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Review

Seizing the clinical presentation in adult onset Still's disease. An extensive literature review ☆

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ABSTRACT

Adult onset Still's disease is an inflammatory disorder with a wide clinical presentation ranging from arthralgia and arthritis to rash and high-grade fever. Etiology of this rare disorder remains a mystery. We present two cases at the extreme ends of clinical presentation diagnosed with AOSD along with literature review for the same. Case one was self limiting, requiring only NSAIDS as treatment. The other was an unusual central nervous system manifestation of repeated seizures that were only responsive to pulse dose of methylprednisolone. Both met Yamaguchi criteria for adult onset Still's disease.

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1. Introduction

Adult-onset Still's disease (AOSD) is a rare inflammatory disorder involving multiple systems. Due to the wide spectrum of clinical presentation, there is no consent on the incidence or prevalence of the disease across the globe. Characteristic features of the disease are joint pain or arthritis, salmon colored rash and high-grade fever. Etiology of the disease remains debatable [1].

It is a diagnosis of exclusion with a clinical presentation ranging from self-limiting to chronic arthralgias and multiple rare manifestations have been reported. Several classification criteria have been proposed with the most validated being the Yamaguchi's criteria (Table 1). The presence of two or more major criteria has a sensitivity of 96.2% and specificity of 92.1% [2].

We present two cases with a wide spectrum of clinical presentation. One is a self-limiting case and the other is an unusual central nervous system (CNS) manifestation of seizures in AOSD. Both met the Yamaguchi criteria for AOSD.

2. Case 1

A 24-year-old male presented to the emergency room 10 days after the onset of fatigue, headaches, fever, and rash. According to the patient, he was on a family vacation in Daytona Beach for a few days, and, on the last day of his trip, they went to a light house where there were lots of mosquitoes. On his way back home a day later, he developed a low

Abbreviations: AOSD, adult-onset Still's disease; CNS, central nervous system; EBV, Epstein–Barr virus; CMV, cytomegalovirus; MRI, magnetic resonance imaging; CT, computed tomography; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; Ab, antibody; NSAIDs, non-steroidal anti-inflammatory drugs; DMARDs, disease modifying antirheumatic drugs; IVIG, intravenous immunoglobulin.

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Table 1
Yamaguchi classification criteria for adult-onset Still's disease [17].

Major criteria	Minor criteria	Exclusion criteria
Fever > 39 °C, intermittent greater than or equal to one week	Sore throat	Infections
Arthralgia > 2 weeks	Lymphadenopathy and/or splenomegaly	Malignancies
Characteristic rash	LFT abnormal	Rheumatic diseases
WBC > 10,000/mL (>80% granulocytes)	Negative ANA/RF	

Five or more criteria required, of whom 2 or more must be major.

grade fever of 37 °C with fatigue and headaches which persisted. He was empirically treated with amoxicillin by his mother since they had a few doses left at home. At that time, he noted a rash in between his fingers bilaterally. He went to see his primary care physician two days after starting antibiotics, and by this time his fever had progressed to 39 °C. Antibiotics were switched to ceftin, the symptoms were thought to be secondary to a viral infection and the rash a side effect of the amoxicillin.

When, despite treatment, his fever rose to 39 °C, he was asked to come to the emergency room. He was initially monitored with negative blood cultures, and in the evening, when his fever dissipated, he was discharged only to be readmitted a day later with a high-grade fever and rash all over. By this time he was also complaining of generalized arthralgia that included his left and right ankle and wrist bilaterally with generalized fatigue. He reported no muscle pain or weakness proximal or dorsal.

By the time he was admitted to the hospital, the rash had spread to his anterior torso, abdomen, arms, and legs. It was non-pruritic and not painful. He reported that he was not sexually active and had no history of alcohol or drug abuse. He had no chest pain, back pain, nausea or vomiting, mouth ulcers, eye pain, redness in the eyes, vision change, or urinary symptoms. He was noted to have chills with the fever. His temperature on admission was 38.3 °C with sinus tachycardia, a normal respiratory rate, and he was normotensive with saturation on room air of ninety eight percent.

On exam he had maculopapular rash on his body as described above, coalescing in places, non-pruritic, and salmon-colored. No blisters or desquamation were noted. No active synovitis or joint inflammation was noted on exam, and he had a good range of motion in all extremities. As per Table 2, the patient was seen to have hyperferritinemia and transaminitis with elevated inflammatory markers and neutrophilia.

The rest of his labs were negative for infectious etiology, including negative cultures (bacterial, fungal, and viral) and negative serology for Epstein–Barr virus (EBV), syphilis, cytomegalovirus (CMV), dengue, HIV, hepatitis, malaria, and chikungunya. Imaging studies, including chest xray, computed tomography (CT) scan of the chest, magnetic resonance imaging (MRI) of the brain, and ultrasound of the abdomen, were all negative and within normal range. A biopsy of the rash showed mild superficial dermal perivascular inflammation.

Given his high ferritin levels, with elevated inflammatory markers, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), arthralgias, transaminitis, and rash, and absence of any other cause for the same, a diagnosis of AOSD was made.

He was started on indomethacin 50 mg three times a day with food along with a proton pump inhibitor. All of the symptoms abated within the ten days following. He remained asymptomatic at the 2-month follow-up.

Table 2
Case 1: self-limiting AOSD.

Labs (normal)	Admission	Day 3 of indomethacin treatment	Day 10 of treatment
Ferritin (24–336)	4176 mcg/L HI	1723	363
LD (122–222)	413 u/L HI		
Sed Rate (0–22)	42 mm/hr HI	82	63
CRP (0–8)	94 mg/L	55	4.1
Hgb (13.5–17.5)	11.4 g/dL		
Hct (38.8–50)	32.9%		
WBC (3.5–10.5)	14.6 × 1000		
Platelet (150–450)	171 × 1000		
Creatinine (0.8–1.3)	0.8 mg/dL		
BUN (8–24)	7 mg/dL		
ALT (8–48)	66 u/L	66	51
AST (7–55)	76 u/L	76	19

LD: lactate dehydrogenase; CRP: C-reactive protein; Hgb: hemoglobin; Hct: hematocrit; WBC: white blood cell; BUN: blood urea nitrogen; ALT: alanine aminotransferase; AST: aspartate aminotransferase.

3. Case 2

A 45-year-old African American female first presented with low-grade to high-grade fevers 37 to 38 °C, joint pains that mainly affected her knees, and generalized fatigue. The patient presented to an outside hospital emergency room and was treated symptomatically. The patient's family said that she was prescribed steroids for an unknown diagnosis, but she did not take any at that time and had a history of non-compliance with medical advice.

In June 2014, she was admitted to an outside hospital for septic knee growing Klebsiella, which was being treated with intravenous antibiotics. When the patient felt better, she decided to leave the hospital against medical advice. She was noted to have a ferritin level of 20,000 mcg/L and transaminitis at this point, per chart review, but she was not seen for follow-up since she had left against medical advice.

In July, she presented to another outside hospital after she had two witnessed episodes of tonic clonic seizures requiring EMS activation. On arrival to the emergency room, the patient was intubated, started on keppra and broad spectrum antibiotics for a fever of 38.8 °C and transferred to Mayo Clinic after three days of hospitalization for further management. At the outside facility, she was found to have a high ferritin level of 16,500 mcg/L with ESR of 98 mm/hr. She was found to have microcytic anemia with leukocytosis of 27,000, which was mainly neutrophilia. This had prompted a bone marrow biopsy revealing a hypercellular marrow with 9–10% CD138 positive cells. Cytogenetic testing eventually came back as interleukin (IL)2 R(CD25) negative ruling out malignancy and macrophage activation syndrome. Her infectious serology was negative for HIV, syphilis, and hepatitis, and she had negative blood, urine, cerebrospinal fluid, sputum, and stool cultures. Her imaging studies from the outside facility revealed a CT scan of the brain to be negative for any acute pathology.

On exam after transfer to our facility she was not responsive to verbal or painful stimuli with faint response of eyes to light. She had no rash or signs of active synovitis. She remained afebrile during her hospital stay.

Her labs on admission to our hospital revealed hypertriglyceridemia and elevated inflammatory markers with an ESR of 108 mm/hr and CRP of 106 mg/L. Her ferritin levels were 28,796 mcg/L. She continued to have microcytic anemia, but her white blood cell count had dropped to 10.6. Her transaminitis had improved with negative rheumatological and vasculitic panel.

An MRI of the brain at our facility showed restricted diffusion within the left hippocampus and dorsal left thalamic lobe, likely related to recent seizure activity, with no evidence of acute infarction, intracranial hemorrhage, or venous sinus thrombosis. The CT scan of her chest, abdomen, and pelvis revealed hepatomegaly with steatosis, normal spleen, and a mass anterior and inferior to the pancreatic head measuring 2.4 × 1.8 cm. Her immunoglobulin levels, including IgG4 levels, were within normal limits.

She did have an acute kidney injury, the biopsy of which revealed chronic sclerosis and acute interstitial nephritis with no evidence of an immune complex process on immunofluorescence microscopy or evidence of light chain deposition disease or cast nephropathy.