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Case Report

Internal Medicine Section

Extreme Hyperferritinaemia in Adult-onset Still's Disease Mimicking Infection and Malignancy: A Case Report

ANKIT NOTWANI[1], RAMACHANDRAN VISWANATHAN[2], KISHORE HEMANTH KUMAR[3]

ABSTRACT

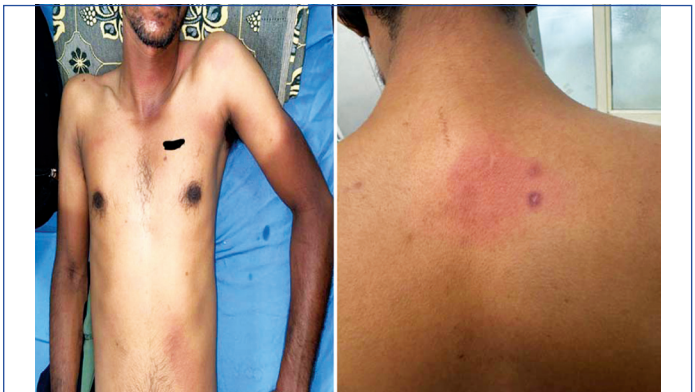
Adult-Onset Still's Disease (AOSD) is a rare systemic inflammatory disorder characterised by quotidian fever, evanescent rash, and inflammatory arthralgia. It often presents as a diagnosis of exclusion due to its clinical heterogeneity and lack of specific diagnostic markers, particularly in patients presenting with Fever of Unknown Origin (FUO). Hyperferritinaemia is a well-recognised laboratory feature, with markedly elevated levels reflecting severe systemic inflammation. However, extreme hyperferritinaemia is not specific to AOSD and may also be observed in infections, malignancies, and hyperinflammatory conditions such as Macrophage Activation Syndrome (MAS), making diagnosis challenging. Hereby, the authors present a case of a 35-year-old male presenting with high-grade fever, migratory polyarthralgia, transient erythematous rash, generalised lymphadenopathy, and significant weight loss, accompanied by markedly elevated serum ferritin levels. Extensive evaluation excluded infectious, malignant, and autoimmune causes. Imaging studies demonstrated reactive lymphadenopathy, splenomegaly, and bone marrow activation, supporting a systemic inflammatory process. The patient showed rapid clinical improvement following corticosteroid therapy. This case is notable for extreme hyperferritinaemia with multisystem involvement in the absence of MAS, along with a presentation mimicking infection and malignancy. It underscores the importance of considering AOSD in patients with FUO and markedly elevated ferritin levels to facilitate timely diagnosis and management.

Keywords: Anaemia, Ferritin, Inflammation mediators, Lymph nodes

CASE REPORT

A 35-year-old male presented with complaints of joint pain, dull aching in nature, intermittent initially and later becoming more persistent, with limitation of routine activities and fever for two weeks, erythematous rash for one week, and vomiting for two days. The patient was apparently well until two weeks prior to admission, when he developed intermittent high-grade fever with temperature of 103.2° F quotidian spikes, associated with chills and rigors. The fever worsened over the preceding two weeks. Over the same period, he developed migratory polyarthralgia, followed by the appearance of an evanescent erythematous rash one week prior to presentation.

The polyarthralgia involved multiple joints (including bilateral knee, ankle and wrist) without associated swelling or redness and was accompanied by generalised body ache, neck pain, anorexia, and unintentional weight loss of approximately 6 kg over one month. One week prior to presentation, he noted erythematous rashes over the right upper limb, abdomen, and back [Table/Fig-1]. The lesions were ill-defined, non-scaly, and lacked vesicles or ulceration. The appearance was consistent with a transient inflammatory rash. Two days prior to admission, he developed three to four episodes of non projectile, non bilious vomiting per day, containing food particles and not associated with abdominal pain.



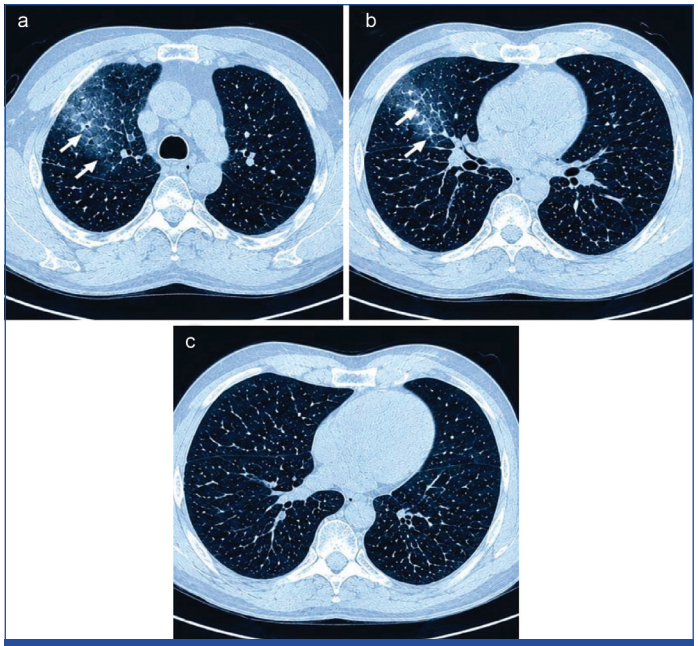
[Table/Fig-1]: Clinical images showing erythematous patches over the anterior chest and posterior upper back, commonly described in systemic inflammatory conditions such as Adult-Onset Still's Disease (AOSD).

The patient had no known co-morbodities or prior history of tuberculosis or malaria. He had been hospitalised two months earlier with similar symptoms, including fever, cough with minimal expectoration, and arthralgia. Computed Tomography (CT) of the chest at that time showed patchy ground-glass opacities with interstitial septal thickening in the anterior segment of the right upper lobe, suggestive of infective pathology [Table/Fig-2a-c]. Bronchoscopy was performed for further evaluation, and bronchoalveolar lavage fluid was sent for microbiological analysis. The culture grew *Pseudomonas* species, while GeneXpert testing for tuberculosis was negative. Based on the culture sensitivity results, targeted antibiotic therapy was initiated. The patient showed gradual clinical improvement, with resolution of symptoms, and was subsequently discharged.

The patient was a former smoker with a ten-year history (abstinence for six months) and had a history of alcohol consumption for ten years, with last intake five months prior to presentation. There was no history of chronic drug abuse. Family history was unremarkable, with no sick contacts or recent travel.

On examination, the patient was conscious, oriented, and febrile. Pallor was present. There was no icterus, cyanosis, clubbing, or pedal oedema. Multiple lymph nodes were palpable in the cervical (levels II and III) and bilateral axillary regions, measuring approximately 1-1.5 cm, firm, mobile, and non-tender, without matting. He was haemodynamically stable with a blood pressure of 130/70 mmHg. Pulse rate was 103 beats per minute, temperature was 103.2°F, and oxygen saturation was 97% on room air.

Systemic examination revealed no abnormalities in cardiovascular, respiratory, or neurological systems. No hepatomegaly or splenomegaly was detected clinically. Musculoskeletal examination



[Table/Fig-2]: Axial High Resolution Computed Tomography (HRCT) images of the chest (lung window) show ground-glass opacities with interstitial septal thickening in the anterior segment of the right upper lobe (arrows); a) Upper lobe slice demonstrating patchy ground-glass opacities and interlobular septal thickening; b) Mid-lung slice showing persistence of the same changes in the anterior segment of the right upper lobe; c) Lower lung slice with no significant abnormalities.

revealed tenderness involving bilateral wrist, knee, and ankle joints without swelling, erythema, or effusion. Range of motion was mildly restricted due to pain.

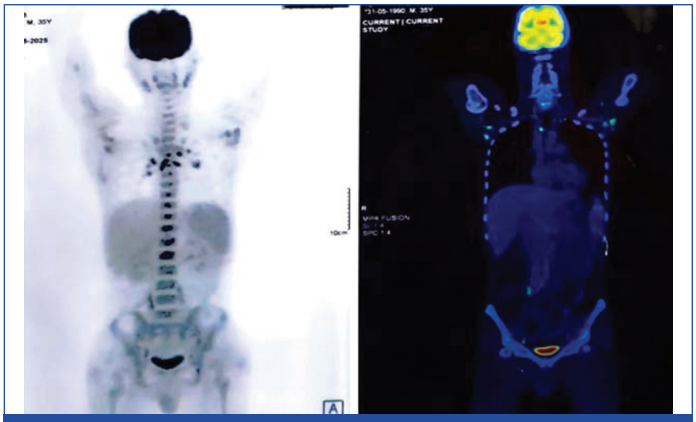
Laboratory evaluation revealed severe anaemia (haemoglobin 6.2 g/dL) and leukocytosis (11,110/µL). Erythrocyte Sedimentation Rate (ESR) as 121 mm/hr and C-Reactive Protein (CRP) was 8.3 mg/dL. Serum ferritin was markedly elevated at 37,450 ng/mL. Lactate Dehydrogenase (LDH) was 428 U/L and fibrinogen was 490 mg/dL. Peripheral smear showed microcytic hypochromic anaemia.

Further evaluation showed mild transaminitis, negative rheumatoid factor, normal complement levels, and no monoclonal gammopathy on serum protein electrophoresis. Procalcitonin was normal (i.e., 0.01ng/mL), and throat culture was negative. Glycosylated ferritin assay was not available. Skin biopsy was not undertaken because the cutaneous lesions were transient, non-specific, and clinically characteristic of the evanescent rash seen in AOSD. In addition, the lesions resolved promptly after initiation of corticosteroid therapy with oral prednisolone at a dose of 1 mg/kg/day and biopsy was not expected to alter clinical management. Bone marrow and lymph node biopsies were deferred due to lack of strong suspicion for malignancy.

Autoimmune markers, including Antinuclear Antibody (ANA) and Anti-Cyclic Citrullinated Peptide (anti-CCP) antibody, as well as viral serology and microbiological cultures, were negative. Imaging studies showed cervical lymphadenopathy on ultrasound. Chest radiography and abdominal ultrasonography were unremarkable. Transthoracic echocardiography demonstrated normal left ventricular systolic function, mild mitral regurgitation, mild pulmonary arterial hypertension, and no evidence of valvular vegetations, although Positron Emission Tomography (PET) scan later demonstrated reactive splenomegaly, lymphadenopathy, and bone marrow activation suggestive of inflammatory aetiology [Table/Fig-3].

The patient was initiated on systemic corticosteroid therapy (with oral prednisolone at a dose of 1 mg/kg/day). A rapid clinical response was observed, with defervescence of fever within 48 hours. Joint pain and rash improved significantly over the subsequent 3-5 days. Inflammatory markers showed a declining trend, and serum ferritin levels reduced progressively during hospital stay.

On follow-up at two weeks, the patient remained afebrile with complete resolution of rash and significant improvement in



[Table/Fig-3]: Whole-body Fluorodeoxyglucose (FDG) Positron Emission Tomography–Computed Tomography (PET-CT) demonstrating reactive splenomegaly, reactive supradiaphragmatic and infradiaphragmatic lymph nodes, reactive bone changes suggestive of autoimmune disorder.

arthralgia. Serum ferritin levels showed a marked decline (480 ng/mL). Prednisolone dose was gradually tapered to 10mg/day and the patient was advised regular follow-up to monitor for relapse or progression to chronic articular disease. On follow-up after three months, the patient remained asymptomatic with no recurrence of fever, rash, or joint symptoms.

DISCUSSION

The AOSD is a rare systemic inflammatory disorder characterised by quotidian fever, inflammatory arthritis, and an evanescent rash [1-4]. Diagnosis is challenging due to the absence of specific biomarkers and the need to exclude infectious, malignant, and other autoimmune causes [1-4]. In this case, the combination of prolonged high-spiking fever, migratory polyarthralgia, erythematous rash, lymphadenopathy, weight loss, and extreme hyperferritinaemia strongly suggested AOSD after extensive exclusion of alternative diagnoses [1-4]. The patient belonged to the second peak age group for AOSD and exhibited classical quotidian fever with fixed daily spikes [2,3]. The transient erythematous rash involving the trunk and upper limbs, along with cervical and axillary lymphadenopathy, reflected systemic inflammatory involvement typical of active disease [2,3]. Articular symptoms were present as migratory polyarthralgia without overt synovitis, consistent with early or systemic predominant AOSD [2,3].

Laboratory evaluation revealed severe anaemia, neutrophilic leucocytosis, markedly elevated ESR and CRP, and extreme hyperferritinaemia (37,450 ng/mL) [1-4]. Ferritin levels exceeding 1,000 ng/mL are characteristic of AOSD, while levels above 10,000 ng/mL raise concern for severe systemic inflammation [5-7]. Negative autoimmune serology, including ANA and anti-CCP antibodies, supported the diagnosis and fulfilled exclusion criteria of the Yamaguchi classification system [1-4]. Imaging studies including PET scan, demonstrated reactive lymphadenopathy, splenomegaly, and bone marrow activation, favouring an inflammatory aetiology over malignancy [3]. Infectious causes were comprehensively excluded through negative cultures, viral serology, GeneXpert testing, and absence of active pulmonary or cardiac infection on imaging and echocardiography [1-4]. Although the patient had a prior episode of pseudomonal pneumonia, the current presentation lacked features of ongoing infection [1].

The present case demonstrated classical features of AOSD, including quotidian fever, polyarthralgia, rash, and extreme hyperferritinaemia. Similar findings have been reported in multiple studies, where ferritin levels exceeding 10,000 ng/mL strongly correlated with active systemic inflammation [6-10]. Previous case series have emphasised that such extreme elevations, although not specific, are highly suggestive of AOSD in the appropriate clinical setting after exclusion of infection and malignancy [9-11]. The transient erythematous rash and generalised lymphadenopathy observed in

this patient are consistent with findings described in prior reports [9-11]. Studies have shown that up to 65-80% of AOSD patients present with evanescent rash, while reactive lymphadenopathy is a frequent but non-specific feature [10,11]. Similar PET scan findings of hypermetabolic lymph nodes and splenomegaly have been documented, often mimicking lymphoma and leading to diagnostic confusion [12,13].

Consistent with previously reported cases, this patient initially mimicked infectious and malignant conditions, particularly in the setting of prior pulmonary infection and lymphadenopathy [3,4,10,11]. The literature highlight that AOSD is frequently misdiagnosed or delayed due to its overlap with sepsis and lymphoma [2,3,10,11]. Negative cultures, absence of malignancy on imaging, and characteristic clinical evolution ultimately guide the diagnosis. A rapid response to corticosteroid therapy, as observed in this case, is a well-documented feature of AOSD and often serves as both a therapeutic and diagnostic indicator [8-11]. Several reports have demonstrated dramatic improvement within 24-72 hours of steroid initiation, supporting the inflammatory nature of the disease and reinforcing the diagnosis when other causes have been excluded [9-11,13]. MAS a life-threatening complication of AOSD, was an important consideration given the extreme ferritin levels [5,6,8,9]. However, preserved fibrinogen levels, absence of pancytopenia, and lack of coagulopathy made active MAS unlikely at presentation, though close monitoring was warranted [5,9,10]. Overall, this patient fulfilled multiple major and minor Yamaguchi criteria, and the clinical profile was highly suggestive of AOSD [1]. Early recognition is essential to prevent progression to chronic arthritis and severe systemic complications [2].

Differential diagnoses considered included Haemophagocytic Lymphohistiocytosis (HLH), Catastrophic Antiphospholipid Syndrome (CAPS), Hepatic necrosis, lymphoma, severe sepsis. HLH was considered given extreme ferritin levels; however, absence of cytopenias, hypertriglyceridaemia, hypofibrinogenaemia, and organ failure made this diagnosis unlikely [14]. HLH is diagnosed based on the HLH-2004 criteria, which require either a confirmed molecular diagnosis consistent with HLH or fulfillment of at least five out of eight clinical and laboratory features. Marked elevated ferritin levels (>10,000 ng/mL) strongly raise suspicion for HLH, though they are not independently diagnostic [14].

Lymphoma was considered due to lymphadenopathy and systemic symptoms. However, PET imaging favoured reactive aetiology, and there was no progressive nodal enlargement or B symptoms suggestive of malignancy [12,13]. CAPS differs from AOSD by its hallmark of widespread thrombosis leading to rapid multiorgan failure. Clinical clues include thrombotic events, positive antiphospholipid antibodies, and organ ischemia, which are not features of AOSD [11]. While ferritin may be elevated in CAPS, it is not the central diagnostic feature as it is in AOSD [6]. Sepsis can mimic AOSD with fever and elevated inflammatory markers, but it is differentiated by the presence of an identifiable infectious source, positive cultures, and haemodynamic instability [2,3]. Unlike AOSD, sepsis does not show the typical quotidian fever pattern or evanescent rash, and ferritin elevation is usually accompanied by clear signs of infection [3]. In hepatic necrosis, hyperferritinaemia results from massive hepatocyte destruction rather than systemic inflammation. It is distinguished from AOSD by markedly elevated liver enzymes, coagulopathy, and clinical features of acute liver failure, without the characteristic fever pattern, arthritis, or rash seen in AOSD [6].

CONCLUSION(S)

The present case emphasises the value of a thorough and methodical diagnostic process when patients have a protracted fever, systemic inflammatory symptoms, and noticeably high ferritin levels. After ruling out viral and malignant causes, clinicians should be prompted by extreme hyperferritinaemia to examine underlying hyperinflammatory syndromes, such as autoimmune and autoinflammatory illnesses. Since a delayed diagnosis may result in organ involvement, illness progression, or potentially fatal consequences such as MAS, early detection of such conditions is essential. Timely therapy commencement, suitable laboratory testing, and meticulous clinical evaluation can greatly enhance results and lower long-term morbidity in impacted individuals.

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PARTICULARS OF CONTRIBUTORS:
1. Junior Resident, Department of General Medicine, Sree Balaji Medical College and Hospital, Chennai, Tamil Nadu, India.
2. Professor, Department of General Medicine, Sree Balaji Medical College and Hospital, Chennai, Tamil Nadu, India.
3. Senior Resident, Department of General Medicine, Sree Balaji Medical College and Hospital, Chennai, Tamil Nadu, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Ankit Notwani,
S/12, E-block Gents Hostel, Sree Balaji Medical College and Hospital,
Chromepet-600044, Chennai, Tamil Nadu, India.
E-mail: ankit.notwani2@gmail.com

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