

## Adult-onset Still's Disease Presenting as Persistent Fever of Unknown Origin: Case Report and Review of Literature

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### Abstract

Adult onset Still's disease (AOSD) is a rare systemic inflammatory disorder of unknown etiology that can raise serious positive and differential diagnosis problems due to the particular complexity of clinical and biological data. One of the most common presentations of the disease is fever of unknown origin. In Romania is also very rare, therefore we present a case report of AOSD who became the *first case* to be notified in our hospital until now. A 24-year-old woman with persistent fever of unknown etiology, rash, arthralgia and myalgia of three weeks duration presented to our hospital. The purpose of this presentation is to describe a case which put uncertainty on differential diagnosis and to review the literature about AOSD from a primary care perspective.

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**Key words:** Adult onset Still's disease, fever of unknown origin, arthritis, ferritin

### Introduction

Adult-onset Still's disease (AOSD), first described by Bywaters in 1971, is a rare multisystem inflammatory disease, characterized by fever, seronegative joint pain and visceral manifestations.<sup>1</sup> In 1896, George Still recognized this triad of daily fevers, evanescent rash, and arthritis in children with what later became known as juvenile inflammatory arthritis.<sup>2</sup> AOSD affects equally both sexes, occurs mostly in the third or fourth decade and the average incidence is approximately 0.16 cases/100000 inhabitants/year.<sup>3</sup> The etiology of AOSD is still unknown, but it was suggested to be caused by a combination of genetic and infectious factors in the setting of an immune dysregulation and an alteration in cytokine production in favor of Th1 predominance.<sup>4</sup> Due to the particular complexity of biological and clinical data, diagnosis of adult Still's disease is one of exclusion.<sup>5</sup> Clinical diagnostic criteria for establishing the diagnosis

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of AOSD were developed by Yamaguchi et al.<sup>6</sup> Determination of the total and glycosylated ferritin levels, although not pathognomonic, can help in diagnosis.<sup>5</sup>

## **Case Presentation**

We describe the first case in our hospital of a patient with AOSD that developed as a persistent febrile syndrome of unknown etiology. A 24-year-old woman presented with three weeks history of spiking fever (39.8°C) more prominent in the afternoon and evening, headache, arthralgia and myalgia at admission. Her arthralgia involved the left tibio-tarsus joint, the left radio-carpal joint, and knees bilaterally. During her febrile episodes she noted a pruritic maculopapular rash on her trunk and limbs.

Her medical and family history were without medical relevance and the patient didn't take any medication prior to admission. At the time of admission, the patient was febrile with an oral temperature of 39.4°C. On examination, the blood pressure was 110/65 mmHg, the pulse was 110 beats per minute and the respiratory rate was 20 breaths per minute. A pruritic erythematous maculopapular rash was observed over the forearms, thighs, abdomen and back. We noticed that the cardiovascular and respiratory systems examinations were normal. Physical examination showed no lymphadenopathy, no hepatosplenomegaly and the clinical evaluation of the genitourinary system was normal.

On the day of admission chest X-ray and electrocardiography were normal. Sinuses radiograph, knee radiograph, abdominal ultrasound and gastroscopy were unremarkable.

Transthoracic echocardiogram revealed no pericardial effusion and no valve vegetation. Laboratory tests at presentation showed a C-reactive protein (CRP) of 77 mg/l, erythrocyte sedimentation rate (ESR) 108 mm/h, hemoglobin 9.8 g/dl, leucocytes  $11 \times 10^3/\text{mm}^3$  (85% neutrophils), platelets  $803 \times 10^3/\text{mm}^3$  and markedly elevated ferritin level (3780 ng/ml) (table I). Liver function tests were not elevated. Serum protein and hemoglobin electrophoresis were normal.

Immunoelectrophoresis and immunofixation showed no pathologic findings. Serological analysis indicated no infection with *Borrelia*, parvovirus B<sub>19</sub>, rubella, HIV, hepatitis B virus (HBV), HCV, HAV, Epstein Barr virus, and cytomegalovirus. Rapid plasma reagin (RPR) test did not detect syphilis antibodies.

Blood cultures and urinalysis had been negative 3 times. Bone marrow aspiration and biopsy were also negative. Computed tomography of the abdomen and chest showed no significant abnormalities.

Rheumatoid factor (IgM-RF), anti-cyclic citrullinated antibodies (anti-CCP), antinuclear antibodies (ANA), anti-neutrophilic cytoplasmic antibodies (ANCA) and anti-dsDNA antibodies were negative. Cultures of blood, urine and feces repeatedly turned out negative.

Examination of the skin biopsy specimen revealed perivascular edema with mixed inflammatory infiltrate composed of lymphocytes and histiocytes located in the superficial dermis.

By differential diagnosis were excluded other causes like malignancy, infectious disease and connective tissue disease. Considering clinical examination and laboratory relevant data, the rheumatologist noticed that the patient fulfill the diagnostic criteria of AOSD, considering Yamaguchi criteria.<sup>6</sup>

As treatment, the rheumatologist proposed daily prednisone 60 mg oral, hydroxychloroquine 400 mg oral, esomeprazole 40 mg oral and oral supplementation with calcium and vitamin D. Within 48 hours after starting glucocorticoids, it was noticed a good clinical response, with resolution of joint pains and fever, subsequent reduction of skin lesions and improvement of inflammatory markers.

## **Discussion**

In Romania, AOSD could easily remain undiagnosed considering the fact that there is no statistical data of the incidence of AOSD in our country and because it is an extremely rare disease. The lack of biomarkers and its similarity to infectious and malignant and rheumatic diseases may lead to a prolongation of its diagnosis.<sup>7</sup>

The particularity of our case is that is the first case of AOSD in our hospital and the differential diagnosis focused primary on infection of unknown origin and non-specific inflammatory process. Acute viral infections can cause fever, arthritis and a diffuse erythematous rash. In our case, the absence of IgM antibodies to parvovirus B19, excludes the presence of this virus. Numerous other viral infections (e.g. acute HIV, acute HBV, HCV, Epstein Barr virus, acute rubella infection) can cause a polyarthritis, but the serological tests for these were negative. Polyarthritis due to acute viral infections usually resolves over days; persistence for a month, as in this case, is uncommon and provides evidence against a viral cause. Subacute bacterial endocarditis was ruled out on the basis of negative blood cultures and transesophageal echocardiography. Secondary syphilis can cause fever, polyarticular synovitis, and a diffuse rash, but was excluded by the negative RPR test. Serological testing for Lyme disease was negative with no history of tick bites or characteristic skin rash and neurologic involvement.

Patients with AOSD typically have an inflammatory response with elevated C reactive protein and erythrocyte sedimentation rate, a neutrophil leukocytosis (probably secondary to bone marrow granulocyte hyperplasia), and abnormal liver function tests (some studies have suggested this can be secondary to use of non-steroidal anti-inflammatory drugs).<sup>8</sup> Unlike other systemic rheumatic diseases, AOSD is not associated with rheumatoid factor (RF) or antinuclear antibody (ANA) positivity, and this fact has been used in various sets of criteria used to define the disease.

The diagnostic difficulties were determined by the combination of fever, rash and musculoskeletal symptoms that raised the suspicion of a collagen-vascular disease. Systemic vasculitis can cause polyarthritis and fever, but not the nonvasculitic rash that was a prominent feature in this case. Pulmonary or renal involvement, common in small or medium-size

vasculitis, were also absent in this case. Our patient didn't meet the minimum 4 out of 11 American College of Rheumatology criteria for systemic lupus erythematosus (SLE).<sup>9</sup> Usually the rashes in SLE are not pruritic and no typical histological features of lupus were observed at skin biopsy. Fever in SLE more commonly occurs when serositis is present. Moreover, the autoantibodies that are commonly seen in SLE were absent.

Acute leukemia and lymphoma may also mimic AOSD.<sup>10</sup> We excluded both diseases after the bone marrow aspirate and biopsy proven to be negative. Computed tomography scans of abdomen and chest were unremarkable.

Serum ferritin is an acute-phase reactant and usually used as a marker of iron storage.<sup>11,12</sup> Nearly 70% of patients have increased levels of serum ferritin.<sup>13</sup> The cause of the extremely high ferritin concentrations in AOSD remains unclear. Inflammation is associated with increased production of ferritin by the histiocytes-macrophage system and/or increased release from damaged hepatocytes.<sup>14</sup> Disease activity correlates relatively well with the serum ferritin level which often normalizes during remission. In addition, serum ferritin might serve as a prognostic marker in AOSD.<sup>12,15,16</sup> A well-known feature of AOSD is increased levels of serum ferritin, which can be observed in our case report.

Our case presented no clinical signs of visceral affection (heart, lung, liver, kidney, nerve or adenosplenomegaly). Their presence was differently reported in the literature.<sup>17-20</sup>

Based on the criteria proposed by Yamaguchi, the diagnosis was positive for AOSD (being fulfilled four major and one minor criterion).

Treatment of patients with AOSD has been empirical for a long time, given the lack of solid data from well-designed double-blinded randomized clinical trials with the majority of evidence deriving from small case series and retrospective studies.<sup>21</sup> Aspirin or NSAIDs are recommended as the initial treatment in AOSD, but the response rate is reported to be as low as 20% to 25%.<sup>22</sup> Novel agents such as TNF inhibitors (etanercept or infliximab), interleukin blockade (anti IL-6 receptor monoclonal antibody, IL-1 receptor antagonist), IL1 blockade (anakinra) and intravenous gammaglobulin have also been tried in different studies.<sup>22-25</sup> In our case, the rheumatologist had chosen oral steroids therapy associated with hydroxychloroquine, a combination of drugs that lead to improved disease symptoms. Treatment could be monitored by clinical symptoms and serial measurement of the erythrocyte sedimentation rate and ferritin values.

In conclusion, AOSD is an important diagnosis to consider in febrile young people with an unknown cause of fever and recognizing the disease based on classic clinical features and laboratory investigations may lead to an early correct diagnosis. The implications of our work will be on long term, the disease may be easily taken into account when a patient present fevers of unknown origin.

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**Table 1:** Laboratory data on admission

Variable	Mean Values	Reference range
White blood cell count (x10 <sup>3</sup> /mm <sup>3</sup> )	11	4-9
Erythrocytes sedimentation rate (mm/h)	108	2-13
C-reactive protein (mg/l)	77	<12
Fibrinogen (mg/dl)	866	200-400
Hemoglobin (g/dl)	9.8	12-15.5
Platelets (x10 <sup>3</sup> /mm <sup>3</sup> )	803	150-380
Serum ferritin (ng/ml)	3780	10-120