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Primary Adrenal Insufficiency Due to Bilateral Adrenal Hemorrhage in a Patient with Antiphospholipid Syndrome

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Abstract

We describe a case of primary adrenal insufficiency due to bilateral adrenal hemorrhage in a patient with Antiphospholipid Syndrome (APS). A 69-year-old male presented with 2-3-month history of unintentional weight loss, weakness and postural dizziness. Investigations revealed low morning cortisol, high ACTH and inadequate response to cosyntropin stimulation test. Additional laboratory testing showed prolonged APTT. He had an established diagnosis of APS and was on anticoagulation. CT abdomen and pelvis demonstrated bilateral enlargement of the adrenal glands. Patient was treated with steroids for adrenal insufficiency secondary to APS. His symptoms improved with steroids and repeat CT scan showed significant decrease in the size of adrenal glands at 3 months and normalization by 8 months. Primary adrenal insufficiency from APS is caused by either spontaneous hemorrhagic infarction or necrosis due to adrenal vein thrombosis. Although recovery of adrenal function is considered irreversible, warranting lifelong therapy with steroids, however, some cases of recovery in the setting of adrenal hemorrhage have been reported.

Introduction

Primary adrenal insufficiency results from destruction of adrenal cortex leading to deficient mineralocorticoid and glucocorticoid production [1]. Manifestations of adrenal insufficiency appear when greater than 90 percent of the cortex is destroyed [2].

Among the many causes of primary adrenal insufficiency, autoimmune adrenalitis is the most common and is responsible for up to 90% of cases as noted by Zelissen, et al. [3], followed by tuberculosis [3,4]. Other unusual causes are metastatic cancer to the adrenal glands, lymphoma or drugs that inhibit cortisol biosynthesis such as ketoconazole [5], fluconazole [6], or increase the metabolism of cortisol like phenytoin, rifampin and barbiturates [7]. Adrenal insufficiency can also be due to bilateral adrenal hemorrhage secondary to use of anticoagulants, thrombo-embolic disease, physical trauma, sepsis, and any cause of severe stress [8,9].

We report a case of 69-year-old man who presented with primary adrenal insufficiency with bilateral adrenal enlargement due to adrenal hemorrhage caused by antiphospholipid syndrome.

Case

Our patient is a 69-year-old male with a past history of latent tuberculosis (diagnosed in 1990s and treated with Isoniazid for 9 months in 2015), Antiphospholipid Syndrome (diagnosed in early 1980s) on warfarin, deep vein thrombosis/pulmonary embolism (diagnosed in in 1982 and 1984 respectively) and interstitial lung disease. He presented to the hospital with a 2-3-month history of poor appetite, unintentional weight loss of 30 lbs., fatigue, weakness and postural dizziness. In addition, he had multiple falls a few weeks prior to his hospitalization. He had watery diarrhea for 2 days prior to admission but denied any recent travel or sick contacts. On examination, BMI 21.9kg/m2, blood pressure 125/69 mmHg, heart rate 86 beats/minute, temperature 100.5 F and oxygen saturation of 95% on 2 liters of oxygen. He appeared very thin and pale. Neck examination revealed no lymphadenopathy. Cardiovascular examination was within normal limits and chest had bilateral basilar crackles. Abdomen was non-tender and soft with normoactive bowel sounds and no rash or ecchymosis was noted on skin exam.

Laboratory testing showed hyponatremia (sodium 130 mEq/L), hyperkalemia (potassium5.1 mEq/L) and random blood glucose of 67 mg%. Complete Blood Count (CBC) revealed mild anemia with hemoglobin of 11.4 g/dl and hematocrit of 33.9 %. 11 am cortisol was low at 1 mcg/dL (normal range 7-23 mcg/dl) with high Adrenocorticotropic Hormone (ACTH) level of 272 pg/ml (normal range 7-69 pg/ml). Serum aldosterone level was <3 ng/dl (normal range <31) and Plasma Renin Activity was 0.8 ng/ml/hr (normal range 0.5-4.0 ng/ml/hr). Activated Partial Thromboplastin Time (APTT) was prolonged to 162.7 sec (normal range 25.1- 36.5 sec) and Prothrombin Time (PT) was 98.6 sec (normal range 9.4-12.5 sec). INR was high at 8.5. A cosyntropin stimulation with 250 mcg of cosyntropin administered intramuscularly, showed inadequate response with cortisol level of 1mcg/dL at 0, 30 and 60 minutes after the injection. 21 alpha hydroxylase antibodies were negative and HIV test was negative.

CT abdomen and pelvis revealed bilateral enlargement of the adrenal glands, right common femoral vein thrombosis and nonspecific prominent mesenteric lymph nodes. CT chest showed calcified granulomas, areas of parenchymal calcification, multiple nonspecific nodules and nonspecific mediastinal lymph nodes (Figure 1). A lung biopsy 6 month prior to admission had demonstrated pulmonary fibrosis with no evidence of granulomas or malignancy.

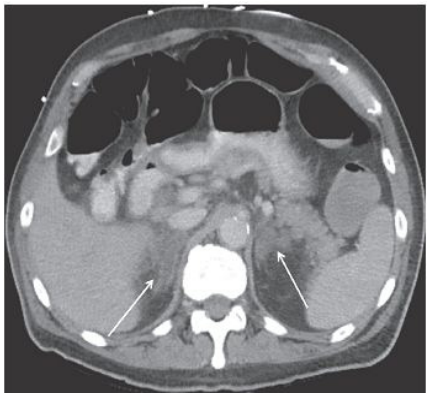

Figure 1: Contrast enhanced CT shows bilateral adrenal gland enlargement with central hypo enhancement.

He was diagnosed with primary adrenal insufficiency and started on treatment with steroids. He was also placed on airborne precautions to rule out active tuberculosis. 3 sputum samples were negative for AFB stain and culture. A bronchoalveolar lavage was also negative for AFB stain, culture and fungal culture. His blood cultures were negative and urinary histoplasma antigen was not detected. A bone marrow biopsy showed no evidence of leukemia or lymphoma.

Given the negative workup for other possible causes, the most likely etiology of his primary adrenal insufficiency was thought to be Antiphospholipid Syndrome (APS), leading to bilateral adrenal hemorrhage. He was initially treated with intravenous methyl prednisolone and then started on oral prednisone replacement. There was significant improvement in his symptoms and he was discharged on prednisone 5mg once in the morning and fludrocortisone 0.1 mg daily. On follow up to the outpatient clinic, he was feeling well, with improvement in appetite and a 3 lb. weight gain. His postural dizziness had resolved completely. A repeat CT scan of the abdomen 3 months after initial presentation showed a slight decrease in the size with persistent thickening of both adrenal glands (Figure 2). 8 months after presentation, both the adrenal glands had returned to normal size (Figure 3). An adrenal gland biopsy was not done in this case, given the resolution of symptoms and improvement in adrenal gland size.

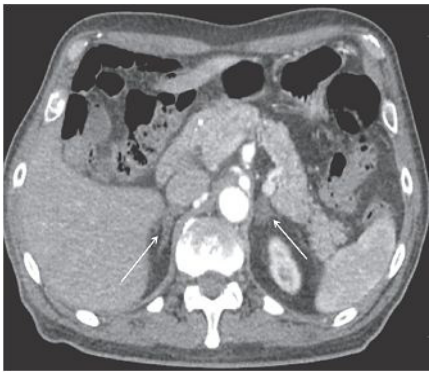

Figure 2: Follow up CT shows decreasing adrenal size with persistent thickening of both adrenal glands.

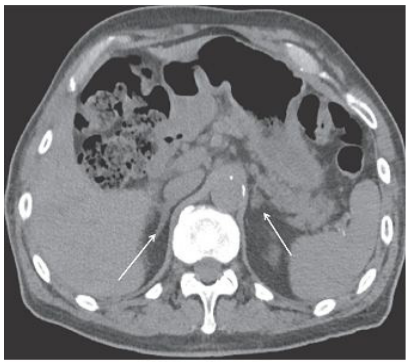

Figure 3: 8 Months after presentation, adrenal glands have returned to normal size.

Discussion

Antiphospholipid Syndrome (APS) is an autoimmune multisystem disorder. It is characterized by arterial, venous, or small vessel thromboembolic events and/or pregnancy morbidity in the presence of Antiphospholipid Antibodies (aPL) i.e. anti-cardiolipin antibodies and/or lupus anticoagulant and/or anti-β2-glycoprotein I antibodies [10].

The diagnosis of APS is made using the Revised Sapporo criteria [10,11]. Patients should meet at least one of the clinical and

laboratory criteria each. Clinical criteria include vascular thrombosis or pregnancy morbidity. Laboratory criteria are fulfilled if the patient has 1 or more of antiphospholipid antibodies: lupus anticoagulant, IgG and/or IgM anti-cardiolipin antibodies and IgG and/or IgM anti-beta2-glycoprotein antibodies on 2 or more occasions, at least 12 weeks apart.

APS is associated with many endocrinologic manifestations with adrenal insufficiency being the most common presentation [12,13]. Other organs including lung, kidney, brain, skin, liver, skin and eyes may also be affected. Other emerging endocrine manifestations include hypopituitarism and Autoimmune Thyroid Disorders (ATD) [12].

Primary adrenal failure in APS is usually caused by spontaneous hemorrhagic infarction due to adrenal vein thrombosis [2]. The vascularity of adrenal glands plays a significant role in pathogenesis. Adrenal glands have rich arterial supply but limited venous drainage and this may predispose to thrombosis [2,14,15]. The adrenal gland is supplied by branches of renal artery, phrenic artery and the aorta but is drained by a single vein that drains into the renal vein on the left and inferior vena cava on the right. The arteries transition to capillaries so abruptly that they form a vascular plexus around the zona reticularis, which leads to the formation of a vascular dam [16,17]. In addition, the adrenal veins are encased by eccentrically arranged muscle bundles that cause turbulent flow within the veins [16]. Additionally, Vella et al proposed that the high concentrations of epinephrine noted in the adrenal veins might be a contributing factor to hemorrhagic necrosis in the setting of increased stress, increased adrenal blood flow, hypotension and/or coagulopathy [17].

Imaging modalities used to visualize adrenal hemorrhage include both CT and MRI. Acute hemorrhage can appear as a hyper intense mass on CT scan [18] and cause enlargement of one or both adrenal glands [18,19]. Acute hemorrhage can also appear as an area of low or mixed attenuation centrally with peripheral enhancement [20]. Our patient's CT scan had similar findings with diffuse low attenuation centrally with associated surrounding fat stranding along with bilateral enlarged adrenals. MRI is highly sensitive and acute hemorrhage appears isointense on T1 weighted images and has low intensity on T2 weighted images, while the subacute hematoma is hyper-dense on T1 weighted images, because of the presence of methemoglobin [21]. Low signal intensity is seen on both T1 and T2 weighted images in chronic hematoma [21].

Our patient had an established diagnosis of APS and was on warfarin prior to admission. His INR was supratherapeutic on admission but he also had prolonged APTT. The etiology of his adrenal hemorrhage was thought to be due to the APS given the prolonged APTT with lupus anticoagulant antibodies. Warfarin was thought to be a possible contributing factor. There has been data to suggest that adrenal hemorrhage due to anticoagulant therapy usually occurs soon after initiation of therapy [22]. Harper, et al. reported this interval to be around 6-13 days [23]. Our patient had been on warfarin for several years prior to admission.

Although adrenal failure secondary to APS is generally considered irreversible with lifelong need for replacement therapy, some reports have described recovery of adrenal function in the setting of adrenal hemorrhage and adrenal infarction [16,24]. It is important for clinicians to consider Antiphospholipid Syndrome (APS) in the differential diagnosis of primary adrenal insufficiency, associated with CT findings of bilateral adrenal gland enlargement and hemorrhage.

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