Still's Got That Fever: Adult-onset Still's Disease in Fever of Unknown Origin

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Abstract: *Still's Got That Fever* is a case report of a patient in her 60s, who presented with a 2-week history of fevers, diffuse arthralgias, and salmon-coloured rash. Given the rarity of this disease, it was almost 1 week into her admission before the diagnosis of adult-onset Still's Disease (AOSD) was made as the cause of her fever of unknown origin. This case highlights the Yamaguchi criteria, which are still the standard in making the diagnosis, which is a clinical one. Our patient underwent extensive investigations to rule out other infectious, malignant, and auto-immune causes. Furthermore, a life-threatening complication of AOSD that clinicians should be aware of is macrophage activation syndrome (MAS). The gold standard investigation to rule out MAS is bone marrow biopsy, which would show hemophagocytosis. Our patient did not develop MAS, was treated with steroids, and showed an immediate clinical response. We highlight other treatment options for AOSD based on disease severity, including methotrexate and biologics.

Key Points:

- Adult-onset Still's Disease (AOSD) is a rare inflammatory disease that is diagnosed clinically, with symptoms including high fevers, arthralgias, and a maculopapular rash.
- Investigations should include an infectious and inflammatory work-up, which typically shows an elevated ESR,[a] CRP,[b] and ferritin, but negative blood cultures, ANA,[c] and RF.[d]
- An important life-threatening complication rarely associated with AOSD is macrophage activation syndrome (MAS). It also presents with high fevers, high ferritin, and abnormal liver enzymes, but can progress to profound cytopenias and liver dysfunction. A bone marrow biopsy is the gold standard to rule out MAS.
- Steroids are the mainstay of treatment in patients with moderate disease (usually 0.5-1 mg/kg/day); however, pulse steroids, methotrexate, and biologic therapies may be considered for more severe-to-resistant disease.

Case Presentation:

A 64-year-old otherwise-healthy female presented with a 2-week history of recurrent fevers (max temperature 40.0°C), chills, bilateral otalgia, sore throat, generalized rash, migratory arthralgias and myalgias, and non-bloody diarrhea. Her exam on admission was pertinent for fever (38.8°C), 0.5 cm tender, mobile anterior cervical lymph nodes, and patches of pruritic rashes over the anterior trunk, and both thighs and arms. Over time, her ear pains and sore throat resolved, but she continued to have daily self-resolving fevers, arthralgias, and developed a salmon-coloured rash.

Her investigations revealed elevated ferritin, ESR, and CRP on day 5 of admission, with imaging evidence of inflammatory arthritis of the wrists, elbows, and knees. Her infectious work-up, including pan-cultures and CT,[e] revealed no source of infection, and her rheumatologic panel (ANA, ENA,[f] ANCAs,[g] rheumatoid factor, anti-CCP,[h] complement studies) were all normal. A bone marrow biopsy was normal. Clinically, she was diagnosed with Still's Disease, and was started on prednisone, which resulted in improvement of her symptoms and inflammatory markers. She was discharged in stable condition on prednisone with outpatient rheumatology follow-up. At her 8-week follow-up, her symptoms remained well-controlled and methotrexate was added as a steroid-sparing agent.

Clinical Manifestations

Patients with adult-onset Still's Disease (AOSD) present with a constellation of symptoms, the most common being severe arthralgias/arthritis, fevers, and subacute rashes.[1] It is a rare disease with an incidence of 1/625,000.[2] As seen with our patient, in about 70% of cases, patients present with a prodromal sore throat prior to manifestation of AOSD symptoms.[3] There is a bimodal age distribution (peaks between 15-25 and 36-46), although our patient was asymptomatic until her 60s, which is a late presentation compared to typical ages of onset.[1]

Fevers in AOSD are usually quotidian, >39˚C, with self-resolution within 2-4 hours.[4] A minority of patients (<20%) have double-quotidian fevers with a second fever spike during the day.[4] Patients tend to feel quite unwell during these febrile spikes. Given these fevers, many patients undergo a work-up for infectious causes which come back negative, and do not respond to antibiotics.

The joint involvement in AOSD may initially start with one or few joints, then most commonly progresses to become polyarticular, affecting both small and large joints.[5] Arthrocentesis usually reveals inflammatory arthritis. Our patient presented with bilateral knee, wrist, and elbow arthralgias. An arthrocentesis was not pursued given her improvement with steroids and our level of diagnostic certainty.

Rash in AOSD is very common, characteristically described as a salmon-coloured, non-pruritic rash usually present on the trunk, arms, or legs.[5] In some patients, this rash is only present during fevers.[4] Our patient indeed had a salmon-coloured rash, but it was quite pruritic, requiring potent topical lotions, and persisting during afebrile periods.

Diagnosis

AOSD is primarily a clinical diagnosis, and a broad differential should always be considered, given the non-specific constellation of symptoms. There is no investigation that confirms AOSD, but the clinical presentation and laboratory findings should be used in conjunction to make the diagnosis. It is usually a diagnosis of exclusion. The Yamaguchi criteria, first described in 1992, have a sensitivity of 96.2% and specificity of 92.1%.[2] A diagnosis of AOSD requires ≥5 criteria (≥2 major criteria) and no exclusion criteria. The criteria are shown in Table 1, with major criteria including fever ≥1 week, arthralgias ≥2 weeks, typical non-pruritic rash, and leukocytosis ≥10,000/mm^3.[2] Our patient met 3 major criteria and 3 minor criteria.

When suspecting AOSD, important investigations include CBC,[i] liver enzymes, ESR, CRP, ferritin, ANA, and RF.[4] An infectious work-up including pan-cultures should be conducted to rule out infectious diseases. As evidenced by our patient, patients commonly will have elevated leukocyte count, ferritin, ESR, and C-RP, but negative ANA and RF. There was no clinical evidence of any other rheumatological disease. Finally, her pan-CT showed no evidence of malignancy. Thus, she did not meet any of the exclusion criteria.

AOSD is typically not a life-threatening disease; however, a rare life-threatening complication of which physicians should be cognizant is macrophage activation syndrome (MAS). Such patients will have high fevers, elevated ferritin, and abnormal liver enzymes, and can deteriorate quickly. A bone marrow biopsy would show hemophagocytosis, and should be strongly considered, to rule out this life-threatening complication.[4] Our patient's biopsy was normal.

Treatment

Given that AOSD is quite rare, treatment is extrapolated from other autoimmune conditions such as rheumatoid arthritis and SLE. AOSD management depends on disease severity, with steroids being the mainstay of treatment.[6]

As there is no well-validated prognostication tool available for AOSD, treatment goals are targeted to control inflammatory signs, symptoms, and laboratory indices.[4] Mild-to-moderate disease, defined by non-disabling symptoms, may be initially treated with NSAIDs[j] and glucocorticoids. Depending on severity and individual patient assessment, initial doses of glucocorticoids, like prednisone, can range from 0.5 mg/kg/day to 1 mg/kg/day.

Moderate-to-severe disease, characterized by persistent debilitating symptoms, may require addition of a biologic agent, like anakinra, or other interleukin-1 inhibitors. Anakinra has shown efficacy as a monotherapy in early disease and in prevention of chronic arthritis and inflammation

Table 1:
Yamaguchi Criteria[2]

Major Criteria	Minor Criteria	Exclusion Criteria
Fever (39°C) lasting ≥ 1 week	Sore Throat	Infection
Arthralgia or arthritis lasting ≥ 2 weeks	Lymphadenopathy	Malignancy
Typical non-pruritic salmon-coloured rash	Splenomegaly	Other rheumatic disease (vasculitis)
Leukocytosis ≥10,000/mm^3 with 80% granulocytes	Abnormal liver enzymes	
	Negative ANA and RF	

later on.[7] At this stage, combination therapy with glucocorticoids may be needed for symptom control. Furthermore, DMARDs,[k] such as methotrexate, may be initiated after 2 weeks of symptom non-resolution, or as steroid-tapering adjuncts long-term. Methotrexate can be used for 3-6 months after discontinuing steroids.

Conclusion

Given its rarity and non-specific symptoms, AOSD is a systemic inflammatory disease that can be challenging to diagnose and treat. Its characteristic spiking fevers, arthritis, rash, and high ferritinemia can elude clinicians. This report highlights the importance of recognizing AOSD to initiate early therapy, and the room for additional research to optimize treatment options.

Glossary:

a. ESR: erythrocyte sedimentation rate
b. CRP: C-reactive protein
c. ANA: anti-nuclear antibodies
d. RF: rheumatoid factor
e. CT: computed tomography
f. ENA: extractable nuclear antigen
g. ANCA: antineutrophil cytoplasmic antibodies
h. anti-CCP: Anti–cyclic citrullinated peptide
i. CBC: complete blood count
j. NSAIDs: Non-steroidal anti-inflammatory drugs
k. DMARDs: Disease-modifying antirheumatic drugs

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Appendix

Table 2:

Bloodwork Trends, by Day of Admission

	Day 3	Day 6*	Day 8	Day 9	Day 12	Day 13
Hb (g/L)	113	120	103	–	120	–
WBC (x 10^9/L)	4.5	5.4	9.4	–	11.3	–
Granulocyte %	80%	83%	92%	–	81%	–
Platelets (x 10^9/L)	242	183	186	–	371	–
ESR (mm/hour)	45	–	63	59	–	–
CRP (mg/L)	30.8	67.1	20	21.1	26	27.4
Ferritin (µg/mL)	6405	>16500	11323	6056	3102	2977

*Prednisone started on day 6 of admission