WebLog Journal of Pulmonology and Respiratory Medicine

Case Report
Published: 06 Apr, 2026

From Pulmonary Embolism to Arterial Pseudoaneurysm: A Case of Aggressive Primary Antiphospholipid Syndrome with DOAC Failure

Nahidi M, Arfaoui H, El Khattabi W, Msika S, Bamha H, Bougteb N, Jabri H and Afif MH*

Department of Respiratory Diseases, 20 August 1953 Hospital, Casablanca, Morocco

Abstract

Introduction: Antiphospholipid Syndrome (APS) is a major cause of acquired thrombophilia, often presenting a diagnostic challenge when clinical manifestations are multifaceted. While venous thromboembolism is common, aggressive arterial involvement represents the "hidden part of the iceberg," carrying a high risk of morbidity and therapeutic failure with newer anticoagulants.

Case Presentation: A 52-year-old male with no prior risk factors presented with acute pulmonary embolism (PE) and a butterfly malar rash. Initial investigations revealed a positive lupus anticoagulant (LA), but the 2023 ACR/EULAR score was insufficient for a formal APS diagnosis. A concurrent lumbar disc herniation caused a diagnostic bias, ascribing limb pain to neurological causes. Despite adherence to Rivaroxaban (DOAC), the patient suffered a "vascular catastrophe," characterized by a recurrent venous thrombosis and a major arterial complication: a pseudoaneurysm of the superficial femoral artery with acute popliteal occlusion. This necessitated urgent complex vascular surgery. Following persistent LA positivity at 12 weeks, the diagnosis of Primary APS was confirmed with a final ACR/EULAR score of 12 points (7 clinical, 5 laboratory).

Discussion: This case highlights the "APS paradox" where initial venous events may mask an underlying, aggressive arterial vasculopathy. It underscores the critical "Red Flag" of thrombotic recurrence under DOAC therapy. In high-risk APS or arterial manifestations, the TRAPS trial and EULAR guidelines confirm the mandatory superiority of Vitamin K Antagonists (VKA) over DOACs. The introduction of Hydroxychloroquine, even with negative antinuclear antibodies, provided a synergistic antithrombotic effect and protection against potential transition to Systemic Lupus Erythematosus.

Conclusion: Clinicians must look beyond the "visible part of the iceberg" in APS. Early identification of arterial fardeau, avoidance of diagnostic biases from incidental findings, and the strict prioritization of VKA over DOACs are essential to prevent life-threatening vascular escalations.

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Correspondence:
Mohammed Nahidi, Department of Respiratory Diseases, 20 August 1953 Hospital, Casablanca, Morocco, Tel: 0766730961;
E-mail: nahidisimo@hotmail.com

Received Date: *19 Mar 2026*
Accepted Date: *04 Apr 2026*
Published Date: *06 Apr 2026*

Citation:
Nahidi M, Arfaoui H, El Khattabi W, Msika S, Bamha H, Bougteb N, et al. From Pulmonary Embolism to Arterial Pseudoaneurysm: A Case of Aggressive Primary Antiphospholipid Syndrome with DOAC Failure. WebLog J Pulmonol Respir Res. wjprm.2026.d0606. https://doi.org/10.5281/zenodo.19673997

Introduction

Antiphospholipid Syndrome (APS) is a systemic autoimmune disorder defined by the association of clinical thrombotic events or obstetric complications with the persistent presence of antiphospholipid antibodies (aPL). In clinical practice, pulmonary embolism and venous manifestations are often merely the visible part of the iceberg.

Arterial involvement in APS, although seemingly less frequent, is significantly underdiagnosed and can present in atypical and severe forms, such as pseudoaneurysms or distal arterial occlusions. A major challenge also lies in the therapeutic strategy: the use of Direct Oral Anticoagulants (DOACs) has shown its limitations, and even its inefficacy, in preventing thrombotic recurrences in high-risk APS patients. The gold standard of treatment must imperatively rely on Vitamin K Antagonists (VKA) to prevent life-threatening complications.

This case report illustrates this dilemma through the history of a 52-year-old patient whose APS, initially revealed by a left pulmonary embolism and treated with DOACs, rapidly progressed under treatment toward a small saphenous vein thrombosis and a complex femoral pseudoaneurysm. This case highlights the critical importance of early diagnosis of arterial involvement and rigorous anticoagulation management with VKA to prevent the failure of revascularization procedures.

Case Presentation

A 52-year-old male, a civil servant by profession, non-smoker, and with no significant medical or surgical history, presented to the emergency department with acute respiratory symptoms that had been evolving for 24 hours. The initial clinical presentation included sudden-onset exertional dyspnea, pleuritic chest pain, and a single episode of small-volume hemoptysis. Upon admission, the physical examination revealed a patient in good general condition (Performance Status: 0) with relative hemodynamic stability (BP 110/60 mmHg, HR 108 bpm), but a mild tachypnea of 19 cycles/min and a peripheral oxygen saturation (SpO_2) of 94% on room air.

A striking semiological feature was noted during the skin examination: the presence of an erythematous malar rash in a "butterfly" distribution (Figure 1), sparing the nasolabial folds. This finding immediately raised suspicion of underlying Systemic Lupus Erythematosus (SLE). However, screening for antinuclear antibodies (ANA) by indirect immunofluorescence was performed twice, 12 weeks apart, and remained consistently negative, making a diagnosis of SLE less likely according to classical criteria.

Regarding the pulmonary status, the chest X-ray (Figure 2) revealed indirect signs of pulmonary infarction: a rounded retrocardiac opacity, an elevated left diaphragmatic dome, and blunting of the homolateral costophrenic angle. Simultaneously, the patient complained of sharp pain in his left lower limb. Although the Homans sign was positive, an emergency venous duplex ultrasound of the lower limbs showed no signs of deep vein thrombosis. To explore this persistent pain, a lumbar MRI was performed, which revealed a degenerative disc herniation. This result acted as a "red herring," initially leading the medical team toward a neurological radicular compression to explain the limb symptoms.

However, given the high clinical suspicion of pulmonary embolism (intermediate Wells score and positive D-dimer), a Computed Tomography Pulmonary Angiography (CTPA) (Figure 3) was performed. This confirmed a proximal left pulmonary embolism, complicated by an infarction in the left lower lobe (LLL) presenting a characteristic "grid-like" appearance. Emergency anticoagulant treatment with Low Molecular Weight Heparin (LMWH) was initiated, followed by an early transition to a Direct Oral Anticoagulant (Rivaroxaban 20 mg/day).

During hospitalization, an exhaustive thrombophilia workup was initiated to elucidate the etiology of this "unprovoked" thrombotic event in a patient with no risk factors (no immobilization, recent surgery, or known tuberculosis contact). Initial laboratory results showed normal renal and hepatic function, as well as the absence of protein C, S, or antithrombin III deficiency. Factor V Leiden and prothrombin mutations were also absent (Table 1).

Table 1: Initial Immunological and Thrombophilia Screening.

Biological Parameter	Result	Interpretation
Antithrombin III	100%	Normal
Protein C / Protein S	90% / 85%	Normal
Factor V Leiden Mutation	Negative	Absent
Prothrombin G20210A Mutation	Negative	Absent
Lupus Anticoagulant (LA)	Positive	Major Criterion of APS
Anti-cardiolipin Ab (IgG/IgM)	Negative	< 40 GPL/MPL
Anti-β2-GP1 Ab (IgG/IgM)	Negative	< 40 U/mL

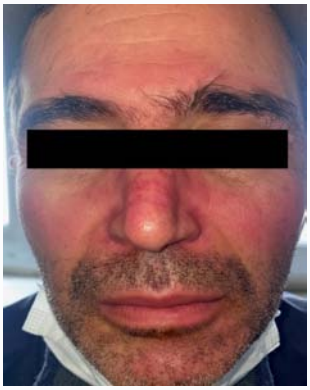

Figure 1: Erythematous malar rash with "butterfly" distribution.

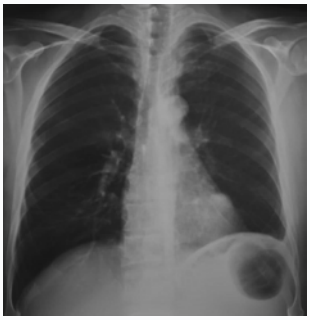

Figure 2: Chest X-ray.

Applying the 2023 ACR/EULAR classification criteria, the patient met the entry criterion. However, the initial total score was only 3 points for the clinical domain (venous thromboembolism) and 1 point for the laboratory domain (isolated positivity for Lupus Anticoagulant). The diagnosis of Antiphospholipid Syndrome (APS) could not be formally established at that stage, and the patient was discharged under Rivaroxaban therapy.

The subsequent clinical course was marked by a flagrant therapeutic failure of the Direct Oral Anticoagulants (DOACs). Despite strict adherence, the patient experienced a thrombotic recurrence in the form of deep vein thrombosis in the left small saphenous vein. Even more severe was the emergence of a major arterial complication: a pseudoaneurysm of the distal third of the left superficial femoral artery, associated with a complete occlusion of the popliteal artery and the tibio-peroneal trunk. This "vascular catastrophe" necessitated extensive surgical management in two stages: first, the resection of the pseudoaneurysm with restoration of continuity using a collagen-coated Dacron prosthetic graft, followed two months later by a revision for prosthetic thrombosis, requiring the placement of a reinforced femoro-popliteal prosthesis.

After a 12-week interval, the persistence of the Lupus Anticoagulant was biologically confirmed. The recalculation of the 2023 ACR/EULAR score then showed a major progression, now reaching 7 points in the clinical domains (reflecting the severity of the combined arterial and venous involvement) and 5 points in the laboratory domains. The diagnosis of Primary APS was definitively established. Given the failure of DOACs in this aggressive form of APS, treatment was substituted with a Vitamin K Antagonist (VKA) with a target INR of 2.0–3.0. Furthermore, in light of the initial

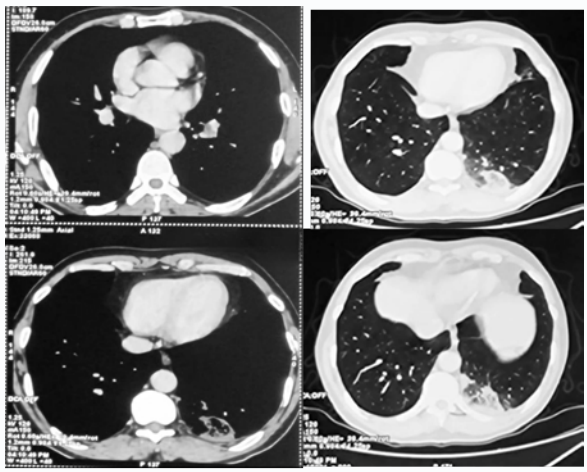

Figure 3: CT Pulmonary Angiography (CTPA) showing left pulmonary embolism and "grid-like" lung infarction.

malar rash and the risk of transition to SLE, Hydroxychloroquine (200 mg/day) was introduced with quarterly monitoring. Following one year of follow-up, the patient shows no thrombotic recurrence or prosthetic complications, confirming the effectiveness of this intensive therapeutic strategy.

Discussion

Antiphospholipid Syndrome (APS) is the leading cause of acquired thrombophilia. It is defined by a diagnostic triad: a specific clinical terrain (primary or associated with an autoimmune disease like SLE), biological positivity (aPL antibodies), and clinical events (thrombotic or obstetrical). In this case, the initial pulmonary embolism represented the venous manifestation, but it was merely the "visible part of the iceberg," masking a far more aggressive systemic vascular pathology [1].

Diagnostic Complexity

The diagnosis was challenging due to the presence of true neurological involvement (documented lumbar disc herniation). However, according to the 2023 ACR/EULAR criteria, clinicians must remain vigilant regarding "presumptive arguments."

The patient presented a malar rash (suggesting an occult autoimmune terrain) and, most importantly, the ultimate "Red Flag" of APS: a thrombotic recurrence (femoral pseudoaneurysm and arterial thrombosis) occurring despite well-managed anticoagulation (Rivaroxaban) [2].

Focus on Arterial Involvement

While venous involvement is the most frequent presentation, arterial involvement represents a major prognostic turning point. According to data from Cervera et al., arterial thrombosis occurs in approximately 26% to 30% of APS patients (3). The spectrum of arterial manifestations is vast [4, 5]:

- Cerebrovascular (~13-20%): Stroke or TIA (the most common arterial manifestation).
- Cardiac (~5-10%): Myocardial infarction, often occurring in patients with angiographically normal coronary arteries.
- Peripheral (~4%): Acute limb ischemia, sudden pain, loss of pulses, and exceptional forms such as the superficial femoral artery pseudoaneurysm observed in our patient.

Pathophysiology of Arterial APS

The "APS Paradox" lies in the *in vitro* prolongation of the aPTT (anticoagulant effect) contrasting with an *in vivo* state of extreme hypercoagulability. Unlike the venous system, arterial involvement involves a complex cellular interaction [6]:

- Cellular Activation: Anti-beta-2GP1 antibodies bind to endothelial cells, monocytes, and platelets.
- Pro-coagulant Cascade: This binding induces a massive expression of Tissue Factor and activation of the complement system. This process weakens the arterial wall and promotes high-flow thrombosis and structural anomalies, such as pseudoaneurysms [7, 8].

DOAC Failure and the Superiority of VKA

A crucial element of the clinical update is the choice of anticoagulant. This patient's deterioration under Rivaroxaban illustrates the failure of Direct Oral Anticoagulants (DOACs) in arterial or high-risk APS. The TRAPS trial confirmed that Vitamin K Antagonists (VKA) remain the gold standard, as they offer superior protection against catastrophic arterial recurrences compared to DOACs [9].

Therapeutic Synergy: The Role of Hydroxychloroquine

Finally, the introduction of Hydroxychloroquine (200 mg/day), even in the absence of confirmed Lupus (negative ANA), is a key strategy. It acts synergistically with VKAs to reduce endothelial activation and the risk of transition to a connective tissue disease, thereby ensuring the patient's long-term stabilization [10, 11].

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