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ADULT-ONSET STILL'S DISEASE: A FORGOTTEN MYTH

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ABSTRACT

Adult-onset Still's disease (AOSD), also known as Wissler-Fanconi syndrome is a rare systemic disorder. Symptoms usually include fever, joint pain, and rash. The diagnosis of ASOD is mostly clinical and excludes other possible causes. In this case report, a 25 years old gentleman, who in the recent past was diagnosed and treated with septic and reactive arthritis. He presented to us with a salmon-colored rash along with arthritis and was diagnosed as AOSD on the basis of clinical criteria, leukocytosis, raised inflammatory markers i.e., serum ferritin after the exclusion of other conditions.

Keywords: Still's Disease; Arthritis; Rash; Leukocytosis; Ferritin

INTRODUCTION

Adult-onset Still's disease is an autoinflammatory condition of unknown etiology, usually affecting people younger than 35 years of age. It is named after Sir George Frederic Still, a British physician who described the association of fever with childhood arthritis in 1896.[1] In 1971 title 'Adult Stills Disease' was used to describe a similar kind of arthritis in adults not fulfilling the criteria for classic rheumatoid arthritis. About 1-1.5 cases per 100,000-1,000,000 people suffer from this disease each year and it affects more women than men[2]. A high index of suspicion is needed for its diagnosis. Clinical and laboratory criteria are combined to overcome the diagnostic difficulties.

In this report, the authors present a case of arthritis which was later diagnosed as Adult-onset Still's disease.

CASE REPORT

A 25 years old, young, unmarried gentleman, student of masters, resident of Skardo presented with two weeks history of bilateral knee pain, high-grade fever (101-103^0 F), and sore throat. There was a history of anorexia and weight loss (undocumented.

He suffered from knee joint pain about 9 months ago. He had a fever too along with a rash on distilling parts of limbs. He was diagnosed, with septic arthritis in a local clinic, based on raised white blood cell count with neutrophilia. Knee joint aspiration was also done and was given antibiotics and analgesics with not much improvement. About 2 months ago symptoms reappeared. He was treated as a case of reactive arthritis although the patient gave no history of urethritis & conjunctivitis when asked retrospectively. Steroids and analgesics were given but he stopped treatment after a few days.

On examination he was clinically anemic but not jaundiced, having fever spikes of 102 ^{o}F. Their throw-away is mildly congested. A maculopapular rash was noticed on the trunk and limbs and face. Spleten was palpable two fingers below the left costal margin. Both knee joints were swollen and moderately tender. Slit-lamp examination of the eyes was normal.

Laboratory investigations revealed a total leucocyte count of 21,000/mm^3 with neutrophilic leukocytosis, Hemoglobin. 7.4 g/dl, mean corpuscular volume 91.1 fl. erythrocyte sedimentation rate was 84mm in 1st hour & C-reactive protein 70.4 mg/dl. Serum ferritin was more than 1000 ng/dl. antinuclear antibodies, Rheumatoid arthritis factor, and anti-CCP antibodies were negative. Aminotransferase and alkaline phosphatase were raised. The radiological examination was normal. Blood & urine culture reports were unremarkable. Ultrasound abdomen showed liver hemangioma and splenomegaly. Serum Alpha-fetoprotein level was normal. Hepatitis B & C were also negative. We also performed an upper gastrointestinal tract endoscopy that was normal.

A diagnosis of Adult-onset Still's disease was made based on clinical features and laboratory findings[3]. Yamaguchi's criteria were used (Table 2). Deltacortil and non-steroidal anti-inflammatory drugs (NSAIDS) were prescribed. After three weeks his arthritis and

Table 1a: Patient's laboratory values

Parameters	Normal Range	Results Before Treatment
Total Leukocyte Count	4-11X103/cmm	21.4 X103 /cmm
Hemoglobin	12.5-16.3 g/dl	7.4 g/dl
Mean Corpuscular Volume	73-96 fl	91.6 fl
Platelet count	152-358/cmm	616 X103 /cmm
Neutrophil	43.5-73.5	89.0 %
Lymphocytes	15.2-43.3	7.8 %
Alanine Transaminase	10-50 U/L	82 U/L
Alkaline Phosphatase	80-360 U/L	839 U/L
Lactate Dehydrogenase	240-480 U/L	873 U/L
Total Bilirubin	0.2-1.1 mg/dl	0.8 mg/dl
Urea	10-50 mg/dl	26 mg/dl
Creatinine	0.4-1.4 mg/dl	0.6 mg/dl
C-reactive protein	0.0-10.0 mg/dl	90.9 mg/dl
Serum Ferritin	Male 17.9 -464 ng/ml	> 1000 ng/dl
HBsAg by ELISA	< 1.0 negative 1.0 -5.0 borderline >5.0 positive	0.27
Anti Hepatitis C by ELISA	< 1.0 negative 1.0-5.0 borderline >5.0 positive	0.14
Dengue NS1 Antigen		Non -reactive
Dengue Anti bodies IgM		Non-reactive
Dengue Anti bodies IgG		Non-reactive
Covid-19 PCR		Negative
Alpha feto protein	0.0-8.8 ng/ml	>2.0 ng/ml
Anti CCP	> 5 IU/ml negative < 5 IU/ml positive	0.9 IU/ml
Serum TSH	0.4-4.50 mIU/l	1.94 mIU/l
Serum Free T4	8-24 pmol/l	19.10 pmol/l
RA Factor	< 8 IU/ml	Negative
ANA		Negative
Serum Uric Acid	160-430 µmol/l	223 µmol/l
Stool for Occult Blood		Negative

Table 1b: Patient's laboratory values

Parameters	Normal Range	Results After treatment
Total Leukocyte Count	4-11X103/cmm	11.9X103/cmm
Hemoglobin	12.5-16.3 g/dl	13.5 g/dl
Mean Corpuscular Colume	73-96 fl	96.8 fl
Platelet count	152-358/cmm	520X103/cmm
Neutrophil	43.5-73.5	78.5 %
Lymphocytes	15.2-43.3	15.4 %
Alanine Transaminase	10-50 U/L	23 U/L
Creatinine	0.4-1.4 mg/dl	0.5 mg/dl

fever subsided, his Total Leukocyte Count decreased, and he was able to mobilize his limbs.

DISCUSSION

AOSD is an autoinflammatory syndrome characterized by recurrent episodes of inflammation due to an abnormality of the innate immune system. This is different from an autoimmune disorder in which the immune system attacks healthy tissues of the body. The pathogenesis of AOSD remains unclear. Evidence of infectious and genetic etiology is suggested by researchers, but the root cause remains unknown[4]. AOSD is not a hereditary disease and does not run in families.

There is the activation of macrophages and neutrophils, followed by a cytokine storm. Interleukin-1, particularly IL-1 beta mediates cell response to inflammation. Interaction between Toll-like receptors and NOD-like receptors generate IL-1 beta, which is a potent pyrogen and facilitates neutrophilic proliferation and diapedesis into the inflamed tissues. Other cytokines involved are IL-6, IL-18, and tumor necrotic factor- alpha[3]. S100A8/A9 activates the Toll-like receptor 4 signaling pathway and may serve as a clinical marker for disease activity in AOSD[4]. Serum s TREM-1 levels are found to correlate with disease activity and are a potential predictor of the chronic course of AOSD[5].

Stills disease often goes unnoticed and is misdiagnosed. Symptoms include high-grade spiking fever, skin rash, myalgia, arthritis, and sore throat. The fever is typically greater than 102°F. The rash is salmon-pink in color, evanescent, and mostly affects the chest trunk, and thighs. Arthritis affects the knee, wrist, ankle, elbow, and hip joints usually[6]. Other symptoms are abdominal pain, loss of appetite, nausea, chest pain, and weight loss. Our patient had recurrent episodes of arthritis, fever, and rash which were overlooked initially. Rash was noticed with fever spikes.

There is no specific test for AOSD. Typically, there is leucocytosis, especially neutrophilia. CRP and ESR levels are raised. Serum ferritin level is raised disproportionately. Oth-

Table 2: Diagnostic criteria of Still's disease

YAMAGUCHI's CRITERIA
Major criteria
Fever of at least 39 0C lasting at least one week
Arthralgia or arthritis lasting two weeks or longer
Characteristic skin rash (non- pruritic macular or maculopapular salmon-color) over trunk or extremities during febrile episodes
Leucocytosis (10,000/ml or greater) with at least 80% granulocytes
Minor criteria
Sore throat
Lymphadenopathy
Hepatomegaly or splenomegaly
Elevation in liver enzymes concentration
Negative RA factor and ANA

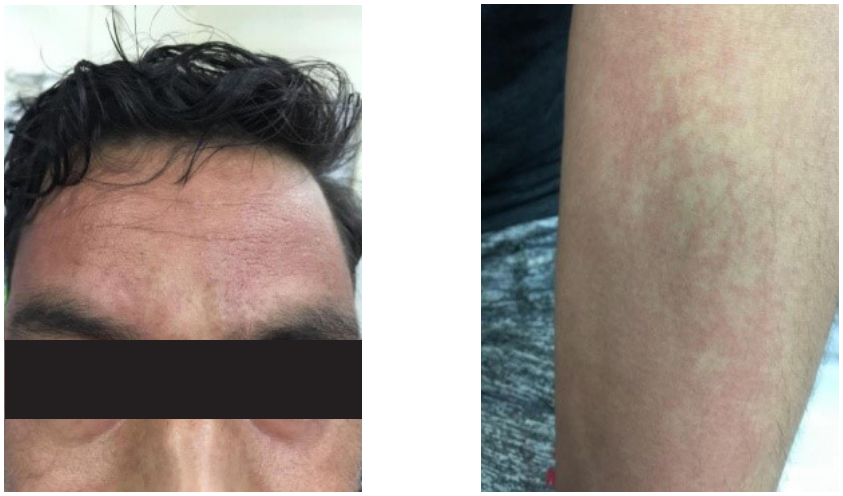

Figure 1: Maculopapular rash

er tests are done to exclude immunological diseases such as ANA, and RA factor[6]. In our patient septic screen was negative, and a Chest x-ray was normal. High TLC and platelet count, and anemia with disproportionally high ferritin levels lead us to think about an inflammatory process.

The Yamaguchi criteria are the most widely used criteria[7]. For the diagnosis of AOSD, it is necessary to fulfill at least five criteria, including two major criteria. Our patient full filled all four major criteria and four minor criteria.

No specific treatment has proven consistently effective in all patients. NSAIDs are used as initial treatment. Corticosteroids are used in patients not responding to NSAIDs and also to treat complications like pericarditis, serositis, and anemia. DMARDS like methotrexate are used as anti-inflammatory and steroid-sparing drugs. Anakinra, an IL-1 blocker is effective in remitting the manifestations of Still's disease and reducing the dose of steroids[8]. Infliximab and Etanercept have shown promise in small studies. Tocilizumab blocks IL-6 and is used to treat systemic juvenile idiopathic arthritis as well as AOSD. Canakinumab, an IL-1 beta blocker is recommended if corticosteroids and methotrexate have not been successful in AOSD[9] and is also approved by FDA in 2020.

About two-thirds of patients go into remission after one or several clinical episodes of AOSD. One-third may develop chronic disease. Most of these patients do well after adopting a healthy lifestyle. Some may develop complications like serositis and pericarditis. Macrophage activation syndrome causes an extreme proliferation of macrophages and is associated with decreased survival[10].

CONCLUSION

Still's disease is a diagnosis of exclusion. In order to prevent complications and improve the prognosis, a detailed history and physical examination along with a multidisciplinary evaluation is needed.

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Author's Contribution

AUN received the case and helped in the write up of the manuscript. SZ, I and AG helped in managing the case and contributed to writing of the manuscript and bibliography. Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflict of Interest

Authors declared no conflict of interest

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Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.