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Adrenal hemorrhage and non-ST elevation myocardial infarction: an antiphospholipid syndrome dilemma

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SUMMARY

Antiphospholipid syndrome (APS) can affect different organ systems, including the heart and adrenal glands. Despite being known for its prothrombotic characteristics, APS can have serious bleeding complications. Occasionally, thrombotic and bleeding episodes can present simultaneously in an APS patient. Whenever these events co-occur, resuming anticoagulation becomes a topic of debate. As such, we present the case of a 43-year-old male with triple positive antiphospholipid antibodies, indicating APS, who presented with chest pain. Anticoagulants were switched one month before presentation from warfarin to a direct oral anticoagulant, rivaroxaban. Non-ST elevation myocardial infarction, as well as new-onset left-sided adrenal hemorrhage, were diagnosed. The patient developed adrenal insufficiency; therefore, corticosteroids were administered, and warfarin was resumed to prevent further thrombotic episodes.

Key words: *Antiphospholipid syndrome, thrombosis, bleeding, imaging.*

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INTRODUCTION

Thrombosis is a hallmark of antiphospholipid syndrome (APS) (1) and is a fundamental part of the clinical criteria of the disease (2). Other clinical criteria include various obstetric complications (2). Previously, international classifications aimed at aiding the diagnosis of APS for research purposes included additional clinical manifestations such as livedo reticularis, splinter hemorrhages, neuropathy, and pulmonary hypertension (3).

Interestingly, APS is not only a pro-thrombotic disease but can also have devastating bleeding complications (4). These complications can actually be disease manifestations or disease treatment complications. Major bleeding events have been reported in 10% of APS patients (5). Prominent manifestations of internal bleeding include diffuse alveolar hemorrhage and adrenal insufficiency secondary to adrenal hemorrhage, which may be the result of renal vein thrombosis. The triggers for adrenal hemorrhage in APS patients include surgical procedures, infections, trauma, and warfarin withdrawal (6). Unusually, thrombotic and bleeding events, such as hematoma and large vessel thrombosis, can co-exist in APS patients (7). In this case report, we highlight the co-existence of acute non-ST elevation myocardial infarction (NSTEMI) and bilateral adrenal hemorrhage in an APS patient who was switched from warfarin to a direct oral anticoagulant (DOAC) one month prior to presentation.

CASE REPORT

A 43-year-old man with a past medical history of APS and a heterozygous factor II mutation presented with acute-onset chest pain. Fifteen years before presentation, he was diagnosed with unprovoked deep venous thrombosis. Diagnostics revealed triple positive antiphospholipid antibodies (aPL) and a heterozygous factor II mutation. He was treated with warfarin. One month before presentation, he was switched to ri-

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varoxaban for convenience and to prevent frequent international normalized ratio (INR) checks. Several days later, he developed severe back pain and was diagnosed with a right-sided adrenal hemorrhage. After he stabilized, warfarin was resumed.

Two weeks later, he presented with acute-onset chest pain. He reported that the chest pain woke him up overnight and was refractory to sublingual nitroglycerine. Dyspnea, orthopnea, paroxysmal nocturnal dyspnea, or palpitations did not occur. Vital signs demonstrated mild tachycardia of 107 beats/min, no hypoxia or hypotension. Laboratory investigations were significant for elevated troponin levels (Table I). No electrocardiogram changes were noted. Therefore, he was diagnosed with acute NSTEMI. A computed tomography angiography ruled out aortic dissection and pulmonary embolism but revealed a new left-sided adrenal gland hemorrhage (Figure 1). An ultrasound of the abdomen also showed bilateral adrenal hematomas (Figure 2). Despite this, heparin infusion was initiated for NSTEMI. Cardiac catheterization was deferred due to the bleeding risk. An echocardiogram demonstrated an ejection fraction of 50-54% with a hypokinetic basal-mid inferior wall.

One day after presentation, the patient's blood pressure dropped to 84/57 mmHg. Despite fluid resuscitation, the blood pressure was persistently low. A suspicion for adrenal insufficiency was raised, and corticosteroid replacement was initiated with

Table I - Pertinent laboratory investigations of our case.

Parameter	Value	Normal value
White blood cell count	7.4	4.0-11.0 thou/uL
Hemoglobin	10.3	13.0-17.7 g/dL
Platelet count	181	150-400 thou/uL
Creatinine	0.9	0.7-1.3 mg/dL
Aspartate aminotransferase	92	<34 U/L
Alanine aminotransferase	126	10-49 U/L
Alkaline phosphatase	117	45-128 U/L
Peak troponin	49,145	<54 ng/L
INR	1.6	
ANA	1:40	<1:40
β-2 glycoprotein Ab, IgG	>112	<20 U/mL
β-2 glycoprotein Ab, IgM	14	<20 U/mL
Cardiolipin Ab, IgG	>112	<20 U/mL
Cardiolipin Ab, IgM	9	<20 U/mL
Lupus anticoagulant	Positive	Negative

INR, international normalized ratio; ANA, antinuclear antibodies; Ig, immunoglobulin.

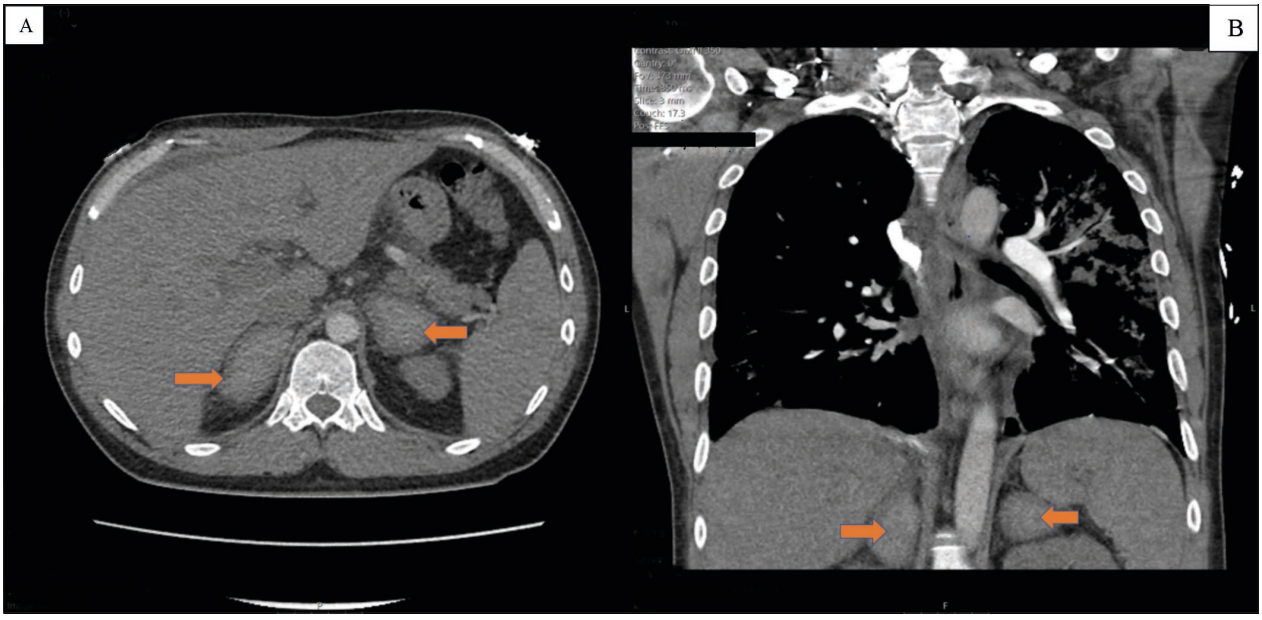

Figure 1 - Computed tomography angiography chest axial view (A) and coronal view, orange arrows show hyperdense, masslike bilateral adrenal glands (B).

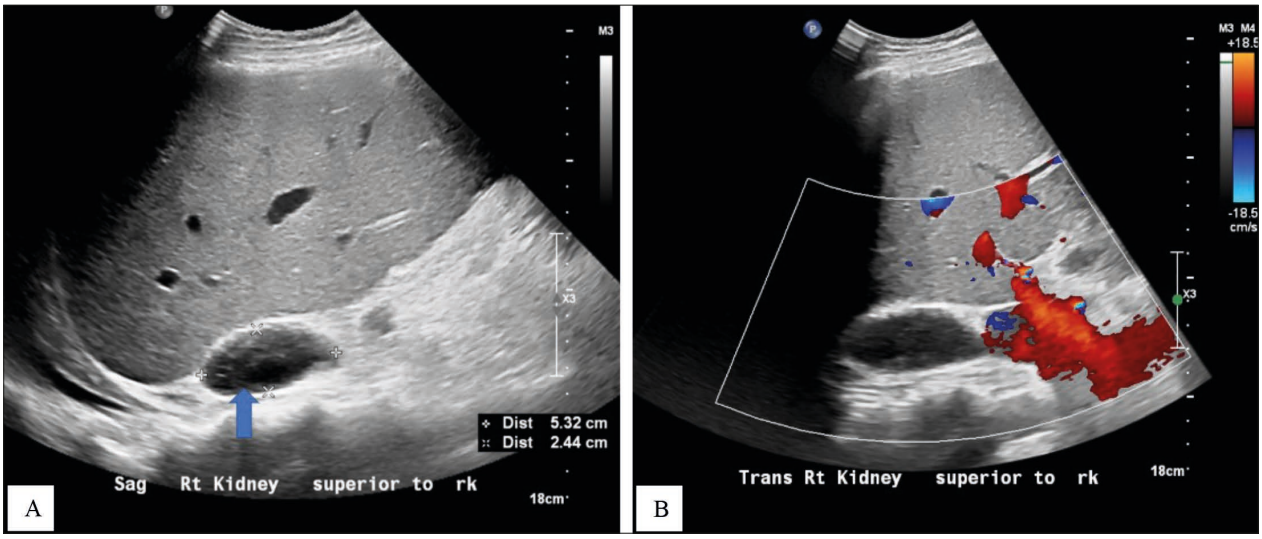

Figure 2 - The abdominal ultrasound with the blue arrow (A) shows a hypoechoic structure at the level of the right adrenal gland with no vascularization on color images (B) and likely corresponding with bilateral adrenal hemorrhage.

hydrocortisone 25 mg three times daily along with fludrocortisone 0.5 mg twice daily. As the blood pressure stabilized, the corticosteroid regimen was later tapered.

Further laboratory investigations were significant for positive antinuclear antibodies, strongly positive antiβ-2 glycoprotein-1, strongly positive lupus anticoagulant, and strongly positive anticardiolipin antibodies, confirming the diagnosis of triple positive APS (Table I). Eventually, warfarin was resumed with no further bleeding complications. Cardiac catheterization was not performed thereafter for loss of follow-up.

DISCUSSION

APS is associated with an increased risk of cardiovascular morbidity and mortality, particularly strokes and coronary artery disease. Several factors can contribute to the likelihood of these outcomes, including elevated levels of low-density lipoprotein cholesterol, increased waist circumference, a sedentary lifestyle, a higher body mass index (BMI), and elevated blood pressure (8). Our patient had a BMI of 34, which may have contributed to his cardiac event.

Myocardial infarction (MI) is a relatively uncommon manifestation of APS. The general prevalence has been reported to be approximately 5.5% (9). It is worth noting that APS can also be associated with clinically silent MI, elevated pulmonary pressure, and coronary atherosclerosis (10). Interestingly, non-thrombotic MI can be a manifestation of APS through a mechanism involving tissue factor activation by inflammatory markers and aPL (11). NSTEMI is less common than ST segment elevation myocardial infarction (STEMI) in APS, with around half the frequency difference (12). Although the isotypes of aPL contributing to STEMI are different from those contributing to NSTEMI, it is still unknown which specific isotypes can increase the risk of NSTEMI (13).

One of the endocrine manifestations of APS is adrenal insufficiency (14). Although the exact mechanism is still to be deciphered, it is thought that aPL can react with organelles in the *zona fasciculata,* leading to microthrombosis and subsequent adrenal hemorrhage (15). Some proposed risk factors include excess anticoagulation or a switch of anticoagulants, especially from warfarin to DOACs, as in our patient (16, 17). Adrenal hemorrhage has been reported in APS patients maintained on warfarin and patients maintained on DOACs (18). Interestingly, adrenal hemorrhage can occur in patients newly initiated on anticoagulation, including warfarin and rivaroxaban (19, 20). In ad-

dition, recurrent thrombosis can still occur while APS patients are on anticoagulation (21). For example, higher-intensity warfarin or the addition of antiplatelet therapy are recommended if thrombosis recurs on standard-intensity warfarin (22). The risk of recurrent thrombosis has been reported to be higher in patients maintained on DOACs than in those maintained on warfarin (23). Warfarin remains the first-line anticoagulation of choice for low- or high-risk APS (24). Alternatively, DOACs may be considered for patients who are already receiving stable anticoagulation with a DOAC, are inadequately anticoagulated with warfarin, are unwilling or unable to undergo INR monitoring, have contraindications or experience serious adverse events due to warfarin (25). Based on a large study population, rivaroxaban is contraindicated in patients with triple positive aPL or those who have experienced an arterial event, such as myocardial infarction (26). Therefore, rivaroxaban was not the initial choice in our case but was implemented based on patient preferences.

Adrenal insufficiency can occur in up to 36% of APS patients (27) and in 13% of catastrophic APS patients (28). Adrenal involvement can be unilateral or bilateral (20, 29), presenting with abdominal pain, hypotension, fever, and vomiting (30). There has been no study that has compared the risk contribution of different aPL profiles to the development of adrenal hemorrhage.

The spontaneous occurrence of both thrombotic and bleeding episodes in APS is unusual and has been limited to a few case reports (Table II) (31-34). No previous case has reported the co-occurrence of acute MI with adrenal hemorrhage complicated by adrenal insufficiency in the setting of APS. The big question that faces the presented case is whether anticoagulation was more harmful than helpful, and vice versa. Certain indications do not warrant long-term anticoagulation in APS patients, including obstetric APS (35), persistently negative aPL (36), and active major bleeding (26). In our case, as both adrenal glands were already affected and there were clinical manifestations of adrenal insufficiency, treatment with long-term anticoagulation along with steroids was initiated to prevent further complications of NSTEMI.

CONCLUSIONS

APS is associated with thrombotic cardiac complications, such as myocardial infarction, unusually NSTEMI. Additionally, APS can be associated with bleeding events such as adrenal hemorrhage. Unusually, simultaneous thrombotic and bleeding events, such

Table II - Literature case reports on the co-occurrence of thrombotic and bleeding events in patients with antiphospholipid syndrome.

Reference	Thrombotic manifestations	Bleeding manifestations	Treatments
Rangel et al. (31)	Distal gangrene Renal microthrombi	Diffuse alveolar hemorrhage	High dose corticosteroids Plasma exchange No anticoagulation
Rodriguez et al. (32)	Brain infarcts	Recurrent epistaxis Hematuria Gastrointestinal bleeding	Corticosteroids Mycophenolate mofetil Low molecular weight heparin Aspirin
Vieregge et al. (33)	Acute thrombotic microangiopathy	Pulmonary hemorrhage	High dose corticosteroids Plasma exchange No anticoagulation
Abdulhai et al. (34)	Extensive inferior vena cava and bilateral common iliac thrombosis	Severe menorrhagia	Corticosteroids IVIG Warfarin
Current case	NSTEMI	Left adrenal hemorrhage	Corticosteroids Warfarin

NSTEMI, non-ST elevation myocardial infarction; IVIG, intravenous immunoglobulin.

as a myocardial infarction and adrenal hemorrhage, can occur. There are various factors that cause such episodes; for instance, a recent bridging between anticoagulants, such as warfarin and rivaroxaban, which is still not recommended for APS patients with an arterial event. The safety of resuming anticoagulation after an adrenal hemorrhage remains a question that needs further research to be answered. Additionally, it is unknown whether a triple positive aPL profile poses an increased risk of the development of simultaneous thrombosis and bleeding.

Contributions
All authors contributed equally.

Conflict of interest
The authors declare no potential conflict of interest.

Patient consent for publication
Verbal consent was obtained from the patient.

Availability of data and materials
Data and materials are available from the corresponding author upon request.

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