Case Report

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Still Disease Is Still Hard to Diagnosis: A Case Report

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ABSTRACT

Adult-onset Still Disease (AOSD) is a rare rheumatologic condition with unrecognized etiology. Spiking fevers, joint involvement (arthralgia or arthritis), rashes, lymphadenopathy, abnormal liver function test data, and leukocytosis are the main features of this disease. Yamaguchi's criteria with the sensitivity and specificity of 96.2% and 92.1%, respectively, is the most beneficial tool for the diagnosis of AOSD, as a rare disease. The uncommon features of the still disease remain confusing for clinicians. about the present study reported a 27-year-old patient who was referred to our hospital with an unknown diagnosis, because of the rare features of Still disease. The explored characteristics of rashes, fever, and para-clinical data, as well as laboratory and imaging data, are described in detail; such features have led to long hospitalization to confirm the diagnosis in this patient. The positive family history of the rheumatologic disease and dramatic response to low dose corticosteroids were other outstanding features of our case. This report highlighted the necessity of conducting randomized clinical trials to address the management of AOSD. Besides, the present study signified the need for providing further awareness among clinicians to prevent long hospitalization.

Introduction

Adult-onset Still Disease (AOSD) is a rare rheumatologic condition with unknown etiology. Spiking fevers, joint involvement (arthralgia or arthritis), rashes, lymphadenopathy, abnormal liver function test, and leukocytosis are the main features of this disease [1, 2]. According to the available limited data, the prevalence of this disease ranges between 1 and 10 cases per million [3]. women are more affected by this condition and individuals aged >16 years can present AOSD. Still disease is a rare condition remaining confusing to clinicians with uncommon features. The different categories of disease from malignancies, like lymphoma to infectious diseases, like endocarditis can mistakenly be diagnosed for AOSD; accordingly, such errors could lead to long hospitalizations and complications in them. Yamaguchi's criteria with the sensitivity and specific-

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ity of 96.2% and 92.1%, respectively, is the most beneficial scale for the diagnosis of AOSD [4].

According to this criteria, evanescent salmon-colored non-pruritic maculopapular rashes are the characteristic skin manifestations of AOSD with a prevalence of approximately 87% [5]. Different types of Pruritic Persistent Eruptions (PPEs) are also mentioned as atypical rashes in the literature and have still disease remained confusing in the clinical setting [5]. We described a patient with the uncommon features of AOSD, who was referred to our referral center after several workups.

Case Presentation

A 27-year-old patient has referred to our center after 21 days of unknown diagnosis. She was a known case of hypothyroidism who experienced 3 weeks of high-grade spiking fever (>40˚C) without a special pattern, non-exudative pharyngitis, non-massive splenomegaly, bilateral submental lymphadenopathy, arthralgia, and generalized pruritic maculopapular rash. Notably, our patient's family history was positive for rheumatologic disorders. Her brother was diagnosed with Wegener's granulomatosis 2 years ago. Furthermore, her sister was a recognized case of Takayasu's arteritis. Her habitual and drug use history was negative before the onset of disease and she had not been to endemic areas. Sore throat preceded other symptoms; fever, generalized rash, and lymphadenopathy were progressively added to the clinical scenario. Her rashes initially started from the lower extremities without any relation to her fever spikes and were distributed all over the body. Besides, some of them were vesicular and she complained about scratching.

In her physical examination, a high fever of 40˚C and increased heart rate (110/min) in concordance with fever were significant parts of vital signs. Maculopapular rashes were observed all over her skin, i.e. vesicular in some part of her extremities. Except for semi-firm submental lymph nodes, there was no lymphadenopathy in the palpation of other parts. Other examinations' data were healthy.

Laboratory findings are mentioned in Tables 1, 2 and 3. Brucellosis and Tuberclosis (TB) were excluded by tests and viral markers were negative, except immunoglobulin G for rubella, cytomegalovirus, and HSV. None of the tests in rheumatologic workups were positive. However, blood cell count was equal to 20000 with neutrophil dominancy. Firstly, the ferritin level was detected as 700 ng/mL; however, the second ferritin level equaled 4939 ng/mL (normal: 15-148 ng/mL). The microscopic details of a skin biopsy revealed a perivascular dermatitis pattern with the exocytosis of some lymphocytes into the lower portions of the epidermis.

The patient had undergone antibiotic therapy with endocarditis diagnosis due to the transthoracic report of strand-like mass in the right atrium with 24×8cm when she was referred to our center. Transesophageal echocardiography was negative for vegetation. Blood and urine analysis and culture were also negative. Additionally, no source of infection was observed in physical examination. Antibiotics were stopped, subsequently.

Table 1. Laboratory tests data of the reported patient

	Before Treatment			After Treatment
WBC	15000	17500	Before treatment 24300	12800
Hb	14.1	12.7	9.9	12.5
PLT	190.000	298.000	402.000	606.000
AST	26	530	179	140
ALT	19	147	147	132
ALP	234	287	187	287
Bil T	1	0.8	1	1
Bill D	0.6	0.2	0.3	0.4
ESR	44	59	49	143
CRP	24	54	48	78

Table 2. Laboratory tests data of the reported case

Tests	Antibody	Results
Anti-CMV	Ig-G	151.1 (Pos)
	Ig-M	0.37 (Neg)
Anti-HSV	Ig-G	182.1 (Pos)
	Ig-M	18 (Neg)
Anti-Rubella	Ig-G	42.7 (Pos)
	Ig-M	0.88 (Neg)
Anti toxo	Ig-G	0.03 (Neg)
	Ig-M	0 (Neg)
EBV	Ig-G	0.02 (Pos)
	Ig-M	41.04 (Neg)

According to Yamaguchi's diagnostic criteria and the existence of several lymph nodes in the submandibular area and both peri-jugular regions, we were suspicious of lymphoma. The size of the largest lymph node in sonography was measured as 3 cm.

Our plan was an initial excisional biopsy; however, fine needle aspiration was conducted, because the size of the lymph node was decreased on the day of surgery (day 3 of admission). The pathology report was negative for malignancy and inflammation was reported. Considering the aforementioned data, we started low-dose prednisolone (15 mg/d) for our patient. Dramatic response to corticosteroid was under notable point in this case. Her fever stopped and skin rashes began to scale. Accordingly, the general condition of the patient improved. Furthermore, by informing of the second level of ferritin, the diagnosis of AOSD was established. The studied patient was discharged after one week and her disease has been remitted until the date of this article submission.

Discussion

AOSD is a rare and potentially life-threatening inflammatory disease. Spiking fever, arthritis, characteristic salmon-pink maculopapular rash, and a white cell counts 10000< are the main features of this disease [6]. AOSD may be monocyclic, polycyclic, or chronic. In the monocyclic type, the patient experiences an acute course of the disease, followed by complete and permanent remission. In the polycyclic type, the patient experiences at least two acute exacerbations and a remission between the exacerbations. The chronic form of the disease can be systemic; however, it is often a poly-articular disease, which resembles rheumatoid arthritis [6].

The pathophysiology of AOSD remains unclear; however, studies have addressed the genetic background as well as the role of microbial agents, especially viruses, such as Epstein-Barr virus, cytomegalovirus, rubella, HCV, and HBV [3, 7]. The familial cases of the disease are rare; however, the reported patient had a strong family history of rheumatologic diseases. Thus, such data may indicate a genetic role in the disease. Besides, the reported case presented positive IgG for HSV, rubella, and CMV, which represent the influence of these pathogens on the disease pathogenesis. There are two age peaks for disease; the age ranges of 15-25 years and 36-46 years [7].

There are two best-known criteria for the diagnosis of AOSD. Yamaguchi criteria were introduced in 1992 and Fautrel's criteria in 2002 [8, 9]. In this study, a patient was reported who met both criteria. As per the literature, Yamaguchi's criteria, with a sensitivity of 93.5% is the most sensitive diagnostic criteria. Besides, Fautrel's criteria, with a specificity of 98.5%, is the most specific criteria; however, because of its lower sensitivity (80.6%), Yamaguchi's criteria should be used to rule out AOSD [10]. In this case report, the second ferritin level was extremely high. Using elevated ferritin levels for diagnosis purposes is limited. This is because it is a nonspecific finding, and in other diseases, such as malignancies and infections, it may be very high; however, it may be a prognostic marker in combination with oth-

Table 3. Laboratory tests data of the reported patient

Tests	Results
ANA	Neg.
RF	Neg.
C- ANCA	Neg.
P-ANCA	Neg.
Anti-CC	Neg.
C3	261.6 (90-180)
C4	53.7 (10-40)
CH50	>90
Anti.ds DNA	0.1
Antiphospholipid Ab-IgG	6.2 (NORMAL,<10)
Antiphospholipid Ab-IgM	9 (NORMAL,<10)
Anti Cardiolipin Ab-IgG	3.5 (NORMAL,<10)
Anti Cardiolipin Ab-IgM	7 (NORMAL,<10)
B2 Glycoprotein syndrome	8 (up to 10)
Anti-SSA/RO-IgG	1.1 (<15 Negative)
Anti-SSB/La-IgG	1.0 (<15 Negative)
FANA	Neg.

Table 4. Still disease diagnostic criteria

Yamaguchi's Criteria	Fautrel's Criteria
Major criteria 1. Fever (≥39, for ≥1 week) 2. Arthralgia or arthritis (lasting ≥1 week) 3. Typical rash 4. Leukocytosis (≥10000) Minor criteria 1. Sore throat 2. Lymphadenopathy and/or splenomegaly 3. Liver dysfunction (abnormal liver function tests) 4. The absence of rheumatoid factor and antinuclear antibody Exclusion criteria ● The absence of infection, malignant diseases, or other inflammatory diseases that mimic AOSD	Major criteria 1. Spiking Fever (39 or above) 2. Arthralgia 3. Transient erythema 4. Neutrophil polymorphonuclear count (≥80%) 5. Glycosylated ferritin fraction (≤20%) Minor criteria 1. Typical rash 2. Leukocytosis (≥10000)
At least 5 criteria consisting of ≥2 major criteria and no exclusion criteria are required for the diagnosis of AOSD.	At least four major criteria or three major and 2 minor criteria are required for the diagnosis of AOSD.

er findings, particularly when the ferritin level remains high after adequate treatment, it can predict a chronic joint disease [6].

Most patients can be treated on an outpatient basis; however, the disease is rare and its diagnosis is challenging and can lead to a long hospitalization. Besides, a retrospective study reported a mean diagnosis time of 4 months for this illness [7, 10]. From the onset of symptoms to the diagnosis of the disease, the patient may be subjected to numerous therapeutic and diagnostic measures. Additionally, the absence of appropriate treatment during this period may lead to disease progression. The major differential diagnoses are malignancies, autoimmune diseases, and infections. In a study of patients with fever of unknown origin, those who were eventually diagnosed with AOSD received antibiotics in 90% of the cases prior to the definite diagnosis (Table 4) [10].

Mild disease may respond to NSAIDs; however, >85% of patients require corticosteroid treatment. The presented case provided a dramatic clinical response to corticosteroid therapy. Moreover, her fever and rashes began to decrease and the general condition improved. However, corticosteroids and NSAIDs generate several adverse effects, including osteoporosis and peptic ulcer; therefore, their use is limited, particularly in the long-term. In the case of complications, drug dependence, or failure of treatment with corticosteroids, disease-modifying anti-rheumatic drugs are used, and methotrexate is the best option [10].

Still's rash and polyarthritis are associated with poor functional outcomes. Secondary complications consist of disseminated intravascular coagulation, thrombotic thrombocytopenic purpura, diffuse alveolar hemorrhage, and pulmonary hypertension [3, 10].

Conclusion

Medical science is based on experience and evidence; that is why the diagnosis and treatment of rare diseases have always been challenging. The present study reported a patient with AOSD, as a rare disease, to emphasize the need for greater awareness among physicians to prevent patient's long-term hospitalization and delay in treatment.

Ethical Considerations

Compliance with ethical guidelines

All ethical principles are considered in this article.

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Conflict of interest

The authors declered no conflict of interest

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