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RESEARCH ARTICLE

ADULT-ONSET STILL'S DISEASE – A CASE REPORT

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ABSTRACT

This article is prepared on Adult onset Still's disease, which is a rare disorder. The most accepted pathophysiology is the autoinflammatory response. We here report a young lady diagnosed with AoSD who presented with complaints of fever, joint pain and sore-throat.

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INTRODUCTION

Adult-onset Still's Disease is rare systemic inflammatory disorder of unknown etiology affecting usually young adults, characterized by fever, arthralgia and distinctive salmon-colored rashes (1) . Adult-onset Still's disease (AoSD), called Wissler–Fanconi syndrome at the beginning of the twentieth century, with an incidence of 1–3 cases per 1 million, is considered one of the most difficult diagnoses of febrile diseases. It has an estimated prevalence lower than 1 case per 100,000 people. Adult-onset Still's disease, as a category of connective tissue diseases, constitutes approximately 59% of cases of pyrexia of unknown origin (2). The correct pathophysiology of the disease is still not completely understood. The etiology of AoSD is unknown. The hypothesis remains that AoSD is a reactive syndrome in which various infectious agents may act as triggers in a genetically predisposed host. Both genetic factors and a variety of viruses, bacteria like *Yersinia enterocolitica* and *Mycoplasma pneumoniae,* and other infectious factors have been suggested as important (3). However, diagnosing AoSD is often difficult due to the presence of several nonspecific symptoms and the absence of characteristic serological biomarkers. AoSD is typically considered as a diagnosis of exclusion and a definitive diagnosis should be made based on the Yamaguchi or Fautrel criteria only after excluding infectious, malignant, and other connective tissue diseases (4).

CASE REPORT

25-year-old female from Bhutan, with no known comorbidities presented to the emergency medicine department of a tertiary care hospital with complaints of on and off fever with rash and multiple small and large joints pain for approximately 6 months duration. The patient had low grade fever, relieving on antipyretics, associated with sore throat, asymmetric small and large joint pain and erythematous rashes over the body. No history of nocturnal rise in temperature, increased frequency of urination, burning micturition, cough, running nose and sneezing, exertional dyspnea, shortness of breath, abdominal pain, altered bowel habits, headache or weight loss. No history of any thyroid disorders, diabetes mellitus, hypertension or other endocrine disorders. The patient was not on any regular medications. No history of travel to anywhere outside the home town. No history of similar illness or any endocrinological or rheumatological disorders in the family. On physical examination, the patient had stable vitals with no active fever. Physical examination revealed scattered erythematous maculopapular rashes over the flexor aspect of the arm, extensor aspect of thigh and V of the neck and cervical lymphadenopathy. Joints on examination were tender, erythematous and range of movements restricted due to pain.

Abdominal examination showed mild hepatosplenomegaly. Chest auscultation showed normal vesicular breath sounds and cardiac auscultation Revealed normal heart sounds and no murmurs.

Laboratory investigation

Sample – EDTA Whole blood

Total WBC count = 7530/mm^3 → 16090/mm^3→ 8490/mm^3→ 24070/mm^3
DLC = N72L21M06E01
Hb = 9.4g/dl → 10.0g/dl
RBC count = 4.07 x 10^6/ul
Platelet = 5.08lakhs/mm^3→ 6.63lakhs/ul
ESR = 23/mm in 1st hr → 92mmin 1st hr → 82mm in 1st hr
MCV = 75.6fl
MCH = 23.0pg
MCHC = 30.4g/dl

Sample – Serum

Total bilirubin = 0.30mg/dl
Direct bilirubin = 0.10mg/dl
SGOT = 44U/L → 18U/L
ALP = 128U/L → 34U/L
GGT = 51U/L → 51U/L
Albumin = 3.3g/dl → 3.2g/dl
Globulin = 4.3g/dl → 3.8g/dl
A:G ratio = 0.77 → 0.84
Urea = 13.00mg/dl
Creatinine = 0.43mg/dl
Sodium = 139.0mEq/L
Potassium = 4.4mEq/L
CRP = 70.30mg/dl →113mg/dl →20.70mg/dl → 50.00mg/dl
CK NAC = 31U/L
LDH =138U/L
FERRITIN Assay = 3264.73ng/ml → 1023.33ng/ml
IL-6 = 74.32pg/ml

Serum biomarkers

HBsAg = Non-Reactive
Anti-HCV= Non-Reactive
HIV Ag/Ab 1&2 = Non-Reactive

To rule out any infective etiology:

Urine routine: WNL
Chest X-RAY: Normal radiograph of the chest
2D ECHO: LVEF=60%. No abnormalities seen.

To rule out auto-immune disorders:

RA factor = Negative
Anti-nuclear antibodies = Negative
C-ANCA= Negative
P-ANCA= Negative
ANA Profile = Negative

To rule out metastatic diseases:

FDG PET-CT = Low grade metabolically active multiple bilateral axillary lymph nodes with preserved architecture (SUVmax 2.1) – likely reactive. Few foci of focal hypermetabolism in left lung parenchyma with no significant corresponding CT changes (SUVmax 11.0) – likely non-significant uptake. Mild diffuse hypermetabolism in marrow of visualized axial and proximal appendicular skeleton. No abnormal focal hypermetabolism seen anywhere in the whole-body scan.

To rule out myopathy of dermatomyositis: MRI Thigh = Minimal muscle edema at bilateral obturator externus as well as around the muscles of ischial tuberosity. No other remarkable findings seen.

The patient was started on IV METHYL PREDNISOLONE (500MG) for 3 consecutive days and then converted into oral PREDNISOLONE 40MG daily along with weekly METHOTREXATE. The patient responded to the steroid pulse therapy, fever and arthralgia resolved along with the disappearance of rashes, total count, ESR, and CRP were normal at the time of the discharge. The patient was discharged with advice of tapering dose of oral PREDNISOLONE, daily HCQs (300MG), weekly METHOTREXTAE (15MG), vitamin supplements and other supportive medication. The patient was advised to use barrier method of contraception and to consult the specialist atleast 3 months prior to planning pregnancy.

DISCUSSION

AoSD is a rare, but well known systemic autoinflammatory disorder whose etiology still remains idiopathic. The disease was 1st described by Eric Bywaters. It owes its name to George Still who published in 1897 his monograph, On a form of chronic joint disease in children, describing 22 children with signs and symptoms of the disease entity currently known as systemic onset juvenile idiopathic arthritis. In 1971, Eric Bywaters described 14 adults with similar presentation with paediatric Still's disease, convincingly establishing the new disease entity. There where evidence of the same in many articles even before the description of the AoSD (5)(6). The exact incidence of AoSD is unknown, but it is thought to affect between 1 and 34 people per million, depending on the population studied. Because of the highly variable symptoms and rarity of the disorder, it often goes undiagnosed or misdiagnosed, making it difficult to determine its true frequency in the general population. AoSD seems to affect men and women in equal numbers, although some reports state that the disorder affects women slightly more often than men. It primarily affects young adults between the ages of 16-35 but can also occur in older individuals (7) (8)(9).

The cause of AoSD is unknown (idiopathic). Researchers believe that the disorder might be caused by a combination of genetic factors and an abnormal or exaggerated response to infections or other environmental exposures. AoSD is not a hereditary disease and usually does not run in families (7). AoSD is considered as a Systemic autoinflammatory disorder (SAID) rather than an autoimmune disorder. SAID is defined as monogenic periodic fever syndromes characterised by intense inflammation with periodic fever, tissue inflammation depending on the disease, increased leukocyte and neutrophil count, elevated erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) level, absence of any specific biomarkers, and, more recently, a pathogenic role of inflammasome and response to interleukin-1(IL-1) blockade (10). The complete pathogenesis of AoSD is still hypothetical. Any danger signals are transmitted to the macrophages and neutrophils and leads to caspase activation and overproduction of active IL-1, which in turn leads to intense innate immune cell activation and overproduction of pro-inflammatory cytokines like IL-6, IL-8 and TNF and leading to cytokine storm. This overactivity can be due to the failure or deficiency of regulatory or anti-inflammatory mechanisms (11) (12).Bacteria or viruses are the usual suspects for the danger signals. Numerous case reports describe the occurrence of AoSD after viral infection (rubella; measles; mumps; Epstein-Barr virus; hepatitis A, B, or C virus; HIV; cytomegalovirus; parvovirus B19; adenovirus; echovirus; human herpes virus 6; influenza and parainfluenza viruses; Coxsackie virus) or bacterial infection (Yersinia enterocolitica**,** Campylobacter jejuni**,** Chlamydia trachomatis **or** pneumoniae**,** Mycoplasma pneumoniae**,** Borrelia burgdorferi) (13) (14). The underlying genetic predisposition of AoSD is largely unknown with the disease being present around the world in different ethnic groups (12). Most individuals with AoSD develop some combination of the symptoms normally associated with systemic inflammatory disease. These include a spiking fever, a skin rash, muscle pain (myalgia), and joint pain

(arthralgia) and inflammation (arthritis). The fever seen in AoSD is typically greater than 102.2°F (39°C), with spikes occurring once or twice a day, usually in the late afternoon or early evening. The rash of AoSD, which usually but not always develops during a fever episode, is pink or salmon coloured. It mostly affects the chest and thighs, but can also affect the arms, legs and face. It may or may not be itchy (pruritic) and tends to disappear quickly (evanescent). Affected joints may become swollen, stiff and inflamed. The knees, wrists, ankles, and hips are most commonly affected. Muscle and joint pain can be intense and is often worse during a fever episode. Other symptoms that can be seen in AoSD include a sore throat, abdominal pain, nausea, loss of appetite (anorexia), weight loss and enlargement of the spleen (splenomegaly), liver (hepatomegaly) and lymph nodes (lymphadenopathy). Rarely it may cause inflammation of internal organs leading to pericarditis, myocarditis, pleuritis and even pleural effusion, presenting as chest pain and shortness of breath and may even be mild to be asymptomatic and picked up in the imaging (3) (15) (16).

The 3 main subtypes associated with AoSD includes

- Monophasic pattern – single episode of symptoms which last weeks to months but less than 1 year
- Polyphasic / Intermittent pattern – more than 1 episode of symptoms, with symptom free period for weeks to years. The subsequent episodes tend to be less severe and shorter in duration.
- Chronic pattern – persistent symptoms over time leading to joint destruction (7) (17).

Laboratory investigations show values similar to any inflammatory disorders, leukocytosis, and/or thrombocytosis and anemia. This can be associated with elevated serum acute phase reactants like ESR, CRP, fibrinogen and serum immunoglobulin. Additionally, some patients have high blood levels of enzymes that are released by the liver, namely alanine aminotransferase (ALT), aspartate aminotransferase (AST) and lactate dehydrogenase (LDH). To exclude other auto-immune disorders, levels of certain antibodies such as antinuclear antibodies (ANA) and rheumatoid factor (RF) are usually measured. However, these antibodies are typically absent in patients with AoSD. High serum ferritin level, an indicator of macrophage activation, has ben frequently reported. A more specific diagnostic marker than ferritin may be its glycosylated fraction. In inflammatory diseases, saturation of glycosylation mechanisms causes the glycosylated fraction to drop to 20–50%. This phenomenon is particularly prevalent in AOSD, where the glycosylation of ferritin is often <20%. Radiographs during the initial acute phase of the disease are not usually very helpful in establishing the diagnosis, being either normal or showing soft tissue swelling, joint effusion, or mild periarticular demineralisation (3)(11) (15)(18)(19)(20). Different sets of diagnostic criteria have been approved, with Yamaguchi et al. being most sensitive (96.3%) and specific (98.2%). Diagnosis requires at least five criteria consisting of two major and no exclusion criteria (21).

Major criteria

- Fever of at least 102.2°F (39°C) that lasts at least one week
- Arthralgia or arthritis lasting at least 2 weeks
- Appearance of a pink or salmon-coloured rash during fever spikes
- Elevated white blood cell count (leukocytosis)

Minor criteria

- Sore throat
- Lymphadenopathy
- Hepatomegaly or splenomegaly
- Elevated liver enzymes
- Negative tests for antinuclear antibodies and rheumatoid factor

Exclusion criteria

- Infection
- Malignancy
- Other rheumatic diseases

Main treatment of AoSD includes symptomatic and supportive treatment. Symptomatic treatment includes NSAIDs like aspirin, acetaminophen, and indomethacin, which requires regular evaluation of LFT to rule out NSAIDs induced liver disease. Corticosteroids are usually required to induce symptom remission. Optimal dosing relies on medium to high doses (i.e., 0.5–1 mg/kg/day of prednisone equivalent). Patients with serious visceral involvement might achieve a quick response with intravenous infusion of high-dose methylprednisolone. Methotrexate along with other DMARDs are used as an immunomodulatory agent and is efficient in controlling AoSD disease activity and allowing for steroid dose sparing. The targeted therapies studied and approved for AoSD mainly includes, Anakinra, a recombinant IL-1 receptor antagonist, Canakinumab, a fully human antibody against IL-1β, Tocilizumab, IL-6 receptor antagonist (22) (23) (24) (25). Some life-threatening complications of AoSD includes, Reactive Hemophagocytic Lymphohistiocytosis (RHL), Coagulation Disorders, Cardiac and Pulmonary Involvements, Amyloidosis (26) (27) (28).

CONCLUSION

AoSD is rare disease with symptoms of any systemic inflammatory disease, which should always be considered as a differential diagnosis for pyrexia of unknown origin. The basic work up should be done along with antibodies to rule out any auto-immune disorders and serum ferritin levels. The diagnosis is made by exclusion and the prompt treatment by steroids and other biological markers should be initiated depending upon the disease severity. We present this case to highlight the difficulties regarding the diagnosis due to its intricacy of the symptoms and its resemblance with many other diseases and hence the delay in the correct treatment of the disease.

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