Case Report

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# The Effect of Steroid Dosage in the Treatment of Adult-Onset Still's Disease: A Case Report

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## Abstract

**Introduction:** Adult-onset Still's disease (AOSD) is a rare systemic inflammatory disorder of unknown etiology accompanied with high spiking fever, arthralgia, arthritis, myalgia, salmon-colored evanescent rash and leukocytosis. However, the clinical presentation of AOSD is heterogeneous and the spectrum of differential diagnoses-including infection, neoplasia and other autoimmune disorders, which should be ruled out before the diagnosis of AOSD can be made- is wide.

**Case Report:** The case of a 25-year-old male with no significant medical history presented with fever, arthralgia and evanescent, salmon-pink, maculopapular eruption for two days. His laboratory tests demonstrated particularly the presence of leukocytosis with neutrophilia, elevated AST and ALT and marked hyperferritinemia. Throughout his hospitalization, the patient was evaluated for other potential differential diagnoses. After an extensive workup, the patient was diagnosed with AOSD based on Yamaguchi criteria. He was promptly started on i.v. pulse methylprednisolone (1 gr/day for 3 days) and followed by oral corticosteroid (40 mg/day for 4 weeks). Once the patient became asymptomatic, the oral steroid dose was decreased related to side effects (4 mg/p.o./daily), and he was started on methotrexate 20 mg/s.c./weekly. However, the dosage of steroid had to be increased again because of the onset of fever and rash in the patient.

**Conclusion:** Although methotrexate (MTX) is well known to control both chronic systemic symptoms and arthritis and as a steroid-sparing agent for tapering dose of steroid, it seems that prednisolone (especially high dose) own a significant place in the treatment of Adult-onset Still's disease.

**Key Words:** Adult-onset Still's disease, Steroid therapy, Methotrexate therapy

## Introduction

Adult-onset Still's disease (AOSD) is an uncommon, systemic autoinflammatory disease of unknown etiology characterized by intermittent high spiking fevers, arthralgias/arthritis, myalgia, maculopapular rash, leukocytosis, sore throat, pharyngitis, anorexia, nausea, weight loss, generalized lymphadenopathy, liver dysfunction and splenomegaly. AOSD, one of the most important causes of fever of unknown origin, is diagnosed after ruling out infection, malignancy, and rheumatologic diseases[1]. AOSD is generally treated with non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and disease-modifying anti-rheumatic drugs (DMARDs) such as methotrexate, azathioprine, tacrolimus and cyclosporine. The biological agents including tumor necrosis factor (TNF) inhibitors, tocilizumab or anakinra have also been shown to be beneficial in the management of patients with AOSD refractory to corticosteroids or conventional DMARDs or in patients presenting life-threatening manifestations[2].

The optimal management of AOSD is corticosteroids ± methotrexate. The patients with AOSD are treated initially with high dose steroids for control of disease activity. The dose of steroids needs to be reduced to the minimum, when the disease is controlled and inflammatory parameters have returned to normal. Methotrexate generally provides a complete remission of the disease or at least a significant reduction in daily corticosteroid intake[3].

In this paper, it was aimed to report a case that occur quickly relapse in spite of adding methotrexate to reduce the dosage of steroid when the patient's symptoms and biological parameters returned to normal after initially high dose of steroid treatment.

## Case Report

A 25-year-old male presented to the emergency department with spiking fever with maximum temperature of 40°C and chills for two days, accompanied with loose stools, decreased appetite, evanescent rash, myalgia and generalized joint pain. He also had a salmon pink, maculopapular rash observed with the fever spike localized on the trunk and both lower extremities (Figure 1). He complained of joint pain affecting knees,

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**Table 1**. Yamaguchi Criteria (1992)

| Major Criteria | Minor Criteria |
|---|---|
| 1) Fever of at least 39°C | 1) Sore throat |
| 2) Arthralgia > 2 weeks | 2) Lymphadenopathy or splenomegaly |
| 3) Still rash | 3) Liver dysfunction |
| 4) Neutrophilic leukocytosis > 10.000 | 4) RF and ANA negativity |

wrist, and hands. Her past and family history was insignificant. He was admitted to the department of Infectious Diseases to investigate the etiology of fever. He had been given Ceftriaxone 1 g/i.v./twice a day and Metronidazole 500 mg/i.v./3 times a day as empirical treatment. His significant laboratory findings showed marked leukocytosis (11,700 elements/mm$^3$; 80,6% neutrophils), elevated C reactive protein (CRP) of 132,27 mg/L, elevated erythrocyte sedimentation rate (ESR) (60 mm) and slightly elevated AST (62 IU/L) and ALT (61 IU/L). Ferritin level was also high at 1650 ng/mL. TORCH (toxoplasma, rubella, cytomegalovirus, herpes simplex virus) and EBV (Epstein-Barr virus) panels were both negative. Salmonella and Brucella tube agglutination, Rose Bengal tests, hepatitis panel, tumor markers and HIV/AIDS and VDRL tests were all negative. No proliferation was observed in the throat, blood, stool and urine cultures. Chest X-ray, echocardiography and computerized tomography (CT) of the chest, abdomen and pelvis, also abdominal ultrasonography (USG) did not show any abnormal finding. Despite the use of antibiotic treatment, the patient remained cyclically febrile. At this point, the department of Physical Therapy and Rehabilitation was consulted and noted a non-pruritic generalized erythematous maculopapular rash occurring only during febrile episodes. Rheumatoid factor (RF), anti-CCP (anti-cyclic citrullinated peptide), anti-nuclear antibody (ANA), anti-neutrophilic cytoplasmic antibody (ANCA), and anti-double-stranded DNA (anti ds-DNA) were negative and complement dosage was normal. In light of the available examinations and tests, AOSD was diagnosed according to the classification criteria of Yamaguchi et al. (Table 1)[6]. The patient received intravenous pulse methylprednisolone therapy (1 g daily for 3 days), followed by oral corticosteroids (40 mg daily for 4 weeks). He had an excellent therapeutic response to methylprednisolone during his hospital stay with a decrease in febrile frequency. Once the patient became asymptomatic, the oral steroid dose was decreased related to side effects (4 mg/p.o./daily), and he was started on methotrexate 20 mg/s.c./weekly and then discharged in a stable condition with normal laboratory findings. One week later, while he was on tapering dose of steroid, he applied to the outpatient clinic with complaints of fever and rash again. The dosage of oral steroid was increased from 4 mg/day to 40 mg/day and methotrexate was continued. He continued to remain complete remission on methotrexate and methylprednisolone as maintenance therapy after six months.

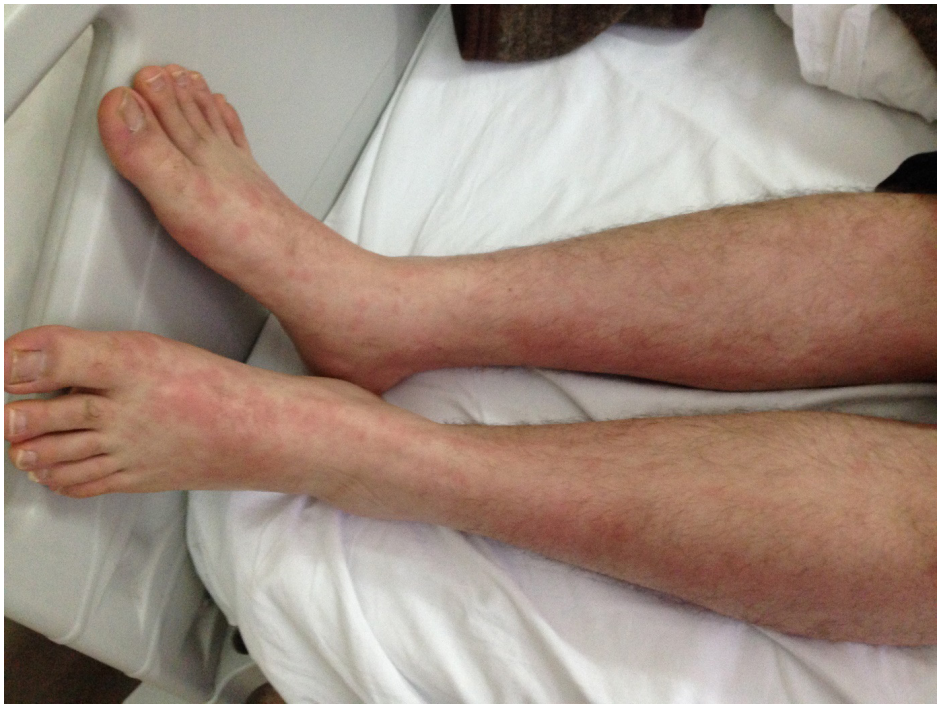

**Figure 1.** Diffuse maculo-papular erythema in legs

## Discussion

AOSD is a rare disease. The incidence of AOSD is estimated to be about 0.16 per 100,000[1]. The age of AOSD onset had a bimodal range with two group: 15–25 and 36–46 years of age[4]. The pathogenesis of AOSD is not clear. Several factors have been suggested to contribute to the disease occurrence, including genetics, viral and bacterial infections, and immune dysfunction. The pro-inflammatory cytokines such as tumor necrosis factor (TNF)-α, interleukin (IL)-1, IL-6, IL-18and IFN-γ seem to play a major role in this disorder. The diagnosis of AOSD can be very difficult. The diagnosis of AOSD requires the exclusion of other possible disorders because it lacks specific clinical and histopathological findings. There is no specific laboratory or imaging test available for diagnosing AOSD and diagnosis is usually based on a symptom complex. AOSD is a multi-systemic inflammatory disorder accompanied by a triad of spiking fever, salmon-colored rash and arthralgia[5]. Yamaguchi's criteria are the most widely used and sensitive diagnostic tool to diagnose AOSD (Table 1)[6]. The patient had four major features of Yamaguchi criteria: fever, arthralgia, leukocytosis and rash. He also met two features of Yamaguchi minor criteria: hepatic dysfunction and negative ANA and RF.

Laboratory findings in AOSD are leukocytosis (mostly neutrophils), anemia, elevated ferritin, C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), abnormal liver function tests (AST and ALT) and ANA and RF negativity[6]. Our patient also had high levels of ferritin, ESR, CRP, AST, ALT and leukocytosis and ANA/RF negativity.

Early diagnosis and intervention may help prevent the development of complication and improve the patient outcomes[7]. AOSD treatment is based on anti-inflammatory medications, including steroids, NSAIDs, and anti-rheumatic agents to control symptoms such as fever, joint pain and systemic inflammation. Non-steroidal anti-inflammatory drugs have limited efficacy, and corticosteroid therapy and disease-modifying anti-rheumatic drugs are usually required. Corticosteroids are usually the first-line treatment. In general, the treatment of AOSD involves corticosteroids, generally medium-high to high doses (0.5–1 mg/kg/day) of prednisone equivalent[8]. Presence of high fever attacks, severe articular symptoms or internal organ involvement may justify corticosteroid (usually prednisolone) use at a dose of 1 mg/kg. The response to corticosteroids is often quick and it occurs within a couple of hours or a few days. The tapering begins usually after 4 to 6 weeks[9]. It was preferred intravenous infusion therapy of high-dose methylprednisolone as initial treatment to achieve quicker response. In this case, intravenous infusion of high-dose methylprednisolone therapy dramatically reduced the fever and rash within 3 days. Then, intravenous steroid was switched to peroral methylprednisolone 40 mg/day.

With inadequate response to corticosteroids, methotrexate appears the best choice to control disease activity and allow for tapering of steroid use. In addition, methotrexate (MTX) was introduced to avoid chronic use of high doses of corticosteroid[6].Unfortunately, steroid dependence occurs in 42% to 45% of the cases. This exposes the patients to serious mid- and long-term side effects. Thus, methotrexate should be added to prednisone when the latter fails to control the disease or in case of steroid-dependence (9).The reason why we added methotrexate to methylprednisolone therapy are: 1) to decrease the dosage of steroid, 2) to prevent the side effects of steroid, 3) to avoid the steroid-dependence. In addition, it was reduced the dosage of steroid from 40 mg/day to 4 mg/day for adding methotrexate. However, the dosage of steroid had to be increased again because of the onset of fever and rash in the patient.

## Conclusion

Although methotrexate (MTX) is well known to control both chronic systemic symptoms and arthritis and as a steroid-sparing agent for tapering dose of steroid, it seems that prednisolone (especially high dose) own a significant place in the treatment of AOSD.

## Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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