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Case Report

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Persistent Pyrexia of Unknown Origin and Deep Vein Thrombosis in a Patient with Sjögren's Syndrome: A Case Report

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Abstract

Background: Sjögren's Syndrome (SS) is a systemic autoimmune disorder primarily affecting the exocrine glands but often presenting with significant extraglandular manifestations, including systemic vasculitis, hematological abnormalities, and antiphospholipid syndrome (APS). Atypical presentations, such as pyrexia of unknown origin (PUO) or thrombotic events, can delay diagnosis.

Case Presentation: We report a 57-year-old male with persistent fever, anemia, and leukocytosis. Initial blood cultures identified Pseudomonas aeruginosa, and antibiotic therapy resulted in temporary improvement. Persistent febrile episodes prompted further evaluation, revealing bilateral hilar lymphadenopathy on HRCT thorax and strong anti-SS-A (Ro-52) antibody positivity, confirming SS. Despite no classical sicca symptoms, systemic inflammation and autoimmune markers led to the diagnosis. One month later, the patient developed deep vein thrombosis (DVT), confirmed by Doppler ultrasound. Positive antiphospholipid antibodies and lupus anticoagulant established APS. The patient was managed with anticoagulation and hydroxychloroquine, achieving clinical stability.

Conclusion: This case highlights the diagnostic challenges in atypical SS presentations, emphasizing the need for a high index of suspicion in PUO. Multidisciplinary management addressing systemic inflammation, thrombotic risks, and infections is essential to improving outcomes in SS patients with extraglandular manifestations.

Keywords: Sjögren's syndrome; Antiphospholipid syndrome; Deep vein thrombosis; Pyrexia of unknown origin; Autoimmune disease; Thrombotic complications.

Introduction

Sjögren's Syndrome (SS) is a chronic systemic autoimmune disorder predominantly affecting the exocrine glands, leading to the hallmark symptoms of dry eyes (xerophthalmia) and dry mouth (xerostomia). However, the disease exhibits a broad spectrum of manifestations, extending beyond glandular involvement to systemic and extraglandular complications. These complications include systemic vasculitis, pulmonary abnormalities, peripheral and central nervous system involvement, and hematological disorders such as anemia, thrombocytopenia, and thrombotic events [1]. The heterogeneity of SS often presents significant diagnostic challenges, particularly in atypical cases where classical sicca symptoms are absent. First described by Henrik Sjögren in 1933, SS is now recognized as one of the most prevalent autoimmune diseases, with a female predominance, primarily affecting middle-aged individuals [2]. The disease may occur as primary SS

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or in association with other autoimmune conditions such as rheumatoid arthritis or systemic lupus erythematosus. The diagnosis of SS relies on clinical features and serological markers, including anti-SS-A (Ro) and anti-SS-B (La) antibodies, which are critical in identifying the disease, particularly in atypical or extraglandular presentations. Antiphospholipid syndrome (APS), a prothrombotic disorder characterized by the presence of antiphospholipid antibodies, represents a severe extraglandular complication of SS [3]. The presence of APS introduces additional diagnostic complexity, as it may lead to life-threatening thrombotic events such as deep vein thrombosis (DVT), pulmonary embolism, and strokes. APS in SS is relatively uncommon, with a prevalence of 5–20%, but its implications are clinically significant and require vigilant screening and management. Pyrexia of unknown origin (PUO) is another rare but challenging presentation of SS. PUO in SS is often attributed to systemic inflammation, vasculitis, or underlying hematological abnormalities, and it can mask coexisting infections or thrombotic events. Infections, particularly in the setting of immune dysregulation, are more frequent in SS and further complicate the clinical picture. These overlapping presentations demand a comprehensive diagnostic approach to identify the primary driver of the patient's symptoms [4]. This case report describes a 57-year-old male with an atypical presentation of SS characterized by persistent PUO, pseudomonas sepsis, and subsequent development of DVT secondary to APS. The absence of classical glandular symptoms posed a significant diagnostic challenge, while the coexistence of autoimmune and infectious processes underscored the complexity of managing systemic autoimmune diseases. This report highlights the importance of a multidisciplinary approach to accurately diagnose and manage SS, particularly in patients with atypical or overlapping presentations.

Case Presentation

A 57-year-old male, with a known history of type 2 diabetes mellitus, presented to the outpatient department with a one-month history of recurrent high-grade fever (maximum temperature 39.5°C), associated with chills and profound fatigue. The patient reported decreased appetite but denied significant weight loss, night sweats, or localized symptoms. Notably, there was no history of classical sicca symptoms, including dry eyes or dry mouth, joint pain, or photosensitive rashes. He also denied any history of recurrent infections, deep vein thrombosis (DVT), or family history of autoimmune diseases. Despite being treated with oral antipyretics, the febrile episodes persisted. During this time, he also experienced mild breathlessness during routine activities. His history was unremarkable for any recent travel, occupational exposures, or contacts with tuberculosis. Upon admission, he appeared systemically unwell and mildly dehydrated, with vitals indicating ongoing inflammation. His temperature was 38.5°C, pulse rate was 96 beats per minute, respiratory rate was 18 breaths per minute, and blood pressure was 130/85 mmHg. Physical examination revealed no lymphadenopathy, oral ulcers, or parotid swelling. Chest and abdominal examination were unremarkable, and there was no evidence of arthritis or neurological deficits. Given his recurrent fever and fatigue, he was admitted for further evaluation.

Investigations

The initial investigations suggested systemic inflammation, as outlined in Table 1. His complete blood count showed leukocytosis and anemia, with a significantly elevated erythrocyte sedimentation rate (ESR). Blood cultures identified Pseudomonas aeruginosa, and he was treated with targeted antibiotic therapy (meropenem). Repeat blood cultures obtained after completing the antibiotic course were sterile, yet febrile episodes persisted, raising concerns of an underlying systemic disorder.

Imaging Findings

To investigate the fever of unknown origin (PUO), a high-resolution computed tomography (HRCT) of the thorax was performed. It revealed bilateral hilar lymphadenopathy and minor pulmonary nodules, without significant interstitial changes or pleural effusion (Figure 1). These findings were consistent with possible systemic inflammation or an autoimmune process rather than an active infection. An ultrasound of the abdomen revealed mild hepatosplenomegaly and minimal ascites, further supporting a systemic inflammatory or autoimmune etiology.

Autoimmune Workup

Given the lack of resolution with antimicrobial treatment and the imaging findings, an autoimmune workup was pursued. This revealed strong positivity for anti-SS-A (Ro-52) antibodies and a positive antinuclear antibody (ANA) test (titer >1:320), both highly suggestive of Sjögren's Syndrome (SS). Schirmer's test confirmed moderate dry eyes, although the patient remained asymptomatic for sicca symptoms. Tests for rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP) were negative, ruling out rheumatoid arthritis. Direct Coombs test was also negative, eliminating autoimmune hemolytic anemia as a contributing factor (Table 1).

Diagnosis and Initial Treatment

Based on these findings, the patient was diagnosed with primary Sjögren's Syndrome (SS) with systemic involvement presenting as PUO. Hydroxychloroquine (200 mg twice daily) was initiated to manage the systemic inflammation, resulting in significant clinical improvement. He was discharged afebrile, with instructions for close follow-up and symptom monitoring.

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Table 1: Summary of Investigations

Category	Test	Result	Remarks
Baseline Laboratory	Total Leukocyte Count	14,900/mm³ (High)	Suggestive of leukocytosis
	Hemoglobin	7.6 g/dL (Low)	Indicative of anemia
	Erythrocyte Sedimentation Rate	75 mm/hour (Elevated)	Reflects systemic inflammation
Microbiological	Blood Cultures	Growth of *Pseudomonas aeruginosa*	Treated with meropenem
	Follow-up Blood Cultures	Sterile	Cleared bloodstream infection
Imaging	HRCT Thorax	Bilateral hilar lymphadenopathy, minor pulmonary nodules (**Figure 1**)	No significant interstitial findings
	Abdominal Ultrasound	Hepatosplenomegaly, mild ascites	Consistent with systemic involvement
Autoimmune Workup	Antinuclear Antibody (ANA)	Positive (titer >1:320)	Suggestive of autoimmune disease
	Anti-SS-A (Ro-52) Antibodies	Strong positivity	Diagnostic for Sjögren's Syndrome
	Schirmer's Test	Moderate dry eyes	Asymptomatic
	Rheumatoid Factor (RF)	Negative	
	Anti-Cyclic Citrullinated Peptide	Negative	
	Direct Coombs Test	Negative	
Thrombophilia Panel	Antiphospholipid Antibodies (IgM)	Positive	Indicative of APS
	Lupus Anticoagulant	Positive	Confirms thrombophilia

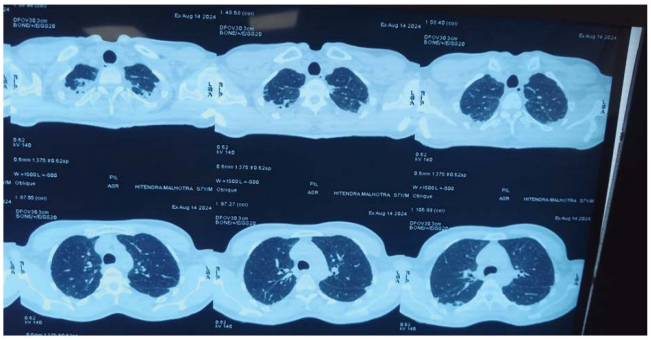

Figure 1: HRCT Thorax demonstrating bilateral hilar lymphadenopathy and minor pulmonary nodules.

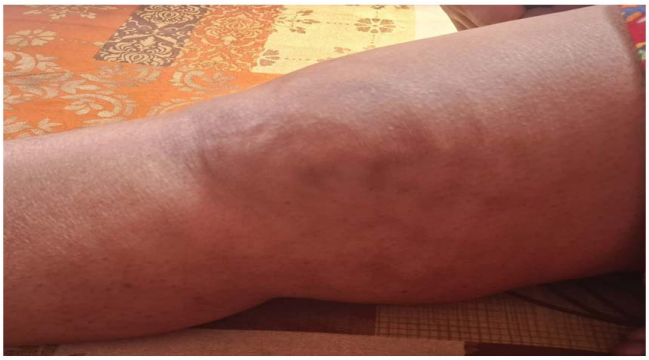

Figure 2: Clinical photograph showing chronic changes in the lower limb, consistent with systemic immune dysregulation and secondary thrombotic complications.

Development of Deep Vein Thrombosis (DVT)

Approximately one month later, the patient presented with bilateral lower limb swelling, redness, and pain. On examination, there was tenderness along the superficial veins and mild pitting edema. Doppler ultrasound confirmed superficial vein thrombosis. A thrombophilia panel identified positive antiphospholipid antibodies (IgM) and lupus anticoagulant, confirming a diagnosis of antiphospholipid syndrome (APS), a known extraglandular manifestation of SS (Table 1). The patient was started on enoxaparin (60 mg subcutaneously every 12 hours for 5 days) and transitioned to apixaban (2.5 mg twice daily) for long-term anticoagulation. Hydroxychloroquine was continued for immunomodulation. His symptoms of DVT gradually resolved with treatment.

Discussion

Sjögren's Syndrome (SS) is a systemic autoimmune disease primarily affecting the exocrine glands, but its presentation often extends beyond glandular symptoms to include extraglandular manifestations, systemic inflammation, and, in rare cases, thrombotic complications such as antiphospholipid syndrome (APS). This case highlights the diagnostic and therapeutic challenges associated with atypical presentations of SS, particularly when classical sicca symptoms are absent, and demonstrates the complexity of distinguishing autoimmune activity from infection-related phenomena [5].

Persistent Pyrexia of Unknown Origin (PUO) and Sjögren's Syndrome

Fever of unknown origin (PUO) is an unusual but recognized initial presentation of SS. Persistent systemic inflammation, vasculitis, or underlying hematological abnormalities are among the mechanisms that can contribute to PUO in SS. While PUO is observed in less than 10% of SS cases, its occurrence can delay diagnosis due to its nonspecific nature. In this case, the patient's fever persisted despite targeted antibiotic therapy for pseudomonas sepsis, indicating that the febrile episodes were likely driven by the underlying autoimmune process rather than an unresolved infectious focus [6]. The presence of hilar lymphadenopathy and minor pulmonary nodules on HRCT thorax, alongside hepatosplenomegaly and elevated inflammatory markers, raised suspicion for a systemic inflammatory or autoimmune disorder. These findings, combined with positive anti-SS-A (Ro-52) antibodies and ANA positivity, confirmed the diagnosis of SS with systemic involvement. This underscores the importance of maintaining a high index of suspicion for autoimmune diseases in patients with unexplained systemic inflammation.

Antiphospholipid Syndrome in Sjögren's Syndrome

APS, characterized by the presence of antiphospholipid antibodies and a hypercoagulable state, is a recognized but uncommon complication of SS, with an estimated prevalence of 5–20% in primary SS patients. The exact mechanism linking SS and APS is not fully understood but is believed to involve immune-mediated endothelial dysfunction, complement activation, and enhanced platelet aggregation, culminating in a prothrombotic state. In this case, the development of deep vein thrombosis (DVT) one month after the initial presentation highlighted the thrombotic potential of APS in the context of SS. The identification of positive lupus anticoagulant and antiphospholipid antibodies confirmed the diagnosis of APS, emphasizing the need for routine thrombophilia screening in SS patients presenting with unexplained thrombotic events or systemic inflammation [7].

Role of Immune Dysregulation in Pseudomonas Sepsis

Patients with SS are at an increased risk of infections due to underlying immune dysregulation, which can impair both humoral and cellular immune responses. This susceptibility is compounded by other comorbid conditions, such as diabetes mellitus, which further compromise immune function. The patient's pseudomonas bloodstream infection can be attributed to this altered immune status. However, the persistence of fever despite clearance of the bloodstream infection suggests that the systemic autoimmune activity associated with SS was the primary driver of his febrile episodes.

Challenges in Diagnosing Atypical Sjögren's Syndrome

This case illustrates the diagnostic challenges posed by atypical presentations of SS, especially in the absence of classical sicca symptoms. While dry eyes and dry mouth are hallmark features of SS, up to 20% of patients with SS may lack significant glandular symptoms, leading to diagnostic delays. In such cases, the presence of extraglandular manifestations, such as PUO, lymphadenopathy, or thrombotic events, should prompt a thorough autoimmune workup. Serological testing for anti-SS-A and anti-SS-B antibodies remains critical for diagnosing SS in these atypical cases. The strong positivity for anti-SS-A (Ro-52) antibodies in this patient, combined with the systemic features and radiological findings, provided a clear diagnostic pathway. The use of HRCT thorax was instrumental in identifying systemic involvement, as it revealed hilar lymphadenopathy and minor pulmonary nodules, which are consistent with autoimmune activity in SS.

Management Strategies

The management of this patient required a multidisciplinary approach addressing both the autoimmune and thrombotic components. Hydroxychloroquine, a cornerstone of SS treatment, was used to modulate systemic inflammation and prevent disease progression. The initiation of anticoagulation therapy with enoxaparin followed by apixaban effectively managed the APS-related DVT, reducing the risk of recurrent thrombotic events [8].

Key aspects of the patient's management included:

1. **Immunomodulation:** Hydroxychloroquine was initiated to control systemic inflammation and reduce autoimmune activity. This intervention was crucial in alleviating the persistent fever and preventing further systemic complications.
2. **Anticoagulation:** The use of low molecular weight heparin (enoxaparin) followed by a direct oral anticoagulant (apixaban) was tailored to manage APS-associated thrombosis effectively.
3. **Infection Control:** Targeted antibiotic therapy cleared the pseudomonas bloodstream infection, addressing one potential source of systemic inflammation.
4. **Monitoring:** Regular follow-up was essential to monitor treatment efficacy, detect potential complications, and adjust therapy as needed.

Clinical Implications and Lessons Learned

This case underscores several important clinical lessons:

- **High Clinical Suspicion:** Atypical presentations of SS, such as PUO, require a high index of suspicion and

comprehensive evaluation to identify the underlying autoimmune etiology.

- **Integration of Findings:** Diagnostic success in this case relied on integrating clinical, serological, and imaging findings. HRCT thorax and autoimmune markers played pivotal roles in uncovering the systemic nature of the disease.
- **APS Screening:** Routine screening for antiphospholipid antibodies is essential in SS patients with unexplained thrombotic events or systemic inflammation, as APS is a potentially life-threatening complication.
- **Infection-Autoimmune Interplay:** Immune dysregulation in SS can increase susceptibility to infections, which may further complicate the clinical picture. Distinguishing infection-driven inflammation from autoimmune activity is critical for optimal management.

Conclusion

The coexistence of PUO, pseudomonas sepsis, and APS in this patient highlights the multifaceted nature of SS and the challenges it poses to clinicians. Early recognition of atypical presentations and prompt initiation of targeted therapy can significantly improve outcomes. This case underscores the importance of a multidisciplinary approach in managing systemic autoimmune diseases with overlapping infectious and thrombotic complications.

Ethical statements

Conflict of interest

The authors declare no conflict of interest regarding the publication of this case report.

Funding statement

No funding was received for the preparation or publication of this case report.

Patient consent

Written informed consent was obtained from the patient for the publication of this case report and associated images. Efforts have been made to ensure anonymity, and identifying information has been excluded.

Ethical approval

Ethical approval was not required for this case report as it is a description of routine clinical care and does not involve experimental procedures.

Data availability

Data supporting the findings of this case are available from the corresponding author upon reasonable request.

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Abbreviations

- SS: Sjögren's Syndrome
- APS: Antiphospholipid Syndrome
- PUO: Pyrexia of Unknown Origin
- DVT: Deep Vein Thrombosis
- ANA: Antinuclear Antibody
- HRCT: High-Resolution Computed Tomography
- ESR: Erythrocyte Sedimentation Rate
- RF: Rheumatoid Factor
- Anti-CCP: Anti-Cyclic Citrullinated Peptide
- IgM: Immunoglobulin M

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