Adult-onset still’s disease presenting with recurrent fever and sore throat.

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Abstract

Adult-onset Still’s Disease (AOSD) is a rare systemic auto-inflammatory disorder characterized by a triad of spiking fever, rash, and arthralgia that may be associated with multiple systemic manifestations. Diagnosis is clinical, which can be challenging. While definitive diagnostic test is lacking, ferritin and glycosylated ferritin are useful adjuncts to aid in the diagnosis of AOSD. It is important to include AOSD in the differential diagnosis of prolonged fever and sore throat especially if accompanied by other systemic manifestations. Mainstay treatment of AOSD is often with glucocorticoids. Other agents that can also be used include methotrexate, and biologic therapy, such as tumor necrosis factor-α (TNF-α) blockers and interleukin-1 (IL-1) inhibitors. We hereby report a case of a thirty-six years old man who presented with a prolonged course of fever, and recurrent pharyngitis diagnosed as Adult-onset Still’s Disease (AOSD).

Keywords: Adult-onset still's disease, Auto inflammatory disorder, Ferritin, Glycosylated ferritin, Sore throat, pharyngitis.

Introduction

AOSD is a rare systemic auto-inflammatory disorder with annual incidence of 0.16 cases per 100,000 people, with an equal distribution between the sexes.

Auto-inflammatory refers to an emerging family of clinical disorders characterized by episodes of unprovoked inflammation without high-titer autoantibodies. It is characterized by high-spiking fevers, rash, arthralgia or arthritis, and possible multi system involvement.

Though juvenile idiopathic arthritis was described first by the British pediatrician, George Frederick Still; Bywater’s described in 1971, in 14 young adults, a similar clinical feature to that of the systemic form of the pediatric Still’s disease [1].

Case Summary

36-years-old man was referred to our service with spiking fever (39.5°C), arthralgia of elbows, wrists, and knees bilaterally, and sore throat. For the proceeding eight months he experienced recurrent similar attacks with high grade fever, arthralgia, and occasional maculopapular skin rash over the trunk, and face, and extremities, weight loss of twenty-five kilograms, dysphagia, and odynophagia.

Previous investigations revealed leukocytosis with neutrophil predominance, elevated hepatic transaminases, and sedimentation rate. Rheumatoid factor, antinuclear antibodies, double stranded DNA antibodies, Epstein Barr viral Capsid Antigen (EB-VCA) IGM, Salmonella and Brucella serology, HIV, creatine kinase, lactate dehydrogenase. FMF genetic testing, HIV, viral hepatitis B and C were negative. Imaging revealed normal CT of the neck and lungs, and abdominal and pelvic ultrasound.

Examination revealed ill-looking young man, with a temperature of 39.6°C, maculopapular rash (Figure 1), bilateral wrist and elbow tenderness, pharyngeal erythema, but no pus, no lymphadenopathy, hepatomegaly, splenomegaly and he had normal cardiac and pulmonary clinical examination findings. Initial laboratory results revealed significant leukocytosis of 18,500 WBC/μL, with neutrophil predominance (81.1%), ESR 33 after 1 hour, and CRP 104 mg/L. Ferritin was 1473 ng/mL.

Diagnosis of AOSD was made on the basis of Yamaguchi’s, Fautrell’s, and Cush’s criteria and the patient was started on prednisolone 60 mg a day. Glycosylated ferritin was requested (Figure 2, Tables 1-3).

In three days, marked improvement was noted both in symptoms and in acute phase reactants levels. Ferritin was 358.7 ng/mL. After 4 weeks, the patient was totally symptom free, with (C-reactive Protein) CRP 11.9 mg/L, ferritin 87.5 ng/mL. Glycosylated ferritin fraction was 36% [2].

Increasing blood pressure and impaired fasting glycaemia were noted. Tapering off steroids was started and the patient continues to be symptom free after stopping steroids. Twelve weeks after initial treatment he had normal white count, ESR, CRP and ferritin. He kept asymptomatic course with normal laboratory values for one year after the initial encounter.

For the following six years, he had arthralgia, with one attack of left shoulder arthritis, with macular rash but no other systemic manifestations. Symptoms responded to short courses of NSAID.

Eighteen months ago, he had fever, macular rash, generalized arthralgia, and prednisolone 40 mg daily and methotrexate 20 mg a week were prescribed before presenting to our facility again.

When he presented, he was symptom-free, with normal white count, CRP, ESR.
Ferritin was elevated: 592 ng/mL. His blood pressure was 158/95,
fasting blood sugar 130 mg/dL, and glycated hemoglobin 7.1%
[3].

Steroid induced adverse reactions were managed by tapering off
steroids, yet this was associated with recurrence of arthralgia
when decreasing prednisolone to 10 mg a day. The patient was
maintained on 20 mg a day. Infliximab infusion was started after
having normal chest X-ray and negative viral hepatitis serology.

We started Infliximab at 0.3 mg per Kg of body weight then
increased to 0.5 mg per Kg of body weight after three months
because of sub optimal clinical response. It was well tolerated.
After three more months, as the patient was asymptomatic,
Methotrexate and prednisolone were gradually withdrawn in
the following six months.

Three months after complete discontinuation of glucocorticoid
and methotrexate treatment, the patient was still asymptomatic.
On examination, he had a blood pressure of 130/88 mmHg,
and no evidence of skin rash or active synovitis. His last
investigation results revealed ESR of 25 after 1 hour CRP of
10.0 mg/L, Ferritin of 182 ng/dL, Glycated hemoglobin of 5.9%
on no pharmacologic treatment for diabetes, normal hemogram,
and normal liver function test results [4].

Infliximab maintenance at 0.5 mg per Kg of body weight will
be continued with no add-on therapy as long as the remission is
well maintained.

**Discussion**

**Clinical course**

The clinical course of AOSD can be divided into three main
patterns:

1. Monocyclic with predominance of systemic manifestations, a
course that lasts weeks to months and completely resolves in less
than a year in most cases.

2. Polycyclic systemic with multiple systemic disease flares that
may or may not be associated with arthritis. Flares tend to be less
severe and of shorter duration than the first disease episode and;

3. Chronic articular patterns that may overlap with the systemic
cyclic pattern [5].

Recent data have suggested that these three patterns may
be grouped into only two: a systemic form that includes the
monocyclic and the polycyclic patterns; our patient is an
example, and another chronic articular form. In fact, it is
probable that the immunological imbalance would be different
between the two forms, which would explain the difference in

<table>
<thead>
<tr>
<th>Major criteria</th>
<th>Minor criteria</th>
<th>Exclusion criteria</th>
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<tbody>
<tr>
<td>fever &gt; 39 degrees C (102.2 degrees F) for ≥ 1 week</td>
<td>sore throat</td>
<td>infection</td>
</tr>
<tr>
<td>arthralgia or arthritis for ≥ 2 weeks</td>
<td>lymphadenopathy</td>
<td>malignancy, particularly malignant lymphoma</td>
</tr>
<tr>
<td>typical rash</td>
<td>hepatomegaly or splenomegaly</td>
<td>other rheumatic disease, particularly systemic</td>
</tr>
<tr>
<td>leukocytosis (white blood cells &gt; 10,000/mm) with ≥</td>
<td>abnormal liver function tests</td>
<td>vasculitides</td>
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<td>80% granulocytes</td>
<td>absence of rheumatoid factor and antinuclear antibody</td>
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**Table 1.** Yamaguchi’s criteria. Diagnosis based on presence of ≥ 5
criteria, including ≥ 2 major criteria.

<table>
<thead>
<tr>
<th>Major criteria</th>
<th>Minor criteria</th>
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<tr>
<td>spiking fever &gt; 39 degrees C (102.2 degrees F)</td>
<td>maculopapular rash</td>
</tr>
<tr>
<td>arthralgia</td>
<td>leukocytosis ≥ 10,000/mm</td>
</tr>
<tr>
<td>transient erythema</td>
<td></td>
</tr>
<tr>
<td>pharyngitis</td>
<td></td>
</tr>
<tr>
<td>polymorphonuclear cells ≥ 80%</td>
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<tr>
<td>glycosylated ferritin ≤ 20%</td>
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**Table 2.** Fautrel’s criteria. Diagnosis based on presence of ≥ 4 major
criteria or presence of 3 major plus 2 minor criteria.
Adult-onset Still’s Disease (AOSD) is a rare systemic auto inflammatory disorder that may present with symptoms that may mimic other rheumatologic, infectious, or neoplastic diseases. Including it in the differential diagnosis of prolonged Fever of Unknown Origin (FUO) is warranted. When there is no clear diagnosis or no adequate response to treatment for conditions presenting similarly, AOSD should be suspected, and serum ferritin and glycosylated ferritin improved specificity to 98.5%.

**Treatment and prognosis**

Treatment is based on small case series and case reports with Non-steroidal Anti-inflammatory Drugs (NSAIDs) as a supportive measure and in the prediagnosis phase. The mainstay initial treatment and treatment for systemic flares is with glucocorticoid 0.5-1 mg/Kg/day with tapering off after normalization of all clinical and laboratory markers of the disease, usually after 4-6 weeks. Disease Modifying Anti-rheumatic Drugs (DMARDs) can be used for steroid resistance or dependence. Early addition of steroid-sparing treatment may be warranted in patients with risk factors for steroid dependency (young age at onset, splenomegaly, low glycosylated ferritin, elevated erythrocyte sedimentation rate). The best results achieved were with methotrexate 7.5-20 mg/week though other DMARDs may be used.

For refractory disease, biologic agents may be used, with TNF-alpha blocking drugs (infliximab has the best outcome results) as the preferred agents for articular disease, and interleukin-1 (IL-1) inhibitors; mostly anakinra, and interleukin-6 (IL-6) inhibitor tocilizumab for refractory systemic disease.

For AOSD during pregnancy and for life threatening complications, higher doses of glucocorticoids and IV Immunoglobulin (IVIG) may be needed [7].

**Prognosis**

AOSD is a relatively benign disease. Life threatening complications are rare. Negative prognostic factors are polyarthritis, erosive arthritis, and lack of response to glucocorticoid treatment.

**Conclusion**

Adult-onset Still’s Disease (AOSD) is a rare systemic auto inflammatory disorder that may present with symptoms that may mimic other rheumatologic, infectious, or neoplastic diseases. Including it in the differential diagnosis of prolonged Fever of Unknown Origin (FUO) is warranted. When there is no clear diagnosis or no adequate response to treatment for conditions presenting similarly, AOSD should be suspected, and serum ferritin and glycosylated ferritin assessed [8].

**References**


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