Case Report

A puzzling case of stress cardiomyopathy with persistent leukocytosis

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ABSTRACT

Adult-onset Still's disease (AOSD) is a rare autoinflammatory multisystem disorder with diverse clinical manifestations, making diagnosis challenging. It remains a diagnosis of exclusion and requires a high index of suspicion. We report a 42-year-old female presenting with fever, sore throat, arthralgia, and dyspnea on exertion. Laboratory evaluation revealed leukocytosis. Echocardiography showed a left ventricular ejection fraction of 45% with regional wall motion abnormalities, and an initial diagnosis of stress cardiomyopathy and acute coronary syndrome was made. After excluding infectious, autoimmune, and hematological causes, she fulfilled the Yamaguchi criteria for AOSD. The patient responded to pulse steroid therapy but experienced relapses requiring initiation of biologics. The absence of standardized international guidelines highlights the need for robust diagnostic tools to enable early recognition and reduce disease-related morbidity and mortality. AOSD is a diagnostic dilemma, but treatment is even more challenging.

Key words: Acute phase reactants, Adalimumab, Adult-onset Still's disease, Stress cardiomyopathy, Tocilizumab, Yamaguchi criteria

Adult-onset Still's disease (AOSD) is a rare systemic autoinflammatory disorder of unknown etiology. Still's disease was first described by G. Still in 1897 as Juvenile chronic polyarthritis in 22 children. 75 years later, Eric Bywaters described the first 14 cases of Still's disease in young women aged 17–35 years. It is characterized by quotidian (daily) high spiking fever, arthralgia with or without arthritis, evanescent salmon pink-colored skin rash, sore throat, leukocytosis, liver dysfunction, lymphadenopathy, hepatosplenomegaly, and other manifestations. AOSD can present in three different patterns: Monocyclic, polycyclic, and chronic patterns. Monocyclic (9–44%) have a single flare and achieve complete remission after several weeks or months, polycyclic (10–41%) have multiple recurrences with remission time in between the flares, and in a chronic pattern, the disease may progress into erosive arthritis seen in 35–67% of cases [1,2]. The annual incidence of AOSD is estimated to be between 0.16 and 0.62/100,000 individuals and prevalence to be 0.73–6.77/100,000 individuals worldwide, irrespective of ethnicity [3].

CASE REPORT

A 42-year-old female patient, diagnosed with hypertension 1 month ago, with no other comorbidities, was admitted to the Department of Internal Medicine with complaints of sore throat, dysphagia of 3 days duration, fever, and generalized body ache for 2 days. The fever was double quotidian with the highest temperature recorded at 103°F. During her stay in the hospital, the patient developed pain in the joints involving the shoulder, wrist, and ankle. There was no history of morning stiffness, ocular symptoms, or any recent contact with any infected person. While in the hospital during the febrile period, the patient developed macular rashes on the chest and lower extremities.

Examination revealed a well-built, sick-looking female patient with a fever of 103°F. Her vitals were stable. There was no lymphadenopathy. Chest on auscultation was normal, cardiovascular, and per abdominal, and neurological examination was unremarkable. On examination of the oral cavity, mild congestion of the posterior pharyngeal wall was noted.

Hematological examination showed Leukocytosis 19000/µL with neutrophils 92%, hemoglobin 11.8 g/dL, hematocrit 36.8%, and platelets 109000/µL, elevated alanine transaminase 197 U/L, and aspartate transaminase 40 U/L. The acute phase reactants, such as lactate dehydrogenase (LDH) 793 U/L, C-reactive protein (CRP) 1.2 mg/L, erythrocyte sedimentation rate (ESR) 120 mm in the 1st h, and fibrinogen 751 mg/dL were raised. Renal and coagulation profiles were normal. Tests for the malarial parasite and an enzyme-linked

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immunosorbent assay for dengue were negative. HIV, hepatitis B, and C were non-reactive.

On the 3rd day of admission in hospital, the patient complained of dyspnea on exertion, and her saturation at room air was 92%. Electrocardiogram (ECG) showed normal sinus rhythm with 2 mm ST elevation in leads V2-V3 and upsloping ST in leads V5-V6. An echocardiogram (ECHO) indicated akinetic basal inferior, mid, and posterior wall, distal one-third of the interventricular septum, and the apex with Grade 2 diastolic dysfunction and left ventricular ejection fraction (LVEF) of 45% with normal cardiac chambers. A provisional diagnosis of stress cardiomyopathy (SCMP) and acute coronary syndrome (ACS) was made. Troponin T was positive, and the patient was treated as per the ACS protocol and treated for heart failure. Dyspnea improved, and as per cardiologist advice, ECHO was repeated 2 days later, which showed LVEF 55%, normal-sized cardiac chambers, an akinetic apex tip with the rest of the area recovered. Repeat echo 15 days later revealed an ejection fraction of 60% with no regional wall motion abnormality. Table 1 shows serial ECHO findings depicting progressive improvement to complete recovery of cardiac functioning of the patient over 15 days.

Despite treatment, the patient continued to have high-grade intermittent fever, sore throat, arthralgia, with tenderness, swelling in the bilateral wrist joints, and persistent leukocytosis with raised acute phase reactants. Fig. 1 shows the progressive increase in the leukocyte counts, which on admission was 19000/µL and increased to a maximum of 27500/µL over the next 10 days. Serum ferritin was raised to 3740 µg/mL. Blood, throat swab, urine, and high vaginal swab culture showed no growth. Antinuclear antibody (ANA) and rheumatoid factor (RF) were negative. Interferon-gamma (IFNϒ) release assay for *Mycobacterium tuberculosis* was negative, computed tomography (CT)-chest and CT-neck showed a normal study, and CT-abdomen revealed mild hepatomegaly. Bone marrow aspiration and biopsy showed no evidence of hematological malignancy, and the positron emission tomography-CT whole body was not significant.

Based on her clinical features, such as daily fever, sore throat, arthralgia, and the laboratory evaluations, significant for elevated serum ferritin and in the absence of another identifiable cause, including infectious, autoimmune, and hematological etiology, she met the Yamaguchi criteria, and the diagnosis of AOSD was made. She was treated with non-steroidal anti-inflammatory drugs (NSAIDs) and pulse therapy of methylprednisolone 1 g for 3 days. There was a subsequent drastic improvement in her clinical symptoms with the decline in levels of acute phase reactants and leukocytosis. Fig. 2 shows the levels of acute phase reactants before and after pulse therapy with methylprednisolone, where ESR reduced from 120 to 65 mm at 1st h, serum ferritin reduced from 3740 to 2026 µg/L, emphasizing the autoinflammatory nature of the disease. She was discharged on a tapering dose of oral steroids and hydroxychloroquine (HCQ) 200 mg OD in August 2023.

During the follow-up period, she was readmitted with complaints of pain in the left wrist and swelling, and was treated with high-dose intravenous methylprednisolone 500 mg for 3 days. She improved symptomatically and was discharged on oral steroids, HCQ 200 mg OD, and methotrexate (MTX) 10 mg weekly.

In December 2023, she was admitted with complaints of persistent fever and pain in the left wrist, right elbow, and bilateral knees (hand joints spared). Treatment was changed, and she was discharged on azathioprine 50 mg BD, MTX 5 mg weekly, and prednisolone 7.5 mg OD. During this time, a coronary angiography (CAG) was attempted thrice, but the procedure was cancelled each time as she developed shivering after dye injection (Inj). Due to the complaints of persistent joint pain, she was started on weekly etanercept Inj 50 mg subcutaneous in January 2024 and continued till March 2024. Moreover, the lack of response to etanercept warranted switching of treatment, and the monthly Inj of adalimumab 40 mg subcutaneous was started from April 2024.

In October 2024, she was admitted again with complaints of constitutional symptoms, inflammatory polyarthritis, and symptoms of neuropathy in both feet and hands. Slit skin smear was negative for Hansen's disease, and a nerve biopsy showed non-specific changes. Treatment was changed to Inj MTX 25 mg, with a tapering dose of oral steroids. However, the patient reported no response to treatment when deflazacort was tapered below 12 mg. Further, she was on regular follow-up and due to complaints of persistent pain in the joints, involving both wrists and occasionally in the small joints of hands, and with a new onset of pain in both hip joints and presence of swelling and early morning stiffness, she was started on Inj of tocilizumab (8 mg/kg). 560 mg of Inj of tocilizumab was administered in March 2025. The first dose was tolerated well by the patient.

Table 1: Serial echocardiographic findings of the patient on days 4,7 and 15

Parameters	Day 4 of admission	Day 7 of admission	After 15 days of admission
LVEF (%)	45	55	60
Cardiac chambers	Normal sized	Normal sized	Normal sized
RWMA	Akinetic basal inferior, mid, posterior wall, distal 1/3 of IVS, apex	Akinetic apex tip with the rest of the area recovered.	No RWMA
Valves	Normal	Normal	Normal
LVDD	Grade II DD	Grade I DD	Grade I DD

LVEF: Left ventricular ejection fraction, RWMA: Regional motion wall abnormality, LVDD: Left ventricular diastolic dysfunction, DD: Diastolic dysfunction, IVS: Interventricular septum

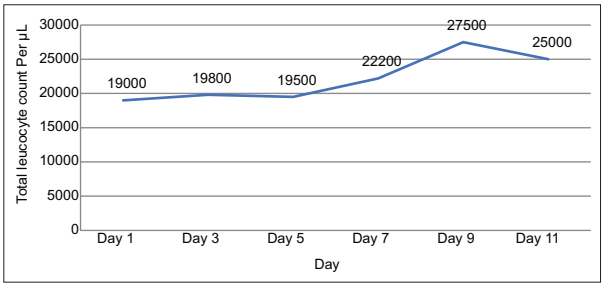

Figure 1: Depicts the progressive increase in serial total leucocyte counts/µL recorded during the hospital stay of the patient

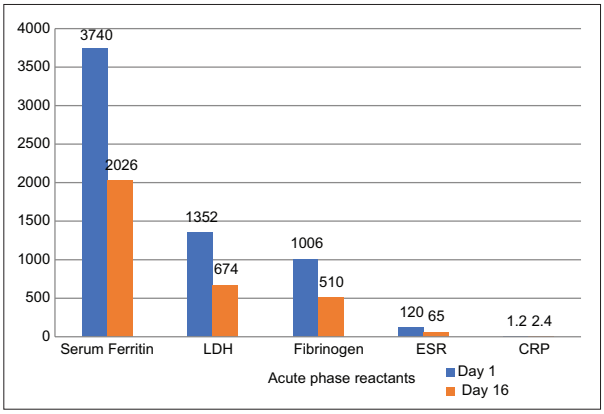

Figure 2: Acute phase reactants before and after pulse therapy with methylprednisolone. Day 1 represents values before pulse therapy, and Day 16 represents values after pulse therapy. LDH: Lactate dehydrogenase, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein

However, during the subsequent dose, she complained of urticaria with allergic rashes all over her body. As the patient had tolerated the first dose of tocilizumab well and after ruling out infection with routine evaluation, and attributing the allergic reaction could be due to faulty technique, Inj of tocilizumab 125 mg subcutaneously was given following premedication with Inj hydrocortisone 100 mg and Inj avil. She tolerated the Inj well and had no adverse reaction. The laboratory parameters following Inj of tocilizumab, except ESR, which was 60 mm at 1st h, other investigations, such as complete blood count, renal function test, liver function test, CRP, ECG, and ECHO, were unremarkable.

Currently, the patient is on Inj of tocilizumab 162 mg subcutaneously once in 2 weeks with a tablet of deflazacort 18 mg OD with symptoms free period for 2–3 days following Inj with mild symptoms thereafter. Fig. 3 shows the timeline of the treatment given to the patient with AOSD.

DISCUSSION

Clinical manifestations of AOSD are highly variable, making diagnosis very challenging and difficult. The disease has no clinical, histological, or radiological hallmark. Lack of specificity can be one of the causes of missed diagnosis. On the other hand, a delay in diagnosis can lead to a chronic disease course, affect response to therapy, and increase the risk of serious complications such as macrophage activation syndrome (MAS). Here, we present a case of middle-aged female patient presenting with complaints of fever, joint pain and during her stay in the hospital, she developed new-onset left ventricular dysfunction and was diagnosed as SCMP, even though CAG could not be done due to dye-related adverse reaction, because, the patient was a female with physical trigger in the form of ongoing disease processes which was later diagnosed as autoinflammatory disease-AOSD, and emotional trigger associated with pain and apprehension related to the disease processes and absence of ST-segment depression and scored high on InterTAK score, i.e., ≥50 points. The prompt recovery of cardiac function to normal with treatment also favors the diagnosis.

The disease has a bimodal age distribution between 15–25 and 36–46 years of age. The disease is equally seen between males and females with a slight female preponderance. No familial association has been attributed to this disease. Laboratory findings often present as neutrophilic leukocytosis, elevated ESR and CRP, hyperferritinemia, and increased inflammatory factors with ANA and RF negative. The pathogenesis of AOSD is not yet clearly understood. It is suggested that it is caused by an imbalance between innate and adaptive immunity and increased inflammatory cytokines, which is related to genetics and abnormal immune function, and infection acts as a starting point [1,4].

Delay in diagnosis can lead to a chronic disease course, affect response to therapy, and increase risk of serious complications such as MAS in up to 23% of patients [5] and is associated with a high mortality rate of 10–15% [6]. Other complications include thrombotic thrombocytopenic purpura, respiratory distress syndrome, diffuse alveolar hemorrhage, pulmonary arterial hypertension, myocarditis, pericardial effusion, cardiac tamponade, cardiopulmonary shock, fulminant hepatitis, multiple organ failure, and joint deformities [1,4,6].

The Yamaguchi criteria for the diagnosis of AOSD include major and minor clinical features. The major criteria consist of fever of at least 39°C (102.2°F) lasting for 1 week or longer; arthralgia or arthritis persisting for 2 weeks or more; a non-pruritic, salmon-colored macular or maculopapular rash typically appearing over the trunk or extremities during febrile episodes; and leukocytosis of 10,000/µL or greater, with at least 80% granulocytes. The minor criteria include sore throat, lymphadenopathy, hepatomegaly or splenomegaly, abnormal liver function tests, particularly elevated aspartate aminotransferase, alanine aminotransferase, and LDH, and negative tests for ANA and RF. For a diagnosis of AOSD, the Yamaguchi criteria require the presence of at least five features in total, with a minimum of two being major criteria [7].

First-line treatment of AOSD included NSAIDs and corticosteroids. Monocyclic disease often remits early, whereas polycyclic or chronic arthritis requires disease-modifying antirheumatic drugs, commonly

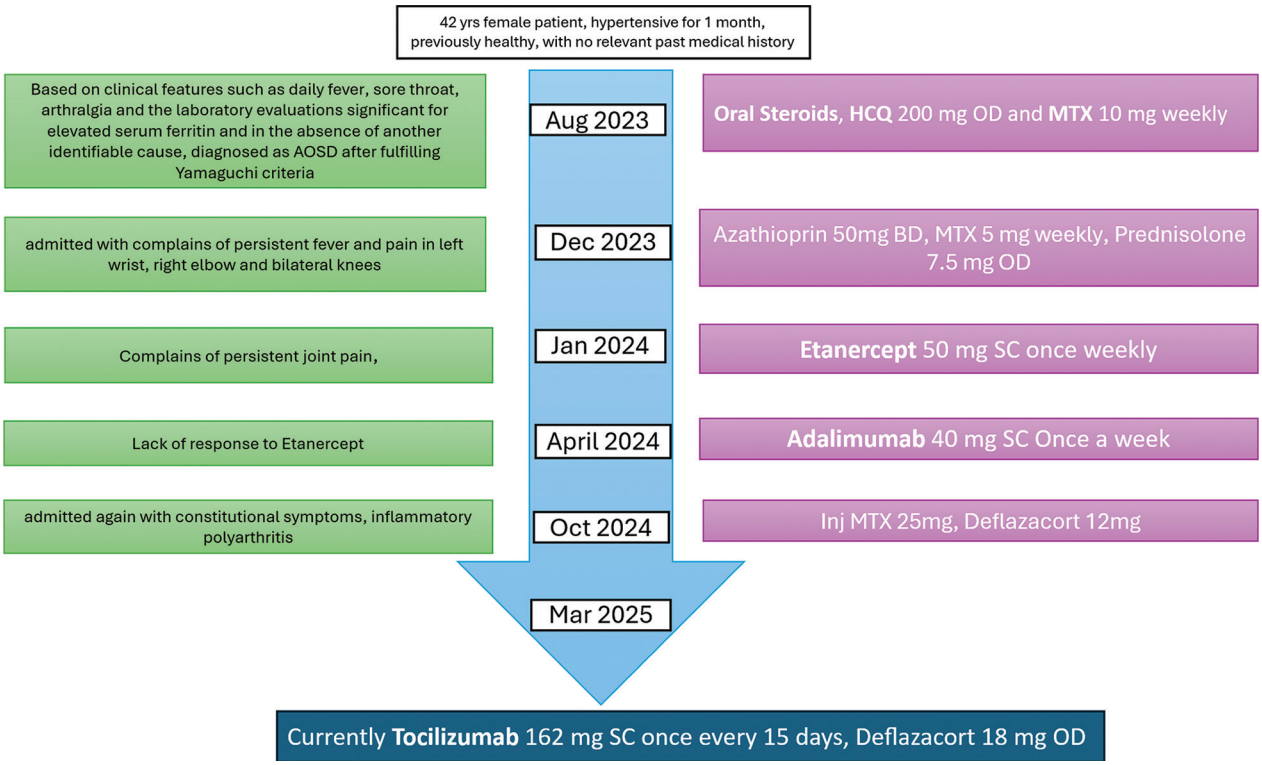

Figure 3: Flow chart with timeline of the treatment received by the patient with AOSD. AOSD: Adult-onset Still's disease, HCQ: Hydroxychloroquine, MTX: Methotrexate, SC: Subcutaneous

MTX, or biologics such as interleukin (IL)-1 inhibitors (anakinra, canakinumab, and rilonacept). Canakinumab is Food and Drug Administration-approved [5]. Tocilizumab (IL-6 inhibitor) was studied mainly in refractory AOSD with arthritis. Tumor necrosis factor-α blockers: Infliximab, etanercept, adalimumab, Anti-IFNϒ antibodies: Emapalumab were tried in AOSD associated with MAS [1]. The latest EULAR/PReS recommendations for optimal therapeutic strategy rely on early use of interleukin (IL-1 or IL-6 inhibitors) with high-dose glucocorticoids (GC) in patients with high disease activity, and a low or intermittent dose of GC for a short duration in patients with remission or clinically inactive disease. MAS treatment should rely on high-dose GCs, IL-1 inhibitors, cyclosporine, and IFNϒ inhibitors [8].

SCMP, also called takotsubo cardiomyopathy, is characterized as a reversible cardiomyopathy that is often precipitated by a stressful or emotional event. The presentation can be indistinguishable from ACS, ranging from chest pain, ST-T changes on ECHO, raised cardiac markers, heart failure with characteristic echocardiographic features of apical and mid-segment hypokinesis with compensatory basal segment hyperkinesia [9]. The final diagnostic proof of SCMP is coronary angiography (CAG) performed to exclude acute obstruction in the epicardial coronary artery. In certain situations, when unnecessary coronary intervention may be harmful, the diagnosis of SCMP relies on the clinical picture and non-invasive imaging only. Recently, a new diagnostic criterion has been proposed to predict the probability of SCMP, especially helpful in unusual cases, called the International Takotsubo Diagnostic Criteria (InterTAK Diagnostic Criteria) [10]. Here, points are allotted to different criteria's; female sex-25, emotional trigger-24, physical trigger-13, absence of ST-segment depression-12, psychiatric disorders-11, neurologic disorders-9, and QTc prolongation-6. Patients with a score of ≥50 showed 85% diagnostic accuracy [11].

Due to a high index of clinical suspicion by the treating clinician, the diagnosis of AOSD was made after fulfilling the Yamaguchi criteria. AOSD is a diagnostic dilemma, but treating it is even more challenging. There have been no standard treatment guidelines until recently, when it has been advocated that the use of biologicals such as IL-1 or IL-6 inhibitors early in the disease processes, along with GCs, yet treatment remains challenging. Our patient here did respond to tocilizumab, but could not be made steroids-free. Newer avenues must be looked for treatment as the disease is not only physically disabling but also has a lot of emotional, psychological, and financial impact on the patient and family.

CONCLUSION

AOSD being one of the rare diseases, conducting large-scale studies is difficult. Clinical presentation of AOSD is heterogeneous, and the lack of specific diagnostic tests accounts for the delay in the diagnosis of the disease. The existing diagnostic criteria mandate the exclusion of a large number of clinical conditions. There are no internationally recognized guidelines for AOSD. A robust diagnostic tool that could aid in early diagnosis without the need for exclusion of many other conditions and hence, decrease the morbidity and mortality associated

with the disease is the need of the hour. AOSD is a diagnostic dilemma, but treatment is more challenging. More research in the field is needed before the existing treatment is proven to be ineffective in patients.

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