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RESEARCH ARTICLE

AN UNUSUAL CASE OF PYREXIA OF UNKNOWN ORIGIN DIAGNOSED AS ADULT-ONSET STILL'S DISEASE: A CASE REPORT

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ABSTRACT

Still's disease, including systemic-onset juvenile idiopathic arthritis (sJIA) and adult-onset Still's disease (AOSD), is a rare systemic autoinflammatory disorder. It presents with quotidian fever, evanescent salmon-pink rash, arthritis/arthralgia, and systemic manifestations. **Case Presentation:** We report a 34-year-old woman who presented with prolonged fever, generalised lymphadenopathy, arthralgia, and elevated inflammatory markers. Workup revealed striking hyperferritinemia and elevated cytokines. Bone marrow biopsy showed features suggestive of macrophage activation syndrome (MAS). Diagnosis was established based on Yamaguchi criteria. The patient responded initially to corticosteroids and was later transitioned to biologic therapy. She achieved sustained remission on upadacitinib mono therapy. **Conclusion:** This case highlights the diagnostic challenges in AOSD presenting as pyrexia of unknown origin (PUO) and the role of targeted immune modulator therapy in refractory disease.

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INTRODUCTION

Adult-onset Still's disease (AOSD) is a rare systemic autoinflammatory condition characterized by daily high-spiking fever, arthritis or arthralgia, evanescent rash, and systemic inflammation (1). It shares similarities with systemic-onset juvenile idiopathic arthritis (sJIA) but occurs in adults, typically between the ages of 16 and 35 (2). Though its exact etiology remains unknown, overproduction of pro-inflammatory cytokines such as interleukin (IL)-1, IL-6, and IL-18 plays a critical role in its pathogenesis (3,4). The diagnosis of AOSD is primarily clinical, requiring exclusion of infectious, neoplastic, and autoimmune causes. Yamaguchi criteria are the most widely used classification system, with high sensitivity in clinical practice (5). Laboratory findings often include leukocytosis, elevated erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), abnormal liver function, and notably elevated ferritin levels—often >3000 ng/mL, and in some cases >10,000 ng/mL (6). AOSD can present in various forms: monocyclic, polycyclic, or chronic articular. Severe systemic cases may be complicated by macrophage activation syndrome (MAS), a potentially life-threatening hyperinflammatory state (7). Initial treatment relies on corticosteroids, but biologic agents targeting cytokine Adult-onset Still's disease (AOSD) is a rare systemic autoinflammatory condition characterized by daily high-spiking fever, arthritis or arthralgia, evanescent rash, and systemic inflammation (1). It shares similarities with systemic-onset juvenile idiopathic arthritis (sJIA) but occurs in adults, typically between the ages of 16 and 35 (2). Though its exact etiology remains unknown, overproduction of pro-inflammatory cytokines such as interleukin (IL)-1, IL-6, and IL-18 plays a critical role in its pathogenesis (3,4).

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CASE PRESENTATION

A 34-year-old female with a history of hypothyroidism (Hashimoto's thyroiditis with a complex thyroid cyst) and a prior isolated seizure episode presented in August 2021 with recurrent high-grade fevers and generalised lymphadenopathy. Lymph node biopsy showed reactive hyperplasia without malignancy.

Between December 2021 and May 2022, she experienced daily fevers, malaise, and joint stiffness—particularly in hands and fingers. On admission in May 2022, vital signs showed febrile spikes >39°C. Physical examination revealed non-tender cervical and axillary lymphadenopathy and arthralgia without active synovitis.
Laboratory findings included:

- Haemoglobin: 10.2 g/dL (microcytic)
- WBC: 11.7 ×10⁹/L
- ESR: 125 mm/hr
- CRP: 150 mg/L
- Serum ferritin: 10,617 ng/mL (peaked at 28,668 ng/mL)
- AST: 222 U/L, ALT: 126 U/L, ALP: 221 U/L
- ANA and RF: Negative
- IL-18: >300,000 pg/mL
- Soluble IL-2 receptor: 10,911 U/mL
- CXCL9: 10,556 pg/mL

Bone marrow biopsy showed normocellular tri lineage haematopoietin, megakaryocytic hyperplasia, and occasional haemophagocytosis, but no evidence of lymphoma or leukemia. The patient fulfilled the Yamaguchi criteria for AOSD and had features consistent with MAS. High-dose intravenous dexamethasone was initiated, followed by oral prednisone, leading to resolution of fever and normalisation of inflammatory markers. However, she experienced relapses during steroid tapering. Biologic therapy with canakinumab(under brand name -ilaris) (IL-1β inhibitor) was started but was later discontinued due to limited response. She was switched to upadacitinib (under brand name -rinvoq)(a JAK1 inhibitor, 15 mg daily), which resulted in sustained remission. As of August 2025, she remained asymptomatic off corticosteroids, with normalised CRP (2.4 mg/L), ESR (10 mm/hr), and Haemoglobin (11.6 g/dL), and no recurrence of fever, rash, or arthralgia.

DISCUSSION

AOSD is a diagnostic challenge due to its nonspecific symptoms and broad differential diagnosis, including infections, malignancies, and autoimmune conditions (1,5). In our patient, the presentation as PUO with systemic inflammation and high ferritin prompted extensive investigation. Her laboratory profile and exclusion of other causes supported the diagnosis. Hyperferritinemia is a hallmark of AOSD and MAS (macrophage activation syndrome) Ferritin levels >10,000 ng/mL, as seen in this case, suggest a severe inflammatory response and may correlate with cytokine activity, particularly IL-18 and CXCL9 (6,7). These cytokines reflect IFN-γ-driven macrophage activation, often seen in macrophage activation syndrome (7,9). Bone marrow findings of haemophagocytosis further supported MAS(macrophage activation syndrome) diagnosis, although not pathognomonic. The presence of elevated soluble IL-2 receptor and CXCL9 further substantiated hyper-inflammatory activity (9). Initial corticosteroid therapy led to rapid improvement, but disease flares during tapering required escalation to biologic therapy. IL-1 inhibitors like canakinumab are approved for AOSD and MAS(macrophage activation syndrome) however, our patient showed better response to upadacitinib, a selective JAK1 inhibitor .

This case illustrates several key points:

- The importance of considering AOSD in PUO with systemic inflammation and hyperferritinemia
- The diagnostic value of Yamaguchi criteria in appropriate clinical contexts
- The utility of ferritin and cytokine levels in guiding diagnosis and treatment decisions
- The emerging role of targeted therapies like JAK inhibitors in refractory AOSD

CONCLUSION

This case highlights the diagnostic complexity of AOSD presenting as PUO with MAS. Elevated ferritin and cytokine levels can provide essential diagnostic clues. Early immunosuppressive therapy is vital, and biologics like JAK inhibitors offer promising options in refractory or steroid-dependent cases.

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