

## CLINICAL VIGNETTE

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# Bilateral Adrenal Hemorrhage in the Setting of Antiphospholipid Syndrome

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### Case Presentation

A 48-year-old male presented with right sided abdominal and back pain. He was admitted to this hospital one month prior for bilateral pulmonary emboli. He had left lower extremity thrombosis, with significant clot burden and right heart strain on echocardiogram. He was discharged on apixaban. The patient reported a fever to 101.4F one day prior to presentation and constipation for five days. Exam was notable for mild tachycardia and a benign abdominal exam. CT scan of the abdomen with contrast revealed mildly dilated loops of small bowel as well as swelling and hypoenhancement of the left and right bilateral adrenal glands with associated periadrenal mesenteric stranding. MRI of the abdomen with gadolinium confirmed the presence of large right and small left adrenal hemorrhage. The patient's apixaban was discontinued and an IVC filter was placed. On further evaluation, the patient had baseline elevated partial thromboplastin time. He was subsequently found to have markedly elevated beta-2-glycoprotein, a positive Dilute Russell Viper Venom Time (DRVVT), and elevated cardiolipin antibody. The diagnosis of Anti-Phospholipid Antibody Syndrome was made and he was started on enoxaparin. Though the patient's cortisol and ACTH were within normal limits, physiologic hydrocortisone replacement therapy was started due to concern for worsening of adrenal hemorrhage in the setting of resumption of anticoagulation therapy. Aldosterone level was low and he was initiated on fludrocortisone. The patient did well and was bridged to and eventually discharged on warfarin.

### Discussion

Bilateral adrenal hemorrhage (BAH), excluding Waterhouse-Friderichsen syndrome (adrenal hemorrhage secondary to disseminated meningococcal disease), is rare. It is generally not associated with bleeding at other sites, although some cases of BAH associated with retroperitoneal hemorrhage have been described. Prior to the advent of CT imaging, most cases were discovered at autopsy, with reported incidence of 1.1% in adults, based on a 1978 autopsy series of 2000 patients. This study, which included a literature review as well as an autopsy series, BAH was associated with co-morbid illnesses including sepsis, heart failure, and extensive burns as well as use of anticoagulation.<sup>1</sup>

Antiphospholipid syndrome is defined by 1) the presence of an antiphospholipid antibody (i.e. anticardiolipin antibody, anti-beta2-glycoprotein antibody, abnormal dilute Russell viper

venom time) and 2) history of arterial or venous thromboembolism as well as adverse pregnancy outcome. There was no mention of antiphospholipid syndrome (APS) in the 1978 study, but this may be because APS was not well characterized until the 1980s. Since 1988, a number of case reports of Addison's syndrome in APS patients have been published<sup>2</sup> and adrenal insufficiency has been reported in 0.4% of APS cases.<sup>3</sup>

Espinosa literature search documented APS with adrenal involvement in 86 patients. Fifty five percent of the patients were male with a mean age of 43. Seventy one percent had primary APS, 24% were diagnosed with SLE or "SLE-like syndrome" (discoid or drug-induced lupus), and 2% had paraneoplastic APS. Thirty six percent presented with adrenal insufficiency as first clinical manifestation. Most patients (79%) presented with acute symptoms, including 33% with catastrophic APS. Fourteen percent presented with chronic adrenal insufficiency, with no time course reported in the remainder. Symptoms included abdominal pain (55%), hypotension (54%), fever (40%), nausea or vomiting (31%), weakness/malaise (31%), lethargy/confusion (19%), weight loss (13%), skin hyperpigmentation (10%), ileus 6%), diarrhea (4%), renal insufficiency (14%). Labs most frequently showed hyponatremia and/or hyperkalemia (85%), thrombocytopenia (62%), and hemolytic anemia (48%). Lupus anticoagulant was found in 97% of patients, anticardiolipin antibodies in 95% of patients; and both were positive in 89% of patients (anti-beta2-glycoprotein antibodies not reported). CT or MRI was performed on 69 of the patients; 67% showed some degree of adrenal hemorrhage (either alone or with adrenal infarction) with another 23% showing adrenal abnormalities ranging from infarction alone, enlargement, mass, or necrosis; adrenal involvement was bilateral in 77% of patients. Of the 22 patients with histopathology for study; 55% had hemorrhagic infarction with vessel thrombosis and 27% had adrenal hemorrhage alone; another 14% had adrenal infarction alone or normal appearing adrenals. There was no evidence of vasculitis in any of the cases.<sup>2</sup>

Pathogenesis of BAH in APS is unclear, but two mechanisms have been proposed. The first is secondary hemorrhage from adrenal vein thrombosis. The adrenals have high risk of hemorrhage due to their unique vascular supply, with three arteries that divide into 50-60 branches with an abrupt transition to a capillary plexus forming a "vascular dam". The plexus is then drained by medullary sinusoids into a single central vein.

Additionally, the musculature of the adrenal vein is longitudinal rather than concentric, which has been suggested could lead to pockets of stasis and turbulence and predispose to thrombus formation. The second presumed mechanism is hemorrhage without evidence of thrombus, which has been seen in the setting of recent surgery or anticoagulant therapy.<sup>2</sup> Interestingly, the Xarli study, found BAH in the setting of anticoagulation typically developed early in the course of anticoagulation, between the 3rd and 18th days.<sup>1</sup>

Forty-three percent of patients in the Espinosa study had precipitating stressors ranging from major surgery (14%), infection (13%), post-partum (3%), trauma (5%), biopsy (2%), to vigorous exercise (1 patient).<sup>2</sup> Xarli's study also noted an association with states of increased "stress" such as infection, heart failure, and severe burns. The presence of intense stimulation of endogenous ACTH (perhaps leading to increased adrenal blood flow) during these episodes of stress could be a contributing factor to adrenal hemorrhage based on animal studies that showed administration of endotoxin to rabbits would induce adrenal gland hemorrhage only with pre-treatment with ACTH.<sup>1</sup>

Unfortunately, recognition of BAH can be delayed as the symptoms can be non-specific and lab abnormalities can be mild; especially in presence of co-morbidities. Once recognized, patients with adrenal insufficiency need to be treated with steroids. However, if shock has developed, high dose steroids may not be sufficient as even transient hypotension can worsen underlying co-morbidities and lead to decompensation.<sup>4</sup>

In patients with known thromboembolism, management of anticoagulation poses further challenges. In a case report by Aldajani, a patient with APS and h/o DVT/PE six months prior on warfarin, was found to have BAH. Initially, anticoagulation was held and patient was started on ASA 81mg daily with worsening of hemorrhage on repeat imaging. Given concern that hemorrhage was secondary to venous thrombosis, anticoagulation was carefully restarted with interval improvement on imaging. Their conclusion was that patients with APS and BAH should be immediately treated with anticoagulation to avoid further complications.<sup>3</sup>

### **Summary**

Our 48-year-old male with newly diagnosed PE/DVT and undiagnosed APS presented with BAH with initiation of anticoagulation. In many ways, patient's presentation fits the typical presentation with the recent stress of a PE/DVT and initiation of anticoagulation a week prior to diagnosis of BAH. Patient was very fortunate that his BAH was diagnosed before development of biochemical adrenal insufficiency. It remains unclear if patient's abdominal pain was secondary to adrenal insufficiency or BAH or from his PE or ileus/constipation. He subsequently improved with careful anticoagulation and was empirically treated with steroids given known hemorrhage with re-initiation of anticoagulation. On follow-up, patient had intact adrenal function and has been advised to taper off steroids. He

continues on anticoagulation for APS and was found to have secondary APS with diagnosis of SLE.

### **REFERENCES**

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