International Journal of Science and Research (IJSR)
ISSN: 2319-7064
Impact Factor 2025: 7.089

A Diagnostic Challenge in Adult-Onset Still's Disease Presenting with Bilateral Pleural Effusions: A Case Report

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Abstract: ***Adult-onset Still's disease (AOSD) is a rare systemic autoinflammatory disorder characterized by fever, arthralgia, rash, leukocytosis, and hyperferritinemia. Owing to its heterogeneous clinical presentation and lack of specific diagnostic biomarkers, it remains a diagnosis of exclusion. Serosal involvement is an uncommon manifestation and may mimic infectious, autoimmune, or malignant diseases, resulting in diagnostic uncertainty and delayed recognition. We report a patient who presented with prolonged fever, constitutional symptoms, and evidence of multisystem involvement, including pleural effusion. Extensive evaluation excluded infectious, malignant, and autoimmune causes. Laboratory investigations revealed significant systemic inflammation, hematological abnormalities, liver function derangement, and markedly elevated serum ferritin levels. Despite comprehensive diagnostic workup, no alternative etiology was identified. In the context of persistent fever, hyperferritinemia, serositis, and exclusion of other causes, a diagnosis of adult-onset Still's disease was established. Treatment with corticosteroids resulted in rapid clinical improvement, resolution of serosal manifestations, and normalization of inflammatory parameters. This case underscores the importance of considering adult-onset Still's disease in patients presenting with prolonged fever, unexplained serositis, and marked hyperferritinemia after exclusion of more common etiologies. Early diagnosis and prompt initiation of immunosuppressive therapy can lead to favorable outcomes and help prevent disease-related complications.***

Keywords: Adult-onset Still's disease, Hyperferritinemia, Serositis, Pleural Effusion, Prolonged Fever

1. Introduction

Adult-onset Still's disease (AOSD) is a rare systemic autoinflammatory disorder characterized by quotidian high-spiking fevers, evanescent salmon-colored rash, arthritis or arthralgia, and a spectrum of systemic manifestations resulting from excessive cytokine-mediated inflammation. The disease represents the adult counterpart of systemic juvenile idiopathic arthritis (sJIA) and was first recognized as a distinct clinical entity by Bywaters in 1971, who described a series of adults presenting with clinical features resembling those originally reported in children by Sir George Frederic Still in 1896 [1].

The estimated annual incidence of AOSD ranges from 0.16 to 0.4 cases per 100,000 persons, with a prevalence of approximately 1-10 cases per million population, making it an uncommon but clinically significant inflammatory disorder [2]. Although the exact etiology remains unknown, current evidence suggests that AOSD results from dysregulated activation of the innate immune system, leading to overproduction of proinflammatory cytokines including interleukin (IL)-1β, IL-6, IL-18, tumor necrosis factor-α (TNF-α), and interferon-γ. This cytokine storm contributes to the characteristic systemic inflammatory manifestations and, in severe cases, may precipitate life-threatening complications such as macrophage activation syndrome (MAS), disseminated intravascular coagulation, and multiorgan dysfunction [3,4].

The clinical presentation of AOSD is highly heterogeneous and often overlaps with a wide range of infectious diseases, autoimmune and rheumatologic disorders, and hematologic malignancies. Consequently, AOSD remains a diagnosis of exclusion, requiring meticulous evaluation to eliminate alternative etiologies before a definitive diagnosis can be established [5]. Several classification criteria have been proposed to facilitate diagnosis, among which the Yamaguchi criteria [6] remain the most widely utilized because of their high sensitivity, while the Fautrel criteria incorporate hyperferritinemia and glycosylated ferritin levels to improve diagnostic specificity [7].

Marked hyperferritinemia is a hallmark laboratory finding in AOSD and may aid in raising clinical suspicion, although it is not pathognomonic. The disease course can vary considerably, ranging from a self-limited monocyclic illness to recurrent polycyclic flares or chronic destructive arthritis, underscoring the importance of early recognition and prompt initiation of therapy [8]. Given its rarity and the absence of specific diagnostic biomarkers, delayed diagnosis remains common, often resulting in prolonged morbidity and extensive investigations. We present a case of AOSD in a patient who initially manifested with prolonged fever and systemic inflammatory features, highlighting the diagnostic challenges and the importance of maintaining a high index of suspicion for this uncommon condition.

2. Case Presentation

A 46-year-old woman from North Kerala presented with a three-month history of intermittent high-grade fever associated with nonproductive cough, diffuse myalgia, generalized fatigue, anorexia, and significant unintentional weight loss. There was no history of tuberculosis exposure, recent travel, skin rash, joint swelling, or other significant comorbidities.

Initial radiological evaluation revealed bilateral pleural effusions, mild on the right side and moderate on the left. [Figure1] Diagnostic thoracentesis was performed, and pleural fluid analysis demonstrated an exudative effusion with low adenosine deaminase (ADA) levels. Cytological examination showed scattered lymphocytes, neutrophils, multinucleated giant cells, and small clusters of pleomorphic round cells. Tuberculosis polymerase chain reaction (TB-PCR) testing of the pleural fluid was negative. Cell block analysis did not reveal evidence of malignancy.

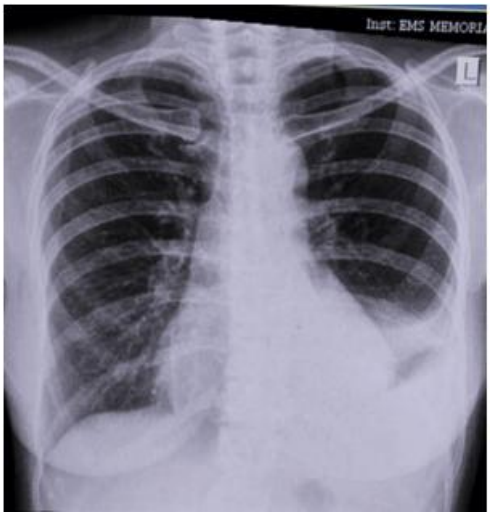

Figure 1: Chest xray showing bilateral pleural efffusion left>right

Further cardiac evaluation with transthoracic echocardiography demonstrated dilatation of the right atrium and right ventricle, mild pericardial effusion, mild tricuspid regurgitation, and pulmonary arterial hypertension, with preserved left ventricular systolic function. Computed tomography pulmonary angiography (CTPA) with high-resolution computed tomography (HRCT) of the thorax showed patchy ground-glass opacities involving the left upper and lower lobes, bilateral pleural effusions (gross on the left and mild on the right), cardiomegaly, and pericardial effusion measuring approximately 17 mm in thickness. No evidence of pulmonary thromboembolism was identified. [Figure2,3] Ultrasonography of the abdomen was unremarkable.

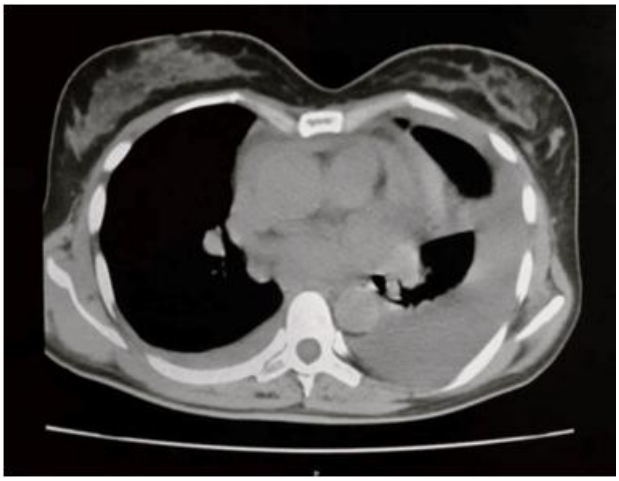

Figure 2: HRCT Thorax showing HRCT Thorax showing right sided mild pleural effusion and left sided gross pleural effusion along with cardiomegaly and moderate pericardial effusion

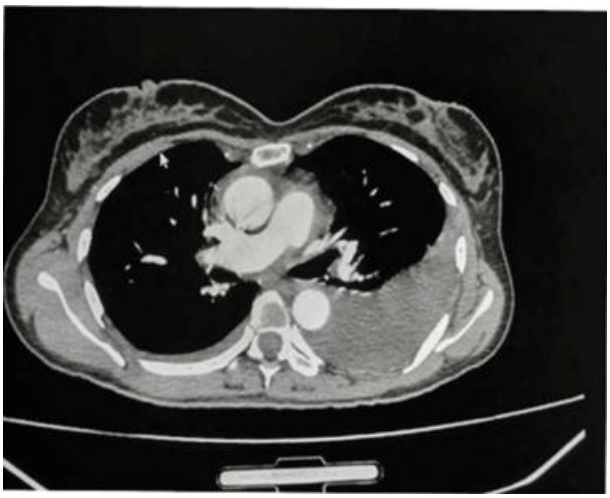

Figure 3: CT pulmonary angiogram showing no evidence of pulmonary thromboembolism

Laboratory investigations revealed anemia, leukocytosis, thrombocytosis, elevated inflammatory markers, deranged liver function tests, markedly elevated serum ferritin levels, and increased D-dimer levels. Thyroid function tests were within normal limits. An extensive autoimmune workup, including serological testing for connective tissue diseases and vasculitides, was negative. [Table 1]

Table 1: Lab investigation reports

	Admission	Discharge	Reference Range
Hemoglobin	10 gm/dl	12.1 gm/dl	12-15.5 gm/dl
Total count	16 *10^3 cmm^3	5.7 *103 cmm^3	4-7 *103 cmm^3
Platelet count	754 *10^3 cmm^3	353 *103 cmm3	150-450 *103 cmm3
ESR	35		0-20
SGOT	50 U/L	31 U/L	10-40 U/L
SGPT	157 U/L	39 U/L	7-56 U/L
Total protein/ albumin	6.1/ 2.9 gm/dl		6-8.3 / 3.5-5 gm/dl
ALP	447 U/L	158 U/L	44–147 U/L

D-dimer	16410 ng/ml	340 ng/ml	<500 ng/ml
Ferritin	2548ng/ml	119 ng/ml	13–150 ng/ml
LDH	285 U/L		140–280 U/L
TSH	3 µIU/mL		0.5-4 µIU/mL
Creatinine	0.7 mg/dl		0.6-1.2 mg/dl
ANA-IF	Negative		
Beta-2 Glycoprotein 1 IGM	1.06 U/ml		<20 U/ml
Cardiolipin antibody IgM	4.5 MPL U/ml		<15 MPL U/ml
Anti-Phospholipid IgM	3.8 MPL U/ml		<15 MPL U/ml
Lupus anticoagulant	Negative		
Anti TPO	8 IU/ml		< 35 IU/ml
PLEURAL FLUID ANALYSIS			
TC	30000 cells/mm^3		
Poly/Lymph/Others	10%/40%/50%		
LDH	253 U/L		
ADA	8 IU/L		<40 IU/L
AFB	Negative		
CBNAAT	MTB not detected		

Given the presence of atypical pleomorphic round cells in the pleural fluid, a hematology-oncology consultation was obtained to exclude an underlying malignancy. Subsequently, a positron emission tomography-computed tomography (PET-CT) scan was performed and did not demonstrate any metabolically active primary or secondary malignant lesions. [Figure 4] The overall evaluation effectively excluded malignancy as the underlying etiology.

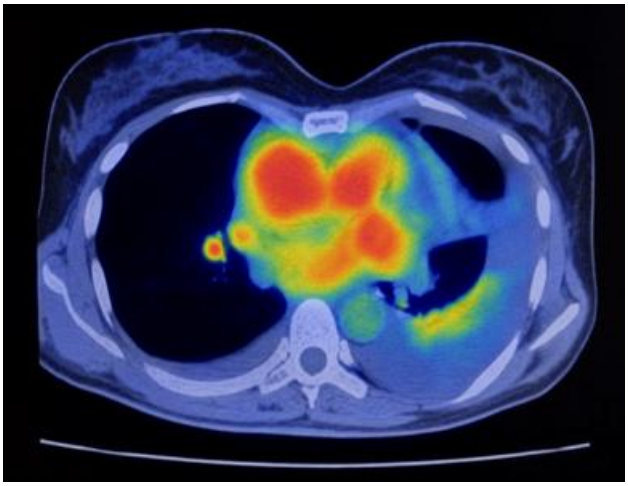

Figure 4: PET-CT scan showed no evidence of metabolically active primary or secondary malignant lesions

In view of the persistent systemic symptoms, elevated inflammatory markers and ferritin levels, serositis in the form of pleural and pericardial effusions, and the absence of evidence supporting infectious, autoimmune, or malignant causes, a provisional diagnosis of adult-onset Still's disease (AOSD) was considered. The patient was initiated on low-dose corticosteroid therapy along with anti-inflammatory medications and supportive care.

A pleural biopsy was initially planned to further evaluate the exudative effusion; however, the procedure was deferred because of the patient's marked clinical improvement following treatment initiation. Serial clinical and radiological assessments demonstrated significant resolution of the pleural effusions, reduction in cardiomegaly, and overall symptomatic improvement. [Figure 5]

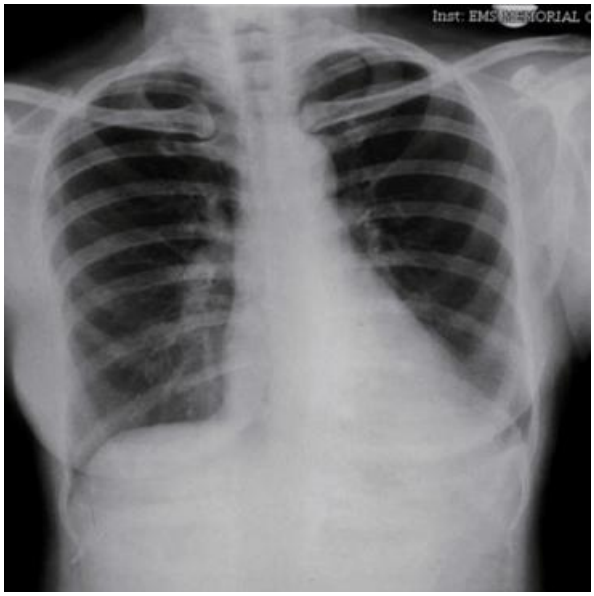

Figure 5: Serial Chest x-ray showing resolution of pleural effusion

The patient was subsequently discharged on oral corticosteroid therapy with advice for regular outpatient follow-up. At follow-up, she continued to demonstrate sustained clinical improvement without evidence of disease progression or emergence of an alternative diagnosis.

3. Discussion

Adult-onset Still's disease (AOSD) is a rare systemic autoinflammatory disorder characterized by excessive activation of the innate immune system and overproduction of proinflammatory cytokines. The disease exhibits considerable heterogeneity in its clinical manifestations, disease severity, and long-term outcomes, often posing a significant diagnostic challenge for clinicians. Because no single clinical feature or laboratory test is pathognomonic, AOSD remains a diagnosis of exclusion and requires careful evaluation to rule out infectious, malignant, and autoimmune etiologies before a definitive diagnosis can be established [9,10].

The clinical course of AOSD has traditionally been categorized into three major patterns: monophasic,

polyphasic, and chronic disease [Table 2]. The monophasic form is characterized by a single episode of systemic inflammation lasting less than one year, followed by complete remission. The polyphasic form consists of recurrent flares separated by symptom-free intervals that may range from weeks to years, whereas the chronic form is marked by persistent inflammatory activity, frequently associated with destructive arthritis and long-term disability.

Table 2: Clinical Patterns of Adult-Onset Still's Disease (AOSD)

Disease Pattern	Clinical Characteristics
Monophasic	Single episode of systemic disease lasting less than one year followed by complete remission.
Polyphasic (Intermittent)	Recurrent episodes of disease activity separated by symptom-free intervals lasting weeks to years. Relapses are generally less severe than the initial episode.
Chronic	Persistent inflammatory activity with ongoing systemic symptoms and/or chronic destructive arthritis.

Adapted from Gerfaud-Valentin et al. (2014) (Ref. 3)

The hallmark clinical manifestations of AOSD include quotidian high-spiking fever, arthralgia or arthritis, myalgia, and an evanescent salmon-colored rash. The characteristic rash typically appears during febrile spikes and predominantly involves the trunk and proximal extremities. Other commonly reported manifestations include sore throat, profound fatigue, weight loss, hepatomegaly, splenomegaly, generalized lymphadenopathy, and elevated inflammatory markers [11]. Laboratory abnormalities frequently include neutrophilic leukocytosis, thrombocytosis, anemia of chronic inflammation, elevated liver enzymes, and markedly increased serum ferritin levels. Hyperferritinemia is considered one of the most useful laboratory clues supporting the diagnosis and often correlates with disease activity.

The diagnosis of AOSD in the present case was particularly challenging because the patient lacked several of the classical manifestations such as the characteristic rash and clinically significant arthritis at presentation. Instead, the predominant features were prolonged fever, constitutional symptoms, bilateral pleural effusions, pericardial effusion, pulmonary hypertension, elevated inflammatory markers, and markedly raised serum ferritin levels. Such an atypical presentation initially raised suspicion for infectious diseases, connective tissue disorders, and malignancy.

Serosal involvement in AOSD is well recognized but relatively uncommon. Pleuritis and pericarditis occur in approximately 20-40% of patients and are usually associated with active systemic inflammation [12]. However, massive pleural effusions as the predominant presenting feature are rarely reported. The presence of bilateral pleural effusions in our patient prompted an extensive evaluation for tuberculosis, malignancy, and other causes of exudative pleural disease. Pleural fluid analysis demonstrated an exudative effusion with low ADA levels and negative TB-PCR, making tuberculous pleuritis unlikely. Furthermore, cell block analysis did not reveal malignant cells, and subsequent positron emission tomography-computed tomography (PET-CT) failed to identify any metabolically active neoplastic process. These findings effectively excluded two of the most important differential diagnoses in the regional setting.

Pulmonary manifestations of AOSD are uncommon but have gained increasing recognition in recent years. Reported thoracic abnormalities include transient pulmonary infiltrates, ground-glass opacities, pleural effusions, acute respiratory distress syndrome, diffuse alveolar hemorrhage, interstitial lung disease, and pulmonary arterial hypertension (PAH). The HRCT findings in our patient demonstrated bilateral pleural effusions accompanied by ground-glass opacities and pericardial effusion, while echocardiography revealed pulmonary arterial hypertension. Although PAH remains a rare complication of AOSD, its occurrence has been associated with significant morbidity and may reflect severe systemic inflammatory activity [13].

Current understanding of AOSD pathogenesis implicates dysregulated activation of the innate immune system, resulting in excessive secretion of cytokines such as interleukin (IL)-1β, IL-6, IL-18, tumor necrosis factor-α, and interferon-γ.[14] These mediators orchestrate systemic inflammation through activation of type 1 and type 3 immune pathways and are responsible for many of the constitutional, hematological, and serosal manifestations observed in affected patients . Elevated IL-18 levels, in particular, have been associated with disease activity, hyperferritinemia, and the development of severe complications such as macrophage activation syndrome (MAS). Macrophage activation syndrome, considered a secondary form of hemophagocytic lymphohistiocytosis (HLH), represents one of the most feared complications of AOSD and is associated with substantial mortality.[15] Clinical features include persistent fever, cytopenias, coagulopathy, liver dysfunction, hyperferritinemia, and multiorgan failure. Although our patient exhibited markedly elevated ferritin and D-dimer levels, there was no evidence of cytopenias or organ dysfunction suggestive of overt MAS.

Several classification criteria have been proposed for AOSD, among which the Yamaguchi criteria [Table 3] remain the most widely utilized because of their high sensitivity (96.2%) and specificity (92.1%). These criteria require the presence of at least five criteria, including two major criteria, after exclusion of infections, malignancies, and other rheumatic diseases.

Table 3: Yamaguchi Classification Criteria for Adult-Onset Still's Disease

Major Criteria	Minor Criteria
Fever ≥39°C lasting ≥1 week	Sore throat
Arthralgia or arthritis lasting ≥2 weeks	Lymphadenopathy
Typical evanescent salmon-pink rash	Hepatomegaly and/or splenomegaly
Leukocytosis >10,000/mm³ with ≥80% neutrophils	Abnormal liver function tests
	Negative rheumatoid factor (RF) and antinuclear antibody (ANA) tests

Exclusion Criteria: Infections, malignancies, and other rheumatic diseases.

Diagnostic Requirement: Presence of ≥5 criteria, including at least 2 major criteria.
Diagnostic Performance: Sensitivity 96.2%; Specificity 92.1%.
Adapted from Yamaguchi et al. (1992) (Ref. 6).

The Fautrel criteria [Table 4], which incorporate glycosylated ferritin levels, demonstrate higher specificity (98.5%) and may be particularly useful when ferritin measurements are available.

Table 4: Fautrel Classification Criteria for Adult-Onset Still's Disease

Major Criteria	Minor Criteria
Spiking fever ≥39°C	Typical maculopapular (salmon-colored) rash
Arthralgia	Leukocytosis ≥10,000/mm³
Transient erythema	
Pharyngitis (sore throat)	
Neutrophils ≥80% of total leukocyte count	
Glycosylated ferritin ≤20%	

Diagnostic Requirement: Four major criteria or three major criteria plus two minor criteria
Diagnostic Performance: Sensitivity approximately 80%; Specificity 98.5%.
Adapted from Fautrel et al. Medicine (Baltimore), 2002 (Ref. 7).

In the present case, the patient fulfilled the Yamaguchi classification criteria through the presence of prolonged high-grade fever, leukocytosis with neutrophilia, abnormal liver function tests, negative antinuclear antibody (ANA) and rheumatoid factor (RF) testing, and exclusion of infectious, malignant, and autoimmune causes. The presence of bilateral pleural effusions, pericardial effusion, and pulmonary arterial hypertension represented an uncommon manifestation of the disease.

The favorable clinical response to corticosteroid therapy further supported the diagnosis. Glucocorticoids remain the cornerstone of treatment for moderate-to-severe systemic disease, while disease-modifying antirheumatic drugs and biologic agents targeting IL-1 and IL-6 pathways are increasingly employed in refractory cases [16]. The rapid resolution of pleural and pericardial effusions, reduction in cardiomegaly, and improvement in constitutional symptoms following corticosteroid initiation underscore the inflammatory nature of the disease process and reinforce the diagnosis of AOSD.

This case highlights an uncommon presentation of AOSD with predominant serosal involvement manifesting as bilateral pleural effusions, pericardial effusion, and pulmonary arterial hypertension. In regions where tuberculosis and malignancy are common causes of exudative pleural effusions, such atypical presentations may result in extensive diagnostic investigations and delayed diagnosis. Clinicians should therefore maintain a high index of suspicion for AOSD in patients presenting with prolonged fever, unexplained serositis, hyperferritinemia, and negative infectious, autoimmune, and malignant workups. Early recognition and timely initiation of immunosuppressive therapy can lead to rapid clinical improvement and prevent potentially life-threatening complications.

4. Conclusion

Adult-onset Still's disease (AOSD) remains a challenging diagnosis because of its rarity, heterogeneous clinical manifestations, and the absence of specific diagnostic biomarkers. This case highlights an unusual presentation of AOSD with predominant serosal involvement manifesting as bilateral pleural effusions, pericardial effusion, and pulmonary arterial hypertension, features that initially raised concerns for tuberculosis, malignancy, and autoimmune disease. The diagnosis was ultimately established through a combination of characteristic clinical findings, marked hyperferritinemia, exclusion of alternative etiologies, and fulfillment of the Yamaguchi classification criteria.

This report underscores the importance of considering AOSD in the differential diagnosis of prolonged fever of unknown origin associated with unexplained pleural or pericardial effusions and elevated inflammatory markers. In regions where infectious diseases such as tuberculosis are highly prevalent, atypical presentations may lead to extensive investigations and delays in diagnosis. Recognition of hyperferritinemia as an important diagnostic clue, coupled with a systematic exclusion of infectious, malignant, and rheumatologic causes, can facilitate earlier diagnosis and treatment. The favorable clinical and radiological response to corticosteroid therapy observed in our patient further supports the diagnosis and highlights the importance of timely initiation of immunosuppressive treatment to prevent disease progression and potentially life-threatening complications. Clinicians should maintain a high index of suspicion for AOSD in patients presenting with fever of unknown origin, serositis, and hyperferritinemia after exclusion of infectious, malignant, and autoimmune etiologies, as early diagnosis and prompt treatment can significantly improve patient outcomes.

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