International Journal of Research in Dermatology
Jain R et al. Int J Res Dermatol. 2018 Mar;4(1):87-92
http://www.ijord.com

DOI: http://dx.doi.org/10.18203/issn.2455-4529.IntJResDermatol20180119

Case Report

Adult onset Still's disease: a diagnostic challenge

Rahul Jain[1], V. K. Joglekar[1], Kriti Jain[2]*

[1]Department of General Medicine, Grant Govt. Medical College, Mumbai, Maharashtra, India
[2]Department of Dermatology, Subharti Medical College, Meerut, UP, India

Received: 14 December 2017
Revised: 12 January 2018
Accepted: 13 January 2018

***Correspondence:**
Dr. Kriti Jain,
E-mail: kriti3k@gmail.com

ABSTRACT

Adult Still's disease (ASD) is a systemic inflammatory disorder of unknown etiology, typically characterized by a clinical triad of daily spiking high fevers, evanescent rash, and arthritis. This report described a 26-year-old male who presented with these symptoms along with raised liver enzymes and hyperferritinemia. After ruling out systemic infections, localized infections, malignancies and other rheumatological diseases, Adult onset Still's disease diagnosis was made according to Yamaguchi criteria (having 4 major features and 3 minor features). AOSD is a heterogeneous and rare disease and the lack of serologic markers as a true gold standard makes diagnosis difficult.

Keywords: Fever, Skin rash, Arthralgia, Adult onset Still's disease

INTRODUCTION

Juvenile idiopathic arthritis (JIA) is classified into seven major types (Table 1), including systemic-onset, rheumatoid factor (RF)-positive polyarticular, RF-negative polyarticular, and oligoarticular. Systemic- onset JIA (SoJIA), also known as Still's disease, is characterized by an evanescent, erythematous eruption that typically accompanies spiking fevers.[1] Cutaneous manifestations are less common in the other types, although the RF-positive subgroup of polyarticular JIA can present with rheumatoid nodules and other skin findings similar to those of adult rheumatoid arthritis, and nearly all patients with psoriatic arthritis have cutaneous and/or nail psoriasis.[2]

In 1897, George Still described systemic onset juvenile idiopathic arthritis in 22 children, owing to which the disease is called "Still's disease". Similar to this clinical entity with arthritis and features of juvenile RA were described in 14 adults by Bywaters, in year 1971.[3] Since then multiple reports of fever of unknown origin or "rheumatoid arthritis" have appeared. In the French and German literature occasional reports of Adult onset Still's disease (AOSD) are found, then called "subsepsis allergica" or "Wissler's syndrome" and later the "Wissler-Fanconi syndrome".[4]

Adult-onset Still's disease should always be considered in an adult with fever of unknown origin (defined as fever >38.3°C on several occasions over a period of at least 3 weeks or uncertain diagnosis after 1 week of hospitalization). The differential diagnosis is similar to that of SoJIA (Table 1). Additionally, Schnitzler's syndrome should be considered in an adult patient with recurrent fevers, arthralgia and an urticarial eruption. In addition to non-pruritic urticaria, patients have recurrent fevers, bone pain (lower extremity, iliac and vertebral due to hyperostosis), and a monoclonal IgM gammopathy. Angioedema is observed in about 15% of patients with Schnitzler's syndrome, and lymphoplasmacytic malignancies in 10–15%.[5]

Table 1: Classification of juvenile idiopathic arthritis.

Classification of juvenile idiopathic arthritis	
Systemic onset (20%) (Still's disease)	*Features required for diagnosis* • High episodic fevers– daily for ≥2 weeks and documented to be quotidian for ≥3 days • At least one of the following: evanescent eruption, generalized lymphadenopathy, hepatomegaly or splenomegaly, serositis • Symmetric polyarthritis >oligoarthritis (erosive in 20%) *Other features* • Leukocytosis with neutrophilia, anemia (often severe), thrombocytosis, elevated ESR, elevated ferritin and C-reactive protein levels • Occasionally myocarditis, pneumonitis, anterior uveitis (<1%), CNS involvement, macrophage activation syndrome (6–13%); rarely amyloidosis • RF- and ANA- negative in >95% of patients
RF-negative polyarthritis (5%)	• 3–9 years of age • ≥5 joints in the first 6 months • Small joints of the hands & feet > knees, wrists, ankles; erosive arthritis (15%) • RF- negative; ANA- negative
RF-positive polyarthritis (15%)	• 10–16 years of age • ≥5 joints in the first 6 months • Small joints of the hands & feet >knees, wrists, ankles; erosive arthritis (>50%) • Rheumatoid nodules, low-grade fever, mild anemia, weight loss • RF- positive (100%); ANA- positive (70%)
Oligo/pauci-articular arthritis (60%) • Type I– 50% • Type II– 10%	• ≤4 joints in the first 6 months† • Knees >ankles, wrists; often asymmetric • Type I: 1–8 years of age; uveitis 30–50%; ANA-positive- 60%; RF-negative • Type II: 9–16 years of age; HLA-B27; RF- negative; ANA-negative
Enthesitis-related arthritis	• Arthritis and enthesitis (or) • Arthritis or enthesitis plus ≥2 of the following: sacroiliac joint tenderness/spinal pain, HLA-B27, family history of HLA-B27-associated disease in first- or second-degree relative, anterior uveitis, onset of arthritis in a boy after age 8 years
Psoriatic arthritis	• Arthritis and psoriasis (or) • Arthritis and ≥2 of the following: dactylitis, nail abnormalities, family history of psoriasis in ≥1 first-degree relative • Other features: anterior uveitis, ANA-negative
Other arthritis	• Children with arthritis of unknown cause persisting ≥6 weeks that does not fulfill criteria for any other categories or fulfills criteria for more than one category

†The persistent oligoarthritis subtype never affects more than 4 joints, whereas the extended oligoarthritis subtype affects a cumulative total of ≥5 joints after the first 6 months of disease.

Although some patients respond to high-dose aspirin or NSAIDs, the majority require oral corticosteroids (e.g. 40–60 mg prednisone daily) to control acute systemic features. When corticosteroids cannot be tapered, methotrexate is the most commonly employed second-line therapy. As in SoJIA, biologic agents that inhibit the IL-1 receptor or IL-6 receptor (e.g. tocilizumab) appear to be promising.[6,7] A therapeutic response to TNF-α inhibitors has also been reported.

The rarity of the disease, presence of all the features satisfying the criteria for diagnosis and the case being managed as various other clinical entities in the past are few of the many reasons to report this case. We are

hereby reporting a case of a young male with AOSD, with his case history, clinical manifestations, differential diagnosis, diagnostic workup, criteria and treatment modalities.

CASE REPORT

A 26 year, old unmarried male came to our hospital with chief complaints of evening rise of temperature associated with chills on and off since 6 months, along with intermittent cough, multiple small and large joint pains since 3 months and skin rash on upper back and bilateral thighs since 2 weeks.

On history, patient had been started on ATT, based on the symptoms, with initial response. However, fever recurred within 2 to 3 weeks of treatment after which he was investigated with negative tests for tuberculosis. He was then labeled as a case of pyrexia of unknown origin. Patient developed non-specific joint pains, on and off 3 months back, resolving on medication but recurring thereafter. Patient was then treated as a case of rheumatoid arthritis with no improvement. Patient had noticed darkening of skin 2 weeks before presenting to us, seen on the upper back and inner thigh region, with redness in the surrounding area. Lesions were not itchy, not associated with any fluid filled lesions. Assuming this to be a drug rash, all his medications were put on hold. A right sided neck swelling was also noted by the patient, about 1.5 cm in size, around 7 days back, which was non tender.

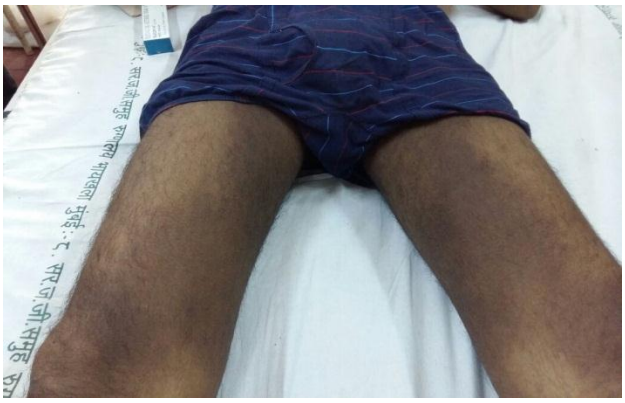

Figure 1: Clinical photograph of violaceous hyperpigmented macules on the inner aspect of bilateral thighs.

On physical examination, patient had pallor present along with right cervical lymphadenopathy, which was non-tender, non-matted and firm in consistency. Mild non-tender hepatomegaly and mild splenomegaly recorded on bimanual examination.

Dermatological examination showed multiple well defined hyper-pigmented to pink colored macules present over the inter-scapular region and inner side of bilateral thighs, (Figure 1 and 2). The various differentials with which the patient came were rheumatoid arthritis, Fever of unknown origin, tuberculosis, drug rash and any hematological malignancy.

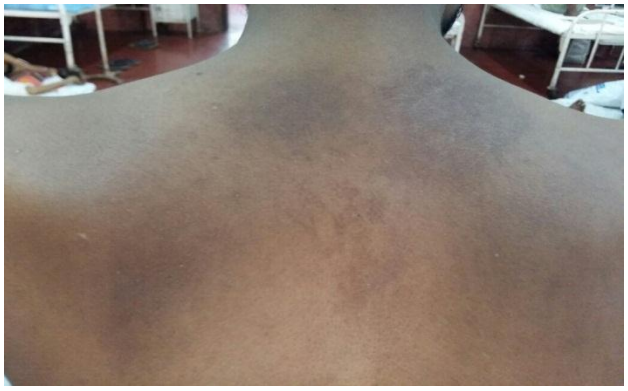

Figure 2: Clinical photograph of hyperpigmented to salmon colored macule present over the upper back.

Investigations

In order to investigate the plausible etiology, a thorough laboratory work up was done revealing a hemoglobin of 7.9 g/dL with microcytic hypochromic anemia; leuko-cytosis of 13 000 cells/µL with neutrophilia (88%) with rest of the parameters on hematogram and serum electrolytes being within normal limits. Transaminases were elevated (SGOT 62 IU/ml, SGPT 108 IU/ml), along with positive C reactive protein (9.6 mg/dL), raised ESR (110 mm, 1st h) and ferritin levels (7050 ng/mL). However, transferrin saturation (24%) and serum Iron levels (94 mcg/dL) were within normal range. Extensive investigations were conducted regarding infectious as well as autoimmune etiologies (Table 2).

ECG and chest radiography did not show any abnormality. X-ray of bilateral wrist joints, joints of hands, feet, knee and Hip were all within normal limits. USG Abdomen confirmed mild hepatomegaly with altered echo texture along with mild splenomegaly. Non-necrotic cervical lymphadenopathy was seen on Contrast enhanced CT of neck and thorax, biopsy of the lymph nodes was suggestive of reactive lymphadenopathy.

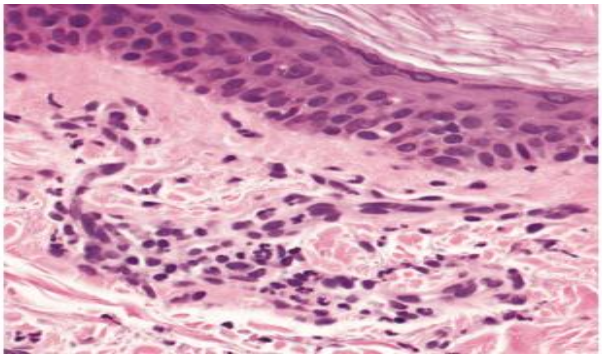

Figure 3: H & E staining showing an interstitial and perivascular dermal infiltrate.

Histopathology of skin biopsy revealed an interstitial and perivascular dermal neutrophil-dominant mixed infiltrate (Figure 3).

With fever, rash and polyarthralgia as the main presenting features along with highly raised serum Ferritin levels, systemic onset juvenile idiopathic arthritis becomes an important differential. After ruling out systemic infections, localized infections, malignancies and other rheumatological diseases, finally AOSD diagnosis was made according to Yamaguchi criteria (having 4 major features and 3 minor features).

Table 2: Investigations done in our case to rule out infectious and autoimmune etiologies.

Peripheral smear for malarial parasite dengue NS 1 antigen	Negative
Dengue IgG dengue IgM	
Widal	
IgM leptospirosis	
Weil Felix test	
Brucella antigen	
Blood culture sensitivity	No organism isolated
Urine culture sensitivity	
Blood fungal culture sensitivity	
CSF culture sensitivity	
TB quantiferon test, gamma interferon	1.67
HIV	Non-reactive
HBsAg	
HCV	
Rheumatoid factor (RF)	Negative
Anti-double-stranded DNA (dsDNA)	
Anti-nuclear antibodies (ANA)	
Anti-neutrophil cytoplasmic antibodies (cANCA & pANCA)	
HLA B 27	

Table 3: AOSD diagnostic criteria.

Yamaguchi et al [13]	Cush [14]	Fautrel et al [15]
Major		
Arthralgia >2 weeks	(2 points)	Spiking fever ≥39°
Fever >39°, intermittent, ≥1 week	Quotidian fever >39°	Arthralgia
Typical rash	Still's (evanescent) rash	Transient erythema
WBC >10 000 (>80% granulocytes)	WBC >12.0+ESR >40 mm/1st h	Pharyngitis
	Negative RF and ANA	PMN ≥80%
	Carpal ankylosis	Glycosylated ferritin ≤20%
Minor		
Sore throat	(1 point)	
Lymphadenopathy and/or splenomegaly	Onset age <35 years	Maculopapular rash
LFT abnormal	Arthritis	Leucocytes ≥10×10^9/l
(-)ve ANA and RF	Prodromal sore throat	
	RES involvement or abnormal LFTs	
	Serositis	
	Cervical or tarsal ankylosis	
Diagnostic combination		
Exclusion criteria		
Infections	Probable AOSD: 10 points with 12 weeks' observation	4 major criteria or 3 major+2 minor
Malignancies	Definite AOSD: 10 points with 6 months' observation	
Rheumatic diseases		
Diagnosis		
5 criteria (at least 2 major)		

The patient was administered Inj. methyl prednisolone 1 gm IV once daily for 3 days which was followed by oral administration of tablet Prednisolone 1 mg/kg/day daily along with non-steroidal anti-inflammatory drugs. He showed considerable improvement and was discharged after one week on prednisolone 1 mg/kg/day daily with tapering dose of 5 mg weekly. With proper treatment, now he is completely symptom free and living a healthy life.

DISCUSSION

Despite the improvement in diagnostic techniques, the fever of unknown origin (FUO) remains a challenge to overcome, comprising 50% of the cases without clear etiology.[8] AOSD is a rare inflammatory disorder that affects the entire body (systemic disease). The cause of the disorder is unknown (idiopathic). Affected individuals may develop episodes of high, spiking fevers, a pink or salmon colored rash, joint pain, muscle pain, a sore throat and other symptoms associated with systemic inflammatory disease. The specific symptoms and frequency of episodes vary from one person to another and the progression of the disorder is difficult to predict.

In some individuals, the disorder appears suddenly, disappears almost as quickly and may not return. In other people, AOSD is a chronic, potentially disabling, condition. It has an estimated prevalence of 1.5 cases per 100,000–1000,000 people. It has been described 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.[9] Although it usually affects the younger adult population, it can also affect elderly people.[10] The disease affects predominantly females as compared to males.[11] Because of the highly variable symptoms and rarity of the disorder; it often goes undiagnosed or misdiagnosed making it difficult to determine its true frequency in the general population.

Hence, AOSD remains a difficult diagnosis, relying on six different sets of classification criteria (Glodman, Calabro, Cush, Reginato, Kahn and Yamaguchi).[12] The Yamaguchi, Cush and Fautrel criteria (Table 3) are the ones recognized for their superior accuracy, as it was shown in Masson et al study in 1996.[12-15] The two greatest obstacles concerning these criteria are: the fact that, despite being a diagnosis of exclusion, there is not a clear set of diagnosis to exclude before assuming AOSD, nor helpful complementary diagnosis techniques to help supporting the hypothesis; the other limitation is the absence of ferritin levels (or its glycosylated form) in the criteria.[15]

AOSD is a diagnosis of exclusion. Differential diagnoses are infections, such as endocarditis and deep-seated occult infections, or neoplastic etiology, especially lymphomas and autoimmune diseases like vasculitis and polymyositis. These conditions should be excluded before AOSD is diagnosed.

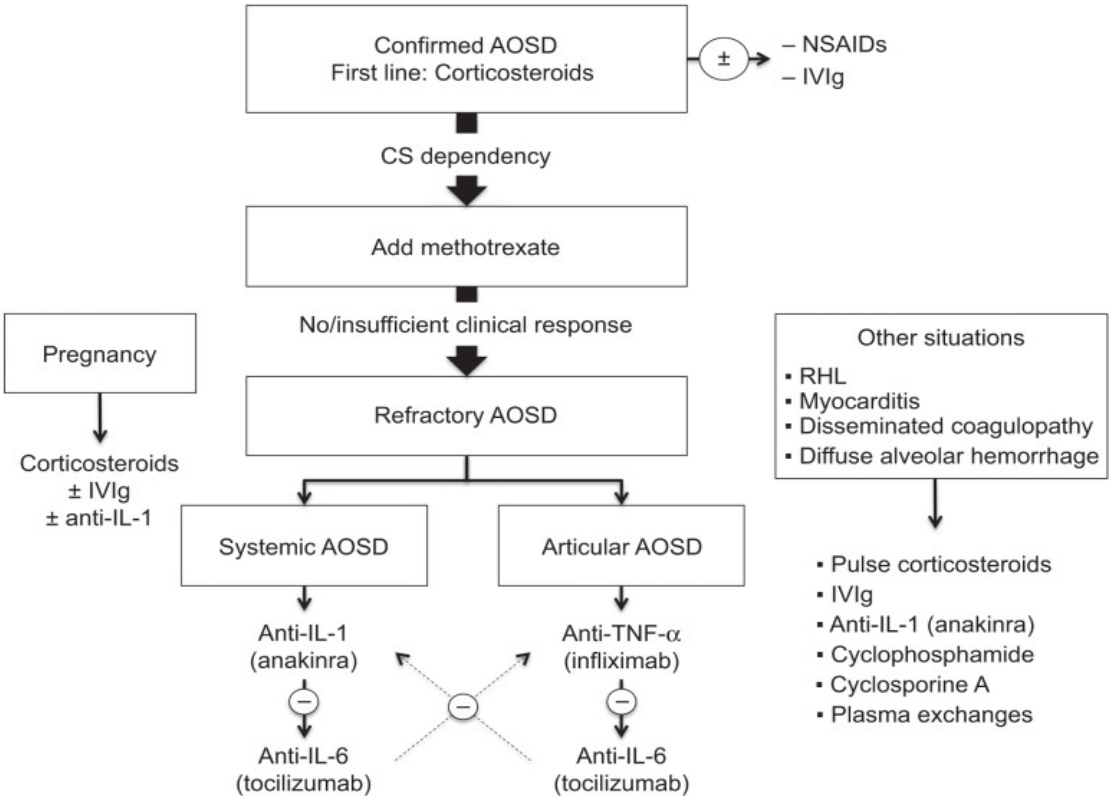

Figure 4: Treatment algorithm.

The treatment generally relies on NSAIDs and steroids, however, in some refractory cases, hydroxychloroquine, gold salts, methotrexate and cyclosporine have been used (Figure 4). The intricacy of the symptoms and the lack of accurate diagnostic techniques make the clinical approach to AOSD patients the hallmark to the right management of this condition.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

REFERENCES

1. Petty RE, Southwood TR, Baum J, Bhettay E, Glass DN, Manners P, et al. Revision of the proposed classification criteria for juvenile idiopathic arthritis: Durban, 1997. The Journal of rheumatology. 1998;25(10):1991-4.
2. Bolognia J, Jorizzo J, Schaffer J. Dermatology. 3rd ed. Elsevier Saunders; 2012: 671-675.
3. Pouchot J, Sampalis JS, Beaudet F, Carette S, DÉcary F, Salusinsky-sternbach M, et al. Adult Still's disease: manifestations, disease course, and outcome in 62 patients. Medicine. 1991;70(2):118-36.
4. Larson EB. Adult Still's disease—recognition of a clinical syndrome and recent experience. West J Med. 1985;142(5):665–71.
5. Efthimiou P, Paik PK, Bielory L. Diagnosis and management of adult onset Still's disease. Ann Rheum Dis. 2006;65(5):564–72.
6. Kötter I, Wacker A, Koch S, Henes J, Richter C, Engel A, et al. Anakinra in patients with treatment-resistant adult-onset Still's disease. Semin Arthritis Rheum. 2007;37:189–97.
7. Puechal X, DeBandt M, Berthelot JM, Breban M, Dubost JJ, Fain O, et al. Tocilizumab in refractory adult Still's disease. Arthritis Care Res. 2011;63:155–9.
8. Bleeker-Rovers CP, Vos FJ, de Kleijn EM, Mudde AH, Dofferhoff TS, Richter C, et al. A prospective multicenter study on fever of unknown origin: the yield of a structured diagnostic protocol. Medicine (Baltimore). 2007;86(1):26-38.
9. Owlia M., Mehrpoor G. Adult onset still's disease: a review. Indian J Med Sci. 2009;63(5):207–21.
10. Ichiki H., Shishido M., Nishiyama S. Two cases of adult onset of Still's disease in the elderly. Nippon Ronen Igakkai Zasshi. 1992;29(12):960–4.
11. Cagatay Y, Gul A, Cagatay A, Kamali S, Karadeniz A, Inanc M, et al. Adult-onset still's disease. Int J Clin Pract. 2009;63(7):1050–5.
12. Crispin JC, Martinez-Banos D, Alcocer-Varela J. Adult-onset Still disease as the cause of fever of unknown origin. Medicine (Baltimore). 2005;84(6):331-7.
13. Yamaguchi M, Ohta A, Tsunematsu T, Kasukawa R, Mizushima Y, Kashiwagi H. et al Preliminary criteria for classification of adult Still's disease. J Rheumatol. 1992;19:424–30.
14. Cush JJ, Medsger TA, Jr, Christy WC, Herbert DC, Cooperstein LA. Adult-onset Still's disease. Clinical course and outcome. Arthritis Rheum. 1987;30:186–94.
15. Fautrel B, Zing E, Golmard J L, Le Moel G, Bissery A, Rioux C, et al Proposal for a new set of classification criteria for adult-onset still disease. Medicine (Baltimore). 2002;81:194–200.

Cite this article as: Jain R, Joglekar VK, Jain K. Adult onset Still's disease: a diagnostic challenge. Int J Res Dermatol 2018;4:87-92.