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Bilateral Adrenal Hemorrhage in a Patient with Antiphospholipid Syndrome

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INTRODUCTION

Bilateral adrenal hemorrhage is relatively uncommon, with a reported incidence in the United States of 0.3-1.8% in hospital post-mortems[1].Clinical manifestations of adrenal hemorrhage are widely variable, making diagnosis a challenge. Left undiagnosed and untreated, bilateral adrenal hemorrhage may lead to cardiovascular collapse and/or death. Here we present a rare case of bilateral adrenal hemorrhage in a patient with antiphospholipid syndrome; the aim of this case, and the corresponding literature review, is to highlight risk factors for and management of this condition.

CASE PRESENTATION

A 50-year-old woman with recent bilateral knee replacements developed crampy, diffuse abdominal pain for two days. The pain was associated with subjective fevers, nausea, and one episode of non-bloody emesis. A CT of the abdomen and pelvis done at an outside facility showed no abnormalities. Due to persistent symptoms for two days, the patient returned to the emergency department for evaluation. Her co-morbidities included antiphospholipid syndrome, prior deep vein thromboses and pulmonary embolism, recent IVC filter placement, lupus, and hypertension. She was receiving maintenance anticoagulation with warfarin for her history of thromboses with goal INR of 2-3, however admission labs revealed an INR of 6.61. Initial vitals were significant for a fever of 100.7ºF, heart rate of 124, and blood pressure of110/71. Physical examination revealed diffuse tenderness to palpation on abdominal exam with normal bowel sounds. No rebound, guarding, flank bruising, or costovertebral angle tenderness was noted. Admission labs showed WBC 12.4, Hb 10.8, Plt 68, INR 6.61, Na 124, K 3.4. Repeat CT of the abdomen and pelvis showed hyperdensities in both adrenal glands concerning for bilateral adrenal hemorrhage (**Figure 1**).

The patient's warfarin was reversed with Vitamin K 2.5mg PO as well as Vitamin K 2mg IV, and four units of fresh frozen plasma. Due to concerns about the development of adrenal insufficiency, she was started on Hydrocortisone 50mg IV q8hr. The patient was managed supportively, with no surgical intervention. Her hemoglobin was serially monitored, and she did not require any blood transfusions. Due to the patient's high risk of thrombosis from antiphospholipid syndrome, she was restarted on therapeutic anticoagulation as soon as she was deemed stable from a bleeding perspective. Repeat CT scans showed no continued bleeding. The patient's subsequent hospital course was complicated by thrombocytopenia, septic shock requiring intubation, ventricular fibrillation cardiac arrest, and Takutsubo cardiomyopathy. The patient ultimately recovered after a 28-day hospital stay and was sent home on a taper of hydrocortisone with instructions to follow up with hematology and endocrinology. She was to obtain an outpatient CT abdomen/pelvis four weeks after discharge to evaluate for resolution of hemorrhage, however the patient was lost to follow up.

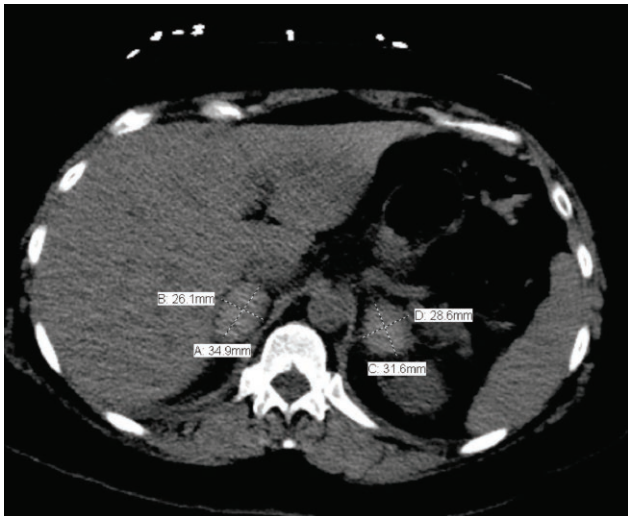

Figure 1. Both adrenal glands are enlarged, oval in shape, and relatively hyperdense. There is surrounding periadrenal fat stranding bilaterally, more extensive on the left.

DISCUSSION

Bilateral adrenal hemorrhage is a rare but potentially fatal condition. Existing literature suggests that bilateral adrenal hemorrhage occurs at an incidence of 4.7-6.2 per million in developed countries.[2] However, inadequate detection and vague clinical presentation often prevents appropriate and timely management of this condition.

The exact pathophysiology of adrenal hemorrhage is not well understood, but case reports suggest that it may represent a multifactorial etiology. The first theory of the development of adrenal hemorrhage relates to the adrenal blood supply. Each adrenal gland is supplied by 50-60 arterioles, which drain into the medullary sinusoids via relatively few venous channels. Each adrenal gland is drained by a single central vein, composed of thick longitudinal muscle, creating increased resistance to flow. During periods of stress, ACTH hormone is released, causing an influx of blood flow to the adrenal glands which may exceed the ability of the singular adrenal vein

to adequately drain. This may lead to hemorrhage of the capillaries at the cortico-medullary junction. A second theory relates to the effect of circulating catecholamines on the adrenal glands. Catecholamine surge promotes vasoconstriction and platelet aggregation, which may induce vasospasm and hemorrhage of the fragile capillary vessels. A final theory connects adrenal hemorrhage to arterial thrombosis. Some evidence suggests that the adrenal vessels are prone to the development of platelet thrombi and stasis during periods of catecholamine surge. This outflow obstruction may result in hemorrhage of the capillary vessels.[1] This final theory may account for the association between antiphospholipid syndrome and adrenal hemorrhage, and may be the underlying etiology of hemorrhage in the patient presented in this case report.

The potential causes of adrenal hemorrhage are vast. Approximately half of all reported cases are associated with a stressful event or illness. Sepsis, infection, surgery, blunt trauma, myocardial infarction, heart failure exacerbation, and pregnancy complications have all been implicated as precipitants of adrenal hemorrhage. There is an increased risk in patients on anticoagulation; more commonly with patients on heparin.[3] Thromboembolic diseases, such as antiphospholipid syndrome or heparin induced thrombocytopenia, can potentiate the risk of adrenal hemorrhage as well.[4] The patient in this report presumably developed adrenal hemorrhage as a result of antiphospholipid syndrome in the setting of a supratherapeutic INR, complicated by sepsis. Less common causes of adrenal hemorrhage include tuberculosis, amyloidosis, and metastatic tumors to the adrenal glands.

The most concerning complication of bilateral adrenal hemorrhage is the development of acute adrenal insufficiency. If left untreated, adrenal crisis may lead to critical illness and death. Clinical manifestations of adrenal insufficiency are typically not noted until 90% of the adrenal cortex has been destroyed, and insufficiency does not typically develop in unilateral adrenal hemorrhage. Death in bilateral adrenal hemorrhage more often occurs due to the underling precipitating condition rather than due to the hemorrhage itself, with a mortality rate as high as 15%.[4]

Presentation of adrenal hemorrhage is highly variable and often vague. In 65-85% of published cases, the most common complaint was nonspecific pain. Pain has been reported in the epigastrium, flanks, upper and lower back, pelvis, precordium, and thorax, highlighting the diagnostic challenge in identifying this condition. Some patients may present with fatigue, dizziness, arthralgias, anorexia, nausea, and vomiting, which may be moreso related to the development of adrenal insufficiency than due to hemorrhage itself. The most common physical exam findings associated with adrenal hemorrhage are fever, tachycardia, and orthostatic hypotension. In rare cases of meningococcal infection, adrenal insufficiency may develop as a component of Waterhouse Friderichsen syndrome, with an associated maculopapular rash. Approximately 15-20% of patients show signs of acute abdomen related to hemorrhage. An estimated 20-40% of patients may exhibit altered mental status, related to underlying disease or development of adrenal insufficiency.[1]

Workup of adrenal hemorrhage and associated adrenal insufficiency is limited. As with any bleeding event, serial hemoglobin monitoring must be performed to screen for persistent bleeding. A basic metabolic panel may reveal hyponatremia, hyperkalemia, and prerenal azotemia, suggesting the presence of adrenal insufficiency. The absence of these characteristics should not exclude a diagnosis of adrenal insufficiency in an acutely ill patient with bilateral adrenal hemorrhage. A baseline cortisol level may be obtained to stratify patients suspected to have adrenal insufficiency, or patients requiring additional cosyntropin stimulation testing. The imaging of choice for adrenal hemorrhage is CT of the abdomen and pelvis without contrast. Evidence of adrenal hemorrhage is evident in areas of higher attenuation (50-60 Hounsfield units), possibly with surrounding fat stranding or signs of inflammation. In a patient with confirmed bilateral adrenal hemorrhage and suspected adrenal insufficiency, treatment with stress-dosed steroids should not be delayed while waiting for the results of laboratory testing.

Treatment of bilateral adrenal hemorrhage is directed at treatment of the hemorrhage itself, and of any resulting adrenal insufficiency. In the 1990's, most patients with adrenal hemorrhage received surgery (adrenalectomies, adrenal repairs). Current literature endorses supportive therapy as the mainstay for patients with hemorrhage, as better outcomes have been observed in patients who do not undergo surgery.[4] This includes serial hemoglobin measurements, blood transfusions as needed, and fluid and electrolyte resuscitation. Current recommendations dictate that if there are no other indications for exploratory surgery in a trauma patient with adrenal insufficiency, supportive therapy is preferred if bleeding has stabilized. If persistent bleeding occurs, patients should be sent for embolization rather than open surgery. It is imperative to follow these patients with serial CT imaging to verify resolution of adrenal hematomas. No absolute recommendations have been made regarding timing of repeat imaging. Steroid replacement should be initiated with Hydrocortisone IV 150mg-300mg in divided doses for a total of 2-3 days. After this period, therapy can be tapered as tolerated. At higher doses, Hydrocortisone has both mineralocorticoid and glucocorticoid effects, however, once the total daily dose of Hydrocortisone is decreased to 50mg, additional mineralocorticoid therapy should be given. Many patients recover some, if not all, adrenal function, and may only require steroid replacement for a finite length of time. An outpatient cosyntropin test should be obtained to evaluate for the recovery of adrenal function.

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