An interesting case of FUO - Adult-onset Still's disease

POORNIMA RAJ

Department of General Medicine,
MADRAS MEDICAL COLLEGE AND GOVERNMENT GENERAL HOSPITAL

Abstract: Adult-onset Still's disease (AOSD) is a systemic inflammatory disorder of unknown etiology and pathogenesis. AOSD remains a painstakingly difficult clinical diagnosis, largely because of its rarity, protean manifestations and a lack of pathognomic features or diagnostic tests. An elderly female presented to us with fever for 6 months duration and she was diagnosed to have AOSD. We report this case since AOSD is one of the rare causes of FUO and even more rare at this age as only 8 percent of the cases present at more than 50 years.

Keyword: Adult-onset Still's disease, fever of unknown origin, serum ferritin

CASE REPORT:
A 55 year old female presented with fever for 6 months and joint pain and swelling of legs for 3 months. Fever was high grade to a peak of 104 degree Fahrenheit, intermittent, not associated with chills or rigors and relieved temporarily with antipyretics. Generalized arthralgia was present not associated with joint swelling or tenderness. Patient also had complaints of pedal edema, easy fatigability, loss of weight and loss of appetite. There is no history of cough or expectoration, night sweats, chronic diarrhea, burning micturition, jaundice, vomiting, bleeding manifestations, abdominal pain, head ache, altered sensorium, photosensitivity, alopecia or skin rashes. For these complaints patient was hospitalized repeatedly but her symptoms did not improve. Patient did not have any similar illness in the past. She is not a diabetic or hypertensive. No history of tuberculosis or anti-tuberculous therapy in the past. No history of contact with pet animals or exposure to poultry. No history of previous blood transfusions or surgeries in the past. She attained menopause 5 years back. On examination she was febrile and pale. Axillary and inguinal lymph nodes enlarged to a size of 1 x 2 cm, firm in consistency, mobile and were not tender. Bilateral soft, non-tender, pitting pedal edema was present extending up to knees. There was no icterus, clubbing, rashess, petechiae or sternal tenderness. She had tachycardia, temperature of 104 degree Fahrenheit and a normal blood pressure. JVP was not elevated. Cardiovascular and respiratory system examination was normal. There was no organomegaly per abdomen and there was no neck stiffness or focal neurological deficits. Hemogram showed elevated total count with increased polymorphonuclear cell, hemoglobin of 8 g/dl and an elevated ESR of 120 mm in 1 hour. LFT was deranged with elevated bilirubin (3 mg/dl, direct 1.2 mg/dl), mildly elevated enzymes (SGOT: 57 IU/l, SGPT: 66 IU/l, GGT: 47 IU/l, ALP: 151 IU/l) and decreased serum albumin (1.5 g/dl). Albumin-globulin ratio was reversed. Coagulation profile and renal function tests were within normal limits. Stool examination for occult blood was negative. Mantoux and sputum for AFB were negative. MP QBC, MSAT and Widal were negative. Blood, urine and sputum cultures showed no growth. HIV-ELISA was non-reactive. Patient was negative for anti-HCV, HBsAg and Brucella antibodies. ECG showed sinus tachycardia. Chest X-ray, echocardiography and HRCT chest were normal. USG and CECT abdomen showed mild hepatomegaly.
symptoms that include highspiking fevers, a characteristic rash and cytokines [IL-2, IFN and TNF and IL-6 and IL-18]. AOSD is a triad of etiopathogenesis of AOSD. There is increased levels of Th1 shown altered cytokine production as a major factor in burgdoferi in the pathogenesis of AOSD. Recent studies have proposed parvovirus B19, hepatitis B and hepatitis C. Other studies have the highest temperatures seen in the late afternoon or early evening. arthritis/arthralgias. Fever is the most common symptom with an Coxsackie virus B4, adenovirus, in fluenza A, human herpes virus 6, echovirus 7, cytomegalovirus, Ep steinBarr virus, parainfluenza, syndrome secondary to various infections such as rubella, mumps, B17, B18, B35 and DR2. Others have suggested it to be a reactive disorder. It is named after George Still who in 1897 described 22 children with signs and symptoms of the disease entity presently known as systemic onset juvenile idiopathic arthritis. In 1971, Eric Bywaters described 14 adults with presentation similar to pediatric Still's disease, establishing the new disease entity. In the French and German literature this condition is called the "WisslerFanconi syndrome". AOSD is very rare and it is slightly more common in females than in males. The disease characteristically affects younger people, with nearly 75% of the patients having onset between 16 and 35 years of age. Several cases have also been reported after the age of 60. Stress has been suggested as an important risk factor for all ages. The etiology and pathogenesis is presently not known. Few studies have shown association with HLA B17, B18, B35 and DR2. Others have suggested it to be a reactive syndrome secondary to various infections such as rubella, mumps, echorivirus 7, cymegalovirus, EpsteinBarr virus, parainfluenza, Coxsackie virus B4, adenovirus, influenza A, human herpes virus 6, parvovirus B19, hepatitis B and hepatitis C. Other studies have proposed Mycoplasma pneumoniae, Chlamydia pneumoniae, Yersinia enterocolitica 3 and 9, Brucella abortus and Borrelia burgdofeni in the pathogenesis of AOSD. Recent studies have shown altered cytokine production as a major factor in etiopathogenesis of AOSD. There is increased levels of TNF cytokines [IL-2, IFN and TNF and IL-6 and IL-18]. AOSD is a triad of symptoms that include highspiking fevers, a characteristic rash and arthritis/arthralgias. Fever is the most common symptom with an incidence of around 95%. It usually exceeds 39°C, transient, lasting around 4 hours and is most commonly quotidian in pattern, with the highest temperatures seen in the late afternoon or early evening. The typical rash is an evanescent, salmonpink, maculo-papular eruption, predominantly found on the proximal limbs and trunk, with rare involvement of the face and distal limbs and is usually accompanied by fever. Arthralgia and arthritis are found in the majority of patients with AOSD. Joints affected most frequently are the knees, wrists and ankles, although involvement of the elbow, shoulder, proximal and distal interphalangeal joints, metacarpophalangeal joints, metatarsophalangeal joints and temporomandibular joints. Carpal and pericapitate abnormalities are typically higher than in cases of rheumatoid arthritis. The pattern of arthritis is typically symmetric and is associated with fever spikes. Other common manifestations include myalgia and liver abnormalities including hepatomegaly and abnormal liver function test. Less common manifestations include pleuritis, pericarditis and splenomegaly. Cardiac complications include tamponade and myocarditis. Pulmonary manifestations include fibrosis, pleural effusions and rarely, adult respiratory distress syndrome. Renal involvement manifests as interstitial nephritis, subacute glomerulitis, renal amyloidosis or collapsing glomerulopathy. Haematological complications (thrombocytopenic purpura, pure red cell aplasia) and neurological complications (cranial nerve palsies, seizures, aseptic meningoencephalitis, MillerFisher syndrome) are rarer still. Erythrocyte sedimentation rate and C reactive protein levels are often elevated. Anemia, leucocytosis with striking neutrophilia is a common feature. Liver enzymes (LDH, AST,ALT) and bilirubin is often elevated. Liver biopsy shows perportal inflammation with monocyte infiltration. Serum ferritin level is elevated and is usually greater than 5 times the normal upper limit. Serum ferritin level correlates with disease activity and it normalizes during remission. Glycosylated fraction of ferritin is more specific. In AOSD less than 20% of ferritin is glycosylated compared to 50 - 80% in normal subjects. It cannot be used to assess disease activity as levels continue to be low for many months. X-ray is not much useful. In acute phase it shows soft tissue swelling, joint effusion and mild periartricular deminerlization. Specific features include intercarpal and carpometacarpal joint space narrowing producing ankylosis. Several diagnostic criteria exist. Yamaguchi criteria is shown to be the most sensitive followed by Cush and Calabro.

**Yamaguchi criteria**

**Major criteria**
- Fever of at least 39 degree Celsius for 1 week
- Arthralgia or arthritis for at least 2 weeks
- Non pruritic salmon colored rash (usually over trunk or extremities while febrile)
- Leucocytosis ( 10,000 cells/µl) with granulocyte predominance

**Minor criteria**
- Sore throat
- Lymphadenopathy
- Hepatomegaly or splenomegaly
- Abnormal liver function tests
- Negative anti-nuclear antibodies and rheumatoid factor

Five features are required for diagnosis with at least two being major diagnostic criteria. A new criteria proposed by Faurel et al also includes ferritin levels but is yet to be validated.
Treatment is aimed at minimizing inflammation and retarding disease progression. NSAIDs are initially started and along with steroids shown to have marked improvement. Intra-articular steroid injections may be used in severe and chronic joint disease. DMARDs and biological agents like anakinra and tocilizumab (humanized anti-IL-6 receptor monoclonal antibody) are used in resistant cases. Refractory cases are treated with plasmapheresis and IV immunoglobulin.

REFERENCES: