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# COMPLEX ANTIPHOSPHOLIPID SYNDROME SUCCESSFULLY CONTROLLED FOR 17 YEARS WITH PERSONALIZED ENOXAPARIN THERAPY

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## ABSTRACT

Antiphospholipid syndrome (APS) is a systemic autoimmune disease characterized by the presence of antiphospholipid antibodies and venous and arterial thrombotic events, including obstetric complications. We describe the case of a 56-year-old female diagnosed with APS with triple antibody positivity and multiple disease-associated manifestations, namely recurrent purpuric lesions, adrenal insufficiency due to infarction, acalculous cholecystitis, and three spontaneous abortions. Her follow-up was marked by severe thrombotic and haemorrhagic events, notably splanchnic vein thrombosis and haemorrhagic shock after a renal biopsy, as well as the diagnosis of systemic lupus erythematosus 8 years after the APS diagnosis. Chronic anticoagulation with enoxaparin, with dosage guided by anti-factor Xa activity, resulted in stability without complications over 17 years. This case emphasizes the importance of personalized therapeutic strategies and close monitoring in patients with APS.

## KEYWORDS

Antiphospholipid syndrome, antibody triple positivity, splanchnic vein thrombosis, long-term enoxaparin anticoagulation, personalized therapeutic strategies

## LEARNING POINTS

- This patient presented with rare manifestations of antiphospholipid syndrome (APS), such as acalculous cholecystitis, Budd-Chiari syndrome, and Addison's disease, all linked to ischemic events caused by vascular thrombosis. These atypical presentations highlight the varied and severe clinical spectrum of APS, requiring physicians to be vigilant about unusual complications.
- After multiple severe thrombotic and haemorrhagic events, the patient was successfully managed with long-term enoxaparin, with dose adjusted according to anti-factor Xa activity (which allowed for a significant dose reduction in comparison with the predicted empiric dose).
- The patient remained event-free for 17 years, reflecting the importance of personalizing anticoagulation therapy.

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## INTRODUCTION

Antiphospholipid syndrome (APS) is an autoimmune disease characterized by the presence of antiphospholipid antibodies and the occurrence of venous and arterial thrombotic events, as well as obstetric complications. The antiphospholipid antibodies typically tested are lupus anticoagulant, anticardiolipin antibodies, and anti-β2-glycoprotein I antibodies. Patients with APS can present a wide spectrum of clinical manifestations with extremely variable severity[1].

The classification criteria for APS from the American College of Rheumatology/European League Against Rheumatism[1] were updated in 2023, reflecting new perspectives and advances in the understanding of the disease. The main differences from the previous criteria include different weightings for the presence of various antibodies (with a higher score for the persistence of lupus anticoagulant versus a single-time detection, and a higher score for triple positivity), as well as the incorporation of antibody titre evaluation, considering high titres as a significant risk factor. The new criteria also consider the presence of cardiovascular risk factors and include additional clinical manifestations related to microvascular circulation impairment, such as livedo racemosa and adrenal gland haemorrhage (either manifested by organ pathology or identified through imaging).

## CASE DESCRIPTION

We present the case of a woman with APS, currently 56 years old, born and residing in an urban centre, and working as a supermarket employee. Her family history is remarkable for ischemic events before the age of 55 (father and paternal uncles), and breast cancer (mother, died at age 45). Her medical history is notable for recurrent purpuric lesions *(Fig. 1A)* since the age of 22, Raynaud's phenomenon, microvasculitic lesions on her hands *(Fig. 1B)*, livedo reticularis since the age of 25, and a diagnosis of Addison's disease at the age of 28, for which she is undergoing replacement therapy with hydrocortisone. She also has a history of recurrent thrombophlebitis in the left lower limb and two first-trimester spontaneous miscarriages (gravida 2, para 0, abortions 2). At age 31, she experienced a missed miscarriage at 15 weeks of gestation, requiring a curettage procedure. Six days later, she developed fever and pain in the right abdominal quadrants, with a positive Murphy's sign. Abdominal ultrasound confirmed acalculous acute cholecystitis, and she was hospitalized. During hospitalization, she was found to have thrombocytopenia (60,000 platelets/μl), persistently prolonged aPTT (60 seconds), and elevated D-dimer levels.

Further testing revealed the presence of lupus anticoagulant, high levels of IgG anticardiolipin antibodies (>120 UGPL/ml), and IgG anti-β2GP1 antibodies (>100 UGPL/ml), confirmed by repeat tests after 12 weeks. Remaining thrombophilia workup (protein C, protein S, antithrombin, factor V Leiden mutation, homocysteine, and plasminogen activator inhibitor type 1) was negative. The autoimmune panel, including antinuclear antibodies (ANA), double-stranded deoxyribonucleic acid (dsDNA) antibodies, and antineutrophil cytoplasmic antibodies (ANCA), was also unremarkable. A diagnosis of APS was made, based on triple positivity of antiphospholipid antibodies, previous venous thrombotic and obstetric events, haematological abnormalities (thrombocytopenia and prolonged aPTT), recurrent purpuric lesions, Raynaud's phenomenon, and livedo reticularis. Acalculous acute cholecystitis and Addison's disease could also be linked to APS, with the latter confirmed by imaging evidence of adrenal gland infarction. She was treated with acenocoumarol after demonstrating resistance to warfarin. At age 37 she became pregnant again, and her anticoagulation therapy was switched to therapeutic doses of low-molecular-weight heparin (LMWH) (1 mg/kg every 12 hours) and 100 mg of aspirin per day. At 8 weeks gestation, she developed fever, shortness of breath, and right upper quadrant abdominal pain. Physical examination revealed painful hepatomegaly, and lab tests showed elevated aspartate transaminase (AST) levels, twice the upper limit of normal. Doppler ultrasound of the abdomen documented thrombosis of the hepatic veins, leading to a diagnosis of Budd-Chiari syndrome. A medical termination of pregnancy was performed, and she resumed anticoagulation with acenocoumarol.

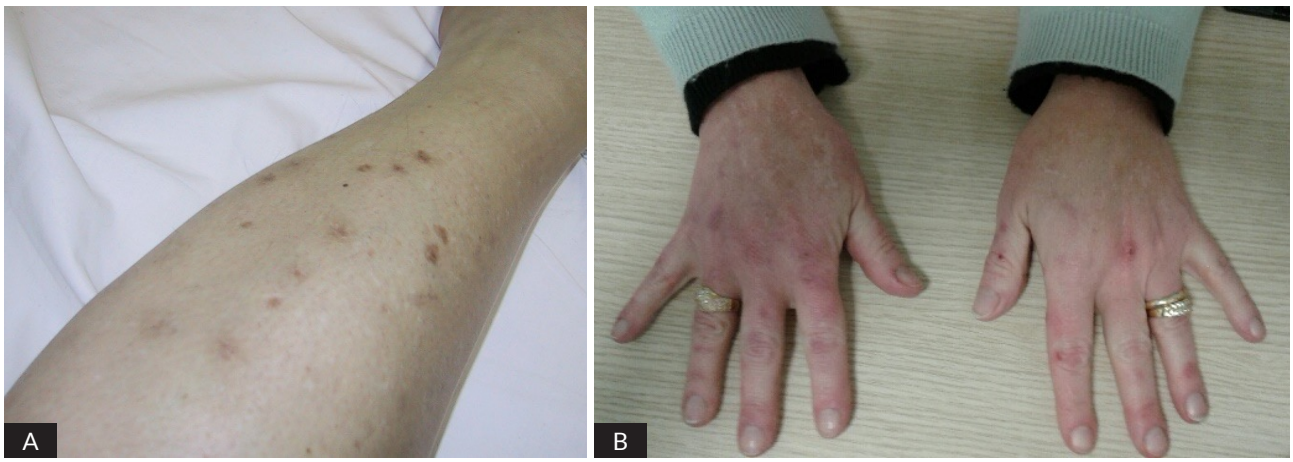


*Figure 1. A) Purpuric skin lesions on the lower limbs; B) Microvascular lesions on the hands.*

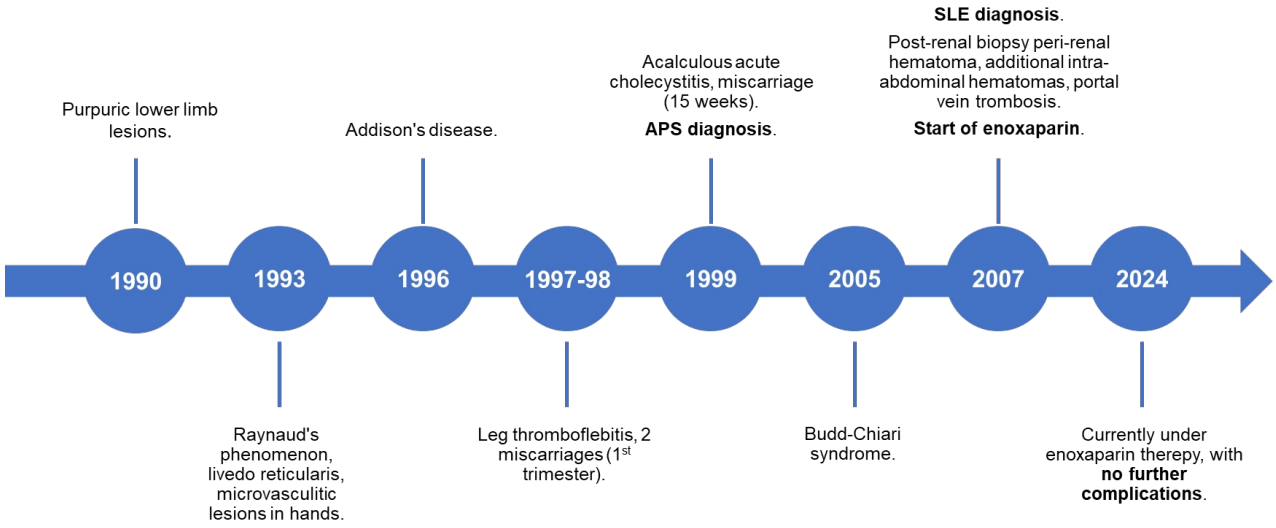


*Figure 2. Key time points of the case. Abbreviations: APS, antiphospholipid syndrome; SLE, systemic lupus erythematous.*

At age 39, 8 years after the APS diagnosis, she presented at the Autoimmune Diseases Clinic with complaints of non-erosive polyarthritis and marked fatigue. Laboratory tests showed positive ANA (titre 1:640) and dsDNA antibodies (320 IU/ml), as well as proteinuria >500 mg/day, without elevated nitrogen retention parameters. A renal biopsy, performed with anticoagulation bridging to LMWH, was consistent with class II lupus nephritis. A diagnosis of systemic lupus erythematosus (SLE) was made, and she started treatment with hydroxychloroquine, prednisone, and azathioprine. Two weeks after the biopsy, while back on acenocoumarol, she developed a perirenal hematoma complicated by haemorrhagic shock, managed with supportive therapy, and anticoagulation was suspended. The hematoma fully resolved, and she resumed anticoagulation, this time with enoxaparin. Two months later, she presented to the emergency department with sudden-onset epigastric abdominal pain, dizziness, hypotension, and syncope. An urgent computed tomography (CT) scan showed spontaneous hematomas in the left perirenal area (measuring 12 cm), in the posterior cavity of the omentum (measuring 12 cm), and at the esophagogastric junction (measuring 5 cm). Due to the severity of these haemorrhagic complications, anticoagulation was once again suspended, and she remained hospitalized for observation. On the 24$^{th}$ day of hospitalization, she developed fever and left upper quadrant pain. A contrast-enhanced abdominal CT scan revealed thrombosis in the left branch of the portal vein, and anticoagulation with enoxaparin was resumed. Since then, and in alignment with the patient's preference, she has remained on chronic anticoagulation with enoxaparin. The dose has been adjusted according to anti-Xa activity, with the patient on a single daily dose of 80 mg, providing greater convenience in dosing. She continues to be monitored at the Autoimmune Diseases Clinic and has not experienced any new thrombotic or haemorrhagic episodes in the past 17 years. *Figure 2* highlights the key time points of the case, specifically the occurrence of complications and the initiation of enoxaparin therapy.

## DISCUSSION

The case highlights several important aspects of APS, particularly the potential severity of manifestations, especially in cases of triple antibody positivity, the complexity of managing simultaneous thrombotic and haemorrhagic events, and the uncertainties in choosing anticoagulant medications. The triple positivity for antiphospholipid antibodies and the high antibody titres observed in this patient are associated with a worse prognosis and a higher likelihood of recurrent thrombotic events[1]. These characteristics reinforce the need for close monitoring of anticoagulation therapy to prevent new thrombotic events. This case was also notable for unusual manifestations of APS, such as acalculous cholecystitis, which in this case occurred due to ischemia of the gallbladder, having been described both in primary APS and secondary to SLE. A second rare gastrointestinal manifestation of APS in this patient was Budd-Chiari syndrome, caused by an obstruction to hepatic circulation due to thrombosis of the hepatic veins. Other reported gastrointestinal manifestations of APS include oesophageal, splenic, hepatic, intestinal, or pancreatic ischemia. Addison's disease is a third rare manifestation of APS in this patient, with a reported prevalence of less than 1% of cases. A literature review found that in 36% of primary adrenal insufficiency cases associated with APS, adrenal insufficiency was the first manifestation of APS. Imaging findings commonly showed adrenal haemorrhage, while histopathological findings revealed haemorrhagic infarction with vascular thrombosis. Almost all patients (97%) tested positive for lupus anticoagulant[2].

The diagnosis of SLE, established 8 years after the APS diagnosis, is also relevant to the case. In a prospective study involving 1,000 APS patients[3], 36% of cases were secondary to SLE. In this study, patients with SLE and secondary APS had a higher occurrence of thrombotic events (arterial, venous, and obstetric) compared to primary APS patients. This adds to the patient's already elevated risk.

Anticoagulation is the cornerstone of APS therapy, with indefinite treatment using warfarin or other vitamin K

antagonists (VKA) being the standard approach. The role of direct oral anticoagulants (DOAC) is not definitively established but is commonly used in cases of single venous thrombosis in patients with low-risk antiphospholipid antibody profiles. However, DOAC use is discouraged in arterial thrombosis or triple antibody positivity, based on results from the TRAPS study[4]. For the first venous thrombotic event, the international normalised ratio (INR) target is typically set at 2-3, but for arterial thrombotic events the optimal intensity of anticoagulation is not well-established, and an INR target of 3-4 may be considered, considering the individual risk of thrombosis recurrence and bleeding. In patients with APS and recurrent thrombosis despite adequate VKA treatment, increasing the INR target to 3-4 (if not already established), adding low-dose acetylsalicylic acid, or switching from VKAs to low-molecular-weight heparin (LMWH) can be considered[5]. Due to its short half-life, LMWH is often used as a bridging agent in patients on VKAs, such as in cases of thrombotic recurrence under standard-dose VKA or in the perioperative period. It is also useful in cases of thrombocytopenia due to its low risk of heparin-induced thrombocytopenia.

In patients positive for lupus anticoagulant, this can affect phospholipid-dependent coagulation tests, making aPTT unreliable for monitoring LMWH activity. In such cases, the anti-factor Xa activity test is more appropriate. In this patient, personalizing the dose of enoxaparin was crucial, allowing for a significant reduction in the estimated dose (calibrated to 80 mg/day in a patient with a body weight of 120 kg). The management of haemorrhagic and thrombotic phenomena occurring in close succession was particularly challenging in this patient, illustrating the delicate balance between haemorrhagic and thrombotic risk. Given the patient's warfarin resistance and significant haemorrhagic complications, the medical decision, respecting the patient's expressed wishes, was to maintain enoxaparin as the chronic anticoagulant. The safety profile of this drug, the ability to adjust its dose according to anti-factor Xa activity, and the possibility of reversing its effects in the case of haemorrhagic events were key factors in this decision. The patient has not experienced any new thrombotic or haemorrhagic episodes over the past 17 years, further reinforcing the efficacy of this treatment regimen and the appropriateness of the therapeutic decision in this particular case.

## CONCLUSION

This case illustrates the need for an individualized therapeutic approach and continuous monitoring to optimize clinical outcomes in patients with APS.

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