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Antiphospholipid Syndrome in a Patient with Systemic Lupus Erythematosus: A Case Report

Vidhya Lekshmi K[1], Chitra Thara S[1], Revanth R[3*], Venkateswaramurthy N[4]

[1] *Department of Pharmacy Practice, J.K.K.Nattraja College of Pharmacy, Affiliated to The Tamil Nadu Dr.M.G.R.Medical University, Guindy, Chennai, India*

[2] *Assistant Professor, Department of Pharmacy Practice, J.K.K.Nattraja College of Pharmacy, Affiliated to The Tamil Nadu Dr.M.G.R.Medical University, Guindy, Chennai, India*

[3] *Professor and Head, Department of Pharmacy Practice, J.K.K.Nattraja College of Pharmacy, Kumarapalayam*

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ABSTRACT

Antiphospholipid Syndrome (APS), also known as Hughes syndrome, is an autoimmune disorder characterized by hypercoagulability and the presence of antiphospholipid antibodies (aPL). It may occur as a primary condition or secondary to other autoimmune diseases, most commonly Systemic Lupus Erythematosus (SLE). We report a case of secondary APS associated with SLE, highlighting the diagnostic and management challenges. A 48-year-old female with a history of rheumatoid arthritis, hypothyroidism, and hypertension presented with severe hypoxemia, with oxygen saturation of 51%. Laboratory investigations revealed mild anemia (8.2 g/dL), prolonged prothrombin time (15.2 seconds), and a subtherapeutic INR (1.1) despite ongoing anticoagulation therapy. Autoimmune panel testing confirmed SLE, and specific antiphospholipid antibody testing was positive for lupus anticoagulant, with elevated anticardiolipin IgG/IgM and anti-β2 glycoprotein I antibodies, consistent with secondary APS. Although she was receiving Acitrom, inadequate anticoagulation raised concern for thrombotic complications, including pulmonary embolism. Azathioprine was discontinued due to the heightened risk of infection in the setting of immunosuppression and respiratory compromise. This case underscores the importance of considering APS in patients with autoimmune conditions presenting with thrombotic manifestations, particularly in the presence of SLE. It highlights the need for meticulous monitoring of anticoagulation, prompt recognition of thrombotic risks, and careful management of immunosuppressive therapies to reduce infectious complications. A multidisciplinary and individualized therapeutic strategy remains essential in managing such complex autoimmune overlap syndromes.

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Introduction

Antiphospholipid Syndrome (APS), also known as Hughes Syndrome or Antiphospholipid Antibody Syndrome**,** is an autoimmune disorder characterized by a state of hypercoagulability, which can lead to the formation of blood clots (thrombosis) in all parts of the vascular system (1). This condition can manifest either as a primary, isolated entity (Primary Antiphospholipid Syndrome), or it can emerge secondarily in the context of other autoimmune disorders, most notably Systemic Lupus Erythematosus (SLE) (2). In the 1930s, syphilis was estimated to affect more than 10% of the American population. As a response to this significant public health burden, the U.S. Congress passed the National Venereal Disease Control Act in 1938. This legislation established specific measures aimed at controlling syphilis and subsequently led to the widespread adoption and use of Wasserman's test by healthcare practitioners (3).

Historically, the understanding of these antibodies primarily focused on their reactivity against complexes of phospholipids and phospholipid-binding proteins, with beta-2-glycoprotein I (β2GPI) being considered the most important cofactor (1). However, contemporary research

***Corresponding author**: Revanth R, Assistant Professor, Department of Pharmacy Practice, J.K.K.Nattraja College of Pharmacy, Affiliated to The Tamil Nadu Dr.M.G.R.Medical University, Guindy, Chennai, India*
Email: revram95@gmail.com

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has begun to challenge this singular focus, presenting compelling evidence that cofactor-independent antiphospholipid antibodies (aPL) are also pathogenic and are present in patients with APS (4).

Beyond the primary characteristics of thrombosis and obstetric morbidity, the clinical presentation of Antiphospholipid Syndrome (APS) is remarkably diverse. It includes a wide range of symptoms and conditions that extend beyond the established classification criteria, often referred to as "extra-criteria" features (5).

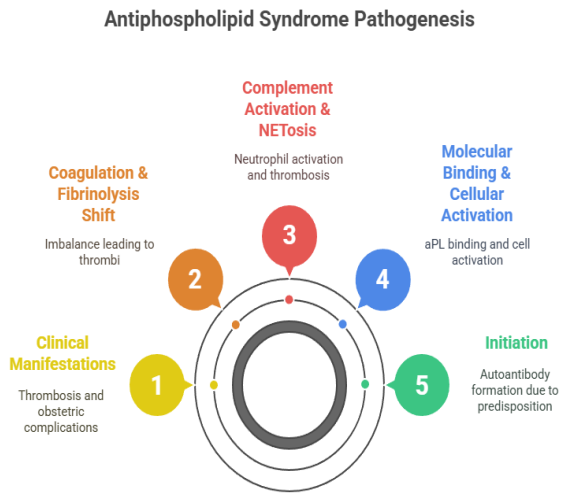
These extra-criteria manifestations can impact numerous organ systems, including the neurological, cardiac, hematological, dermatological, renal, gastrointestinal, ocular, pulmonary, and adrenal systems (2). This expanded understanding of the clinical spectrum is vital for a thorough diagnostic approach. It prompts healthcare professionals to consider APS in patients who present with unexplained systemic symptoms, even when classic thrombotic or obstetric events are absent, especially if other autoimmune features are present.

The exact mechanisms behind Antiphospholipid Syndrome (APS) are complex and not yet fully understood. The condition involves intricate interactions among antiphospholipid antibodies (aPL), various proteins that bind to phospholipids, and components of the coagulation cascade (5). The wide variety of clinical complications observed suggests that multiple, distinct pathogenic processes are simultaneously at work, contributing to the diverse ways the disease presents in patients (6).

Significant advancements in understanding APS pathogenesis include the identification of domain I-specific anti-β2-glycoprotein-I (aβ2GPI) antibodies as crucial pathogenic features (7).

These specific antibodies are believed to trigger a series of events within the blood vessels. This includes activating endothelial cells (EC), leading to the release of pro-inflammatory cytokines, and fostering a widespread prothrombotic state (a tendency to form blood clots) (2). Beyond their direct impact on coagulation, the activation of endothelial cells and the complement system are increasingly recognized as pivotal contributors to APS pathogenesis. This highlights the important role of inflammatory and immune responses in the development of the disease.

Antiphospholipid Syndrome (APS) is a complex and varied autoimmune disorder that carries substantial risks for patient illness (morbidity) and, in its most severe form, death (mortality). Our understanding of APS has advanced considerably. Initially, the focus was primarily on thrombosis and obstetric complications. However, there is now a broader recognition of its widespread impact on various body systems, including numerous "extra-criteria" manifestations. The underlying pathophysiology, driven by a diverse group of antiphospholipid antibodies, is increasingly understood to involve intricate interactions that extend beyond simple blood clotting, now encompassing the activation of endothelial cells and the complement system.



Case Description

A 48-year-old female patient presented with significantly reduced oxygen saturation, measured at 51% on admission.

Past Medical History

The patient has a history of hypothyroidism diagnosed 15 years ago, rheumatoid arthritis and hypertension for the past 4 years,

Current Medications

The patient was prescribed a regular medication regimen, including:

- Acitrom 2 mg (anticoagulant) (0-0-1-0)
- Hydroxychloroquine 200 mg (antimalarial) (1-0-1)
- Azathioprine 50 mg (immunosuppressant, recently discontinued)
- Nifedipine 10 mg (calcium channel blocker) (1-0-1),
- Calcium (500 mg) and Vitamin D3 (250 IU) supplementation (1-0-0)

Diagnosis on Further Investigation

Further evaluation confirmed diagnoses of **secondary Antiphospholipid Syndrome (APS),** occurring in association with **Systemic Lupus Erythematosus (SLE),** which is the most common autoimmune condition linked to secondary antiphospholipid syndrome (APS) and systemic lupus erythematosus (SLE). APS is an autoimmune disorder characterized by antiphospholipid antibodies, which increase the risk of thrombosis and pregnancy complications. SLE is a systemic autoimmune disease that can affect multiple organs and is frequently associated with APS.

Clinical Considerations

The patient's severe hypoxemia may result from several potential causes, including thromboembolic events or lupus-related pulmonary involvement. Given her APS diagnosis, pulmonary embolism or other vascular complications are significant concerns. Although the patient was receiving Acitrom, the therapeutic efficacy of

this anticoagulant requires evaluation, with potential dose adjustments based on clinical and laboratory findings.

Reason for Azathioprine Discontinuation

Azathioprine was discontinued in this patient due to an increased susceptibility to infections. As an immunosuppressive drug, Azathioprine weakens the body's immune response, making the patient more susceptible to infections, including opportunistic infections like tuberculosis (TB). This risk is particularly elevated when combined with the patient's existing autoimmune disease (SLE) and potential thromboembolic complications. The decision to stop Azathioprine was likely made to reduce the risk of such infections.

Laboratory Findings on Admission

- Hemoglobin: 8.2 g/dL, indicating mild anemia, commonly associated with chronic autoimmune conditions like SLE.
- **Lupus Anticoagulant (LA):** Positive
- **Anti-Cardiolipin Antibodies (aCL):**
  IgG: **92 GPL units/mL** *(Reference: <20 GPL = Negative).*
  IgM: **38 MPL units/mL** *(Reference: <20 MPL = Negative)*
- **Anti-β2 Glycoprotein I Antibodies (aβ2GPI):**
  IgG: **75 SGU/mL** *(Reference: <20 SGU = Negative)*
  IgM: **29 SMU/mL** *(Reference: <20 SMU = Negative)*
- Prothrombin Time (PT): 15.2 seconds, slightly prolonged compared to the patient's previous PT of 12.8 seconds.
- International Normalized Ratio (INR): 1.1, indicating subtherapeutic anticoagulation for a patient on long-term Acitrom therapy.

These findings underscored the need for close monitoring of anticoagulation status, as subtherapeutic INR values in patients with antiphospholipid syndrome (APS) may increase the risk of thrombotic complications.

Case Discussion

48-year-old female presented with complaints of severe breathlessness, generalized weakness, and hypoxemia. She was a known case of hypothyroidism for 15 years and had a history of rheumatoid arthritis and hypertension for the past 4 years. There was no significant history of smoking, alcohol use, recent surgery, immobilization, malignancy, or oral contraceptive use. Family history of autoimmune or thrombotic disorders was not reported. On physical examination, the patient appeared dyspneic and cyanotic. Vital signs revealed oxygen saturation of 51% on room air, tachycardia, and tachypnea. Respiratory examination showed bilateral basal crepitations, while cardiovascular examination revealed tachycardia without significant murmurs. Mild pallor and pedal edema were present. No focal neurological deficits or cutaneous manifestations such as malar rash or livedo reticularis were observed. Laboratory investigations demonstrated positive antiphospholipid antibodies with elevated inflammatory markers. ANA positivity supported the diagnosis of systemic lupus erythematosus. Coagulation profile monitoring revealed subtherapeutic anticoagulation despite Acitrom therapy. Arterial blood gas analysis confirmed severe hypoxemia. Radiological evaluation including chest imaging showed bilateral pulmonary infiltrates suggestive of thromboembolic or inflammatory pulmonary involvement. Clinical findings, laboratory evidence, and autoimmune profile collectively supported the diagnosis of antiphospholipid syndrome associated with systemic lupus erythematosus.

The patient was receiving Acitrom, an anticoagulant, before admission, reflecting prior recognition of her thrombotic risk. However, her acute presentation with severe hypoxemia, despite ongoing anticoagulation, underscores a critical clinical challenge: ensuring therapeutic efficacy. For patients on vitamin K antagonists like Acitrom, close monitoring of the International Normalized Ratio (INR) is essential to maintain the target therapeutic range (typically 2.0–3.0 for secondary prophylaxis in antiphospholipid syndrome [APS]). In cases of acute thrombotic events or subtherapeutic INR, adjustments to the anticoagulant regimen—potentially including bridging with parenteral anticoagulants such as heparin—are vital to prevent further clot progression. This case highlights that, even with established anticoagulation, patients with APS remain at risk of recurrent thrombotic events, emphasizing the need for ongoing vigilance and adherence to therapeutic targets.

A key decision in this patient's management was the discontinuation of azathioprine. As an immunosuppressive agent commonly used in autoimmune conditions such as systemic lupus erythematosus (SLE) and rheumatoid arthritis, azathioprine increases susceptibility to infections. In a patient presenting with acute respiratory distress and underlying systemic autoimmune diseases, the risk of opportunistic infections, such as tuberculosis, is significantly heightened. Discontinuing azathioprine was likely a strategic decision to reduce this infection risk, particularly in a patient with compromised respiratory status, where an infection could severely exacerbate her condition. This case underscores a core principle in managing complex autoimmune patients: balancing effective control of autoimmune disease activity with minimizing iatrogenic risks, especially immunosuppression-related infections, which can be life-threatening in acute settings.

In conclusion, this case clearly demonstrates the diagnostic and therapeutic complexities of coexisting antiphospholipid syndrome (APS) and systemic lupus

erythematosus (SLE). It highlights the critical need for heightened suspicion of thrombotic events, such as pulmonary embolism, in APS patients, even those receiving anticoagulation therapy. Additionally, it emphasizes the importance of closely monitoring and adjusting anticoagulant therapy to ensure its effectiveness. The case also serves as a vital reminder for clinicians to carefully weigh the risks and benefits of immunosuppressive therapies in patients with acute clinical deterioration or heightened infection risk. Ultimately, it underscores the need for a comprehensive, individualized, and multidisciplinary approach to optimize outcomes for patients navigating the complex challenges of APS and related autoimmune conditions.

Practical Recommendations

Patients with systemic lupus erythematosus presenting with unexplained hypoxemia or thrombotic manifestations should be promptly evaluated for antiphospholipid syndrome. Early antiphospholipid antibody testing, regular INR monitoring, and timely optimization of anticoagulation therapy are essential to prevent life-threatening thromboembolic complications. Clinicians should maintain a high index of suspicion for pulmonary embolism in APS patients with severe hypoxemia. Careful monitoring is also necessary during immunosuppressive therapy because of the increased susceptibility to opportunistic infections. A multidisciplinary approach involving rheumatologists, pulmonologists, hematologists, and clinical pharmacists may improve patient outcomes.

Conclusion

This case highlights the complex interplay between Antiphospholipid Syndrome (APS) and Systemic Lupus Erythematosus (SLE), demonstrating the diagnostic and therapeutic challenges associated with coexisting systemic autoimmune diseases. The patient's presentation with severe hypoxemia raised strong clinical suspicion for pulmonary thromboembolic complications, a potentially life-threatening manifestation of APS. Despite being on anticoagulation therapy, her acute presentation emphasized the need for continuous monitoring and individualized adjustment of therapeutic strategies to ensure optimal anticoagulant efficacy. The discontinuation of Azathioprine due to increased infection risk further underscores the critical balance between immunosuppression and infection control in managing patients with overlapping autoimmune conditions. This case reinforces the importance of a multidisciplinary approach, early recognition of systemic involvement, and tailored therapy in improving outcomes for patients with APS and SLE.

- **Abbreviations**
- **SLE** – Systemic Lupus Erythematosus
- **APS** – Antiphospholipid Syndrome
- **aPL** – antiphospholipid antibodies
- **β2GPI** – beta-2-glycoprotein I
- **EC** – endothelial cells
- **TB** – tuberculosis
- **LA** – Lupus Anticoagulant
- **aCL** – anticardiolipin antibodies
- **IgG** – Immunoglobulin G
- **GPL** – IgG Phospholipid units
- **IgM** – Immunoglobulin M
- **MPL** – IgM Phospholipid units
- **aβ2GPI** – anti-β2-glycoprotein I antibodies
- **SGU** – Standard GPI Units (for IgG)
- **SMU** – Standard M Units (for IgM)
- **PT** – Prothrombin Time
- **INR** – International Normalized Ratio
- **PE** – Pulmonary Embolism

Ethics approval and consent to participate

Ethical approval was not required for this case report in accordance with institutional policy. Written informed consent was obtained from the patient for participation and use of the clinical information for academic purposes.

Consent for publication

Written informed consent was obtained from the patient for publication of this case report and any accompanying clinical details.

Availability of data and materials

All relevant data supporting the findings of this case report are included within the article. Additional information is available from the corresponding author upon reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Vidhya Lekshmi K, performed the literature review, collected and interpreted the clinical data, and wrote the complete manuscript. **Chitra Thara S**, critically edited the manuscript.
Revanth R reviewed the manuscript and provided valuable intellectual input. **Venkateswaramurthy N** supervised the work, provided expert guidance throughout the preparation of the manuscript, critically reviewed the content, and approved the final version. All authors read and approved the final manuscript.This version reflects a typical contribution for a senior author or guide.

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