiently and also found in rapidly reducing the glucocorticoids dosage during the treatment of refractory AOSD.[16] In our case the tocilizumab was added on day 5, as the patient was not responding to corticosteroid treatment, despite of adding two corticosteroids (methylprednisolone and prednisolone) he had lot of pain in leg. Combination of tocilizumab and glucocorticoids can partially reduce symptoms such as fever and rash, reduce inflammatory markers and hence contribute to withdrawal of glucocorticoids.[16] TOCILIZUMAB is used as an alternative to methotrexate in steroid sparing treatment.[7]

Table 3: RIFLE criteria and AKIN classification for diagnosis of AKI.[19]

GFR Criteria		Urine Ouput Criteria	
R - RISK	⬆ Serum creatinine- 1.5 times (OR) GFR ⬇ > 25%	Urine output < 0.5ml/kg/hr X 6hrs	
I – INJURY	⬆ Serum creatinine- 2times (OR) GFR⬇ > 50%	Urine output < 0.5ml/kg/hr X 12hrs	HIGH SENSITIVITY
F – FAILURE	⬆ Serum creatinine- 3times (OR) GFR ⬇ > 75% (OR) Serum creative ≥ 4mg/dl Acute rise ≥ 0.5mg/dl	OLIGURIA Urine output < 0.3ml/kg/hr X 24hr OR ANURINA X 12 hrs	HIGH SPECIFICITY
L- Loss of Kidney Function	Persistent acute renal failure (ARF) = complete loss Of kidney function > 4 weeks		
E- ESRD (end stage renal disease	END STAGE RENAL DISEASE (> 3 months)		

Table 4: Stages of acute kidney injury (AKI).[19]

Stage	Serum Creatinine (SCr)	Urine Output (UO)
1	SCr: X 1.5-1.9 times baseline serum creatinine. [OR] Increase in serum creatinine level ≥ 0.3mg/dl (≥ 26.5µmol/l)	UO < 0.5ml/Kg/hr for 6-12 hr
2	SCr: X 2.0-2.9 times baseline serum creatinine.	UO < 0.5ml/kg/hr for ≥ 12 hr
3	SCr: X 3.0 times baseline serum creatinine. [OR] Increase in serum creatinine ≥ 4.0mg/dl (≥ 353.6µmol/l) [OR] Renal replacement therapy initiation [OR] In patients with age less then l8years and eGFR decreased to less then 35ml/min per 1.73 m².	UO < 0.3ml/Kg/hr for ≥ 24 hr Or ANURIA: for ≥ 12 hr

The patient was continuously hypotensive and was not maintaining blood pressure, in hypotensive patient there is less blood supply to the kidney which may lead to acute kidney injury which can be fatal and it is very difficult to manage both AKI (acute kidney injury) and hypotension.[17,18] In our case the patient developed acute kidney injury due to hypotension which was confirmed by evaluating laboratory parameters which showed a high blood urea nitrogen (26mg/dl), a high uric acid levels (7.5mg/dl), a high serum creatinine levels (1.7mg/dl) and glomerular filtration rate was also reduced to < 50% (43.42%) and patient also developed ascites (INJ. FUROSEMIDE was given to reduce ascites and also pleural effusion). According to RIFLE criteria (Table 3) AKI was confirmed as when compared it shows decrease in GFR less than 50% (i.e. 43.42%).

According to the above staging of AKI (Table 4), in our case the patient had stage 1 AKI with serum creatinine 1.7mg/dl and a glomerular filtration rate (GFR) 43.42% (<50%).

The patient developed severe hypotension which led to inadequate blood supply to various organ and the patient had multiple organ dysfunction. He was shifted to MICU and was intubated, put on ventilator support, there he continued to worsen, he developed cardiac arrest (refractory shock which is lethal manifestation of cardiovascular failure, which occurs when a high dose of vasopressor fails to show adequate hemodynamic response), CPR (cardio pulmonary resuscitation) was initiated as per ACLS protocol (advanced cardiac life support) but could not be revived and death was declared.

It is always not possible to establish the precise, final cause of death as the patient may finally present a multiorgan failure which can be difficult to differentiate from a septic state.[20]

In our case the patient developed refractory shock with multiorgan dysfunction which led to death.

One study showed that a higher systemic score (a cut- off at 7.0 of the systemic score) and the presence of AOSD

– related complications (such as macrophage activation syndrome, disseminated intravascular coagulopathy, thrombotic thrombocytopenic purport, respiratory distress syndrome, thrombotic microangiopathy, pulmonary arterial hypertension, myocarditis, tamponade, diffuse alveolar hemorrhage, constrictive pericarditis, endocarditis, shock, multiorgan failure, fulminant hepatitis and amyloidosis) at the time of diagnosis were significantly associated with mortality and shows a strong prognostic impact in identifying patients at risk of AOSD related death.[21]

Table 5: ELAR/ ACR approved classification criteria for MAS.[22]

Ferritin >684 ng/ml
And any 2 of the following:
Platelet count ≤ 181 ×10⁹/liter
Aspartate aminotransferase > 48 units / liter
Triglycerides >156 mg/dl
Fibrinogen ≤ 360 mg/dl

Table 6: Assessment of MAS in our patient.

Laboratory parameters	Values
Ferritin	1551.6 ng/ml
Platelet count	1.3 lakhs
Aspartate aminotransferase (SGOT)	51 units/ liter
Triglycerides	NA
Fibrinogen	NA

Macrophage activation syndrome (MAS) is a life-threatening complication of AOSD which is characterized by an overactive inflammatory reaction due to an uncontrolled and dysfunctional immune response resulting in massive hypersecretion of proinflammatory cytokines due to continual activation and expansion of T- lymphocytes and macrophages.[22]

ELAR (European league against rheumatism- executive committee)/ ACR (American college of rheumatology-board of director) approved classification criteria for MAS shown in Table 5.[22]

According to the above ELAR/ ACR classification criteria for MAS our patient had MAS (Table 6) at the time of diagnosis indicating a poor prognosis and a high risk of mortality in our patient.

There are several scoring systems for AOSD according to various diagnostic criteria (Table 7):

Table 7: Different Scores for Adult Onset Stills Disease (AOSD) and its Comparison.[23]

Manifestation	Goldman	Cush	Culabro	Reginato	Kahn	Yamaguchi	Fautrel	Crsispin
Fever	++	++	++	++	++	++	++	++
Serological Factors:								
Leukocytosis	++	+	+	++	++	++	++	18
Liver Dysfunction				+		++		
Negative ANA	++	++	++		++	+		
Negative RF	++	++	++			+		
Ferritin							++	
Organ Manifestation:								
Rash	+	+	++	++	++	++	++	5
Arthralgia or Arthritis	++	++	++	++	++	++	++	10
Sore Throat or Pharyngitis				+	+	+	++	7
Pleuritis/ Pericarditis	+	+		+	+			
Splenomegaly	+	+	+	+				5
Lymphadenopathy		+	+	+		+		
Hepatomegaly		+		+				
Organ Involvement				+				
Myalgia			++		+			
Similar Episode in Childhood					++			
Positive Diagnosis	5 major, > 1 minor	3 major, 2 minor	4 major, 2 minor	4 majo, or fever+ arthritis + 1 major+ 1 minor	4 major or 3 major+ 2 minor	5 positive criteria, 2 major	4 major or 3 major+ 2 minor	≥30 points

++: major criteria, +: minor criteria, ANA-antinuclear antibody, RF- rheumatoid factor

Table 8: Scoring in our patient according to Yamaguchi criteria.[23]

Manifestations	Positive Diagnosis
Fever	++
Serological Factors:	
Leukocytosis	++
Liver Dysfunction	++
Negative ANA	
Negative RF	
Ferritin	
Organ Manifestation:	
Rash	++
Arthralgia	++
Sore Throat or Pharyngitis	
Pleuritis/ Pericarditis	
Splenomegaly	
Lymphadenopathy	+
Hepatomegaly	
Organ Involvement	
Myalgia	
Similar Episode in Childhood	
Positive Diagnosis	6 positive criteria = 5 major criteria + 1 minor criteria

RF- rheumatoid factor, ANA- antinuclear antibody

Table 9: Assessment of clinical manifestation and scoring in AOSD patient according to Pouchet *et al.*[21]

Clinical Manifestation	Score Proposed by Pouchet *et al.*[22]	Score in Our Patient
Fever	1	1
Typical Rash	1	1
Pleuritis	1	1
Pneumonia	1	1
Pericarditis	1	
Hepatomegaly or Abnormal Liver Function Tests	1	1
Splenomegaly	1	1
Lymphadenopathy	1	1
Leukocytosis > 15,000/mm^3	1	1
Sore Throat	1	
Myalgia	1	
Abdominal Pain	1	
Total Score	12	8

The systemic score which was proposed by Pouchet *et al.* for AOSD assigns 1 point to each of the 12 manifestations (Table 9) .[21]

The systemic score in our patient was found to be 8 (Table 9), therefore a systemic score of greater than 7 indicates a high risk of mortality.

Early detection of systemic score and understanding the clinical presentation of AOSD could be helpful in deciding the therapy between glucocorticoids alone or in combination with biological drugs or immunosuppressive drugs as first line treatment. Early detection and early initiation of therapy including immunosuppressive or biological drugs along with glucocorticoids may be helpful in avoiding the risk of death to the patient and may provide comfort and improve patient`s condition.[21,24]

Here we present a case in which the patient was exhibiting clinical presentations of AOSD from a long period of time but was not evaluated, when the condition got worsened the disease was ruled out and started with glucocorticoids but the patient did not respond to the therapy despite of adding 2 corticosteroids and also the TOCILIZUMAB was added on the 5th day as the patient was not improving with corticosteroid therapy. Even though TOCILIZUMAB was added it was too late as the patient developed complications associated with AOSD such as, the patient complicated with pneumonia and hypotension, contributing to AKI and refractory shock. Development of refractory shock and multiorgan dysfunction led to death.

CONCLUSION

Early detection of systemic score, assessing and understanding the clinical manifestation and evaluation of life-threatening complication of AOSD will help in predicting the risk of mortality and also help in planning an appropriate treatment and early initiation of biological agents and immunosuppressive drugs which may be helpful in preventing the negative influence on survival in patient with a systemic score greater than 7 and the presence of life threatening complication during the diagnosis.

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CONFLICT OF INTEREST

We declare that this case report does not have any conflict of interest.

ABBREVIATIONS

AOSD: Adult onset stills disease; **AKI:** acute kidney injury; **ARF:** acute renal failure; **AKIN:** Acute kidney injury network; **CRP:** C- reactive protein; **ESR:** Erythrocyte sedimentation rate, **IL:** Interleukin; **TNF:** Tumor necrosis factor; **GLK:** germinal center kinase- like kinase; **CMV:** Cytomegalovirus; **HSV 1:** Herpes simplex virus 1; **PET:** Positron emission tomography; **SGOT:** Serum glutamate oxaloacetate transaminase; **SGPT:** Serum glutamate pyruvate transaminase; **ALP:** alkaline phosphatase; **GGT:** Gamma glutaryl transferase; **HBsAg:** Hepatitis B surface antigen; **HIV:** Human immune deficiency virus; **INJ:** injection; **TAB:** tablet; **PLE:** protein loosing enteropathy; **AFB:** Acid fast bacilli; **KOH:** Potassium hydroxide; **BUN:** blood urea nitrogen; **CT:** computed tomography; **MICU:** Medical intensive care unit; **CPR:** Cardio pulmonary resuscitation; **ACLS:** Advanced cardiac life support; **PMN:** Polymorphnuclear cells; **WBC:** white blood cells; **ANA:** antinuclear antibody; **RF:** rheumatoid factor; **RBC:** rood blood cell; **GFR:** Glomerular filtration rate; **A/G RATIO:** albumin/globulin ration; **NSAIDs:** Non-steroidal anti-inflammatory drugs; **DMARD:** Disease- modifying antirheumatic drug; **MAS:** macrophage activation syndrome; **ELAR:** European league against rheumatism; **ACR:** American college of rheumatology.

SUMMARY

We present a case report of 47 years male patient who was presented with the signs and symptoms of AOSD (Adult Onset Stills Disease) including fever, polyarthralgia, lymphadenopathy, hepatospleenomegaly and also cough, pyoderma, anemia. The laboratory abnormalities including hyperferritinemia, abnormal liver function test which is the characteristics of AOSD was also seen. He was complicated with pneumonia as in AOSD patient`s pulmonary manifestations are frequently seen. The patient had a past history of colitis and herpes oral ulcer which was excluded and the diagnosis of AOSD was confirmed based on Yamaguchi criteria which is the most frequently used diagnostic criteria. The patient was started with prednisolone which is one of the drug of choice for AOSD. The patient was inadequately managed due to late admission and delayed diagnosis. According to one study a higher systemic score (a cut of at 7.0 of the systemic score) and presence of AOSD related complication at the time of diagnosis were significantly associated with mortality and shows a strong prognostic impact in identifying patient at risk of AOSD related death. In our patient the systemic score was 8 and also met with ELAR/ ACR classification criteria for MAS. Early diagnosis, detection of systemic score and detection of MAS will help to decide the treatment (including early initiation of TOCILIZUMAB) and may help in preventing the risk of death by improving quality of life. In our patient the tocilizumab was at later date, despite of adding 2 corticosteroids and TOCILIZUMAB the patient did not improve. The patient developed complication associated with AOSD such as hypotension contributing to AKI and refractory shock. Development of refractory shock and multiorgan dysfunction led to death, although CPR was initiated the patient was unable to recover and the death was declared.

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