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CASE BASED REVIEWS

Adrenal failure as an antiphospholipid syndrome manifestation: case-based review

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ABSTRACT

Adrenal involvement in antiphospholipid syndrome (APS) is rare but potentially life-threatening. Early recognition reduces morbidity and mortality. We report a 56-year-old male with chronic thrombocytopenia and prolonged activated partial thromboplastin time who developed fatigue, anorexia, and weight loss. On admission, he presented with hypotension, hyperkalemia, thrombocytopenia, anemia, and elevated inflammatory markers. After hospitalization, he underwent an extensive workup study. PET-CT revealed bilateral adrenal uptake, and hormonal tests confirmed primary adrenal insufficiency (PAI). Autoimmune studies showed persistently positive lupus anticoagulant, and high-titer antinuclear and anti-double-stranded DNA antibodies, establishing systemic lupus erythematosus and APS with secondary PAI. Treatment with mineralocorticoids, hydroxychloroquine, anticoagulation, and subsequently high-dose glucocorticoids led to clinical and laboratory improvement. Review of published cases shows that, although APS is more frequent in women, adrenal involvement occurs predominantly in men and usually presents acutely with abdominal pain, hypotension, and electrolyte imbalance. Our patient's atypical presentation delayed diagnosis. Awareness of such variable presentation is crucial, as early recognition and treatment significantly improve outcomes. Clinicians should consider APS in new-onset adrenal failure and systematically evaluate adrenal involvement in APS patients with compatible symptoms.

Keywords: Antiphospholipid syndrome; Adrenal insufficiency; Adrenal hemorrhage.

INTRODUCTION

Antiphospholipid syndrome (APS) is an acquired, multisystemic autoimmune thrombophilia characterized mainly by recurrent macro and/or microvascular thrombotic events and/or pregnancy morbidity, with persistent antiphospholipid antibodies (aPLs)[1]. APS can be primary or secondary, the latter most often associated with systemic lupus erythematosus (SLE)[2]. Although virtually any vascularized organ may be affected[3], endocrine involvement is rare, particularly as a presenting feature[2,4] .When it does occur, the adrenal glands are the most frequently implicated, typically bilaterally, presenting as primary adrenal insufficiency (PAI) (also known as Addison's disease)[2].

Despite its rarity [PAI reported in 0,4% of APS patients, of which 10-26% in catastrophic APS (CAPS), and APS detected in <0.5% of all Addison's disease patients], its complications can be severe and life-threatening if untreated[2,3,4,5]. The diagnosis may be delayed due to nonspecific symptoms and frequent absence of classical signs, compromising the disease outcomes[4].

Here, we present a case of a postponed APS manifesting by PAI diagnosis in a tertiary Portuguese hospital, in Lisbon, in March 2022. Clinical data were extracted from electronic medical records, and the case description was based on CARE guidelines and checklist[6]. A comprehensive literature search was conducted in PubMed using the terms Antiphospholipid syndrome AND adrenal insufficiency OR Addison's disease OR adrenal involvement OR Adrenal hemorrhage OR adrenal infarction OR adrenal failure, reviewing all the published articles between 1990 and 2025. We aimed

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to synthesize the current literature, highlighting epidemiological and clinical aspects, and thus stressing the differences between our patient and previously reported cases. Lastly, we aimed to raise awareness among clinicians about the relevance of recognizing APS-associated PAI to improve the outcomes of a potentially severe manifestation.

CASE REPORT

A 56-year-old caucasian male with chronic mild thrombocytopenia first documented in 2013, with a nadir of 78,000 x10^6/L [reference range (RR) 150-400,000x10^6/L] in 2014. This had been previously evaluated in an internal medicine follow-up visit and was assumed to be related to alcohol consumption (around 50 g/day). Searching in medical, laboratory and imaging records, no signs of alcoholic stigmas or chronic hepatic disease were found. In 2021, a prolonged activated partial thromboplastin time (aPTT) of 61.3 seconds (RR 23–38 seconds) was found, with a simultaneous thrombocytopenia of 111,000x10^6/L.

In March 2022, he presented to the emergency department with 3 months of intense fatigue, anorexia, and a 20% unintentional weight loss. He denied comorbidities, chronic medication or ongoing alcohol use. On admission, he was hypotensive (blood pressure 100/54 mmHg), afebrile, with no other remarkable findings. Laboratory evaluation revealed normocytic normochromic anemia [Hemoglobin (Hb) 9.9 g/dL], thrombocytopenia (94,000 x10^6/L), prolonged aPTT (76.4 seconds), hyperkalemia (7.11 mmol/L, RR 3.5–5.2), and elevated C-Reactive Protein (CRP 2.25 mg/dL, RR <0.5) and Erythrocyte Sedimentation Rate (ESR 118 mm/h, RR <30). Leucocyte count, serum sodium, renal and liver tests, and urine sediment were normal.

The patient was admitted to the internal medicine department. An extensive diagnostic workup was initiated to exclude malignancy and infectious etiologies. Chest, abdominal, and pelvic computed tomography (CT) scans and transthoracic echocardiography were unremarkable, as were serial blood cultures and tuberculosis test (Interferon Gamma Release Assay negative). A fluorodeoxyglucose positron emission tomography-CT (FDG PET-CT) revealed intense bilateral adrenal uptake with areas of necrosis, predominating on the right (Figure 1A). The Endocrinology department was consulted, and hormonal assessments revealed a low serum cortisol (1.9 µg/dL; RR 6.2-19.4) and a high adrenocorticotropic hormone (ACTH 626.0 pg/ml; RR 7.2-63.3). PAI was assumed, and intravenous hydrocortisone (200 mg/day) was started, leading to clinical (blood pressure, constitutional symptoms) and some laboratory (platelet count 101,000 x10^6/L, CPR 0,72 mg/dL, ESR 93 mm/h) improvement. The main causes for PAI, namely autoimmune adrenalitis (21-hydroxylase antibodies negative), tuberculosis, medications (exclusion of previous steroid therapy) and human immunodeficiency virus infection, were ruled out. The Rheumatology department was consulted for further assessment. Autoimmune workup revealed persistently positive lupus anticoagulant (on two occasions, 12 weeks apart; other aPLs were negative), antinuclear antibodies (ANAs) at a titer of 1:1280 (homogeneous pattern), elevated anti-double-stranded DNA (anti-dsDNA) antibodies (517 IU/mL), and weakly positive anti-nucleosome antibody. C3 and C4 complement fractions were normal. Concerning anemia, there was no hemolytic, blood smear or nutritional changes, and massive blood loss was also excluded. The final diagnosis was SLE and APS overlap with bilateral adrenal, hematological and immunological involvement. Other SLE features, such as cutaneous or articular, were absent both at the time of diagnosis

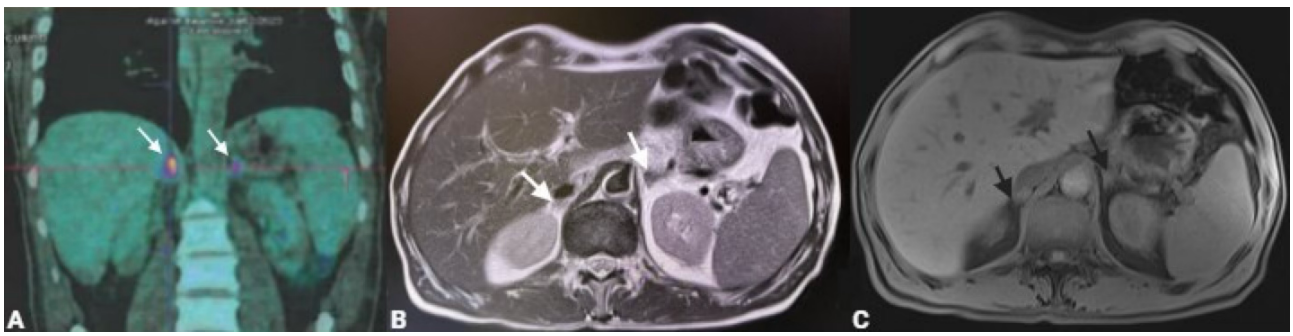

Figure 1. Adrenal involvement radiological evolution. **A:** FDG PET-CT at diagnosis moment, showing intense uptake in both adrenal glands (white arrows); **B:** abdominal MRI (T2-sequence) 3 months after the diagnosis, showing atrophy of both adrenal glands (white arrows); **C:** abdominal MRI (Dixon method) 6 months after the diagnosis, showing almost complete disappearance of both adrenal glands (they supposed to be placed where black arrows are pointing out), comparing to the previous MRI. FDG PET-CT, fluorodeoxyglucose positron emission tomography-computed tomography; MRI, Magnetic resonance imaging.

and in the past, according to the patient's information. Treatment was adjusted accordingly, with the addition of hydroxychloroquine 400 mg/day, fludrocortisone 0.05 mg/day and warfarin 5 mg (scheme adjusted by International Normalized Ratio). Prednisolone PO 60 mg/day was later introduced (hydrocortisone stopped) because of worsening anemia (Hb 7,5 g/dL) and uncomplete platelet response (100,000 x10^6/L) despite initial treatment. On discharge, adrenal function stabilized with complete clinical response and laboratory normalization (Hb 13.2 g/dL, platelets 190,000 x10^6/L, CRP 0.42 mg/dL, ESR 30 mm/h). Magnetic resonance imaging (MRI) scans at 3 and 6-month follow-up visits showed progressive atrophy of the adrenal glands (Figure 1B and 1C), consistent with the natural evolution of hemorrhagic infarction. A timeline graphic describing the case evolution is shown in Figure 2.

DISCUSSION

This case illustrates an uncommon APS case, presenting with PAI secondary to adrenal involvement. Unlike most cases, which present with acute abdominal pain and/or classic biochemical abnormalities, such as hyponatremia or hypoglycemia, our patient developed insidious constitutional symptoms with markedly elevated inflammatory markers, and no prior thrombotic events. These atypical features highlight the heterogeneity of APS-related adrenal involvement and inform clinicians about the possibility of adrenal failure as a first APS manifestation, even in the absence of thrombotic events or obvious triggers.

The association between APS and PAI was first reported in 1988[5]. Narrative reviews in 2003[7] and 2005[5] and systematic reviews in 2018[8] and 2024[3] consolidated its epidemiology, clinical spectrum, and outcomes features. The main findings from published reviews are summarized in Table I. These reviews also raised awareness of adrenal involvement as a direct and potentially life-threatening microvascular APS manifestation, contributing to its inclusion in the most recent American College of Rheumatology (ACR)/European Alliance of Associations for Rheumatology (EULAR) classification criteria[9]. The current work provides a case-based synthesis, emphasizing practical implications for clinicians.

The APS-associated PAI pathophysiology can be

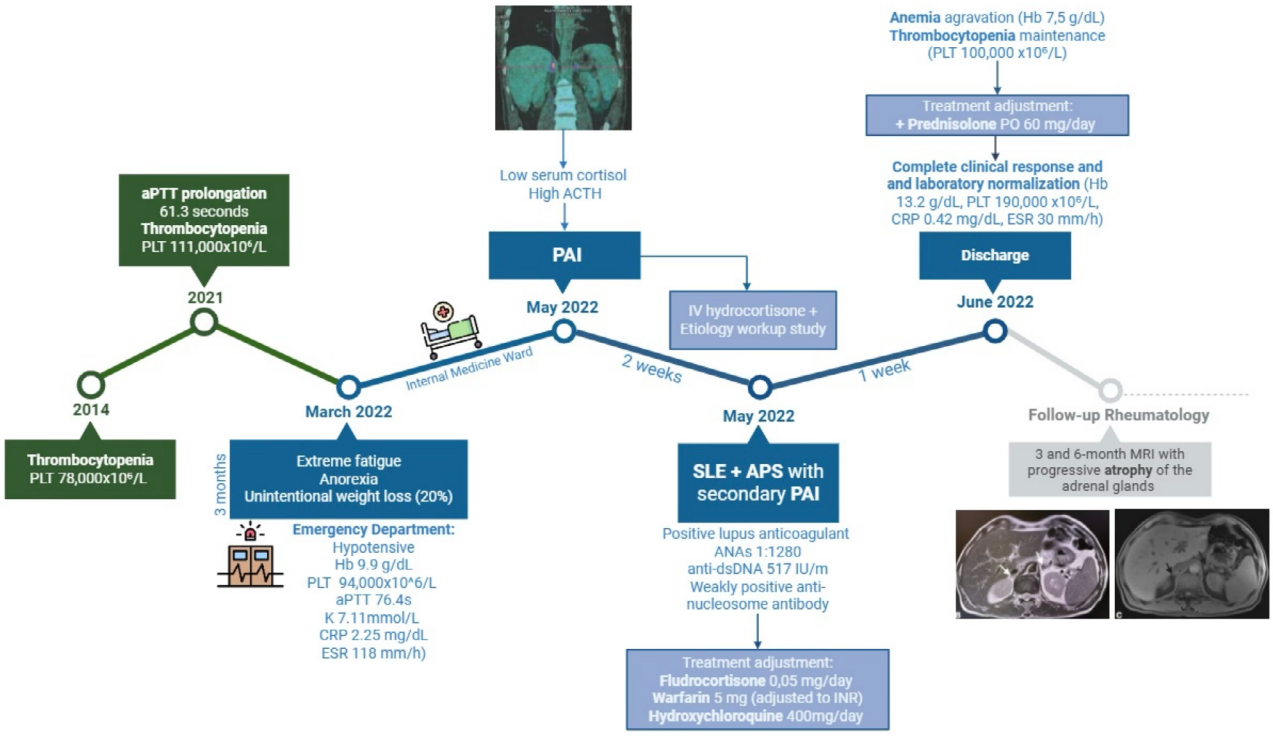

Figure 2. Clinical, laboratory and treatment timeline of the reported case.
PLT, platelets; aPTT, activated partial thromboplastin time; Hb, hemoglobin; K, potassium; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; ACTH, adrenocorticotropic hormone; PAI, primary adrenal insufficiency; IV, intravenous; SLE, systemic lupus erythematosus; APS, antiphospholipid syndrome; ANAs, antinuclear antibodies; anti-dsDNA, anti-double-stranded DNA; INR, International Normalized Ratio; MRI, Magnetic resonance imaging.

TABLE I. Summary of main findings from published reviews on APS-associated PAI

Review (year)	Design (pts included)	Epidemiology	Clinical presentation	Laboratory features	Imaging/ pathology	Key conclusions
Espinosa *et al.* **(2003)**	Multicenter cohort + literature review (86 pts)	Mainly male; middle-aged; often primary APS	Acute abdominal/ flank pain, fever, hypotension	Thrombocytopenia (65%), anemia (47%), prolonged aPTT	Bilateral adrenal hemorrhage/ infarction common	Adrenal involvement is rare but potentially life-threatening; often first manifestation of APS
Presotto *et al.* (2005)	Case report + literature review (39 pts)	Mainly male; most between 30–50 yrs	Abdominal pain is the most frequent, often mimicking a surgical abdomen	Hyponatremia and hyperkalemia frequent	Acute hemorrhage → chronic atrophy	PAI may be a heralding symptom of APS; awareness is crucial for early diagnosis
Lee *et al.* (2019)	Systematic review (111 pts from 47 studies)	Mainly male (male:female ratio 2:1); median age 40s	Abdominal pain (78%), fever (52%), nausea/ vomiting (43%), hypotension (30%)	Hyponatremia (64%), hyperkalemia (55%), cytopenias frequent	CT most used; acute hemorrhage/ infarction followed by atrophy	APS should be suspected in adrenal failure with thrombocytopenia or unexplained prolonged aPTT
Meade-Aguilar *et al.* (2024)	Multicenter cohort + systematic review (36 pts from the cohort + 179 pts from the review)	Mainly male; median age 42	Abdominal pain (70%), fever (60%), hypotension (41%)	Anemia in 77%, thrombocytopenia in 63%	Bilateral involvement in 90%; acute hemorrhage most common	Largest series to date; anemia frequent but etiology unclear; outcomes better with early recognition

explained by both immunological and vascular processes. Recently, aPLs have been shown to target lysobisphosphatidic acid-containing endosomes in adrenal cells, promoting microthrombosis[4] Simultaneously, the unique adrenal glands' vascular anatomy is particularly vulnerable to this hypercoagulability status, because they have a rich arterial supply but single venous drainage through a central vein. The venous stasis caused by microthrombosis leads to a progressive increase in adjacent arterial blood pressure, favoring the development of hemorrhagic infarction[4,5]. This cascade results in irreversible atrophy and adrenal failure (PAI)[1,10]. Although adrenal hemorrhage was initially attributed to anticoagulant therapy of APS patients[5], subsequent observations of hemorrhagic infarction in newly diagnosed APS cases (before anticoagulation introduction) and histopathologic findings confirmed adrenal vein thrombosis and hemorrhage as a direct manifestation of APS[2,5].

Although APS affects predominantly women (82%)[5], adrenal involvement occurs more often in men, especially as a presenting feature, typically in mid-life[3,5,7,8]. Most cases of adrenal insufficiency occur in patients with previously diagnosed APS or thrombotic events. Triggers such as infection, surgery, trauma, postpartum state, vigorous physical exertion, and anticoagulation withdrawal are described in one-third of these cases[3,5,7,8].Lee K. *et al* also assessed PAI in SLE patients without APS, concluding that isolated SLE-related adrenal insufficiency is even rarer and less well-defined than APS-related PAI[8].

Mortality in APS-related adrenal failure remains significant, with reported fatality rates around 16%, mainly due to thrombosis, catastrophic APS, or adrenal crisis[3].

Independent of its cause, PAI typically presents acutely with a variable combination of nonspecific symptoms caused by gluco and/or mineralocorticoid deficiency[8], leading to diagnostic delay and worsened outcomes[11]. The most frequent symptoms are abdominal pain and hypotension, but fever, nausea, vomiting, skin hyperpigmentation, weakness or fatigue, weight loss, and altered mental status can also occur. Laboratory abnormalities commonly found are hyponatremia, hyperkalemia and hypoglycemia[3,5,7,8]. In APS-associated PAI cases, besides PAI symptoms, specific APS symptoms and laboratory abnormalities, such as aPTT prolongation and thrombocytopenia, can also be present. Thrombotic events frequently co-occur, either simultaneously or preceding PAI[3,5,7,8]. Lee K. *et al.* reported that 34% of patients had a history of thrombotic events [notably deep venous thrombosis (DVT) and/or pulmonary embolism (PE)], and 10% had prior obstetric complications at the time of PAI diagnosis in previously unrecognized APS cases[8].

Our case differed by presenting with gradual unspecific fatigue, anorexia, and weight loss associated with elevated inflammatory markers. These symptoms can be "less aggressive" with respect to the tolerance of the patients compared to the most common PAI acute symptoms, such as abdominal pain. On one hand, these highlight the heterogeneity of this condition, challenging the diagnosis and leading to a possibly life-threatening situation. On the other hand, this presentation also misled the initial workup towards infectious or

malignant etiologies, postponing APS diagnosis. Only one other case reported by Kozamernik K. *et al* explicitly documented elevated inflammatory markers[2]. In that case, initial clinical suspicion pointed to pulmonary infection, prompting empirical antibiotics. Adrenal insufficiency was only considered after development of hypotension and hyponatremia associated with no improvement of the symptoms despite treatment. The subsequent workup study confirmed PAI and PE as APS initial manifestations. Additionally, in our case, the absence of previous/simultaneous thrombotic events (contrarily to the case reported by Kozamernik K. *et al*[2]) or associated with some triggering event, could also contribute to APS delayed recognition. However, longstanding thrombocytopenia and prolonged aPTT in our patient may have been unrecognized early markers of APS. Our patient also presented with normocytic and normochromic anemia, noted by Meade-Aguilar J. *et al* as a common laboratory finding (in 77% of patients), though etiology remains unknown[3]. Several mechanisms are possible in SLE/APS patients, namely autoimmune hemolytic anemia, thrombotic microangiopathy, chronic disease anemia (CDA) and coexisting hematological disorders (e.g. bone marrow necrosis and nutritional deficiencies)[12]. There were also some reported cases of massive bilateral adrenal hemorrhage with considerable blood loss to the retroperitoneal space, resulting in acute anemia and hemodynamic instability. Associated with APS, these cases were described only in CAPS patients[13]. Among these etiologies, considering the clinic and laboratory findings, CDA related to the intensive systemic inflammation appeared most likely.

Previous studies have shown that lupus anticoagulant is the most frequently detected aPL, and a significant proportion of patients also met classification criteria for SLE, based on high-titer ANAs and anti-dsDNA positivity[3,5,7,8]. These factors, the male gender and the age of the patient, were the most consistent findings when compared to the previous literature.

PAI is diagnosed by low morning cortisol serum in combination with elevated ACTH[7,10]. Once confirmed, secondary causes should be excluded. Autoimmune adrenalitis is the most common cause in adults, followed by infections (mainly tuberculosis) and sepsis. Rarer causes are genetic disorders, metastasis, lymphomas, infiltrative disorders, bilateral adrenalectomy, and drugs (such as long-term glucocorticoids)[3,8,10,14]. The hemorrhagic or infarction causes of PAI are even rarer, but could be associated, besides APS, with meningococcemia, pseudomonas aeruginosa infection, severe traumas, disseminated intravascular coagulopathy, other coagulopathies, and use of anticoagulants[10]. Imaging (mainly MRI or CT scans) usually demonstrates bilateral adrenal involvement, with hemorrhagic changes in acute settings and atrophic ones in chronic phases[3,5,7,8]. Even in cases with initially unilateral adrenal findings, over half of them progressed to bilateral disease at re-evaluation[3]. In our case, PET-CT was the first chosen modality as cancer was the first diagnosis to rule out, after other unremarkable imaging studies. None of the studies found in literature mentioned the role of PET-CT. The identification of adrenal uptake in our case prompted an endocrinological study, with subsequent PAI diagnosis. The etiology workup study excluded most of the previously mentioned causes, making it more probable its association with APS, considering aPL result, aPTT prolongation and thrombocytopenia. The subsequent MRI scans during follow-up showed the expected atrophic progression after an adrenal hemorrhage, confirming the presumptive diagnosis.

Regardless of its etiology, PAI management requires immediate steroid replacement therapy by hydrocortisone or fludrocortisone[8,10]. Additional treatments may be needed depending on its etiology. In APS-associated PAI, lifelong anticoagulation is essential, and immunosuppressants may be indicated in case of microvascular or non-thrombotic manifestations, such as hematologic manifestations, or in case of overlap with other inflammatory diseases[10,15]. In our patient, hormone replacement and anticoagulation were enough to achieve clinical response, but it was necessary to associate higher doses of glucocorticoid therapy to improve hematological involvement.

In conclusion, adrenal failure is a rare but potentially severe APS manifestation. This case underscores important clinical messages: i) APS-related PAI presentation variability and lack of specificity can extend the time until diagnosis, which may worsen outcomes. ii) Outcomes can be improved by early recognition of this association, which is now facilitated by the recent inclusion of adrenal hemorrhage in ACR/EULAR APS classification criteria[9]. iii) A multidisciplinary approach, early hormonal evaluation, and prompt treatment are also important steps to improve outcomes. iv) clinicians should consider APS in patients with new-onset PAI, even in the absence of thrombotic or obstetric events, especially when imaging reveals hemorrhagic adrenal infarction, and when longstanding cytopenias and prolonged aPTT are present. v) Conversely, rheumatologists should maintain vigilance for adrenal involvement in APS patients presenting with compatible symptoms or biochemical abnormalities, particularly following potential triggers. While the cost-effectiveness of a routine screening for adrenal insufficiency in APS is debated[2], a systematic assessment of symptoms, blood pressure, and basic biochemical parameters (sodium, potassium, glucose) during APS follow-up visits may be a pragmatic approach.

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