

Bilateral Adrenal Hemorrhage in a Patient with Antiphospholipid Syndrome Following Reversal of Warfarin-induced Over-anticoagulation

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Antiphospholipid syndrome (APS) is an autoimmune disease characterized by venous and arterial thrombosis in the presence of persistent laboratory evidence of antiphospholipid antibodies (aPL). A rare clinical manifestation of APS is bilateral adrenal hemorrhage (BAH), which is potentially life threatening [1]. The detection of BAH is a considerable diagnostic challenge. We present a case study and summarize our experience in the diagnosis and treatment of a rare case of BAH in a woman with known APS. We explain the pathogenesis and suggest a potential laboratory predictor for similar patients.

PATIENT DESCRIPTION

A 60-year-old woman presented to the Emergency Department (ED) in November 2019 with anorexia and general weakness. Her medical history included triple positive APS with several previous events of pulmonary emboli (PE) and deep vein thromboses (DVT), for which she was treated with warfarin at dose titrated to achieve a target international

normalized ratio (INR) between 2.5 and 3.5. Some of the previous thrombotic events occurred while she was receiving anticoagulant therapy. In addition, she presented with hypertension and had undergone unilateral nephrectomy following childhood trauma.

Two weeks prior to arrival she presented with bleeding hemorrhoids, and 6 days prior to arrival the patient was hospitalized with flank and epigastric pain accompanied by generalized weakness. Laboratory results showed hemoglobin 8.0 g/dl and INR 6.3. Because of suspected massive lower gastrointestinal bleeding, warfarin was discontinued. Intravenous (IV) vitamin K 5 mg and one unit blood transfusion were administered. Subcutaneous low-molecular weight heparin (LMWH) was initiated. She was discharged with a recommendation to re-initiate warfarin in accordance with INR monitoring and to complete an ambulatory gastroscopy and colonoscopy.

Three days after discharge, she was admitted to our hospital. On arrival, recumbent blood pressure was 121/66, heart rate was 79 beats per minute (bpm). Physical exam revealed epigastric tenderness. Chest X-ray, electrocardiogram and urine analysis were normal. Laboratory results showed Na 120 mmol/L, K 4.1 mmol/L, urea 9.9 mmol/L, creatinine 2.47 mg/dl (creatinine was 0.96 mg/dl at prior discharge), hemoglobin 10.1 g/dl,

platelet count $119 \times 10^9/L$, INR 2.11, and C-reactive protein of 23 g/dl.

Despite IV fluids (0.9% saline) her blood pressure dropped. Septic shock was suspected. Total body computed tomography (CT) scan was performed with findings compatible with BAH. With the highly suspected diagnosis of acute adrenal insufficiency (AI), treatment was initiated with high dose IV hydrocortisone and she was admitted to the intensive care unit. Laboratory testing taken before the initiation of the steroid therapy showed ACTH 103 pmol/L (normal range 2.2–13.3 pmol/L at 8 a.m.) and random serum cortisol < 13 nmol/L (normal range 85–275 nmol/L at 4 p.m.) confirming the diagnosis of acute primary AI. Her blood pressure rapidly improved and she underwent tapering down of oral corticosteroids and was discharged with recommendation to further taper-down oral prednisone until reaching 5 mg while concomitantly starting 0.1 mg of fludrocortisone.

Three months after discharge, the patient returned to the ED having stopped oral mineralocorticoid treatment on her own accord. Blood pressure was 126/85, heart rate was 87 bpm and Na was 131 mmol/L. Abdominal CT was repeated. The scan showed resolution of the BAH. Nonetheless, adrenal function remained abnormal as shown by clinical and laboratory manifestations. As a result, she was advised to continue prednisone and fludro-

cortisone. Her clinical condition stabilized following re-initiation of mineralocorticoid therapy. She continued under close follow-up with an endocrinologist and a hematologist and continued to receive subcutaneous LMWH. She remained reluctant to switch back to warfarin.

COMMENT

We report on a patient with APS presenting with acute AI and BAH in the context of warfarin overtreatment necessitating its discontinuation, antidote therapy with vitamin K, and switch to an alternative therapy. The occurrence of BAH in our patient may be related to the APS itself, the over-anticoagulation (INR of 6.3, 3 days prior to diagnosis), or to the rapid correction of coagulation function with IV vitamin K, despite the initiation of LMWH when warfarin was discontinued.

In 2020 Lee et al. [1], published a systematic review of 105 cases with AI associated with autoimmune diseases including either APS or systemic lupus erythematosus (SLE). They found most cases with AI already had an established diagnosis of the underlying autoimmune disease; however, there was a delay in

diagnosis. Thus, they concluded that AI should be considered as a potential diagnosis in patients with APS or SLE even with no specific features. Hyponatremia, which played an important part in the diagnosis of BAH in our patient, was observed in 53/68 (77.9%) of the cases in which sodium level was reported.

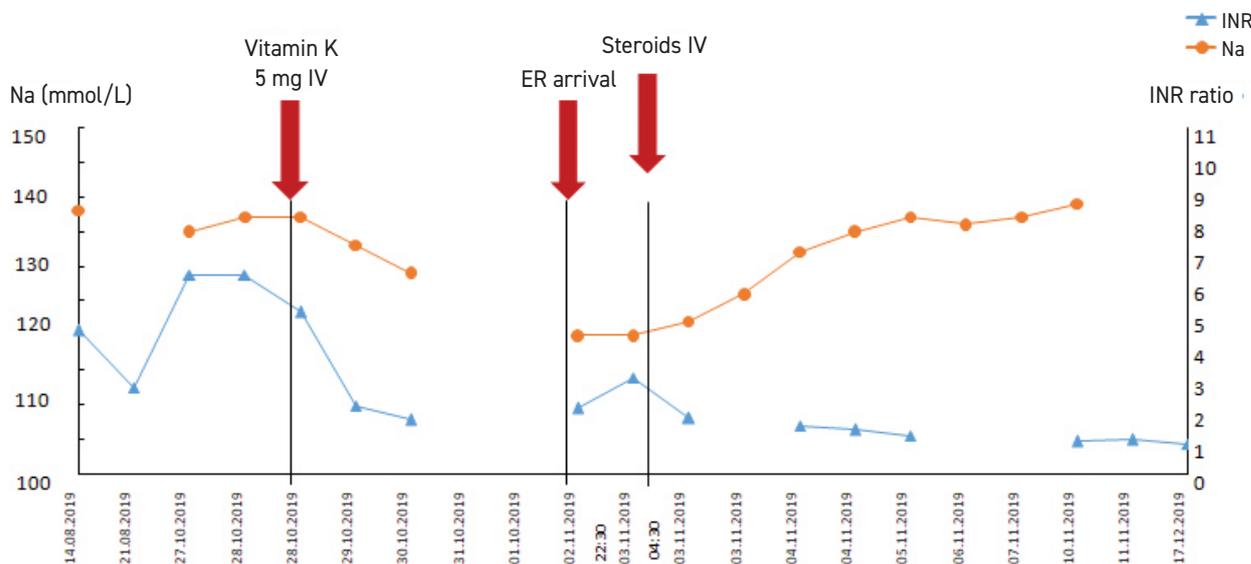
We hypothesize that the abrupt discontinuation of warfarin and administration of a high dose IV vitamin K in a patient with significant hypercoagulable state could have sufficiently disrupted her coagulation system, with subsequent formation of adrenal arteries thrombosis, which were observed on CT scan [1]. Of note, the patient was positive for the three aPL antibodies: anticardiolipin antibodies and anti-beta2-glycoprotein-I antibodies with a titer of over 160 U/ml, positive lupus anticoagulant test, and ANA negative [1]. Spontaneous adrenal bleeding following adrenal microvessel ischemia appears to be the common accepted mechanism in these patients [1]. Specifically in our patient, adrenal ischemia may have been triggered by vitamin K treatment administered due to elevated INR, with subsequent hemorrhage following re-initiation of anticoagulation. Alternatively, sponta-

neous adrenal bleeding due to over-anticoagulation on initial presentation caused AI.

Our patient had lower gastrointestinal hemorrhage with hemoglobin of 8 g/dl and INR of 6.3. Thus, there was a therapeutic dilemma in managing bleeding and reversing over-anticoagulation in our APS patient: Weighing the risk of massive bleeding vs. thrombosis, especially in an aPL triple positive patient. Warfarin was discontinued and changed to LMWH, and IV vitamin K was administered to reverse the warfarin effect. According to clinical guidelines [2], an INR of 4.5–10 requires discontinuation of warfarin with consideration of oral or IV vitamin K depending on the patient's hemodynamic status [2].

Our patient had a hemoglobin level of 8.0 g/dl and bleeding hemorrhoid. She received 5 mg IV vitamin K. As shown in Figure 1, the patient developed hyponatremia (130 mmol/L at discharge) following vitamin K administration, which may have been the first sign of AI. Sodium concentration only normalized following the initiation of steroids [Figure 1]. Hyponatremia is a known sign in Addison's disease [3]. Therefore, it is possible that

Figure 1. Serum sodium and international normalized ratio (INR)



BAH occurred after warfarin reversal and the hyponatremia was the first manifestation of AI.

The diagnosis of acute AI is challenging. Symptoms are non-specific [4]. We observed a correlation between anticoagulation status and hyponatremia. In 2017, Saevik et al. [3] published a retrospective audit of patient records with the aim of identifying biochemical markers for early diagnosis of Addison's disease. Hyponatremia occurred in 207/247 patients (84%). The authors concluded that the most consistent biochemical finding of untreated Addison's disease was hyponatremia independent of the magnitude of glucocorticoid deficiency.

Previous cases reported BAH in patients with APS without anticoagulation. In some BAH was the first presentation of APS. Percik and colleagues [4] showed an increase in AI cases following immunotherapy. Ramon and co-authors [5] found that BAH was the first manifestation of APS in 5 of 16 patients. Almost half of the patients were receiving anticoagulant therapy at the time of the BAH. The BAH was elicited in none of these patients during the reversal of anticoagulation therapy.

We identified one follow-up review published regarding the long-term prognosis of BAH patients [5]. A follow-up CT revealed bilateral adrenal atrophy in 10/16 patients, most of whom had no adrenal response to a synacthen test. In our patient, despite evidence of hemato-ma-absorption on CT, adrenal function failed to recover 3 months following the diagnosis of AI, as witnessed by clinical deterioration following discontinuation of mineralocorticoid treatment.

CONCLUSIONS

BAH can be a manifestation of APS itself, as well as over-anticoagulation or its withdrawal. In this case low sodium blood concentration may have been the earliest manifestation of AI. Our report may raise clinical suspicion in any case of new onset hyponatremia in an APS patient or under the circumstances surrounding drastic changes in anticoagulation therapy. Reversibility of BAH may not be association with normalization of adrenal function. The availability and involvement of a multidisciplinary team including an endocrinologist, hematologist, rheumatologist, and intensive care specialist in the internal medicine de-

partment was essential to the integration of the different aspects in the successful management of this patient.

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I find that the harder I work the more luck I seem to have.

Thomas Jefferson (1743-1826), third president of the United States

A grain of poetry suffices to season a century.

José Martí (1853-1895), Cuban poet, philosopher, essayist, journalist, translator, professor, and publisher

Capsule

Making sense of TCR-pMHC topology

Most T cells use a T cell receptor (TCR) that recognizes major histocompatibility complex molecules bound to peptides (pMHCs) derived from both self- antigens and foreign antigens. Although there is great variability in the interface because of the diversity of both partners, this interaction displays a canonical docking topology for reasons that remain contested. **Zareie** and colleagues tested an assortment of both canonical and reversed-polarity TCRs that were all specific for the same cognate

pMHC-I bearing a peptide derived from influenza A virus (IAV). The authors determined that docking topology was the primary driver of in vivo T cell activation and recruitment when mice were infected with IAV. The canonical topology was required for the formation of a functional signaling complex, suggesting that T cell signaling constraints dictate how TCR and pMHC meet.

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