Adult-onset Still's disease after environmental exposure while working in Africa

Emily L Gilbert , Benjamin Wang

Rheumatology, Mayo Clinic Hospital Jacksonville, Jacksonville, Florida, USA

Correspondence to
Dr Emily L Gilbert;
gilbert.emily@mayo.edu

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SUMMARY

Adult-onset Still's disease (AOSD) is characterised by a constellation of systemic inflammatory symptoms and typical laboratory findings like hyperferritinaemia. A high index of suspicion is needed to identify patients as diagnosis is primarily clinical and significant morbidity can result from delayed diagnosis. While AOSD may be self-limited, some patients experience flares over years and require more aggressive treatment approaches. Aetiology is unknown but can be triggered by viral infections and other environmental factors in a susceptible genetic host. We present a case of AOSD triggered after exposure to a sap-like liquid while working in Africa. This inciting event occurred as part of a hostile act towards the patient and involved medicinal practices traditional to the area. Our case highlights the more chronic course of AOSD, which requires escalating biological treatment to avoid long-term corticosteroids, as well as the juncture between traditional and modern medical practices.

BACKGROUND

Adult-onset Still's disease (AOSD) is a rare, systemic inflammatory disease of unknown aetiology.[1 2] Diagnosis can be difficult as symptoms vary, and no definitive diagnostic test is available. However, astute clinicians need to recognise the possibility of AOSD promptly as serious complications can occur in patients including macrophage activation syndrome (MAS).[1 2] While some cases may be self-limited, other patients experience a chronic course over years. Treatment in these situations can be challenging as long-term steroid use is associated with many pejorative side effects. We present a case of AOSD occurring after environmental exposure in Africa.

CASE PRESENTATION

A Caucasian man in his 50s with a medical history significant for gout was referred to our institution for a second opinion assessment of AOSD. His symptoms began 6 years prior while he and his wife were working in West Africa. After contact with a local individual touching the patient's hands and arms with a liquid, sap-like substance on his hands, the patient developed a high fever along with epistaxis, visual hallucinations, nausea/vomiting, arthralgias and myalgias. He experienced similar fever, nausea, arthralgias and myalgias over the next few days in the evenings with gradual improvement over a week. Symptoms resolved on their own, and he felt well and able to continue his work. Symptoms of high fever, arthralgia, myalgia, fatigue and malaise began to occur approximately once a month in the ensuing months. He was treated for malaria on multiple occasions and eventually returned to the USA in 2017.

INVESTIGATIONS

In 2019, he was hospitalised for fever of unknown origin and presumed sepsis, with no infectious aetiology identified. Table 1 shows pertinent infectious disease tests, laboratory studies, and autoimmune serologies. Chest X-ray was negative. Tagged white blood cell scan was negative. He had a non-diagnostic cancer workup with CT imaging of the chest/abdomen/pelvis and positron emission tomography (PET) scanning. He received treatment with broad-spectrum antibiotics including vancomycin, Zosyn and doxycycline in addition to atovaquone. His local rheumatologist and haematologist became suspicious for the possibility of AOSD when serum ferritin was found to be greater than 5000 ng/mL during one of the patient's flares, which continued to manifest with quotidian fever, sore throat, fatigue/malaise and arthralgias sometimes with knee swelling. Bone marrow biopsy was considered but ultimately not pursued. Leucocytosis and transaminitis were also typical during flares.

TREATMENT

He began treatment with his local rheumatologist for AOSD with courses of corticosteroids during flare with eventual initiation of leflunomide as steroid sparing agent. Unfortunately, he did not improve on leflunomide with increasing frequency of flares and inflammatory arthritis in his knees. He was referred to us for further management. We recommended canakinumab with use of corticosteroids during acute flare.

OUTCOME AND FOLLOW-UP

Four months have passed since the patient's referral to our care centre. The patient has suffered one significant flare since our evaluation lasting approximately a week with quotidian fever, sore throat, knee pain and significant malaise. His ferritin was significantly elevated during this time as well. His local rheumatologist treated this acute episode with corticosteroids and then initiated treatment with canakinumab. He has received two doses of canakinumab and has not suffered additional disease flare. Primary side effect has been vertigo around the time of injection.

DISCUSSION

AOSD remains a poorly understood and often under-recognised systemic, inflammatory disorder

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Table 1 Representative infectious disease tests, laboratory studies and autoimmune serologies during hospitalisation for fever of unknown origin workup

Infectious tests	
HIV	Negative
Hepatitis A IgM	Negative
Hepatitis B surface antigen	Negative
Hepatitis B core IgM	Negative
Hepatitis C Ab	Negative
Blood Cultures × 3	Negative
CSF gram stain, bacterial/fungal culture	Negative
CSF studies: WNV, cryptococcus, EBV, CMV, arbovirus	Negative
Stool Studies: *Clostridium difficile* toxin, culture, O&P, Shiga	Negative
Sputum culture, AFB smear, *Streptococcus pneumoniae*/legionella urine Ag	Negative
Urine culture	Negative
Malaria blood smear	Negative
Dengue fever panel	Negative
Laboratory investigations/autoimmune serologies	
ANA	Negative
ENA panel	Negative
Rheumatoid factor	Negative
Anti-CCP Abs	Negative
ANCA panel	Negative
ESR	55 mm/hour (0–20 mm/hour)
CRP	110.71 mg/L (<8.0 mg/L)
TSH	2.63 uU/ml (0.46–4.68)
Uric acid	6.0 mg/dL
WBC	25.5 (3.4–9.6)
Absolute neutrophils	15.6 (1.4–6.5)
Absolute lymphocytes	0.6 (1.2–3.4)
Haemoglobin/haematocrit	12.5/36.1
Platelets	125 (135–317)
AST	68 U/L (8-48)
ALT	82 U/L (7-55)
Ferritin	5671 ng/mL (22-322)

AFB, Acid Fast Bacillus; ALT, Alanine Aminotransferase; ANA, Anti-nuclear Antibody; ANCA, Antineutrophil Cytoplasmic Antibodies; AST, Aspartate Aminotransferase; CCP, Cyclic Citrullinated Peptide; CMV, Cytomegalovirus; CRP, C Reactive Protein; CSF, Cerebrospinal Fluid; EBV, Epstein-Barr Virus; ENA, Extractable Nuclear Antigen ; ESR, Erythrocyte Sedimentation Rate; O&P, Ova & Parasites; TSH, Thyroid Stimulating Hormone; WBC, White Blood Cell ; WNV, West Nile Virus.

with a prevalence of 1–34 cases per 1 million people.[1 2] In an eponynmous historical context, the paediatric equivalent of systemic juvenile idiopathic arthritis (sJIA) was described in 22 patients in 1897 by Still.[3] Bywaters characterised 14 adult patients with a similar clinical picture to sJIA patients, giving rise to the term AOSD.[4] Pathogenesis of AOSD is complex, and both innate and adaptive immune systems contribute. It is hypothesised that in a genetically susceptible individual, a trigger serves as a second hit promoting the exaggerated inflammatory response and AOSD development.[1] It is important to familiarise ourselves with the presentation of AOSD as diagnosis is primarily clinical and serious complications can occur such as MAS. AOSD flare commonly precipitates this life-threatening complication; therefore, continued vigilance in these patients is warranted with each flare.[1] Thankfully MAS has not been a part of our patient's clinical course.

Disease mimics must be excluded. The Yamaguchi criteria are the most sensitive.[5] Our case highlights three major criteria with fever, arthralgia and leucocytosis as well as several minor criteria with sore throat, liver abnormalities and negative ANA and rheumatoid factor. Biochemical markers typical of AOSD like hyperferritinaemia were seen in our patient as well.[6] Evanescent rash was not part of our patient's disease.

Treatment of AOSD remains a challenge. Our patient had at best a subpar response to steroids with increasing frequency of attacks despite steroids and steroid sparing immunosuppressive agent. Methotrexate is used most frequently as a steroid sparing disease modifying anti-rheumatic drug (DMARD) in AOSD and has been beneficial in some patients both to reduce steroid consumption and to induce disease remission.[7–9] Our patient received leflunomide for several years with progression of his symptoms. Refractory AOSD typically is subdivided into two subgroups with patients experiencing primarily high fever as 'systemic AOSD' and those with primarily joint manifestations as 'rheumatic AOSD;' these subdivisions can be helpful in guiding treatment.[10] For example, IL-6 antagonism with tocilizumab and tumor necrosis factor (TNF) inhibition with etanercept, adalimumab and infliximab can be beneficial in refractory cases with more joint involvement.[7 8 11–15] Along these lines it is quite exciting that the rheumatology community now has the first Food and Drug Administration (FDA) approved medication for treatment of AOSD with canakinumab, an interleukin 1 (IL-1) inhibitor.[16] Aberrant production of proinflammatory cytokines like IL-1 through altered inflammasome activity is important in AOSD pathogenesis as IL-1 promotes cartilage and bone destruction as well as systemic inflammation. Our patient, thus, far has done well following initiation of canakinumab with reduced flares and minimal side effects. Clinical trials are currently examining the role of other cytokines such IL-18 in active AOSD.[1] JAK pathways have also been of interest in animal models of MAS in AOSD and would be a natural interest of possible future trials in humans given the ease of oral dosing and the treatment role they already play in inflammatory arthritis.[1]

The intersection of modern medicine with traditional practices seen more frequently in other parts of the world is an intriguing aspect of our case. Traditional medical practices have been a point of interest dating back to manuscripts in the 1960s and even prior.[17] WHO has defined traditional medicine as the sum total of the knowledge, skill and practices based on the theories, beliefs and experiences indigenous to different cultures, whether explicable or not, used in the maintenance of health and is practised with vegetable, animal and mineral substances by practitioners recognised in the community.[18] In West Africa where our patient worked, disease is viewed as caused by natural forces as well as supernatural agents including witchcraft, sorcery and juju.[19] The most numerous type of traditional practitioner in West Africa is an herbalist, using a combination of herbal preparations and ritual to approach healing/medicine. All parts of plants may be employed including roots, bark, stems, sap, leaves, buds, flowers and seeds often through grinding to powders or boiling to make teas.[19 20]

One of the most interesting aspects of this case is the timing of symptom onset with the cutaneous exposure to the liquid. Most likely the substance that precipitated symptoms in our patient had been concocted by an herbalist. Our patient experienced some atypical findings at the onset of his disease, particularly epistaxis, visual disturbances/hallucinations and nausea/vomiting. It is intriguing that the beginning of his quotidian fever, arthritis and myalgias conincided with the event with the local African practices. Multiple triggers have been postulated

to contribute to AOSD pathogenesis including viruses, bacteria, solid tumours and haematological malignancies.[1 21] Is it possible that the sap-like substance triggered an immunological event in a susceptible host leading to the onset of his disease or mere unfortunate coincidence? The importance of plants and their relationship to medicinal practices is underappreciated in modern societies and largely not thought of in everyday clinical practice; however, prior estimates have shown that 80% of the world's population rely almost entirely on local medicines made from plants.[20] In West Africa specifically, approximately 1000 medicinal plants are thought to occur with about 80% of the population relying on herbal preparations for primary healthcare.[20] Ziblim *et al* detail 47 medicinal plants and 21 rare plants used in West Africa for a number of therapeutic targets ranging from headache, to fever, swelling, rheumatisms, snake bite, cough, stomach issues and stroke.[20] Conversely throughout history, plants as poisons have functioned as means to intimidate or harm, to ascertain innocence or guilt, and to prophecy the future.[17 22] So-called ordeal poisons from the calabar bean, the equatorial tree Erythrophleum, mboundou, djave nuts and many others have been employed throughout Africa as means for proving innocence or identifying guilt. While causality will not be able to be determined definitively, our case serves as an important reminder that indigenous practices are still very much a part of medicine throughout the world and an open mind in medicine is part of the art and humanity inherent in our practice.

Patient's perspective

It has been an extended journey for the patient as he has experienced escalating number of flares over the years with uncertainty as to whether his diagnosis was correct. The lack of long term response to immunosuppressive treatment has been frustrating for him; however, he expressed his hope that the canakinumab injections will continue to be beneficial. Moreover, he has communicated with his colleagues and friends in Africa to attempt to identify the herbal liquid he encountered. The patient expressed his hope that his case is helpful to other patients and that physicians will keep an open mind when considering a diagnosis of Still's disease.

Learning points

- Adult-onset Still's disease (AOSD) is rare and is primarily a clinical diagnosis with potential serious complications if not recognised promptly.
- AOSD should be considered in a patient who presents with a recurring febrile illness, where other causes including infections, haematological malignancies and other autoimmune conditions have been ruled out.
- Treatment of refractory cases should be aimed at targeting the underlying inflammatory pathways responsible for AOSD. IL-1 inhibition is FDA approved for treatment.
- It is important to remember that indigenous practices, herbal supplements and botanicals are a part of medicinal practices throughout the world and can be encountered even in modern medical clinics.

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ORCID iD
Emily L Gilbert http://orcid.org/0000-0003-2108-8315

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