

# Adult Onset Still's Disease With Different Antibodies: A 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. There is not currently any specific serological markers for AOSD, and diagnosis still relying on the exclusion of other likely diagnoses. Yamaguchi's criteria are used as a diagnostic criterion which contains negative serologic markers for other collagen vascular diseases including systemic lupus erythematosus and rheumatoid arthritis. Here we report a 28-year-old woman with arthralgia, fever, rash, leukocytosis, lymphadenopathy, sore throat, abnormal liver function and negative rheumatoid factor and ANA but seropositive for anti-CCP, anti-dsDNA, and C-ANCA. It seems that despite AOSD is considered as a seronegative disorder; it should be remembered in patients with compatible findings who are seropositive.

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## Introduction

Adult-onset Still's disease (AOSD) is a rare systemic inflammatory disorder of unknown etiology, characterized by spiking fever, evanescent cutaneous manifestations, arthralgia or arthritis, and multiorgan involvement (1). The most common cutaneous manifestation is an evanescent salmon-pink or erythematous maculopapular eruption which frequently appears during febrile attacks. The rash is predominantly found in the proximal limbs and trunk, but the involvement of the face and distal limbs is rare. In general, it lasts for hours and may be changed daily, enhancing with the fever spike and fading with the fever down (2).

Yamaguchi's criteria is a diagnostic criterion for Still's Disease, including negative serologic markers for other collagen vascular diseases including systemic lupus erythematosus and rheumatoid arthritis (3). Diagnosis of AOSD is based on fulfilling its diagnostic criteria and exclusion of other diseases such as vasculitis, other collagen vascular disorders, infections, and malignancies. Thus, investigation of serologic and clinical markers of other diseases is essential for a definite diagnosis (4). Despite seronegativity of most patients, there are some reports about detection of

antineutrophil cytoplasmic antibodies (ANCA), anti-citrullinated peptide (Anti CCP), rheumatoid factor (RF) or antinuclear antibodies (ANA) in patients with Still's disease (4-7). Here we report a 28-year-old woman with a final diagnosis of Still's disease whose tests have been positive for different kinds of rheumatologic disorders.

## Case Report

A 28-year-old woman was presented with a two-week-continuous symptom of a sore throat and fever despite using several doses of antibiotics (penicillin G and ceftriaxone). On the physical exam, she had tonsillitis with arthralgia in shoulder, hip, and knees without any sign of arthritis. She was admitted to infectious disease ward for evaluation of pharyngitis and arthritis. The following results were revealed in initial lab tests: mild Leukocytosis=11800 cells/ $\mu$ L, mild anemia (Hgb=11.3), normal platelet count, elevated Erythrocyte sedimentation rate (ESR)=45 mm/h and C-reactive protein (CRP)=28, alanine aminotransferase (ALT)=65, aspartate aminotransferase (AST)=42, antistreptolysin O (ASO)=150.

On the third day of admission, she developed an erythematous and maculopapular rash on both extremities. On the next day as the fever persisted,

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tenderness and swelling on 2,3 and 4th metacarpophalangeal (MCP) and proximal interphalangeal (PIP) joints were appeared. All the tests consisting of Wright, cold agglutinin, human immunodeficiency virus (HIV) antibody, hepatitis B surface antigen (HBs Ag), hepatitis C Virus (HCV Ab) antibody, Epstein-Bar virus viral capsid antigen (EBV VCA) and tuberculin skin test (PPD) were negative.

Echocardiography showed a normal ejection fraction without valvular involvement. In suspicious of stills disease, a rheumatology consult was appealed.

The result of Lab tests has been showed a positive anti-CCP, anti-dsDNA, C-ANCA, normal complements and serum ferritin of 400. CT scan of paranasal sinus and chest did not show any significant abnormality. C-ANCA stayed positive, but antiproteinase 3 (anti PR3) was negative. The patient has been considered as an undifferentiated collagen vascular disease. She was offered a treatment consisting of prednisolone (10 milligrams/day), hydroxychloroquine (200 mg/d) and calcium-D. One month later she kept complaining of generalized arthralgia, fever, chills and weight loss of 6 kg without any improvement. She was advised to be readmitted for more workup. On the second admission, she looked ill, complained of fever, sore throat, and arthritis. Physical examination showed night fever, a painful lymph node in the right axillary area, small joint arthritis of upper limbs and arthralgia in lower limbs and a transient rash in palms (Figure 1).



**Figure 1.** Erythematous macular rash in palm

The result of laboratory investigations revealed elevated ESR (40) and positive CRP, ALT= 67, AST=42. Complete blood cell count (CBC) included a mild leukocytosis (WBC=11600) and anemia (Hgb=11.6 mg/dl). Other biochemistries included: urea=11, creatinine=0.5, fasting blood sugar=91, thyroid stimulating hormone=0.6 and viral markers for HIV, HBS Ag and HCV Ab, blood and urine cultures were negative. The breast sonography showed some lymph nodes in the axillary region. The lymph node biopsy

revealed a reactive lymph node without any malignant changes. Abdominopelvic CT scan didn't show any significant abnormality. Endoscopy and colonoscopy results were normal except for an antral erosion. The result of Screening tests for autoimmune diseases was negative for ANA and RF, and complements levels were normal. Surprisingly the result of C-ANCA, anti-ds-DNA and anti-CCPall was positive with a ratio of (56.2, 23.4, 44.4 with ULN of 18, respectively). The patient was considered as AOSD according to Yamaguchi's criteria because of fever, arthralgias, skin rash, leukocytosis, sore throat, lymphadenopathy, elevations in aspartate and alanine aminotransferase and also the negative tests for ANA and RF(3). A treatment consist of prednisolone (1 mg/kg/d), hydroxychloroquine (400 mg/d) and methotrexate (15 mg/week) was prescribed, and she was discharged afebrile.

With a three month following up on the case, she showed marked improvement of arthralgia and constitutional symptoms.

## Discussion

AOSD is a complicated inflammatory disease. The pathogenesis and etiology of it are still unknown. To date, there are not any specific serological markers for AOSD confirmation, and the diagnosis relies on the exclusion of other likely diagnoses.

According to the Yamaguchi criteria, the diagnosis of AOSD relies on the presence of 5 criteria, at least 2 of which should be the major criteria (3). The most plausible diagnosis based on clinical and laboratory findings and exclusion of other possible causes were AOSD (total 8 Yamaguchi's criterias, 4 majors). An important point in this patient was seropositivity for antiCCP, anti-dsDNA, and C-ANCA. As we exclude other autoimmune diseases, tumors, bacterial and unusual infections this case is considered to be AOSD.

There is some evidence about common pathways and cytokine profile in the pathogenesis of AOSD and other types of collagen vascular disorders such as IL-1, IL-6, and IL-18, tumor necrosis factor alpha (TNF- $\alpha$ ), macrophage colony-stimulating factor, interferon-gamma and tumor necrosis factor-alpha (4,8). In particular, IL-18 is suggested to play a crucial role in activating macrophages, favoring Th1 type cytokine production (9). It seems that there are two subsets of patients with AOSD, patients with high levels of IL-18 or ferritin presented with severe systemic inflammatory disorders and patients with low levels of IL-18 or ferritin which developed severe arthritis (5). Our patients didn't

have a very high level of ferritin level, and it may explain that why she experienced severe arthritis.

To the best of our knowledge; this is the first description of a patient with a diagnosis of AOSD which was seropositive for three different kinds of specific antibodies (anti-dsDNA, antiCCP, and C-ANCA).

The Authors propose that; despite AOSD is described as a seronegative disorder (according to Yamaguchi criteria), it should be considered in patients with compatible findings even they were seropositive.

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