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A case of adult-onset Still's disease that does not fulfill Yamaguchi's and Fautrel's criteria: Sensitivity limitations and improvement proposal

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ABSTRACT

Adult-onset Still's disease (AOSD) is an uncommon inflammatory condition that lacks a universally accepted diagnostic test. The clinical presentation comprises symptoms such as fever, rash, joint pain, sore throat, swelling of lymph nodes, and enlargement of the liver and spleen. The diagnostic criteria developed by Yamaguchi and Fautrel are commonly employed because of their great sensitivity and specificity. However, there are cases in which individuals may not meet these criteria but still demonstrate symptoms of AOSD. In this case, we report an elderly patient who has been diagnosed with AOSD but does not meet the criteria for any of these criteria. We discussed the factors contributing to impaired sensitivity and put forth various suggestions to enhance the sensitivity of these criteria.

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INTRODUCTION

Adult-onset Still's disease (AOSD) is an infrequent inflammatory disease that affects multiple systems in the body. It is recognised by the clinical triad of recurrent high fever, joint pain, and a transient skin rash.[1] AOSD primarily affects young adults, particularly females. The global prevalence of this condition ranges from 0.16 to 0.40 per 100,000 individuals.[1] The precise mechanism still needs to be comprehensively understood, although the innate system is triggered, and there is an increase in pro-inflammatory cytokines such as IL-1b, IL-6, IL-8, IL-17, IL-18, and TNF-alpha.[2] While the exact cause of the disease is uncertain, stressful life events associated with work, family, and health could catalyse AOSD.[3] The clinical symptoms of AOSD consist of recurrent high fevers, joint inflammation accompanied by joint pain and swelling, a distinct rash that is temporary, not itchy, salmon-coloured, and consists of flat or slightly raised lesions (which are uncommon in older individuals), enlargement of lymph nodes, and enlargement of the liver and spleen.[3-5] The laboratory findings of AOSD include an increase in white blood cells with an increase in neutrophils, higher levels of acute-phase reactants, raised liver enzymes, and significantly elevated levels of ferritin.[3] There are two globally recognised criteria for diagnosing AOSD: Yamaguchi's criteria and Fautrel's criteria *(Table 1).* The Yamaguchi's criteria exhibit a sensitivity of 96.3% and a specificity of 98.2%, while the Fautrel's criteria provide a sensitivity of 87.0% and a specificity of 97.8%. The Yamaguchi criteria involve excluding other potential disorders. In contrast, the Fautrel criteria utilise ferritin and glycosylated ferritin (GF) levels as diagnostic indicators for the disease without the need for any exclusion criteria.[6,7] In this case report, we present a patient diagnosed with AOSD, but the criteria for either of these conditions do not match. We shed light on the pitfalls of Yamaguchi's and Fautrel's criteria and how to improve them.

CASE REPORT

A 70-year-old female patient, who has been diagnosed with hypertension and is currently taking ramipril 5 mg, presented at the outpatient general internal medicine clinic with several symptoms, including a sore throat, overall fatigue, malaise, myalgia, unintentional weight loss of 5 kg over the past few weeks, widespread itchy and red skin lesions that peel off, primarily on the trunk, arms, and knees *(Figure 1)* as well as a fever reaching up to 38 °C. Due to the absence of any previous tick exposure or recent travel, the patient was diagnosed with a viral infection and treated conservatively. She experienced a lack of progress in the subsequent days and returned to the outpatient clinic for a second visit. The laboratory tests showed that she had normocytic anaemia and thrombocytopenia, as well as a remarkably high hyperferritinemia level of 33,511 µg/L and high C-reactive protein *(Table 2).* She was admitted to the internal medicine ward for further investigation due

Table 1. Two main diagnostic criteria for diagnosing adult-onset Still's disease

Criteria	Yamaguchi's criteria[6]	Fautrel's criteria[7]
Major	•Fever ≥39 °C lasting 1 week or more	• Spiking fever ≥39 °C
	•Arthralgia lasting 2 weeks or more	• Arthralgia
	•Typical skin rash: maculopapular, nonpruritic, salmon-pink rash with concomitant fever spikes	• Transient erythema
		• Pharyngitis
	•Leukocytosis ≥10,000/mm^3 with neutrophil polymorphonuclear proportion ≥80%	• Neutrophil polymorphonuclear proportion ≥80%
		• GF proportion ≤20%
Minor	•Pharyngitis or sore throat	• Typical rash
	•Lymphadenopathy and/or splenomegaly	• Leukocytosis ≥10,000/mm^3
	•Liver enzyme abnormalities (aminotransferases)	
	•Negative for RF or antinuclear antibodies	
Exclusion	•Absence of infection, especially sepsis and Epstein-Barr viral infection	• None
	•Absence of malignant diseases, especially lymphomas	
	•Absence of inflammatory disease, especially polyarthritis nodosa	
	•At least five criteria, including two major criteria and no exclusion criteria	Four major criteria or three major criteria and two minor criteria

AOSD: adult-onset Still's disease, GF: glycosylated ferritin, RF: rheumatoid factor.

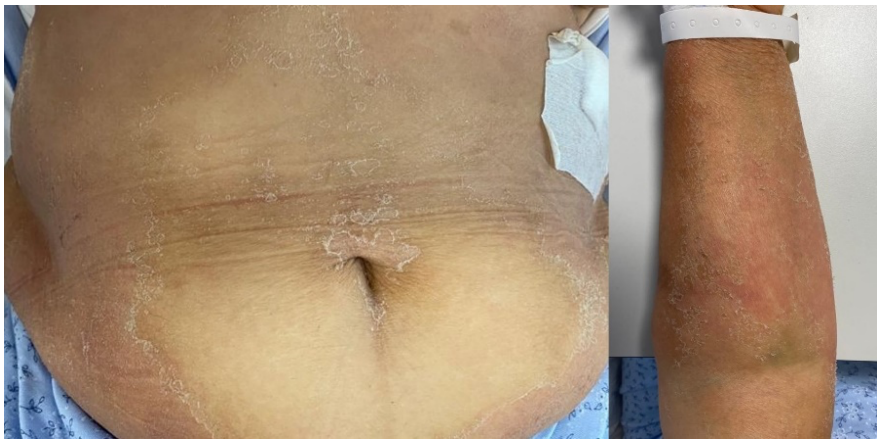

Figure 1. Itchy and red skin lesions that peel off, primarily on the trunk, arms, and knees

to a preliminary diagnosis of cancer, inflammatory illness, or infection. The results of Epstein-Barr virus and CMV serology tests were negative. Imaging tests of the neck, thorax, and abdomen failed to reveal any significant findings other than hepatosplenomegaly. No vegetation was observed on the echocardiography. The blood and urine cultures were negative. A skin biopsy was performed and revealed drug-related inflammation. The peripheral blood smear was insignificant. The bone marrow biopsy did not show any evidence of neoplasia. All rheumatologic markers yielded negative results. After ruling out cancer, infections, and vasculitidis, no apparent reason could explain the significantly elevated ferritin levels. Additionally, the patient continued to experience widespread constitutional symptoms, leading to the conclusion that she likely had AOSD. She underwent assessment using Yamaguchi's and Fautrel's criteria but did not meet the requirements. Nevertheless, no probable diagnosis could account for the patient's

Table 2. Laboratory and imaging results on the first day of admission

Variables	Value	Variables	Value
Hemoglobin (g/dL)	10.9	ALT (U/L)	48
MCV (fL)	79.4	AST (U/L)	120
Leukocyte (/µL)	7,080	ALP (U/L)	61
Neutrophil (/µL)	5,130	GGT (U/L)	42
Lymphocyte (/µL)	820	Total bilirubin (mg/dL)	0.50
Thrombocyte (/µL)	65,000	BUN (mg/dL)	17
ESR (mm/h)	2	GFR (mL/min/1.73 m²)	53
CRP (mg/L)	83.6	Creatinine (mg/dL)	1.05
LDH (U/L)	1109	Sodium (mmol/L)	136
Ferritin (µg/L)	33511	Potassium (mmol/L)	3
Iron (µg/dL)	33	Uric acid (mg/dL)	6.4
Transferrin saturation (%)	16.1	Total protein (g/dL)	5.7
Fibrinogen (mg/dL)	172	Albumin (g/dL)	3.5
Hemolysis markers	Negative	Triglyceride (mg/dL)	391
Viral serology	Negative for HSV, Parvovirus B-19, EBV, CMV, hepatitis viruses		
Urine, blood and throat cultures	All negative		
Thorax CT	No lymph node, no nodule or mass, no sign of infection		
Abdominal CT	Hepatomegaly (170 mm), splenomegaly (142 mm), no lymph nodes		
Peripheral blood smear	Normal erythroid lineage, no sign of myelodsyplasia, lymphocytye abnormality		
Bone marrow biopsy	Hypercellular bone marrow. 80% cellularity ratio; mildly increased megakaryocyte count; no sign of neoplastic infiltration		

ALP: alkaline phosphatase, ALT: alanine aminotransferase, AST: aspartate aminotransferase, BUN: blood urea nitrogen, CMV: cytomegalovirus, CRP: C-reactive protein, CT: computed tomography, EBV: Epstein-Barr virus, ESR: erythrocyte sedimentation rate, GFR: glomerular filtration rate, GGT: gamma-glutamyl transferase, HSV: herpes simplex virus, LDH: lactate dehydrogenase, MCV: mean corpuscular volume.

Table 3. Laboratory results prior to discharge

Variables	Value	Variables	Value
Hemoglobin (g/dL)	10.5	ALT (U/L)	23
MCV (fL)	79.5	AST (U/L)	18
Leukocyte (/µL)	8,840	ALP (U/L)	56
Neutrophil (/µL)	6,500	GGT (U/L)	29
Lymphocyte (/µL)	1,320	Total bilirubin (mg/dL)	0.50
Thrombocyte (/µL)	141,000	BUN (mg/dL)	14
ESR (mm/h)	2	GFR (mL/min/1.73 m²)	63
CRP (mg/L)	<2	Creatinine (mg/dL)	0.9
Ferritin (µg/L)	589	Sodium (mmol/L)	140
Iron (µg/dL)	40	Potassium (mmol/L)	4.6
Transferrin saturation (%)	16.3	Uric acid (mg/dL)	5.1
Albumin (g/dL)	3.8	Triglyceride (mg/dL)	156

ALP: alkaline phosphatase, ALT: alanine aminotransferase, AST: aspartate aminotransferase, BUN: blood urea nitrogen, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, GFR: glomerular filtration rate, GGT: gamma-glutamyl transferase, MCV: mean corpuscular volume.

clinical and laboratory findings. As a result, she was diagnosed with AOSD and started on a regimen of methylprednisolone 24 mg. She was then discharged with close follow-up. Two weeks later, she was evaluated at the outpatient clinic, and her ferritin levels significantly decreased. Her fever, myalgia, malaise, and fatigue symptoms also reduced considerably. The rheumatology department commenced the use of methotrexate along with a tapering plan for methylprednisolone. After a month, her ferritin level decreased to 589 µg/L, and she described her general health as "exceptionally well." Her last laboratory results were shown in Table 3. She is currently taking a weekly dosage of 10 mg of methotrexate.

DISCUSSION

AOSD is a rare condition with an unknown aetiology, characterised by persistent fever, polyarthritis, and rash. Diagnosis is typically established by excluding malignancies, rheumatological disorders, and infections using either Yamaguchi's or Fautrel's criteria.[6,7] The patient presented in this case report did not fulfil any of the criteria above yet was correctly diagnosed with AOSD, and the patient experienced remission with the appropriate treatment. We acknowledge that no criteria can have 100% sensitivity, but we identified several possible causes that lower the sensitivity of these criteria.

Firstly, having a fever of 39 °C and over is a major criterion according to the Yamaguchi and Fautrel criteria[6,7], a finding our patient lacks. It has been shown that fever tends to be lower in older people compared to youngsters.[8] Although no mean age data exists in Yamaguchi's article, in Fautrel's cohort, consisting of 72 patients, the mean age was 35.2±13.5. Moreover, a study by Kim et al.[9] illustrated that only 30% of patients with Still's disease had a fever of 39 °C. A case-based review illustrated that fever was not present in 23.9% of elderly patients (mean age 75) with AOSD but without macrophage activation syndrome (MAS).[10] The markedly lower age of patients in Fautrel's diagnostic criteria and the fact that fever response is blunted as age increases point out the necessity of revising the fever threshold according to age.

Another major criterion of Yamaguchi's criteria is the presence of typical non-pruritic maculopapules described as salmon-pink-colored. Our patient's rash manifested as peeling red lesions with itching. Considering various examples in the literature that show the occurrence of rashes in different variations[11,12] and a lower incidence of typical rash in older people[4], it might be advisable to broaden the criteria to encompass all dermatological lesions. An observational study demonstrated that the prevalence of atypical skin lesions was 14%, with persistent pruritic papules and/or plaques constituting the most frequent non-classical skin findings.[13] While this addition might slightly lower the specificity of the criteria, it is expected to increase the sensitivity significantly.

The major criterion of arthralgia lasting more than two weeks has not been observed in our patient. Instead, the patient reported general, widespread

pain throughout the body. Although we did not encounter a patient in the literature who did not report arthralgia but stated widespread body pain, a patient, later diagnosed with AOSD, from India describing polyarthralgia persisting for 18 months is the most similar presentation to our patients.[14] Moreover, it was shown that more than 25% of elderly patients with AOSD but without MAS did not experience arthralgia or myalgia at all.[9] Generalised body pain may not be expected to become a major or minor diagnostic criterion; further registries should involve widespread body pain to determine its role in diagnosis.

The last point is that glycosylated ferritin can be used as a bioindicator. Although GF has 89% specificity and 63% sensitivity for AOSD[14], it is an expensive and relatively challenging test. Moreover, it is not widely available. Therefore, including this exceptional test in the minor rather than the major criteria may be prudent.

CONCLUSIONS

In conclusion, this case report demonstrated that, despite the high sensitivity and specificity of Yamaguchi's and Fautrel's criteria, their performance may be limited in elderly patients. Age-dependent modifications, both for fever and rash, may improve the sensitivity and specificity of these criteria.

Consent

Consent has been obtained prior to manuscript preparation

Authors' Contribution

Study Conception: ATG, BH, BK, NŞ, AÖ, TIG,; Study Design: ATG, BH, BK, NŞ, AÖ, TIG,; Literature Review: ATG, BH, BK, NŞ, AÖ, TIG,; Critical Review: ATG; Data Collection and/or Processing: ATG, BH, BK, NŞ, AÖ, TIG,; Analysis and/or Data Interpretation: ATG, BH, BK, NŞ, AÖ, TIG,; Manuscript preparing: ATG, BH, BK, NŞ, AÖ, TIG.

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