

CASE REPORTS

THIRTY TWO YEARS MALE PATIENT WITH ADULT STILL'S DISEASE

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Abstract:

A rare systemic inflammatory disorder is Adult onset Still's disease (AOSD), characterized by diverse clinical and laboratory findings, which is often difficult to diagnose. It is responsible for a significant proportion of cases of acute febrile illness in young adults. Adult Onset Still's Disease (AOSD) usually affects multiple organs, but it is a diagnosis of exclusion. Here we describe a case of a 32-year old patient with fever of unknown etiology, arthralgia, sore throat and skin rash. The final diagnosis of Still's disease was made by clinical and laboratory criteria and exclusion of other causes of similar presentation.

Introduction:

Adult onset Still's disease (AOSD) is a rare systemic inflammatory disorder the aetiology of which is unknown, and the quotidian or double-quotidian spiking fevers with an evanescent rash, arthritis, and multiorgan involvement are the characteristic feature. In 1897 George Still published his monograph, in which he describes 22 children with signs and symptoms of the disease entity currently known as systemic onset juvenile idiopathic arthritis. Eric Bywaters described 14 adults with similar presentation in 1971 and establishing the new disease entity with paediatric Still's disease. However, in 1896 the Lancet first published the description of an adult patient with signs and symptoms of AOSD, which is labeled as rheumatoid arthritis. Occasional reports of AOSD are found, in the French and German literature called "subsepsis allergica" or "Wissler's syndrome" and later the "Wissler-Fanconi syndrome". There is no consensus on its incidence and prevalence in different populations as AOSD is rare and not readily diagnosed. The disease characteristically affects younger people, and women are slightly more affected than male. However in different studies it has been found that AOSD can affect all ages, and several cases have been reported after the age of 60. It has been suggested that stress is an important risk factor for all ages.¹

The Case Report:

A 32 year old man hailing from Badda Dhaka, presented to us, at Medicine Out Patient Department, DMCH with 6 weeks history of high fever with rigors

and spikes at night lasts for 4-5 hours and relived with sweating. He had pain in joints involving both knee, shoulder, elbow and metacarpophalangeal joints and erythematous rash all over the trunk. Rash appears prominently with spikes of fever and almost disappeared when temperature subsided. He Also gives history of difficulty in deglutition and throat pain. Review of Systems revealed no alopecia, Raynauds phenomenon, sicca, photosensitivity, or aphthous ulcers. No significant Past medical history, Family history, and allergic history. Social history revealed he is nonsmoker, non alcoholic and no history of intravenous drug use or extramarital sexual exposure. Medications used are Azithromycin and Paracetamol.

On examination he was found to be febrile with Temperature: 39°C, non-itching macular erythematous rash on the trunk. He had tenderness of both knee, elbow, shoulder and metacarpophalangeal Joint with mild restriction of motion of joints, both actively and passively, with redness and swelling. There is pharyngeal erythema but no oral ulcers, no alopecia, no lymphadenopathy or subcutaneous nodules and clubbing. Chest examination is normal, Heart: Regular with no pericardial friction rub or murmur and in Abdomen: no hepatosplenomegaly.

On investigation, Complete blood count and Blood film reveals, WBC - 20.1 X 10⁹/L with a PMN predominance of 88%, Hematocrit - 43%, Platelets - 286 X 10⁹/L, ESR - 100 mm/1st Hr, Hb (Cyn. Meth.) - 12.6 g/dl (normal is 13-17 g/dl), PBF: RBC - Normocytic and normochromic, WBC - Mature

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with Neutrophil Leukocytosis , Plateletes – Normal. Urinalysis is negative for protein or red cells. LFT shows, S.Bilirubin – 2.2 mg/dl, ALT(SGPT) – 102 U/L, AST - 98 U/L, Alkaline phosphatase – 145 U/L, Prothrombin time – 13.5 sec (control 12 sec). HBsAg and Anti HCV by ELISA method is Negative. USG of whole abdomen is normal. No organism is isolated in Blood culture and Urine culture. Chest radiograph is normal. His ASO titer is 298 IU/ml (normal is <200 IU/ml) and CRP – 48 mg/L (normal <5 mg/ml). Serum Ferritin – 599 ng/ml (normal is 28-397 ng/ml), RA test and ANA is negative. ECG is within normal limit.

Discussion:

In this case we have some differentials. Early in the presentation the acute onset of high fever and symmetric arthritis makes it a possibility of viral arthritis, but the longer duration of symptoms and Neuticophilic Leukocytosis in blood count excludes the diagnosis. Systemic lupus erythematosus is another possibility but lack of other clinical features and the negative ANA made this diagnosis very unlikely. Although rheumatoid arthritis can present with these features but the presence of pharyngitis, along with the presence of fever and arthralgia, in this patient also helps to exclude the differential diagnosis, because sore throat is distinctly uncommon in most rheumatic diseases presenting with arthralgias and constitutional symptoms with or without a rash. However, in case of Acute Rheumatic Fever and Adult Onset Stills Disease, Pharyngitis is commonly associated.² In this patient, although ASO titer is a little bit raised, but the age of the patient makes the diagnosis unlikely. Although a solid tumor malignancy, can present with fever and articular symptoms, but the patients young age and lack of other evidence ruled out this diagnosis.

The exact aetiology of AOSD, is currently unknown. A genetic component linking the disease with a number of HLA antigens has been suggested by many studies. One hypothesis has been very popular that AOSD may be a reactive syndrome, where various infectious agents triggers disease activity in a genetically predisposed host, and a variety of organisms have been proposed including self limited viral infections and other microbial triggers, like Mycoplasma Chlamydia etc. in the pathogenesis of AOSD.^{1,2} Recently, it has been suggested that alterations in cytokine production have an important pathophysiological role in AOSD. Serum levels of IL6,

TNF α , and INF γ , were significantly increased with active AOSD when compared with controls.¹ Another proinflammatory cytokine is IL18, which is overproduced in the acute phase of the disease. Genetic polymorphisms of the human IL18 gene and the S01/S01 diplotype is associated with disease susceptibility. Serum levels of soluble IL2 receptors, IL4, and IL18 correlated with chronic articular AOSD activity, while IFN γ , and IL8, TNF α , soluble TNF receptor and IL18 levels were persistently raised, even in disease remission, in both the systemic and the chronic articular forms of AOSD.¹

The triad of symptoms including high-spiking fevers, a characteristic rash, and arthritis/arthralgias are the typical manifestations of ASOD. Fever is usually more than 39C, lasting typically under 4 hours, and is most commonly quotidian or double quotidian in pattern. Fever can herald the onset of other manifestations as well, with serositis, sore throat, myalgias, and arthralgias described. The typical rash is characterized by salmon-pink, maculopapular eruption, predominantly found on the proximal limbs and trunk, the face and distal limbs are rarely involved. The majority of patients with AOSD presented with arthralgia and arthritis. The knee, wrist, and ankles joints are most frequently affected although involvement of the elbow, shoulder, proximal and distal interphalangeal joints, metacarpophalangeal and metatarsophalangeal joints, temporomandibular joints, and hip joint have also been described. The arthritis is typically symmetrical, and joint pain is associated with fever spikes. Approximately 1/3 of patients develop chronic persistent disease with progressive joint damage. The typical changes in the wrist with progressive joint space narrowing in a pericarpitate or carpometacarpal distribution develops 6 months after disease onset, and ankylosis develops after 1.5–3 years. The Another common manifestation is myalgia which is generalised, and most often appears with exacerbations of fever. Hepatic abnormalities like jaundice and acute hepatitis, predominantly hepatomegaly and abnormalities in liver biochemistry, are present but hepatic failure, requiring liver transplantation is rare. Pleuritis, pericarditis, and splenomegaly are less common manifestations of ASOD. Additional cardiac complications like tamponade and myocarditis are also found to a lesser extent. Pulmonary manifestations like fibrosis, pleural effusions, and, rarely, adult respiratory distress

syndrome are also noted. Renal disease may be in the form of interstitial nephritis, subacute glomerulitis, renal amyloidosis and, the more recently described, collapsing glomerulopathy. More rarer manifestations include Haematological complications (thrombotic thrombocytopenic purpura, pure red cell aplasia), and neurological complications (cranial nerve palsies, seizures, aseptic meningoencephalitis, Miller-Fisher syndrome).¹⁻³

The Adult Onset Still Disease is diagnosed mostly clinically with the help of laboratory profile and various sets of Criteria is used to define the disease. The currently available tests: complete blood count and differential, ESR, CRP, ANA, and RF (both negative), liver function tests (LFTs) and albumin, ferritin, and glycosylated ferritin (if available) are done. The erythrocyte sedimentation rate (ESR) was raised in virtually all patients and C reactive protein (CRP) may also be found to be raised a reflection of the systemic inflammation. Leucocytosis, anaemia, and thrombocytosis are common haematological abnormalities. Neutrophilia is probably secondary to bone marrow granulocyte hyperplasia which often accompanies increased disease activity. Anaemia is due to chronic disease, which often returns to normal when the disease subsides. Reactive thrombocytosis is common. Patients with fever and exacerbations of arthritis show frequent increases in lactic dehydrogenase, aspartate aminotransferase, alanine aminotransferase, c-glutamyltransferase, and bilirubin. Liver biopsy typically shows mild periportal inflammation with monocyte infiltration. Recently, serum ferritin and glycosylated ferritin have been used as diagnostic and disease activity markers. Ferritin, an acute phase reactant, is increased in inflammatory processes, including the mechanisms underlying oxidative stress due to increased production of ferritin by the histiocytemacrophage system and/or increased release from damaged hepatocytes. Ferritin levels are usually higher than other autoimmune or inflammatory diseases in patients with ASOD. Glycosylated fraction of ferritin may be a more specific diagnostic marker than ferritin. Normally 50–80% of ferritin is glycosylated, for protection from proteolytic enzymes. Glycosylated fraction drop to 20–50% in inflammatory diseases as glycosylation mechanisms are saturated. In AOSD, This phenomenon is particularly prevalent where the glycosylation of ferritin is often <20%. Ferritin can be used as a disease activity marker as it reduces when disease activity

subside but Glycosylated ferritin cannot be used to monitor disease activity or response to treatment, as it remains low for many months after the disease goes into remission. Better new immunological tests, such as IL18, may be useful in the near future for diagnosis as well as monitoring disease activity and response to treatment. During the initial acute phase of the disease plain radiographs are not usually very helpful in establishing the diagnosis, rather radionuclide bone scan and gadolinium enhanced magnetic resonance imaging may be more sensitive imaging modalities for early diagnosis and successful treatment in follow up.¹⁻⁴

The heterogeneous clinical presentation of AOSD make the spectrum of differential diagnoses wide.¹ The extensive work up is needed to exclude infectious, neoplastic, and autoimmune disorders, before the diagnosis of AOSD can be made.² This costly and time consuming work may be obviated if Several diagnostic criteria sets for AOSD is used.⁵ Among these Yamaguchi's criteria were shown to be the most sensitive (93.5%).¹

Yamaguchi's *M et al* criteria ⁵

Major Criteria

1. Fever > 39C or higher lasting 1 week or more
2. Arthralgia
3. Typical macular evanescent rash
4. Leucocytosis (10,000/cmm), with 80% or more Granulocytes

Minor Criteria

1. Sore throat
2. Lymphadenopathy and/or splenomegaly
3. Liver dysfunction
4. Negative RA and DNA

Presence of total of 5 criteria with 2 or more major criteria have 96.2% sensitivity and 92.1% specificity

Our patient fulfill the 4 major and 3 minor Yamaguchi's criteria. So the diagnosis of Adult Onset Still Disease is confirmed.

The treatment in AOSD is exclusively empirical, and has centred around the use of NSAIDs, steroids, and antirheumatic agents to control fever, arthritis, and systemic symptoms. NSAID is effective in controlling disease in only 7–15% of patients, when used singly and most patients require steroids with responses ranging from 76% to 95%.¹ Different case report also

describes the usefulness of intravenous pulse methylprednisolone (in dose of 1 g/daily during 3 days) and dexamethasone as a prednisone alternative to treat disease refractory to oral prednisone.^{1,4}

The use of antirheumatic drugs should be reserved where the combination of NSAIDs and steroids fails, or in which there is lack of tolerance or adverse events of steroid. Antirheumatic drugs include ciclosporin A, hydroxychloroquine, gold, penicillamine, azathioprine, cyclophosphamide, and methotrexate (MTX). MTX treatment is very much useful in treatment of Polyarthritits but on non-articular manifestations of AOSD the effect of MTX was less well defined.¹ The treatment of flares of AOSD and disease refractory to NSAIDs, with intravenous gammaglobulin (IVIg) at doses ranging from 0.4 to 2 g/kg/day for 2–5 days, has also been described in different studies. In a patient where multiple immunosuppressive drugs and plasmapheresis had failed, TNF blocking agents (Etanercept) was used successfully in conjunction with MTX and corticosteroids. The effectiveness of the monoclonal chimeric anti-TNF α antibody (Infliximab) in AOSD, has also been reported in various open label trials. The use of anti-human IL6 monoclonal antibody (MRA) is also reported in one case which is refractory to MTX, ciclosporin A, and prednisolone. Most recently, a patient with refractory AOSD, for whom multiple disease modifying antirheumatic drugs (MTX, sulfasalazine, ciclosporin A), IVIg, and TNF inhibitors had failed, IL1 blockade (with anakinra) has emerged as a possible new therapeutic option. The patient reported a decrease of arthritic and systemic symptoms within weeks, paralleled by a normalisation of serum acute phase reactants, When anakinra 100 mg subcutaneously/day is used in conjunction with MTX 25 mg/week, prednisolone (20 mg/day), and naproxen.¹

In our case we use a moderate dose of prednisolone (40 mg/day) and Naproxane (250 mg, twice daily). The patient is responded well and his fever, joints symptom subside along with decrease in total count and ESR.

The clinical course and prognosis can be described in three categories. 1. The self limited or monocyclic pattern which is characterised by systemic symptoms (fever, rash, serositis, and organomegaly), remission usually occur within 1 year from the first and only disease episode. 2. The intermittent or polycyclic

systemic pattern characterised by recurrent flares, with or without articular symptomatology and complete remission between the flares. The flare may be years apart and tend to be milder than the initial episode. 3. The chronic articular pattern which is characterised by articular manifestations that can be severe and lead to joint destruction. These patients generally have more disability and worse prognosis than patients with only systemic symptoms.¹

Conclusions:

The diagnosis of AOSD is often very challenging and difficult. The diagnosis must be based on detailed analysis of patient's history, physical examination and laboratory tests. Patients with fever of unknown origin may be diagnosed eventually with AOSD but infections, malignancy, and autoimmune disorders should be ruled out before the diagnosis of AOSD is made. The diagnosis and management of this complex systemic disorder is simplified by the presence of validated diagnostic criteria and better serologic markers reflecting increased immunological activity. Treatment of AOSD is usually done with non-steroidal anti-inflammatory drugs, corticosteroids, immunosuppressive drugs (methotrexate, leflunomide, gold, azathioprine, ciclosporin A, cyclophosphamide), and intravenous gammaglobulin. The recent successful application of biological agents (anti-tumour necrosis factor, anti-interleukin (IL)1, anti-IL6), often in combination with traditional immunosuppressive drugs, has been very promising. So it is important for the physicians to keep in mind about the existence of adult Still's disease in cases of unknown etiology of fever.

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