Asian Journal of Medicine and Health

10(4): 1-8, 2018; Article no.AJMAH.39960
ISSN: 2456-8414

Adult-onset Stills Disease: Advocating for New Markers to Overcome the Diagnostic Challenge

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Authors' contributions

This work was carried out in collaboration between both authors. Author Arun Agarwal was the primary consultant in this case. He contributed to the conception, design and analysis of the case study. He wrote the first draft of the manuscript and approved the final work to be published. Author Aakanksha Agarwal managed the tabulation work, literature searches and final grammar correction of the manuscript. Both authors read and approved the final manuscript.

Article Information

DOI: 10.9734/AJMAH/2018/39960
Editor(s):
(1) Nicolas Padilla-Raygoza, Department of Nursing and Obstetrics, Division of Health Sciences and Engineering, Campus Celaya Salvatierra, Mexico.
Reviewers:
(1) Smita Goorah, University of Mauritius, Mauritius.
(2) Chia-Li Yu, National Taiwan University Hospital, Taiwan.
(3) Shamala Moodley, Mangosuthu University of Technology, South Africa.
Complete Peer review History: http://www.sciencedomain.org/review-history/23530

Case Study

Received 1st January 2018
Accepted 4th March 2018
Published 8th March 2018

ABSTRACT

Adult-onset Still's disease (AOSD), is the adult form of systemic juvenile rheumatoid arthritis (juvenile Still's disease). AOSD is a known cause of fever of unknown origin (FUO). It is characterised by a triad of symptoms: spiking fever (>39°C), salmon-coloured rash and arthritis/arthralgia. However, rash is not easily appreciated in wheatish or dark colour patients as are seen in tropical countries. First described in 1971, it is a rare, difficult to diagnose, idiopathic, autoinflammatory, multisystemic disorder characterised by two subsets according to clinical and laboratory features: systemic or articular. Timely diagnosis and treatment of the disease can prevent complications and lead to a favourable prognosis. We present and discuss a young female patient who presented as FUO and was diagnosed timely as AOSD and treated with corticosteroids and had a desirable outcome and prognosis. We will also discuss the role of some potential biomarkers including procalcitonin and ferritin. Can these markers, along with other biomarkers, like IL 18, s100 proteins and sCD163 be included in diagnostic criteria of AOSD need further research, study and meta-analysis?

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Keywords: Adult-onset stills disease, ferritin, yamaguchi criteria, and fautrel criteria, procalcitonin.

SYNONYMS

Adult Still's disease; AOSD; Wissler-Fanconi syndrome.

1. INTRODUCTION

AOSD has been categorized as a multigenic (or complex) auto inflammatory disorder and put it at the crossroads of autoinflammatory and autoimmune diseases [1]. It is characterised by the classic triad of persistent high spiking fever, arthralgia, and salmon coloured skin rash. It is said that rash is seen in 60-80% of cases, but in tropical countries where skin colour is wheatish to dark, it is not commonly seen. An absence of characteristic serological biomarkers makes diagnosis difficult. In fact, it is a diagnosis of exclusion and a definitive diagnosis is usually made based on the Yamaguchi [2] or Fautrel [3] criteria only after excluding infectious, malignant, and other connective tissue diseases.

According to the clinical presentation of the disease at diagnosis, two distinct AOSD phenotype has been seen clinically may be distinguished:

i) an acute systemic febrile illness, with mono or polycyclic pattern, highly symptomatic, may evolve into a multiorgan dysfunction or failure and can even be fatal if not timely diagnosed and treated and;
ii) A more indolent one with arthritis less of systemic symptomatology, finally evolving into a chronic articular pattern.

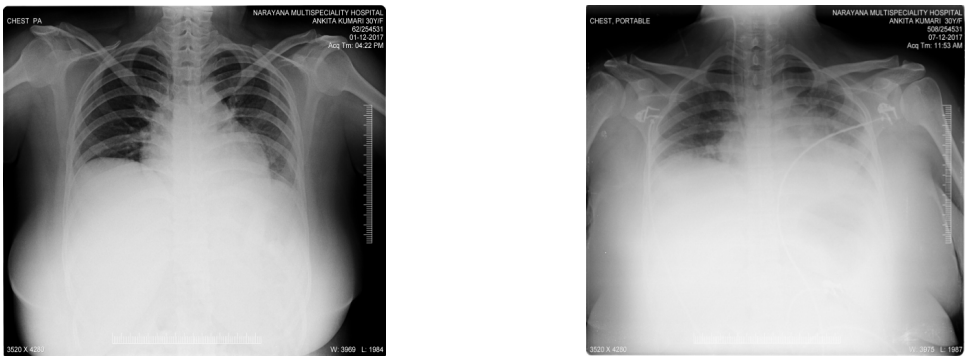
Timely diagnosis and treatment of the disease with corticosteroids followed by maintenance therapy with disease modifying anti-rheumatic drugs (DMARDs) or biologic drugs such as tumour necrosis factor- (TNF-) alpha agents or interleukin (IL-1) antagonists can prevent complications and lead to a favourable prognosis. Steroid and DMARDs refractory cases with the systemic pattern may be benefited by Anakinra, active arthritis with systemic symptoms by tocilizumab and chronic polyarticular refractory AOSD by TNFα-blockers.

2. CASE PRESENTATION

Ms AK, age 30 years, had complaints of high grade fever off and on for 2 months, sore throat and severe pain over left shoulder, lower back and chest so much that she starts crying with difficulty in breathing, and diffuse arthralgia for 15-20 days. She took consult locally in a village where she was evaluated with an electrocardiogram (ECG), x ray chest (XRC) and routine complete blood counts. Her ECG and XRC were normal. In view of high total leukocyte counts ($36x10^3$/cmm.) the patient was treated with antibiotics and NSAID. However, she did not respond and was referred for further management. She attended triage on 01.12.2017, and was advised admission. Her CXR was normal (Fig. 1A). The patient refused admission and was advised non-steroidal anti-inflammatory drugs for body aches. She again attended triage in the evening of the 02.12.2017 with the same complaints and was admitted in a female general ward for further diagnostic evaluation. On 03.12.2017, in morning she had severe pains, breathlessness with fall in peripheral capillary oxygen saturation (SpO_2) and was shifted to MICU.

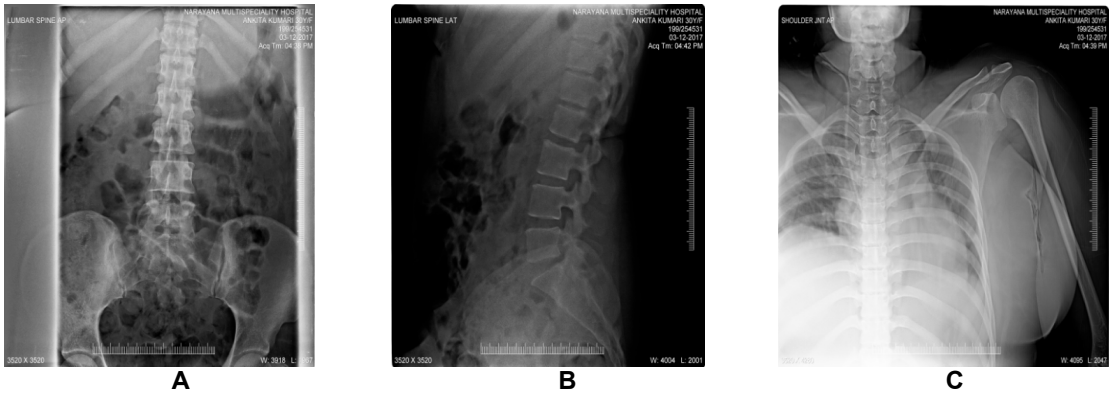
On examination, she had a dark complexion, weighed 85 kg (BMI 34.3 kg/m2), her pulse was regular 105 per minute, blood pressure 114/76 mm Hg, respiratory rate 27 per minute, peripheral capillary oxygen saturation (SpO2) 93%, and temperature 99.6°F. She looked toxic, had bilateral decreased basal air entry, mild hepatosplenomegaly, and mild bilateral pedal edema. Her investigations are in Table 1. XR chest, spine, left shoulder and contrast enhanced computerized tomography (CECT) are in figure 1, 2 and 3 respectively. Investigations revealed mild anemia with leukocytosis, moderate transaminitis, severe hypoalbuminemia, mediastinal lymphadenopathy and Polyserositis (bilateral pleural effusion, and pericardial effusion). Electrocardiogram showed sinus tachycardia. She had daily fever spikes of up to 101°F, paroxysmal severe chest and back pains with associated tachycardia and tachypnea. There was no deep venous thrombosis in legs clinically. Though she had moderate transaminitis with cholestasis, there was no evidence of liver failure. She was initially treated with meropenem, amikacin, tramadol, diclofenac sodium, Pantoprazole and other supportive treatment, awaiting body fluid cultures (Urine and blood). Blood sample for EBV DNA was also negative. Mild pleural fluid could not be aspirated

for biochemical and other analysis. Her laboratory tests such as body fluid cultures, mantoux test, widal test, scrub typhus antibodies, malaria parasite, immunological profile, (antinuclear antibody (ANA), anti neutrophil cytoplasmic antibody (ANCA), complement C3 and C4),extractable nuclear antigens (ENA) panel (U1-nRNP/Sm,Sm,SS-A,Ro-52,SS-B/La,Scl-70,PM-Scl,Jo-1,CENP-B,PCNA,ds-DNA,Nucleosomes,Histones,Rib-P Protein and AMA-M2) were neative. In addition a, polymerase chain reaction (PCR) based detection of bacteria/fungus/viruses from EDTA blood sample and procalcitonin were also negative or unremarkable. The erythrocyte sedimentation rate (ESR) and C reactive protein (CRP) were raised and she had severe hypoalbuminemia. Looking to our past experience when we lost two patients due to late diagnosis of AOSD and having received antibiotics for many days locally, persistent fever, severe myalgias and arthralgias, we suspected AOSD and gave her a pulse of intravenous methylprednisolone 250 mg on 05.12.17 pending reports. On 06.12.17 her reports did not show any evidence of infection, and with raised total leukocyte count, raised inflammatory markers and increasing toxemia possibility of an inflammatory disorders was evaluated. Her serum ferritin was high. We reviewed her laboratory and clinical parameters with a possible diagnosis of adult onset stills disease (AOSD). She fulfilled three major and 4 minor yamaguchi criteria (3 major and 1 minor fautrel etal criteria) and was labeled as AOSD – predominantly systemic inflammation on 06.12.2017. Rash, if any could not be appreciated as she was dark in complexion. Intravenous 250 mg methyl prednisolone was continued for 3 days and later oral prednisolone in doses of 1mg/kg body weight was started. She responded dramatically to the treatment and became afebrile. Her ESR and counts decreased to 50 mm 1 hour and 14100/cmm on 19.12.2017. Her CRP was negative on 09.12.2017. She is presently asymptomatic, under regular follow-up and is on tapering doses of oral steroids (prednisolone) along with hydroxychloroquine and methotrexate.



A B

Fig. 1. CXR dated 01.12.2017 which is normal (A), 07.12.2017 (B) showing bilateral blunt costo and cardio phrenic angles suggestive of pleural effusion



A B C

Fig. 2. X rays dated 03.12.2017. Normal lumbar spine AP view (A), Normal lumbar spine lateral view (B), Normal left shoulder joint AP view(C)

Table 1. Hematological, biochemistry, cultures, and imaging results of case presented

	Normal value	02.12.2017	04.12.2017	07.12.2017	19.12.2017	19.01.2018
Hemoglobin	13-17 gm/dl	10.5	10.1	8.8	11.4	
TLC	4.0-10 X10^3/cmm	33.4	21	12.7	14.1	
DLC	%	P91 L6		P85.5L11.7		
Platelet count	150-400 X103/cmm	232	228	243	255	
PBF		Normal				
ABG		pCO2 31.6 mm Hg,pO2 161.9 mm Hg,pH 7.447,sO_2 99%. HCO3 std 22.7 mmol/L, BE ecf -2.7 mmol/L.				
Serum Creatinine	0.8-1.3 mg/dl	0.84				
BUN	7-18 mg/dl					
Gamma Glutamyl transferase(GGT)	6-23 U/L	123.8	67.9		66.5	
Serum Alkaline phosphatase	82-169 U/L	207.7		138.3	90.5	
Serum total bilirubin	0-1.3 mg/dl	0.49		0.22	0.31	
Serum Total Proteins	6.4-8.6 gm/dl	6.35		6.35	8.29	
Serum Albumin	3.8 5.6 gm/dl	2.21		2.21	3.68	
SGOT(AST)	15–37 U/L	129.9		111.8	25.7	
SGPT(ALT)	30-65 U/L	317.3		233.5	43.5	
PT-INR	< 1.2 ratio	1.09				
Procalcitonin	< 0.5 ng/ml	<0.5				
CPK total	< 190 u/l	<10				
CARDIAC MARKERS						
CK MB	0-4.3 ng/ml	<1				
TNI	0-0.02 ng/ml	<0.01				
BNP	0-100 pg/ml	<315				
ESR	0-15 mm 1 hour	130	140	95	70	50
CRP	0-5 mg/dl	15	26.5	3.9		
Serum Ferritin	10-154 ng/ml	863.4				
ANA(ELISA)	0.0-0.99 Index value	0.79				
ANCA (IFA)	Negative	P and c both negative				
RA factor	<12 IU/ml	<10.40				
Serology						
HIV,HBsAg,anti HCV antibody		Not detected				

Dengue IgM/IgG antibodies	Not detected
Body fluid Cultures (Urine,blood,ET,etc)	sterile
Electrocardiogram (ECG)	TWNL
USG	Mild hepatosplenomegaly,GB calculus, minimal left pleural effusion
ECHO	Mild MR, mild TR, mild to moderate effusion(thickness 8-14 mm)
CT Chest and Abdomen	Multiple mediastinal Lymph nodes-prevascular and perihilar ,largest 18x10 mm,b/l mild to moderate pleural effusion, mild pericardial effusion, subtle ground glass haze in bilateral perihilar regions

TLC: total leukocyte count; DLC: differential leukocyte count; PBF: peripheral blood film; ABG: arterial blood gas; BUN: blood urea nitrogen; BE: base excess; ecf: extra cellular fluid; SGOT: serum glutamic-oxaloacetic transaminase; SGPT: serum glutamic pyruvic transaminase; PT: prothrombin time; RA factor: rheumatoid factor; LDH: lactate dehydrogenase; HIV: human immunodeficiency virus; HBsAG: Hepatitis B surface antigen; HCV: Hepatitis C virus; Igm/IgG: immunoglobulin M/G; USG: ultrasonography; ECHO: echocardiogram; CT: computerized tomography

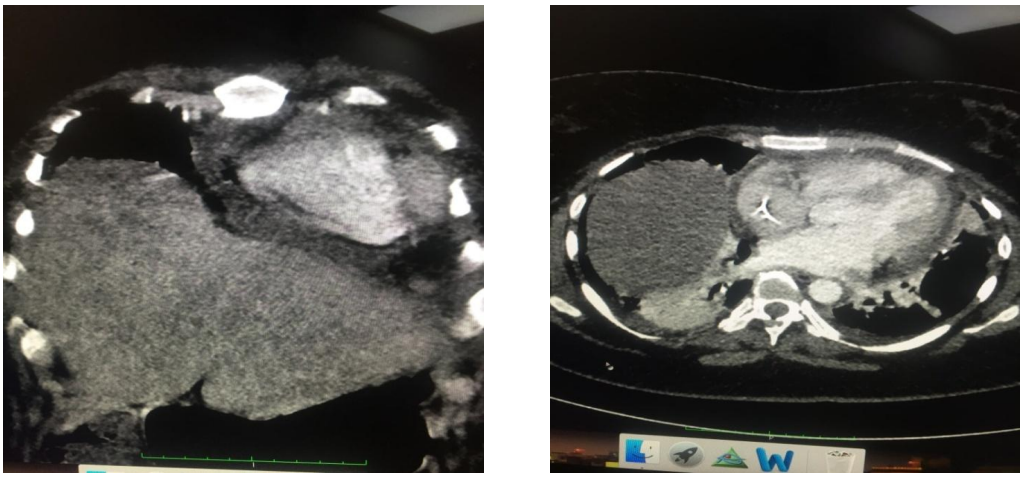


Fig. 3. Axial and coronal view of CECT chest dated 06.12.2017. Bilateral pleural effusions and pericardial effusion along-with underlying atelectasis is seen

Table 2. Yamaguchi criteria for the diagnosis of adult onset still's disease [2]

Major criteria	Fever 39°C lasting ≥ 1 week
	Arthralgia or arthritis lasting ≥ 2 weeks
	Typical nonpruritic salmon-colored rash
	Leukocytosis ≥ 10,000/mm^3 with granulocytes 80%
Minor criteria	Sore throat
	Lymphadenopathy
	Splenomegaly
	Abnormal liver function tests
	Negative tests for antinuclear antibody and rheumatoid factor
Exclusion criteria	Infection
	Malignancy
	Other rheumatic disease (vasculitis)
Criteria for diagnosis of AOSD	≥ 5 criteria are present with ≥ 2 being major criteria and no exclusion criteria.
Sensitivity and specificity	Sensitivity 96.2% and specificity 92.1%

3. DISCUSSION

Adult onset still's disease is a rare systemic inflammatory disease which is under reported and under diagnosed. It may even present as FUO. It was first described by Bywaters in 1971 [4]. Its estimated prevalence is 1.5 cases per 10^5-10^6 people. Cases have been reported from all over the world and has a bimodal age distribution with 2 peaks, the first peak affecting people within 15–25 years of age and the second peak affecting people within 36–46 years of age [5,6]. It usually affects young adults but can also affect elderly people [6,7]. The disease affects predominantly females as compared to males [8]. They represent up to 70% and 50% cases in rheumatologic and internal medicine case series respectively. The authors have reported two fatal cases which were also young adult females [9].

The exact pathogenesis of AOSD is unknown. It is said that a genetic background would confer susceptibility to the development of auto inflammatory reactions to environmental triggers. It is proposed that infection can trigger interplay between host genetic factors, autoimmunity mechanisms, and pathogenic antigens, leading ultimately to the disease pathogenesis [1]. Neutrophil and macrophage activation is said to be a hallmark of AOSD. Serum levels of tumor necrosis factor- (TNF-) alpha, IL-1, IL-6, IL-18, Interferon gamma IFN-γ, IL-8, and Soluble interleukin-2 receptor SIL-2R have been found to be elevated in patients with active AOSD [10].

Table 3. Fautrel et al. criteria for the diagnosis of AOSD [3]

Major criteria	Spiking fever ≥ 39°C (102.2°F) Arthralgia Transient erythema Pharyngitis Polymorphonuclear count ≥ 80% Glycosylated ferritin ≤ 20%
Minor criteria	Maculopapular rash Leukocytes >10,000/mm^3
Criteria for Diagnosis of AOSD	4 major criteria or 3 major + 2 minor criteria
Sensitivity and specificity	Sensitivity 80.6% and specificity 98.5%

Clinically, the most classic manifestations of AOSD are fever (60-100%), macular or maculopapular evanescent salmon pink skin rash (60-80%), sore throat (70%), and arthralgia (70-100%) with fever and arthralgia being the most common among them. Other symptoms reported during AOSD are myalgias (45%),enlargement of the lymph nodes (50%), splenomegaly (40%), hepatomegaly (30%), transaminitis (70%), hypoalbuminemia (76%), serositis-pleuritis (40%)/pericarditis (30%), abdominal pain (30%), pneumonitis (20%) and weight loss (27%) [1,9]. The monocyclic pattern, polycyclic, and chronic patterns are seen in 29, 22, and 33 patients, respectively [11]. Our patient had fever, arthralgias, myalgias, serositis (pleural and pericardial effusion), hepato-splenomegaly, mediastinal lymphadenopathy, transaminitis and hypoalbuminemia. Due to her dark color skin any rash could not be appreciated.

Laboratory investigations are notable for the consistent absence of ANAs and RF and reflect the non-specific systemic inflammatory nature of the disease. Increases in the erythrocyte sedimentation rate, CRP level, and serum ferritin are common in AOSD (90 to 100%) as were seen in the present case. Elevated ferritin level is a nonspecific but common finding and a helpful feature for diagnosing AOSD. However, normal levels of serum ferritin should not rule out the diagnosis of AOSD [9,10,12]. A neutrophil leukocytosis is found in about 80-90% of cases. In the case discussed it was 33,400/μL. Despite extensive work up we could not find any evidence of Infection, malignancy or any rheumatic disease including vasculitis. Although, the case discussed did not had criteria fulfilling possible associated MAS, its prevalence in AOSD ranges from 11% to 15%.

There is no specific serological marker to diagnose AOSD and diagnosing AOSD is often difficult. The diagnosis is clinical, not based on serology and one of exclusion. The Yamaguchi criteria (Table 2) proposed in 1992 are the most widely cited criteria [2]. Diagnosis requires at least 5 features, with at least 2 of these being major diagnostic criteria. Our patient had 3 of the major criteria and all of the minor criteria. In 2002, Fautrel et al. proposed a new criterion which contained 2 new markers: serum Glycosylated ferritin fraction ≤ 20% and ≥80% neutrophil Polymorphonuclear count [3]. Diagnosis of AOSD by Fautrel criteria requires 4 or more major criteria or 3 major and 2 minor criteria. Our patient had 4 major criteria and 1 minor criterion. Transient erythema and still's rash could not be appreciated in this case due to dark skin color. Glycosylated ferritin was not done due to non availability of the test. These criteria were proposed 25 and 15 years back respectively. As reported earlier by us [6] and other authors also, and in the present case, we noticed that negative procalcitonin, hyperferritenemia and severe hypoalbuminemia were more easily picked up and glycosylated ferritin is difficult to get done in routine clinical practice. Can hyperferritenemia and negative procalcitonin along with other biomarkers – IL 18, s100 proteins and sCD163, as proposed by other authors be utilized as diagnostic criteria needs further research, study and meta-analysis [13].

Many different therapies have been tried for individuals with adult onset Still's disease. Besides symptomatic and supportive treatment, nonsteroidal anti inflammatory drugs (NSAIDs) for fever, joint pain and bone pain, corticosteroids for systemic symptoms, Disease modifying anti-rheumatic drugs (DMARDs) methotrexate, hydroxychloroquine (HCQS), azathioprine or tumor necrosis factor (TNF) inhibitors are used depending on disease severity and drug safety. We treated this patient with NSAIDs, pulse methylprednisolone and later on tapering doses of prednisolone along with methotrexate and HCQS. In refractory cases alternative treatments include anti TNF agents (infliximab, etanercept, and adalimumab), IL-1 inhibitors (anakinra, canakinumab and rilonacept) and IL-6 receptor antibody tocilizumab has been shown to induce remission in patients with AOSD. Plasma exchange and intravenous immunoglobulin's are

other treatment options in refractory AOSD patients.

4. CONCLUSIONS

1. AOSD remains as a diagnostic dilemma for physicians. In a case of FUO, consider adult-onset still's disease as an important differential.
2. As AOSD is a diagnosis of exclusion. Newer specific biomarkers able to facilitate differential diagnosis are needed. As discussed ferritin, procalcitonin, IL 18, s100 proteins and sCD163 are some of them.
3. Early and timely diagnosis of AOSD can lead to prompt initiation of appropriate therapy with decrease in morbidity and mortality in the severe form of the disease.

CONSENT

As per international standard or university standard, patient's consent has been collected and preserved by the authors.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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Peer-review history:
The peer review history for this paper can be accessed here:
http://www.sciencedomain.org/review-history/23530