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A Case of Adult Stills Disease: Not So Uncommon Cause of Fever of Unknown Origin

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Authors' contributions

This work was carried out in collaboration between all 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. Author ASK retrieved all patient data, images and photograph. All authors read and approved the final manuscript.

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Case Study

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ABSTRACT

Adult still's disease (ASD) is a defined clinical entity and a known cause of fever of unknown origin (FUO). It is a rare systemic inflammatory disorder characterized by a triad of symptoms: daily (quotidian) spiking fever (>39°C), arthritis and an evanescent salmon-colored rash. First described in 1971, it is a uncommon, difficult to diagnose, auto inflammatory, multisystem disorder. The disease is characterized by two subsets according to clinical and laboratory features: systemic or articular. Early diagnosis and treatment of the disease can prevent morbidity and mortality with a favorable outcome. We present and discuss a young male patient who presented as FUO and was diagnosed timely as ASD and treated with corticosteroids with a favorable prognosis.

Keywords: Auto inflammatory disease; adult onset stills disease; fever of unknown origin; Yamaguchi criteria; Fautrel criteria.

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SYNONYMS

Adult Onset still's disease.
Wissler Fanconi syndrome.

1. INTRODUCTION

ASD is an auto inflammatory disorder characterized by the classic triad of persistent high spiking fever, arthralgia, and salmon colored skin rash. It is said that rash is seen in 60-80% of cases, but in tropical countries where skin color is wheatish to dark, it is not commonly appreciated. Its diagnosis is challenging due to absence of any serological biomarkers making diagnosis difficult. In fact, it is a diagnosis of exclusion and a definitive diagnosis is usually made based on the Yamaguchi [1] or Fautrel [2] criteria only after excluding infectious, malignant, and other connective tissue diseases.

According to the clinical presentation of the disease at diagnosis, two distinct ASD phenotype may be distinguished clinically:

i) An acute systemic febrile illness, with a monocyclic or polycyclic pattern, highly symptomatic, may evolve into a multi organ dysfunction or failure and can even be fatal if not timely diagnosed and treated and;
ii) A more slowly evolving illness with arthritis and 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 tumor necrosis factor- (TNF-) alpha agents or interleukin (IL-1) antagonists can prevent complications and lead to a favorable prognosis. Steroid and DMARDs refractory cases with systemic pattern may be benefited by Anakinra, active arthritis with systemic symptoms by tocilizumab and chronic polyarticular refractory ASD by TNFα-blockers respectively.

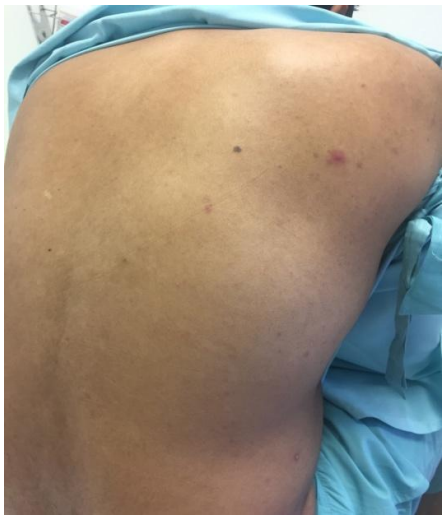
2. CASE PRESENTATION

An Asian male, age 28 years, attended medical out patients department on 17.03.2018 with complaints of daily high grade spiky fever with chills for almost 3 weeks, sore throat with mild cough off and on, severe pains over right lower chest , left ankle and knee pain ,and body aches (myalgias). He took consults locally where he was evaluated with routine blood counts, biochemistry and was being treated with antibiotics- ceftriaxone and azithromycin for presumed enteric fever. His x-ray chest (XRC), sonography whole abdomen done outside was normal and complete blood counts show leukocytosis (Total leukocyte count 13.6 $x10^3$ per cmm). Perusal of his outside reports showed mildly raised creatinine which he related to overuse of NSAID's for body pains since January 2018. He was being treated with antibiotics, paracetamol and supportive treatment for last 15 days. However he did not respond and came for further management. He was admitted and further evaluated.

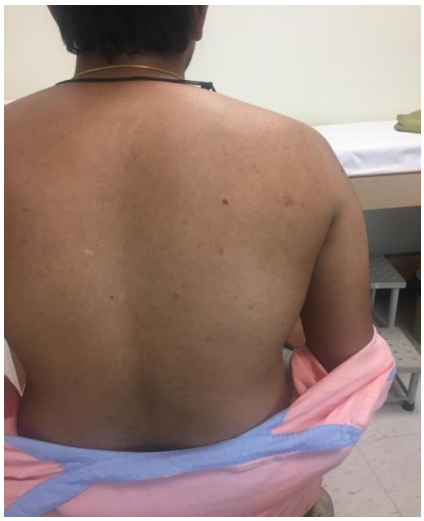
On examination he had fair complexion, his pulse was regular 91 per minute, blood pressure 110/70 mm Hg, respiratory rate 18 per minute, peripheral capillary oxygen saturation (SpO2) 98%, and temperature 102°F. He looked toxic, had few salmon color, non raised maculopapular lesions on back (Fig. 1A), mild hepato-splenomegaly, Left cervical lymph node of 1.5x2 cm size, mildly tender, and freely mobile. His left ankle joint was inflamed. Rest of the clinical examination was essentially normal. His investigations are in Table 1. XR chest and High resolution computerized tomography (HRCT) of chest is in Fig. 2. Investigations revealed mild anemia with neutrophil leukocytosis, minimal transaminitis, mild hypoalbuminemia, and markedly raised inflammatory markers. His electrocardiogram, 2D echocardiography was normal. He had daily fever spikes of up to 102-104°F, paroxysmal severe chest pains with associated restlessness. There was no deep venous thrombosis in legs clinically. He was continued on same antibiotics, paracetamol and supportive treatment and further evaluated. His body fluid cultures (Urine and blood), widal test, IgM/IgG Dengue virus antibody, IgM Scrub typhus antibody, serology for HIV, HBsAG, and HCV antibodies, malaria parasite, ASLO titers, HLA B27, antinuclear antibody (ANA), anti neutrophil cytoplasmic antibody (ANCA), Anti-cyclic citrullinated peptide antibody (Anti CCP), rheumatoid factor, polymerase chain reaction (PCR) based detection of bacteria, fungus, viruses from whole blood sample and procalcitonin were negative or not detected. Looking to our past experience when we lost two patients due to late diagnosis of ASD and having received antibiotics for many days locally, persistent fever, severe myalgias and arthralgias, we suspected ASD and advised him for a pulse of intravenous methylprednisolone 250 mg to

which family refused and instead preferred to take oral prednisolone. On 19.03.2018 his reports did not show any evidence of infection, malignancy, rheumatic disease or vasculitis and with neutrophil leukocytosis, raised inflammatory markers, symptomatology, presence of rash over trunk, hepato-splenomegaly and cervical lymphadenopathy, possibility of an auto inflammatory disorder was evaluated. We reviewed his laboratory and clinical parameters and he was diagnosed as a case of adult stills disease (ASD). He was discharged on 19.03.2018 with an advice to take oral prednisolone along with other supportive treatment.

He responded dramatically to the treatment and became afebrile. He was reviewed in outpatient department on 03.04.2018. He is asymptomatic, rash has disappeared (Fig. 1B) and his ESR and CRP have settled in normal range. However mild transaminitis is persisting, which we expect will settle down in due course. He has been advised to continue with prednisolone for one month and then taper over next two months and report if he experiences any flare up or recurrence of symptoms.

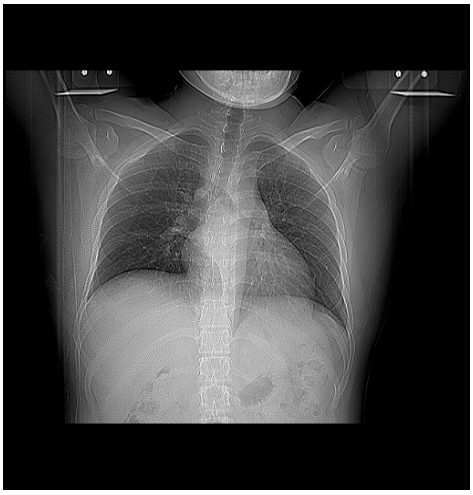


A



B

Fig. 1.A. Salmon color, non raised, stills rash on trunk on 18.03.2018
B:No rash in follow up on 03.04.2018



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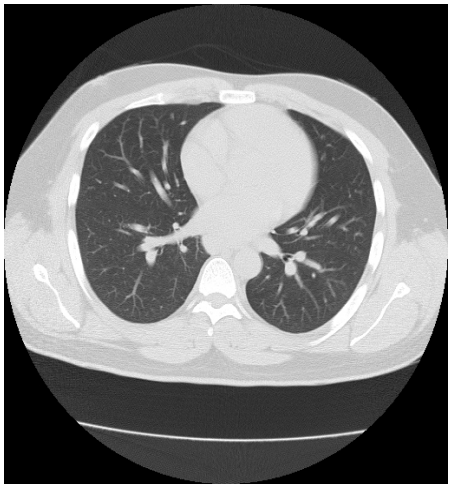

B

Fig. 2. Normal CXR dated 17.03.2018 (A) and normal HRCT chest dated 17.03.2018 (B)

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

	Normal value	13.03.2018	17.03.2018	19.03.2018	01.04.2018
Hemoglobin	13-17 gm/dl		**12.7**	**11.7**	14.5
TLC	4.0-10 X10^3/cmm	**13.6**	**14.8**	**10.4**	12.9
DLC	%	**P87** L9	**P86** L6	**P84** L10	P79 L16
Platelet count	150-410 X103/cmm	350		409	475
PBF		Normal			
Serum Creatinine	0.8-1.3 mg/dl		**1.61**		1.37
Gamma Glutamyl transferase (GGT)	7-64 U/L	**167**	**156**		168.9
Serum Alkaline phosphatase	40-129 U/L		96		
Serum Total Proteins	6.4-8.3 gm/dl		7.2		
Serum Albumin	3.4- 4.8 gm/dl		**3.2**		
SGOT(AST)	0–35 U/L		**41**		78.8
SGPT(ALT)	0 -41 U/L		**57**		169.6
Lactic dehydrogenase	85-227 U/L		**235**		
Procalcitonin	< 0.5ng/ml		0.718		
Creatine Kinase	0-160 U/L		49		
ESR	0-15 mm 1 hour		**90**		20
CRP	0-5 mg/dl	**15.7**	**182.5**		1.4
Serum Ferritin	30-400 ng/ml		203.6		
RA factor	<10 IU/ml		< 8		
Anti CCP antibody				Not detected	
Serology HIV,HBsAg,anti HCV antibody			Not detected		
Dengue IgM/IgG antibodies			Not detected		
Body fluid Cultures (Urine,blood)				Sterile	
Electrocardiogram (ECG)		TWNL			
USG			**Mild epatosplenomegaly, echogenic kidneys.**		
ECHO			Normal study		
HRCT Chest and MRI Brain			Normal study		

- *TLC:Total leukocyte count; DLC:Differential leukocyte count; PBF:Peripheral blood film; SGOT: Serum glutamic-oxaloacetic transaminase;SGPT:Serum glutamic pyruvic transaminase;RA factor: Rheumatoid factor; Anti CCP:Anti-cyclic citrullinated peptide antibody; LDH:Lactate dehydrogenase; HIV:Human immunodeficiency virus; HBsAG:Hepatitis B surface antigen; HCV:Hepatitis C virus; IgM/IgG:ImmunoglobulinM/G; USG:Ultrasonography; ECHO:Echocardiogram; HRCT:High resolution computerized tomography;MR:Magnetic resonance imaging.*
- *Abnormal results have been highlighted*

Table 2. Yamaguchi criteria for the diagnosis of adult 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/mm3 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	$\geq$ 5 criteria are present with $\geq$ 2 being major criteria and no exclusion criteria.
Sensitivity and specificity	Sensitivity 96.2% and specificity 92.1%

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

Major criteria	Spiking fever $\geq$ 39°C (102.2°F) Arthralgia Transient erythema Pharyngitis Polymorphonuclear count $\geq$ 80% Glycosylated ferritin $\leq$ 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%

3. DISCUSSION

Adult still's disease is one of the most frequent aetiology of FUO. In a patient with FUO, a maculopapular rash and/or arthralgia and/or sore throat should raise the suspicion of ASD. In a study by Mert A etal ASD was diagnosed in 20 (15.4%) cases among 130 cases of FUO during the period 1984-2001. [3] The clinical findings are heterogeneous and bacterial infections (e.g. streptococcal pharyngitis and sepsis) are generally considered initially with prescribing of antibiotics as also happened in the case presented.

Adult still's disease is a rare systemic noninfectious inflammatory disease which is still under reported and under diagnosed. It was first described by Bywaters in 1971[4]. Its estimated prevalence is 1.5 cases per 10^5-10^6 people. Noninfectious inflammatory diseases contributed to 17% cases of fever of unknown origin in 1961 and increased to 22% in 2007 [5]. As an internal medicine physician practicing in tertiary care centre based at Jaipur (India) for nearly three decades, I believe this incidence has further increased in last decade, mainly because of increased awareness about the disease and better diagnostic facilities. The authors have previously reported two fatal cases of ASD who were diagnosed late [6] and another patient who was diagnosed timely with a favorable prognosis [7].

The exact pathogenesis of ASD 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 [8]. Neutrophil and macrophage activation is the hallmark of ASD. 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 ASD [9].

Clinically, the most classic manifestations of ASD are daily 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

commonest. Other symptoms reported 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%), and pneumonitis (20%) and weight loss (27%) [6,8]. The monocyclic pattern, polycyclic, and chronic patterns are seen in 29, 22, and 33 patients, respectively [10]. Our patient had mild rash, fever, arthralgias, myalgias, hepato-splenomegaly, cervical lymphadenopathy, minimal transaminitis and mild hypoalbuminemia.

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 ASD (90 to 100%) as were seen in the present case except normal ferritin levels. Elevated ferritin level is a nonspecific but common finding and a helpful feature for diagnosing ASD. However, normal levels of serum ferritin should not rule out the diagnosis of ASD as in the case presented [6,9,11]. Hyperferritenemia is probably an acute phase response and hepatocytes respond to inflammatory cytokines by increasing ferritin synthesis. It is possible that serum ferritin levels were normal in this case as he was diagnosed early within three weeks of his illness and there wasn't any significant transaminitis. Had the diagnosis been delayed, it would have certainly increased. A neutrophil leukocytosis is found in about 80-90% of cases. In the case discussed it was 14,800/μ with 86% neutrophil. 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 ASD ranges from 11% to 15%.

The diagnosis of ASD is clinical, not based on serology and one of exclusion. The Yamaguchi criteria (Table 2) proposed in 1992 are the most widely cited criteria [1]. Diagnosis requires at least 5 features, with at least 2 of these being major diagnostic criteria. Our patient had 4 of the major criteria and all of the minor criteria. In 2002, Fautrel et al. [2] proposed a new criterion which contained 2 new markers: serum Glycosylated ferritin fraction $\leq$ 20% and $\geq$80% neutrophil Polymorphonuclear count. Diagnosis of ASD by Fautrel criteria requires 4 or more major or 3 major and 2 minor criteria. Our patient had 5 major and 2 minor criteria. Glycosylated ferritin was not done due to non availability of the test.

Many different therapies have been tried for individuals with adult 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 is used depending on disease severity and drug safety. We treated this patient with NSAIDs, oral prednisolone and supportive drugs. In refractory cases alternative treatment with 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 ASD. Plasma exchange and intravenous immunoglobulin's are other treatment options in refractory ASD patients.

4. CONCLUSIONS

ASD is still a diagnostic dilemma for physicians and one should have high index of suspicion for it. In most cases; it is clinically distinguishable from other causes of FUO. The key point to remember is that for patients who present with prolonged and unexplained fever despite being treated with antibiotics, combined with musculoskeletal symptoms and macular rash, the differential diagnoses should include ASD. Early and timely diagnosis of ASD can lead to prompt initiation of appropriate therapy with decrease in morbidity and mortality in severe systemic 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

As per international standard or university standard written ethical approval has been collected and preserved by the authors.

COMPETING INTERESTS

The authors declare that there is no conflict of interests regarding the publication of this paper.

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