

Adult Onset Still's Disease (AOSD): Case Report: A Rare Cause of Fever of Unknown Origin (FUO)

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ABSTRACT

Fever of Unknown Origin (FUO) is one the complicated cases, which needs herculean task of extensive evaluation to finally arrive at the destination-diagnosis, especially in developing nations with wide array of infectious diseases. Noninfectious inflammatory diseases are usually the 2nd most common cause of FUO among which Adult Onset Still's Disease (AOSD) is a rare cause. We report a case of 16 years old male presenting with high grade fever, rash and arthralgia. Patient underwent detailed clinical examinations and wide array of investigations to finally arrive at the diagnosis of AOSD after ruling out possibilities of many infectious and non-infectious causes. We are discussing the clinical history, epidemiology, pathogenesis, clinical presentation, diagnosis, treatment, prognosis of Adult Onset Still's Disease.

Keywords: Fever of unknown origin; Adult onset still's disease; Rare diseases

INTRODUCTION

FUO was originally defined by Petersdorf and Beeson [1] in 1961 as an illness of >3 weeks duration with fever of $\geq 38.3^{\circ}\text{C}$ ($\geq 101^{\circ}\text{F}$) on two occasions and an uncertain diagnosis despite 1 week of inpatient evaluation.

FUO is now defined as follows:

Fever $\geq 38.3^{\circ}\text{C}$ ($\geq 101^{\circ}\text{F}$) on at least two occasions

Illness duration of ≥ 3 weeks

No known immune-compromised state

Diagnosis that remains uncertain after a thorough history-taking, physical examination, and the following obligatory investigations: determination of erythrocyte sedimentation rate (ESR) and C-Reactive Protein (CRP) level; platelet count; leukocyte count and differential; measurement of levels of hemoglobin, electrolytes, creatinine, total protein, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, lactate dehydrogenase, creatine kinase, ferritin, antinuclear antibodies, and rheumatoid factor; protein electrophoresis; urinalysis; blood cultures (n=3); urine culture; chest x-ray; abdominal ultrasonography; and Tuberculin Skin Test (TST) or interferon γ release assay (IGRA) [2].

Etiologies of FUO have changed over the time and geographic areas with infectious diseases dominating the majority followed by non-infectious inflammatory diseases and neoplasms so on. Mostly the non-infectious inflammatory diseases are second most common cause of FUO among which Adult Onset Still's Disease (AOSD) is one of the rare cause and a diagnosis of exclusion.

AOSD is characterized by high grade fever, associated evanescent rash over trunk, proximal limbs, arthralgia/arthritides and many nonspecific symptoms. It is the diagnosis of exclusion mostly as there are no specific markers, though recently decreased glycosylated ferritin is taken into consideration. After ruling out infections, other auto immune disorders and neoplasms this must be considered where diagnosis is based on Yamaguchi or Fautrel criteria [3,4]. Diagnosis on time and adequate treatment with initially corticosteroids followed by disease modifying anti-rheumatic drugs (DMARDs) or Biological help in preventing development of complications.

CASE PRESENTATION

16 years male patient presented to out-patient department with fever, rash and joint pain in both knee since two weeks, he was admitted to inpatient department, detailed relevant history was

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taken-revealing he had fever daily mostly in the evening or at night times, associated sweating, no chills but had rash on the trunk and limbs which disappeared sometime after fever settles in. He also had pain in both knees since 2 weeks, no morning stiffness, no swelling, no redness no small joint pains, no difficulty in walking due to pain. He also had history of malaise and back ache. No history of weight loss, reduced appetite, headache, disturbance in vision, ear-discharge, painful eye, no oral ulcers, toothache, no cough, no pain abdomen, nausea vomiting, diarrhoea, no burning micturition, no wounds, swellings. Past Personal and Family history was insignificant. On detailed examination patient comfortably sleeping on bed, height-170 cm, weight-45 kg BMI-15.57, under nourished, patient had temperature 102°, pulse 112/min, blood pressure 100/70 mm of Hg, well hydrated, RR-18 cycles/min. On general physical examination patient had maculo-papular salmon pink coloured rash on trunk and proximal limbs which disappeared after the fever settled, bilateral significant cervical and axillary lymphadenopathy, no joint swellings or redness, local rise in temperature. Respiratory system examination symmetrical chest, air entry bilaterally equal and no added sounds on auscultations in all chest areas, cardiovascular system examination was normal, nervous system examination revealed no focal deficits or any abnormalities and per abdomen examination was normal, no organomegaly was found clinically (Figures 1 and 2). Routine haematological and biochemical evaluation showed:

Hb=11.9 g/dl, Total leucocyte count=14200, 85% neutrophils,

Platelet count=2.42, PBF detail=neutrophilic leucocytosis normocytic normochromic anaemia rest normal study, ESR=106, CRP=51.3 mg/l highly raised, random blood sugar=92 mg/dl, Blood urea=42 mg/dl, creatinine=0.4 mg/dl, total protein=7.6 g/dl, albumin=4.5 g/dl, total bilirubin=0.6 mg/dl, direct bilirubin=0.2 mg/dl, SGOT=77I U/L, SGPT=119I U/L, ALP=268I U/L, BT,CT normal, prothrombin time=20 sec, INR=1.8 serum electrolytes normal, screening for infectious diseases=malaria, enteric fever, dengue, scrubtyphus, leptospira, brucella came negative, Ra factor negative, ASO titre negative, ANA qualitative profile negative, serum uric acid=4.0 mg/dl, serum Creatine kinase (NAC)=64.2U/L. serum ferritin=>1200 ng/ml highly raised, serum protein electrophoresis=normal study, no M band seen ag ratio=0.9, Mantoux test negative. Thyroid profile normal.

Radiological investigations=Chest radiograph, radiograph of both knee joints was normal. Ultrasonography of abdomen and pelvis was normal. Transthoracic 2d echo showed no evidence of rheumatic heart disease or infective endocarditis. Ultrasonography of neck and both axilla showed lymphadenopathy, Patient underwent FNAC of lymph node showing hypocellular smear with hemorrhagic background, later patient underwent excision biopsy of left axillary lymph node, histopathological examination showed features of chronic non-specific lymphadenitis, with no features suggestive of granuloma or malignancies.

Blood and urine cultures came to be negative (n=3).

Patient was initially started with parenteral antibiotics, anti-malarials and antipyretics continued for 1 week by that time

patient's infectious screen had come negative and first set of cultures had come negative, next set of cultures, serum electrophoresis, ANA profile, Serum ferritin, Serum protein electrophoresis were sent and antibiotic were stopped and patient was kept on just antipyretic and NSAIDS. Results were received after a week, within that patient also underwent all the above mentioned investigations. After the infections, malignancies and other connective tissue disorders ruled out patient was diagnosed to have adult onset still's disease by using Yamaguchi criteria.

Once the diagnosis of AOSD was considered patient was started on parenteral high dose corticosteroids for 5 days then shifted to oral dose and tapered over a month, also started on methotrexate low dose once weekly, with folic acid and NSAIDS. Patient improved clinically, fever, rash, joint pain, lymphadenopathy settled on maintenance therapy and patient is completely asymptomatic (Figures 3 and 4).



Figure 1: Showing the salmon pink maculopapular rash over the back of the patient.



Figure 2: Showing the salmon pink coloured rash over the anterior aspect of thigh of the patient.



Figure 3: Showing salmon pink rash over ventral surface of forearm of the patient.



Figure 4: Showing pink coloured rash over the arm of the patient.

RESULTS AND DISCUSSION

fever of unknown origin is one of the challenge to the physician especially in under developed and developing nations as the load of infectious diseases is immense. One may have to rule out so many infections bacterial, viral, fungal and parasitic too. Over that once done with the infectious diseases the never ending list of connective tissue disorders come onto play along with the neoplasms mostly. Among the non-infectious inflammatory diseases Adult Onset Still's Disease (AOSD) is one of the rare causes of FUO.

Still's disease is named after English physician Sir George Fredric Still-Systemic onset Juvenile Idiopathic Arthritis, adult onset variant was characterized by Bywaters,1971 [5].

AOSD is characterized by high grade fever, classic salmon pink evanescent rash, arthralgia or arthritis and associated features include sore throat, lymphadenopathy, hepatosplenomegaly, liver function test derangement with other various systemic

involvement. It is the diagnosis of exclusion, so exclusion of other rheumatological diseases is must and malignancies too. Over this there are no specific markers of AOSD, though ferritin and glycosylated ferritin are considered so, Calprotectin is under investigation [6].

With respect to the epidemiological data, exact incidence and prevalence is not available as the disease is very rare. With respect to age distribution, has bimodal peaks, first appearing in 15-25 years of age and next appearing in 36-46 years of age though affects younger population more can affect elderly too. Gender variation is found with more predominant in females than males [7,8].

Etiological factors can't be pinpointed though genetic factors, environmental factors, infections are being suggested no causative relation has been established. HLA subtypes association has been found in some studies.

Pathogenesis-the path to destination is yet to be dug in AOSD, it has been postulated that immune regulatory pathways are involved major role played by IL-1 which is proved by patients responding to IL-1 inhibitors anakinra, canakinumab treatment [8].

Clinically there are varieties of presentations but chief complaints are fever, high grade usually in the late afternoon, daily spiking or alternate day associated with rash which appears with fever and disappears after some time the fever settles in. In our case patient had high grade fever with evanescent rash which mostly occurred in the evenings. Though in tuberculosis rash is not present evening rise of temperature is very common with associated weight loss, loss of appetite and other features like cough, or lymphadenopathy which dictates ruling out tuberculosis is must in endemic nations. Rash in the AOSD is maculopapular involving trunk, proximal limbs rarely involving distal limbs and face. In our case patient had maculopapular salmon coloured evanescent rash over the trunk, and proximal limbs. Patients also have joint pains-arthralgia, arthritis involving large joints most commonly knee, ankle, shoulder elbow, wrist- in our case bilateral knee joint pain was the complaint but there was no signs of synovitis. Pharyngitis is also one of the common presentations which usually precedes or presents along with other symptoms our patient had no sore throat. Myalgia can be present specially during febrile episodes.

On clinical examination pallor may be present due to normochromic normocytic of chronic disease, rarely jaundice due liver function derangement, lymphadenopathy is found in majority patients usually generalized hence ruling out leukemias, lymphomas, chronic granulomatous infections is must. Our case had generalized lymphadenopathy involving bilateral cervical and axillary lymph nodes. Hepatosplenomegaly is another significant finding which our case didn't have. Musculoskeletal examination may reveal tenosynovitis arthritis involving large joints mostly.

Rarely pleuritis, pericarditis can be manifested. Macrophage activation syndrome one the rare life threatening complication seen in AOSD.

Laboratory findings include normocytic normochromic anaemia, neutrophilic leucocytosis, thrombocytosis, elevation in liver enzymes, kidney function tests are rarely deranged. With elevated inflammatory markers-ESR, CRP persistently elevated, serum ferritin markedly raised, glycosylated ferritin reduced. ANA and RA factors negative in most of the cases. No pathognomonic markers available for AOSD serum calprotectin is under investigation [6].

Diagnosis is made after excluding infectious diseases, other non-infectious inflammatory diseases and malignancies. After the exclusion the most sensitive diagnostic criteria-Yamaguchi's criteria [2] is applied.

Major criteria are as follows:

Fever of at least 39°C for at least a week.

Arthralgia or arthritis for at least 2 weeks.

Nonpruritic salmon coloured rash on trunk/extremities.

Granulocytic leukocytosis.

(10,000/microL or greater).

Minor criteria are as follows:

Sore throat.

Lymphadenopathy.

Hepatomegaly or splenomegaly.

Abnormal liver function tests.

Negative tests for RF and ANA.

Diagnosis requires at least 5 features with at least 2 of them being major criteria.

In 2002 Fautrel et al. proposed a new criteria [4].

Major criteria are as follows:

Spiking fever $\geq 39^\circ\text{C}$.

Arthralgia.

Transient erythema.

Pharyngitis.

Neutrophilic polymorphonuclear count $\geq 80\%$.

Glycosylated ferritin fraction $\leq 20\%$.

Minor criteria are as follows:

Typical Still's rash.

Leukocytosis (10,000/mm³).

Diagnosis of AOSD by Fautrel criteria requires 4 or more major criteria or 3 major and 2 minor criteria.

3 distinct sub categories of AOSD according to clinical presentation [7,8].

Mono cyclic-single episode followed by complete remission.

Poly cyclic-2 or more episodes separated by symptom free period of at least 2 months.

Chronic articular pattern characterized by severe articular presentation with destruction of joints.

CONCLUSION

First line management includes corticosteroids and non-steroidal anti-inflammatory drugs (NSAIDs). Followed by Disease Modifying Antirheumatic Drugs (DMARD) methotrexate, cyclosporine, azathioprine, cyclophosphamide are used for maintenance therapy and also to reduce steroid induced side effects. Recently biologicals have been for management of AOSD-anakinra-recombinant antagonist of IL-1 receptor, canakinumab-human monoclonal antibody against IL-1 β , RILONACEPT-soluble IL-1 trap fusion protein, tocilizumab-monoclonal antibody against IL6. Plasma exchange and intravenous immune-globulins are also treatment option in non-responding cases

Half a century gone from its initial description still the Adult Onset Still's Disease is a diagnostic dilemma to the clinicians with management guidelines yet to be drafted and no pathognomonic markers.

CONFLICT OF INTEREST

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

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