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PUO-Clinicians Dilemma Clinical Profile of Adult-Onset Still's(AOSD)

KEYWORDS: PUO - Pyrexia of unknown origin, AOSD - Adult onset Still's disease, MAS - Macrophage activation syndrome, ANA - Antinuclear antibodies, ARDS – Acute respiratory distress syndrome(ARDS).

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ABSTRACT ***Background:*** *Adult-onset Still's disease (AOSD) is a rare inflammatory disease of unknown etiology, which commonly affects young adults regarding which sparse published data are available from India. In the present paper, we aimed to describe clinical and laboratory spectrum AOSD patients.*
Methods: Retrospective study of 7 patients, who presented with pyrexia of unknown origin (PUO) seen over a 3-year period who were diagnosed to have AOSD after a thorough work-up.
Results: *Their mean age was 28 (range 20-35) years; there were five females. Mean duration of symptoms was 12 week . All patients had spiking fever, 4 patient had arthralgia involving both large and small joints and a negative ANA and RF. Preceding sore throat was noted in 3 cases. Salient laboratory abnormalities were as follows: mean leukocyte count (range 15,800-22,000) /mm3, leukocytosis (n=7), neutrophilia (n=7), anaemia (n=1) hepatic dysfunction (n=3), mean serum ferritin very high (range 10000-40000) ng/mL, (n=7). All cultures were negative for microbial growth. Serositis with minimal pleural fluid collection was noted in 1case. Nuclear scan was done in 2 patients and was S/O acute hepatitis. All patients fulfilled the required Yamaguchi criteria for the diagnosis of AOSD. All patients treated with non-steroidal anti-inflammatory drugs, oral and IV corticosteroids and responded well to treatment.*
Conclusions: *Diagnosis of AOSD is Challenging. Validated diagnostic Yamaguchi criteria and judicious interpretation of serum ferritin in a patient with a compatible clinical presentation can assist in making early and correct diagnosis*

INTRODUCTION

Adult-onset Still's disease (AOSD) is a rare inflammatory disease of unknown etiology, which commonly affects young adults. Although several sets of classification criteria have been developed from retrospectively analyze data,7 most often used criteria for the diagnosis of AOSD are the Yamaguchi criteria.[1] It is usually characterized by high spiking fevers, arthritis, and an evanescent, nonpruritic, macular and salmon coloured rash, appearing on the trunk and the extremities. Organomegaly, lymphadenopathy, serositis, and asepticmeningitis can also occur. Important laboratory findings include leukocytosis, with predominance of neutrophila, negative testing for rheumatoid factor (RF), and antinuclear antibodies (ANA) as well as high serum ferritin levels and low serum glycosylated ferritin levels [2,3,4] Severe disease complications include pericarditis, endocarditis, haemolytic anaemia, and macrophage activation syndrome (MAS). The latter is characterized by thrombocytopenia, markedly elevated ferritin levels, hypofibrinogenemia, and elevated aspartate amino-transferase (AST). AOSD diagnosis can be safely established, after important mimickers including infections, malignancies, and autoimmune diseases are excluded. Treatment of patients with AOSD includes nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and disease-modifying antirheumatic drugs (DMARDs), while our better understanding of disease pathophysiology allowed the identification of biological agents as important targeted therapies.[2,5]

Recent studies have added valuable information in regard to the underlying pathogenetic mechanisms of AOSD. Besides, the exact pathogenesis remains largely elusive, with genetic, environmental, and immunologic contributors being implicated. In the present paper, we aimed to describe clinical and laboratory spectrum of AOSD patients.

MATERIAL AND METHODS

We retrospectively studied the case records of patients, who presented with PUO to department medicine during the period of Jan 2012 to Dec 2015. All these patients were admitted at Smt kashibai navale medical college and general hospital- Pune for evaluation of PUO. In all of them a detailed history was taken and a thorough clinical examination was done. All of them underwent work-up for PUO which included haemogram, smear for malarial parasite, urine examination, blood and urine culture, chest radiograph, abdominal ultrasonography radiological investigation like HRCT lung, CT Thorax ,Abdomen and 2D echo. Anti-nuclear antibody (ANA), rheumatoid factor (RF), liver function test , renal function tests and other relevant serological tests were also done in all patients. Nuclear scan was done in 2 patients. Other investigations were conducted wherever it was indicated. Common causes like infections, malignancy (lymphoma, leukaemia) and other common autoimmune rheumatic diseases were ruled out. AOSD was diagnosed as per Yamaguchi Criteria. All patients were treated with non-steroidal antiinflammatory drugs (NSAIDs) and oral and iv corticosteroids (1 mg/kg body weight and tapered over 6 to 8 weeks). Where ever necessary, oral hydroxy chloroquine (200 mg once a day) was added.

RESULTS

Seven cases of AOSD were diagnosed over a period of 3 years. The clinical characteristics were shown in (Table 1). All patients had spiking fever, 4 patient had arthralgia involving both large and small joints and all patient were negative for ANA and RF with raised ESR and CRP positive. Preceding sore throat was noted in 3 cases. Salient laboratory abnormalities were as follows: mean leukocyte count (range 15,800-22,000) /mm3, leukocytosis (n=7), neutrophilia (n=7), anaemia (n=1) hepatic dysfunction

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(n=3), mean serum ferritin very high (range 10000-40000) ng/mL, (n=7). All cultures were negative for microbial growth . Serositis with minimal pleural fluid collection was noted in 1 cases. Nuclear scan was done 2 patient and was S/O hepatits All patients fulfilled the required Yamaguchi criteria for the diagnosis of AOSD . All patient improved clinically with management.

TABLE 1
Clinical characteristics in 7 patients with adult onset still's disease

Variable	No of patients
Male	2
Female	5
Age of onset (years) Mean Range	 28 20- 35
Duration of illness before Diagnosis (weeks) Mean duration	 12 weeks
Fever	7
Arthopathy	4
Rash	1
Sore thoat	3
Lympadenopathy	3 (Sub centimeter)
Splenomegaly	2
Hepatomegaly	3
Serositis (pleural effusion)	1
CRP	positive
ESR	90 to 100
Sr. Ferritin	10,000 to 40,000
ANA	Negative
RA	Negative
Nuclear Scan	2 patients S/O hepatitis

Discussion
We tried to analyse various case series described in medical literature. The age at onset of AOSD in the present study was 20 years. Where one study conducted in india age of onset was 28 years.[6] In present study mean age at onset was 28 years our observations are similar to one study [6] and 26.2 years in other study [7] We observed a female preponderance (female: male = 5:2). A similar Female preponderance was noted in one study [6] how ever other 3 studies had male preponderance.[8,9,10] The proportion of patients with fever and other systemic manifestations were similar in the present study and other published studies [8,9,10] Serositis in the form of mild pleural effusion was noted in one of the seven cases in our study. But serositis was noted in only two out of 27 in another study. [9] Pericardial effusion was described in 8 out of 28 cases in a study from Iran .[11] pericardial effusion was not noted in our present study.

However, occasionally organ failure associated with this disease or during its drug therapy have been described. In a study [7] of 23 patients, acute liver failure, respiratory insufficiency, myocarditis, progressive anemia due to bone marrow failure, paralytic ileus, peripheral facial nerve paralysis, retro-orbital myositis with a possible intraorbital pseudo-tumor, increased intra-cranial pressure with mental confusion, glomerulonephritis, acute renal failure, rapidly destructive arthritis of hips and knees and septicaemia have been described and have contributed to mortality. But mortality can also occur due to other serious complications like amyloidosis, pericarditis and macrophage activation syndrome (MAS) [12] ARDS is also reported in some cases [13] In contrast to above mentioned studies life threatening complication were not observed in our study except mild form of liver dysfunction. Due to mild lymphadenopathy we could not do lymph node biopsy. However one study showed dynamic Histological spectrum including atypical paracortical hyperplasia burnt out with S-100 +ve histiocytes and Histiocytic reaction , exuberant, immunoblastic reaction and follicular hyperplasia [14] In our study Pulmonary hypertension was not observed. But one study mentions occurence of pulmonary HTN due to involvement of pulmonary vasculature and altered vaso reactivity[15]

Highly Raised serum ferritin levels in thousands and more is observed in our present study is similar to other studies. [16] In 2 patient who under went scintigraphy in this study showed enlargement of right lobe of liver with altered distribution of Tc99m phytate with increased splenic and marrow uptake suggestive of early liver parenchymal dysfunction (Fig no1) and Tc99mmethyl diphosphonate-MDP bone scan showed bilaterally symmetrical arthritis in small and large joints of axial and appendicular skeleton. In our present study all patient treated with non-steroidal anti-inflammatory drugs, intravenous methylpredinsolone and oral corticosteroids, responded well to treatment, which is first line treatment of AOSD practiced globally. How ever Severe refractory, systemic, articular forms associated with complications various new class of drugs have been tried like Disease-modifying antirheumatic drugs like methotrexate, HCQs, leflunomide, and intravenous immunoglobulin. Newer biologic agent like Tocilizumab, anakinra and canakinumab, have showed promising result in some of the studies.

Fig no1:

Conclusions
PUO is one of the most challenging clinical situation encountered by all clinicians which involves ruling out vast categories of diseases like infection, maliganacies, drug fever, collagen vascular disorder, autoimmune diseases etc. AOSD which is polygenic multifactorial disease which is another great mimicker of PUO which manifestes with muti organ involvement.

Diagnosis of AOSD Challenging.Validated diagnosticYamaguchi criteria and judicious interpretation of serum ferritin in a patient with a compatible clinical presentation can assist in making early and correct diagnosis.

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