Definitive bilateral adrenal failure in antiphospholipid syndrome

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ACTA REUMATOL PORT. 2012;37:76-80

ABSTRACT

Antiphospholipid antibodies may signal the formation of vascular thrombi in the Antiphospholipid syndrome (APS). A rare complication of APS is adrenal insufficiency resulting from venous thrombus followed by hemorrhagic infarction. We describe the case of a 42--year-old male with APS presenting with vomiting and abdominal pain. Through laboratory and imaging diagnostic exams, we confirmed the diagnosis of bilateral adrenal hemorrhage and subsequent adrenal failure. We also conducted a search of literature associating bilateral adrenal thrombosis to APS, and describe the two pathological mechanisms most often cited to explain this phenomenon. To our knowledge, this is the first Portuguese case of adrenal insufficiency due to APS-associated bilateral adrenal hemorrhage.

Keywords: Antiphospholipid Syndrome; Adrenal Failure; Adrenal Insufficiency; Addison's Disease.

INTRODUCTION

Primary adrenal insufficiency (AI) is an uncommon condition caused by destruction of the adrenal cortex, resulting in a deficiency in glucocorticoids and mineralocorticoids[1]. It results primarily from three pathogeneses: autoimmune adrenalitis (80%), infectious diseases (15%) and, unusual disorders, such as APS (5%)[2].

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In APS, a family of auto-antibodies promotes thromboembolic events[3]. A diagnosis of APS is based on past clinical episodes of hypercoagulability and on laboratorial evidence of antiphospholipid antibodies detected on two or more occasions, at least twelve weeks apart[4]. Research has identified a link between primary AI and APS. Hypoadrenalism has been reported in 0.4% of APS cases and may be the first manifestation of APS[1,5].

Here we describe a case of AI due to bilateral adrenal gland hemorrhaging in a male patient with primary APS. We review the literature of past clinical cases of adrenal failure in patients with APS and provide two possible pathogenic mechanisms for this phenomenon.

CLINICAL CASE

A 42-year-old male with APS was admitted to the emergency room (ER) for sudden onset abdominal pain and fainting. The patient had been diagnosed two years earlier with APS after recurrent episodes of deep vein thrombosis in the lower extremities and was being treated with enoxaparin (40 mg/ /day). In the preceding week, the patient's medication was switched from warfarin to enoxaparin. According to the patient, this was done in response to a clinical worsening of a varicose ulcer in the right lower extremity. In the ER, the patient was observed by the surgical staff. All diagnostic exams were inconclusive for acute abdominal disease. The patient was discharged and prescribed butylscopolamine and domperidone.

On his way home, the patient began vomiting. He returned to the hospital and was found to be hypertensive (170/100 mmHg) and tachypneic. Abdominal distention and tenderness were observed. A varicose ulcer was noted in the lower right leg. Laboratory tests revealed thrombocytopenia and slightly prolonged activated partial thromboplastin time (Table I). Abdominal

TABLE I. LABORATORY RESULTS FOR A PATIENT WITH APS COMPLICATED BY BILATERAL ADRENAL HEMORRHAGING

	On admission	At diagnosis	Reference values
Hematological			
Hemoglobin	14.6	10.8	14.0-18.0 g/dL
Mean corpuscular volume	83.4	81.0	80.0-95.0 fL
White blood cell count	7.6	3.70	4.50-11.50x10^9/L
Plateletes	91.0	65.0	150.0-450.0x10^9/L
Activated partial thromboplastin time	59.2	81.2	26.0-36.0 sec
International normalized ratio	1.25	1.36	
Fibrinogen	4.9	7.0	2.0-4.0 g/L
Protrombin time	14.8	16.1	9.9-12.8 sec
Protein C		73	70.0-140.0%
Protein S		33.7	60.0-130.0%
Biochemical			
Glycemia	121	75	74-106 mg/dL
Sodium	142	129	136-145 mEg/L
Potassium	3.5	3.2	3.5-4.5 mEq/L
Urea	31	35	14-42 mg/dL
Creatinine	0.9	1.0	0.6-1.3 mg/dL
Amylase	28		8-53 IU/L
Lipase	23		6-51 IU/L
C-reactive protein	0.67	10.46	<0.50 mg/dL
Endocrine			
ACTH		1157.0	4.7-48.8 pg/mL
Renin		85.4	4.4-46.1 uIU/mL
Aldosterone		<20.0	41.0-323.0 pg/mL
Cortisol		1.3	4.3-22.4 ug/dL
Cortisol (urine)		9.0	28-214 ug/24hr
Adrenalin		35.3	0.0-100.0 pg/mL
Noradrenalin		860.4	0.0-600.0 pg/mL
Thyroid-stimulating hormone		4.120	0.350-5.50 mIU/L
Serological			
Anticardiolipin antibodies		Ig G >280 U/mL Ig M <2.0 U/mL	Negative
Lupus anticoagulant antibodies		Positive	Negative
Anti- 2 glycoprotein I antibodies		Ig G 228 Ig M 21	0.0-10.0 U/mL
Antinuclear antibodies		Negative	Negative
Antiplatelet antibodies		Positive	Negative
Antibodies adrenal cortex		Negative	Negative
Anti-dsDNA		Negative	Negative
Coombs test		Negative	Negative
Other			
Treponema pallidum		Negative	Negative

angiogram did not reveal thrombotic or hemorrhagic lesions. The patient was medicated with pethidine and admitted.

Several hours later, vomiting persisted and the patient complained of abdominal pain localized to the left upper quadrant. Seventy-two hours after admission, he began referring acute lumbar pain. He was hypotensive (BP 96/55 mmHg) and febrile (38ºC) with skin pallor and anemic conjunctivae. Blood work showed he had normocytic, normochromic anemia, thrombocytopenia, prolonged activated partial thromboplastin time, hyponatremia, and an elevated C-reactive protein (Table I). A renal ultrasound revealed a nodular, heterogeneous, 6-centimeter mass in the upper extremity of the left kidney. Because of the possibility of an acute abdominal complication, blood and urinary cultures were ordered, and empirical antibiotic treatment with ceftriaxone and gentamicin was initiated.

An abdominal CT scan revealed an extensive left adrenal gland hematoma and a smaller right adrenal gland hematoma (Figure 1).

Primary AI was confirmed by the presence of low serum cortisol levels (1.3 µg/dL after 30 minutes and 1.4 µg/dL after 60 minutes) after an adrenocorticotropic hormone (ACTH) stimulation test with 250 µg of ACTH. Was also observed a low urinary cortisol level, an undetectable aldosterone reading, and high ACTH and renin levels (Table I). Autoimmune serology confirmed the presence of anticardiolipin and anti- 2 glycoprotein I antibodies and negative anti-adrenal cortex antibodies.

Treatment began with intravenous hydrocortisone 100 mg, followed up with daily oral hydrocortisone medication 30 mg. Antibiotic treatment was suspended. Adjustable doses of warfarin were administered to maintain an international normalized ratio between 2.5 and 3.

Since being discharged, the patient has continued treatment and maintained a stable condition. Subsequent abdominal CT scans have revealed a slight reduction of the bilateral hematoma. Blood work has revealed that after six months, cortisol insufficiency remains, indicating irreversible adrenal damage.

DISCUSSION

Still unknown is how APS, a thrombosis-favoring pathology, can lead to adrenal hemorrhaging. Two possible pathogenic mechanisms have been proposed. The first, and most often cited, refers to the unique vascularization of the adrenal gland. The adrenal gland has a rich arterial supply, yet limited venous drainage. Blood is provided by three main arteries that branch out to form smaller arteries. These smaller arteries penetrate the surface of the gland and run along the zona glomerulosa and zona fasciculata. At the zona reticularis, the innermost region of the adrenal cortex, a capillary plexus is formed that drains into the medullary sinusoid and eventually into the large central vein[6].

The transition from artery to capillary plexus is abrupt, functioning as a "vascular dam" that causes the accumulation and stasis of blood[1,7-9]. Additionally, the musculature of the central vein consists of eccentric, longitudinal bundles that when contracted form pockets of turbulence and local stasis[1]. These two factors favor a primary venous thrombotic event, leading to increased localized arterial blood pressure, followed by post-infarction hemorrhaging[7].

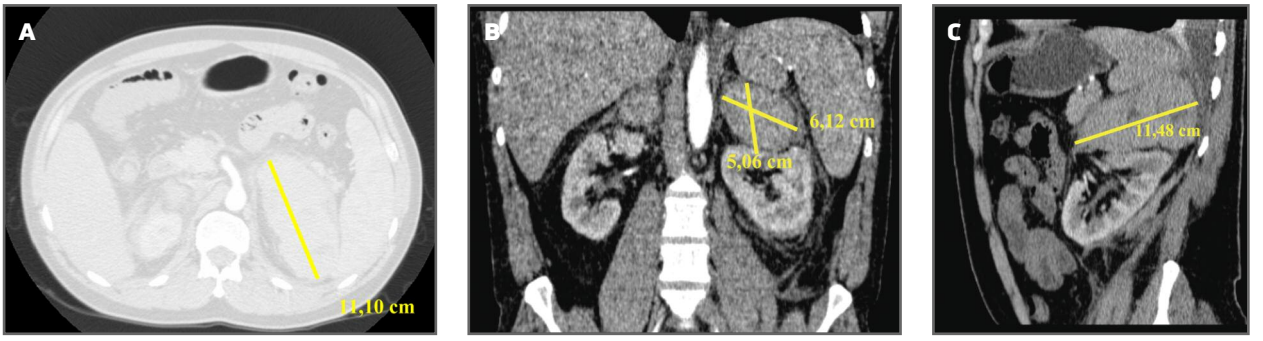

Figure 1. Both the right and left adrenal hematomas can be observed in the A) axial, B) coronal, and C) sagittal images. The left adrenal hematoma is clearly the larger of the two.

The second possible pathogenic mechanism refers to the cellular characteristics of the zona fasciculata, the central region of the adrenal cortex. The cells in this region are rich in cholesterol due to a high number of cholesterol trafficking organelles. The membranes of these organelles contain lysobiphosphatidic acid, a target of anti-phospholipid antibodies. The second proposed pathogenic mechanism suggests that these antibodies, reacting locally, cause the accumulation of cholesterol within the cell, leading to cell death and the release of lysosomal proteinases. The proteinases activate endothelial cells, thus favoring coagulation and causing microthrombosis[10].

A review by Espinosa et al. of 86 cases of AI in patients with APS noted a precipitating factor in 43% of the cases. These factors included surgical procedures, infections, trauma, warfarin withdrawal, and inadequate anticoagulation[5,7]. In the present case, we speculate that the precipitating factor was warfarin withdrawal. As described earlier, a week prior to this incident, the patient suspended warfarin medication and began enoxaparin. As demonstrated by Palareti and Legnani, warfarin withdrawal results in a "rebound phenomenon", creating a hypercoagulant condition[11]. We believe that an initial venous thrombotic event occurred, after warfarin withdrawal, followed by hemorrhaging in the adrenal cortex.

The primary symptom manifestations of AI, as listed by Garcia et al., do not exclusively suggest AI. In 66% of cases, abdominal pain localized to the lumbar, epigastric, umbilical, and pericardial region is observed. In 50% of cases, continuing or intermittent fever is observed. In 12% of cases, altered mental status, lethargy, and asthenia is observed, and in 19% of cases hypotension is observed[8]. Other symptoms include vomiting, weight loss, ileus, and diarrhea[12]. Because its symptoms are common to other pathologies, AI is difficult to diagnose, a difficulty worsened by the rarity of bilateral adrenal hemorrhaging[7]. Adrenal failure should be suspected in all patients with APS who complain of abdominal symptoms. All patients with bilateral adrenal hemorrhaging should be screened for antiphospholipid antibodies[5].

Diagnosis of AI resulting from adrenal hemorrhaging requires suggestive clinical symptoms, radiological images and hormonal evaluation. Formerly, a majority of bilateral adrenal hemorrhage cases were diagnosed post-mortem[8,9]. Today, abdominal CT has become the preferred method to visualize the adrenal gland[13]. The case illustrated in this paper demonstrates how an initially normal abdominal CT scan should not exclude adrenal hemorrhaging. Abdominal CT scans performed in the earlier phases of clinical cases may not reveal abnormalities. CT scans should be repeated to document morphological changes in cases where symptoms persist[9].

Routine laboratory exams may reveal abnormalities typical of AI due to bilateral hemorrhaging, including hyponatremia, hyperkaliemia, anemia, and prolonged activated partial thromboplastin time[13]. However, adrenal failure can be confirmed only through hormonal evaluation. Acute AI is detected by measuring levels of the stimulatory hormones, ACTH and renin, and of cortisol and aldosterone, which are produced by the gland in response to stimulatory hormones. Stable or elevated ACTH and renin levels, accompanied by reduced cortisol and aldosterone values, as seen in our patient, suggest primary adrenal failure. Since bilateral hemorrhaging of the adrenal glands may lead to irreversible damage and chronic adrenal failure, it is important to assess long-term adrenal function[14]. Chronic AI is detected by administering ACTH and taking subsequent measurements of plasma cortisol. Cortisol levels below 18 µg/dL suggest chronic failure[15]. Sixty minutes after adrenal stimulation, we recorded a cortisol level of 1.4 µg/dL in our patient.

Based on initial and subsequent blood work and abdominal CT imaging, we conclude that our patient has chronic, irreversible primary adrenal failure due to bilateral adrenal hemorrhaging.

Recommended medication includes hormonal replacement with hydrocortisone and fludrocortisone, as well as anticoagulation therapy to prevent future thrombotic events[8,14,16]. Six months after the initial event, the patient continued to register undetectable levels of plasma cortisol. One year later, the patient remains on steroid replacement.

Bilateral adrenal hemorrhaging is a rare complication of APS that frequently leads to AI. Diagnosis of AI is complicated by the overlap of its symptoms with that of other pathologies. However, prompt diagnosis of AI is needed to avoid serious complications, including death.

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XXXVIII CONGRESO NACIONAL DE LA SER

Saragoça, Espanha
16 a 18 Maio 2012