ADULT ONSET STILL'S DISEASE-A DIAGNOSIS OF EXCLUSION

Tejasvi H. T[1]

[1]*Senior Resident, Department of General Medicine, ESICMC & PGIMSR, Rajajinagar, Bangalore, Karnataka.*

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PRESENTATION OF CASE

A 27-year-old lady, married came with chief complaints of fever since 1-month duration and pain in both knee joints, since 20 days. Fever was high grade, 2-3 spikes /day, not associated with chills or rigor. Right knee joint pain followed with left knee, not associated with swelling or any skin discolouration.

Patient was worked up extensively for 3 weeks with investigations ranging from complete blood count, Fever profile including– malaria, leptospirosis, dengue, blood culture, Urine routine and culture, Blood for fungal culture, ANA, RA factor, anti- CCP antibody, p- ANCA, c- ANCA, Quantiferon Gold TB test, Bone marrow aspirate and biopsy, IgM for Brucella, IgM for chikungunya, EBV, HIV, HBsAg, HCV, CT brain and CT abdomen which were all negative. Significant investigations were –CBC s/o Leucocytosis and Raised neutrophils count, ESR was raised (110 mm per hour), Ferritin was raised (???), USG abdomen and pelvis reveal mild hepatosplenomegaly, 2D Echo s/o minimal pericardial effusion, CT-Thorax s/o bilateral minimal pleural effusion, Whole body PET scan – s/o bilateral minimal pleural effusion. Patient had received – Antimalarials and antibiotics like Ceftriaxone (for 5 days), Piperacillin+Tazobactum (for 7 days), Meropenem (for 11 days), but still fever persisted even after 4 weeks in a private hospital and hence patient was referred to our Sir J.J.Groups of hospital, Mumbai for further management.

27-year-old married female with symptoms of fever, arthralgia, and intermittent rash of 1-month duration; On Examination the patient was well built, conscious and oriented, patient was febrile 103°F, heart rate of 98b/min, blood pressure of 110/70 mmHg, with Effervescent reddish macular rash over both hands, and normal jugular venous pressure, with no pallor / lymphadenopathy. Mild Hepato-splenomegaly was present, and investigations showing leucocytosis with neutrophilia and raised ESR, Polyserositis, raised ferritin levels with negative ANA and RA-Factor. We diagnosed it as an Antibiotic induced fever / AOSD. We stopped antibiotics soon after the admission but still fever persisted even after 3-4 days. Patient was started on Prednisolone of 1 mg/kg BW and NSAIDS –Diclofenac sodium 50 mg bid.

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Corresponding Author:
Dr. Tejasvi H. T,
Senior Resident, Department of General Medicine,
ESICMC & PGIMSR, Rajajinagar, Bangalore, Karnataka.
E-mail: tejasviht@gmail.com
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Patient became asymptomatic after 2 days and was discharged with advice of Tapering of steroids after 1 month of full course. Patient was asymptomatic when he came for regular check up

DIFFERENTIAL DIAGNOSIS

- Acute and chronic infection
- Haematological malignancy
- Rheumatic fever

CLINICAL DIAGNOSIS

It is mainly diagnosed by Yamaguchi criteria

AOSD is a chronic multi-systemic inflammatory disease of unknown aetiology that predominantly affects young adults. The common presentation of the disease is fever of unknown origin, polyarthritis and skin rash. Ambiguity in presentation and lack of serologic markers make diagnosis difficult. A 27-year-old married female presented with fever, skin rashes and arthralgia for 1 month. On Detailed examination and investigation, she was found to be fulfilling the criteria for Yamaguchi criteria for AOSD[1]. All other causes for acute or chronic infections, haematological malignancies and other rheumatic disorders were excluded by laboratory investigations. Patient was treated with Non-steroidal anti-inflammatory drugs and steroids.

DISCUSSION OF MANAGEMENT

AOSD is characterised by fever, an evanescent skin rash, polyarthralgia, hepatosplenomegaly, leucocytosis and high serum ferritin level. It is a difficult diagnosis to make, as there is no diagnostic test for the disease and it is a great mimicker of other conditions, such as autoimmune disorders and haematological malignancies. AOSD is rare and has a bimodal age distribution in all ethnic groups with peaks at 15- 25 and 36-46 years of age in both sexes with an incidence of 0.16 cases /100000 persons /year. The disease may have a monocyclic (25-30%), polycyclic (25-30%) or chronic course (30-50%).

AOSD was initially described in 1897 by George F. Still, a pathologist. The characteristic features of this illness have subsequently been reported in adults, as detailed by Eric By waters in 1971, exact aetiology is not known but role of infection genetic and environmental factors cannot be ruled out.[2-4] There is a correlation between several cytokines in the pathogenesis of AOSD, including Tumor necrosis factor-alpha (TNF-α), interleukin (IL)-6 and IL-18. The levels of these cytokines are highly elevated in active AOSD.[5]

Patients with AOSD typically present with fever, rash, sore throat and arthralgia.[6] The fever normally exceeds 39.0°C and highest temperatures are seen in late afternoon and early evening.[7]

The typical rash in AOSD is asymptomatic and is described as salmon-pink, maculopapular eruptions mainly affecting the trunk and extremities.[8,9] Sore throat is one of the major signs of AOSD and may be associated with odynophagia.[10] Arthralgia and arthritis mainly involving the knees, wrists, ankles and elbows have also been noted. The flare up of joint symptoms occurs during the febrile spikes.[11,12] Carpal joints are the target of most destructive arthritis in AOSD.[13] Other features of AOSD include lymphadenopathy,[14] hepatosplenomegaly,[15] pericarditis, pleuritis and central nervous system involvement.[16]

Laboratory studies show marked ESR elevation and leukocytosis with predominance of neutrophils. Disproportionately elevated ferritin is characteristic of AOSD.[17] Almost 70% of patients have hyperferritinemia,[10] which was thought to be due to cytokine secretion induced by the reticuloendothelial system or hepatic damage. In most cases however; the ferritin levels increased without obvious liver damage.[18,19] Liver enzymes are elevated in almost three quarters of patients.[20] Rheumatoid factor and antinuclear antibody are generally negative.[21]

In the early stages of the disease, diagnosis of AOSD is difficult. Before making a diagnosis of AOSD, other diagnoses including infections such as infectious mononucleosis, malignancies (especially lymphoma), and other rheumatic diseases such as systemic vasculitides should be ruled out. Investigations were done to rule out the possible causes before this patient's diagnosis was reached. The Yamaguchi criteria (1992), is the most widely used criteria to diagnose AOSD with a 93.5% sensitivity.[22] In these criteria, there are 4 major and 4 minor criteria with 3 exclusion criteria. The 4 major criteria include: arthralgia more than two weeks, fever more than 39°C for more than 1 week, typical rash and leukocytosis for more than 10,000/mm^3 including more than 80% granulocytes. While the 4 minor criteria include: sore throat, lymphadenopathy or splenomegaly, liver dysfunction, negative RF and ANA. Five or more criteria must be met in order to make a diagnosis of AOSD, including 2 or more major criteria, after excluding infections, malignancies or rheumatic diseases. According to Yamaguchi criteria our patient has fulfilled 4 major and 2 minor criteria

Non-steroidal anti-inflammatory drugs (NSAIDs) or aspirin are recommended as the initial treatment in AOSD, but low response rate AHS been reported.[23] Prednisolone should be started for patients for the patients who are not responding to NSAIDs.[24] Disease modifying anti-rheumatic drugs (DMARDs) such as methotrexate have been used to control the acute symptoms, and it is suggested that at least 6 months of therapy should be given to allow ample time for the assessment of the therapeutic effect.[25] Sulfasalazine appears to have severe adverse reactions in AOSD and should be avoided.[26]

For patients who do not respond to conventional medications such as corticosteroids and DMARDs, biological agents should be considered. Since cytokines such as TNF-alpha, IL1 and IL6 involved are implicated in the pathogenesis of AOSD; biologic agents targeting these cytokines have proven to be effective in treating AOSD. Three different patterns have been described in AOSD,[27] And the prognosis is variable. The first category of patients tend to have monocyclic or self-limited pattern with complete remission within a year. The second group have intermittent or polycyclic pattern with recurrence of systemic and articular flares separated by periods of remission as shown in our patient. The final group show chronic joint problems and are prone to joint destruction.

AOSD is a rare disease with unknown etiology and pathogenesis. It should be considered in patients presenting with rash, arthritis and fever after excluding other possible diagnoses such as malignancies, infections and rheumatic diseases.

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