

Antiphospholipid syndrome: is there a preclinical period?

Síndrome antifosfolipídico: ¿existe un periodo preclínico?

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Introduction

Antiphospholipid syndrome (APS) is a systemic autoimmune disease characterized by arterial, venous, or microvascular thrombosis, obstetric morbidity, and various non-thrombotic manifestations in patients with persistently positive antiphospholipid (APL) antibodies^{1,2}. The prevalence of APS is estimated at 50 per 100,000 people and is 5 times more common in women vs men¹. Catastrophic APS is a severe, acute manifestation, accounting for 1% of cases, characterized by microthrombosis in multiple areas, leading to multiple organ dysfunction, with high mortality rates (29% up to 75%)³.

In the absence of diagnostic criteria for APS, clinicians have used “classification” criteria: initially the Sapporo criteria (1999 and revised in 2006)^{4,5}, and more recently, those of the American College of Rheumatology (ACR) and the European Alliance of Associations for Rheumatology (EULAR) (2023)², aiming to include a heterogeneous group of patients, primarily for research rather than for confirmation diagnoses, guiding therapy, or monitoring. Some cases do not meet the classification criteria for APS, yet present diagnostic and therapeutic challenges in clinical practice^{6,7}. This is the case for asymptomatic patients with persistently positive APL antibodies. It is known that these antibodies can also be positive in conditions unrelated to APS (e.g., elderly individuals, neoplastic diseases, pregnancy), reflecting their low specificity^{1,8}. Additionally, the contribution of

each APL antibody type to thrombotic risk varies and may be additive in certain cases². Therefore, the thrombotic event risk in this clinically asymptomatic patient group represents uncertainty for clinicians.

We present an APS case that illustrates the progression from an asymptomatic or preclinical stage, with positive APL antibodies and mild thrombocytopenia, to a catastrophic clinical onset.

Case report

A 55-year-old woman with a past medical history of chronic idiopathic urticaria under follow-up and treatment with the allergy service. A routine blood test revealed confirmed mild thrombocytopenia ($128 \times 10^3 \mu\text{L}$ [reference values: 150-450]) with no abnormalities in the peripheral blood smear. Further testing showed triple positivity for APL antibodies at high titers measured by ELISA: anti- β_2 -glycoprotein I (anti- β_2 GPI) IgG 188 U/mL (reference values: 20-40), anticardiolipin (aCL) IgG 168 GPL (reference values: 20-40), lupus anticoagulant (LA) positive (screened with dRVVT and silica-activated APTT), with positive mixing and confirmatory studies.

A second determination after 12 weeks remained positive.

Prophylactic treatment with acetylsalicylic acid (ASA) was started, and periodic follow-up at the coagulation clinic showed persistent laboratory abnormalities

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(high APL antibody titers > 80 U/mL and mild thrombocytopenia) with no clinical signs consistent with APS or systemic autoimmune disease.

Five years after detecting these laboratory abnormalities, the patient presented to the ER with cyanosis in the first toe of the right foot, evolving over a few hours, along with fever, diffuse abdominal pain, and postprandial vomiting. Blood tests showed mild thrombocytopenia ($100 \times 10^3 \mu\text{L}$), no other cytopenias, no peripheral blood smear abnormalities, and no renal or hepatic dysfunction. Imaging modalities (Doppler ultrasound and angiography) revealed renal and splenic infarcts, as well as thrombosis in the infrarenal abdominal aorta and various portions of the right popliteal artery. No adenopathy, visceromegaly, or lesions suggestive of solid neoplasm were found, and serial blood cultures tested negative. Autoimmune tests were repeated, showing positive APL antibodies only. Anticoagulant treatment with low-molecular-weight heparin (LMWH) (enoxaparin 60 mg subcutaneously every 12 hours) was started, a mechanical thrombectomy was performed, and a transpopliteal revascularization of the distal trunks was attempted with partial success and without further clinical progression of tissue ischemia. No clear trigger or additional cardiovascular or thrombotic risk factor was identified in the medical history.

Given the previous laboratory findings, a diagnosis of probably primary catastrophic APS was established. Treatment was initiated with high-dose corticosteroids (methylprednisolone 500 mg IV/day for 3 days), hydroxychloroquine (200 mg/day orally), immunoglobulins (0.4 g/kg/day IV for 5 days), anti-CD20 monoclonal antibody (375 mg/m² IV in a single dose), and plasmapheresis (5 sessions), achieving a favorable outcome. Subsequently, outpatient follow-up continued with a tapering dose of oral corticosteroids, hydroxychloroquine, ASA, and acenocoumarol to maintain an international normalized ratio (INR) between 2 and 3. Since there was no adequate correlation between capillary (POC device: CoaguChek XS) and venous blood INR measurements (Quick method), it was decided to continue measurement by the Quick method, maintaining a therapeutic range without bleeding complications or new thrombotic events.

Discussion

Patients with positive APL antibodies without defining clinical events of APS (preclinical stage) have an annual thrombotic risk between 1% and 5% in an apparently healthy population, being higher in patients with

systemic lupus erythematosus⁹. Despite the difficulty in predicting thrombotic events in these patients, laboratory variables have been used as potential markers. Traditionally, high-risk cases have been defined as “triple positive,” meaning positivity for all 3 antibodies (LA, aCL, and anti- β_2 GPI); cases with persistently positive LA; “double positives” (aCL and anti- β_2 GPI); and/or high titers of APL antibodies^{8,10}. For these high-risk cases, some experts recommend low-dose ASA (75-100 mg/day) as primary prophylaxis; however, in a prospective study, “triple positive” patients had an annual thromboembolic risk of 5%, which did not decrease with ASA use¹¹. A randomized clinical trial (APSALA) that sought to answer this question (ASA in primary prophylaxis) was stopped early due to the low rate of thrombosis, without detecting a reduction in thrombotic events¹².

Besides ASA, LMWH is often recommended in high-risk situations, albeit with a low level of evidence^{8,10}. Even so, the actual time window to clinical presentation remains an enigma. These antibodies do not, *per se*, cause thrombotic complications in healthy subjects, but they may act as a “first hit” that varies depending on genetic, ethnic, and geographic factors, given the variable distribution of APS in epidemiological studies⁸. According to the “second hit” hypothesis, certain factors can trigger the thrombotic process by acting as biological stressors (e.g., viral infections [hepatitis B, C, human immunodeficiency virus, severe acute respiratory syndrome coronavirus² or bacterial infections [*Coxiella burnetii*]), eventually leading to APS development⁸.

In clinical practice, patients with a positive APL antibody profile but no APS classification criteria should be periodically evaluated for not only thrombotic signs (microvascular, cardiac, obstetric) but also for the dynamic risk of thrombotic events (concomitant systemic autoimmune diseases, as well as cardiovascular and venous thromboembolic disease risk factors)² to establish preventive measures and attempt to mitigate the risk of modifiable factors. However, these measures may be insufficient in some cases, and prospective and comparative studies are necessary to determine which early interventions may be beneficial.

In terms of catastrophic APS, most cases are primary and develop within the first 5 years of follow-up after APS diagnosis; in about half of cases, it is the initial sign³. However, as this is an extremely rare condition, few studies elucidate the true prevalence, incidence, and time window from APL antibody detection. The latest CAPS registry data shows that peripheral arterial involvement, as in our case, is present in only 37% of cases, and renal infarcts in 8.7%¹³. The most common

clinical signs are renal, pulmonary, and peripheral venous system involvement¹³. Despite high mortality, data from this registry show that 66% of cases are symptom-free under anticoagulant therapy at the 67-month follow-up¹⁴. Catastrophic APS should be suspected in cases presenting with this type of severe multisystemic involvement over a short period, to address both potential triggers and the inflammatory and thrombotic storm.

Currently, vitamin K antagonists are the anticoagulants of choice for secondary prophylaxis¹⁰. INR measurement is typically done using the prothrombin time with the Quick method on venous blood^{15,16}. However, given the frequent INR monitoring required in these cases, many patients are monitored with point-of-care (POC) devices, usually obtaining good correlations for INR between 1.5 and 4.5¹⁶. Nonetheless, false INR elevations can occur due to APL interference (mainly with LA and anti- β_2 GPI) with reagents (recombinant thromboplastin times) in POC devices^{15,16}. This may lead to inadequate anticoagulant dosing, with associated risks. A practical approach may be to restrict POC use to APS patients with sustained agreement between digital and venous INR of < 0.5, regardless of LA positivity¹⁵. If there is no concordance, it is preferable to continue INR measurement with venous blood, ideally with the Owren method (less sensitive to interference)¹⁶. Other methods may be useful; however, a therapeutic range has not been systematically established for methods like chromogenic factor X, anti-Xa activity, chromogenic ecarin-based assays, and thrombin generation¹⁵.

Conclusions

There is no standardization for clinical follow-up of patients with positive APL antibodies without APS clinical signs. Despite recommended prophylactic measures for high-risk positive APL antibody cases in preclinical stages, these may still present with catastrophic manifestations of the disease. APL interference can lead to INR discrepancies (capillary vs venous) and thus inadequate control of anticoagulant therapy with vitamin K antagonists in these cases.

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Conflicts of interest

None declared.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article. Furthermore, they have acknowledged and followed the recommendations as per the SAGER guidelines depending on the type and nature of the study.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

Use of artificial intelligence for generating text. The authors declare that they have indeed used generative artificial intelligence, specifically ChatGPT-4, for the efficiency analysis of the 3 treatments, through the analysis of the results reported in the different studies.

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