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Case Report

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Cushing Syndrome due to Ectopic ACTH Secretion Presenting With Lower Limb Edema and Pulmonary Nocardia Infection: Case Report and Review of the Literature

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Abstract

Ectopic ACTH secretion has been described since 1962, but its presentation as only lower limbs edema was rarely described. Symptoms and signs are very similar to Cushing disease, but with a more rapid onset and progression of symptoms. Cushing syndrome presenting as lower limbs edema only has been reported once. We present here a case of a 60-year-old male patient with ectopic ACTH secretion presenting with isolated lower limb edema and developing pulmonary nocardia infection.

Keywords: Ectopic ACTH; Cushing; Nocardia; Limb edema

Introduction

Excess glucocorticoids secretion was first described by Harvey Cushing in 1912. Twenty years later, he postulated that it was due to a primary pituitary abnormality causing adrenal hyperplasia, but it was until 1962 that ectopic secretion of ACTH was characterized. Ectopic ACTH secretion is responsible for 20% of ACTH-dependent Cushing syndrome [1]. Differentiating between ectopic ACTH secretion and Cushing disease remains a challenging problem [1]. Despite detailed investigation, the cause of corticotropin production might remain occult in 5-15% of patients, and these patients need continued follow-up [2, 3]. Several clinical pictures of glucocorticoid excess have been described. Symptoms and signs are very similar to Cushing disease; however, the rapidity of onset and progression of symptoms are more suggestive of an ectopic ACTH secretion. Most frequently reported are muscle weakness, increased body weight, hypertension, menstrual irregularities and hirsutism in women, osteoporosis and hypokalemia with a frequency ranging between 70% and 80%. About half of the patients will complain of diabetes, infections and violaceous striae [4]. However, Cushing syndrome presenting as lower limbs edema only has been reported once [5].

Case Report

A 60-year-old Iraqi man presented to our tertiary care center in Beirut for evaluation of bilateral lower limbs edema of 2 months duration. Relevant past medical history was positive for type 2 diabetes mellitus (DM2) of 13 years duration, with peripheral diabetic neuropathy and nephropathy, hypertension, and dyslipidemia. His home medications included premixed insulin (neutral protamine Hagedorn with regular insulin), rosuvastatin, nebivolol, valsartan, and hydrochlorothiazide and he was recently started on bumetanide 1 mg daily. The patient was clinically euthyroid. On physical exam, he had bilateral lower limbs pitting edema, extending to the knees. His blood pressure was 120/70 mm Hg, he had regular heart sounds and clear lungs and there was no jugular venous distension. No Cushingoid facies, no skin striae or ecchymoses were noted.

Preliminary laboratory workup showed proteinuria of 2.3 g/24 h with normal creatinine of 0.5 mg/dL (0.6 - 1.2 mg/dL), normal sodium 145 mmol/L (135 - 145 mmol/L), hypokalemia of 3.1 mmol/L (3.5 - 5.1 mmol/L) with metabolic alkalosis, bicarbonate of 40 mmol/L (24 - 30 mmol/L), low normal albumin level 35 g/L (36 - 53 g/L) and normocytic anemia with a hemoglobin of 11.4 g/dL (13 - 18 g/dL), white blood count of 10,800/mm^3 (4,000 - 11,000/mm^3) (neutrophils: 85%), and platelets count of 108,000/mm^3 (150,000 - 400,000/mm^3). Echocardiography found an ejection fraction of 50-59% with grade 1 diastolic dysfunction. Thyroid function tests showed TSH was 0.44 (0.27 - 4.2 µU/mL), low FT3 was 0.65 pg/mL (1.8 - 4.6 pg/mL) and FT4 was 0.78 ng/dL (0.93 - 1.7 ng/dL). Ultrasound of the kidneys was normal. Doppler ultrasound of lower extremities did not show evidence of deep venous thrombosis. The hypokalemia was initially attributed to bumetanide use but it persisted and even after discontinuation of the diuretic (2.4 mmol/L). Additional tests were then requested, including a complete pituitary function that revealed normal prolactin level, hypogonadism with testosterone of 95.6 ng/dL (249

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- 836 ng/dL) and low LH of 2.5 mIU/mL (5 - 12 mIU/mL), elevated ACTH of 312 pg/mL (10 - 60 pg/mL) and high morning cortisol level of 40.7 µg/dL (4 - 25 µg/dL). An overnight low dose dexamethasone suppression test did not suppress morning cortisol (cortisol level 36 µg/dL). High dose 8 mg overnight dexamethasone test failed to suppress cortisol level as well: 28 µg/dL. MRI of the sella was performed and was normal. Chest X-ray showed a prominent right hilum. CT chest showed multilobar consolidations likely pneumonic with left apical and right lower lobe lung masses. Spondylotic changes with multiple compression fractures and paraspinal abscess at T12 level were also noted. Blood cultures and culture from abscess grew *Salmonella typhi*. Bronchoscopy was normal and bronchoalveolar lavage was negative for malignancy, but grew Nocardia species. The patient was discharged home on double antibiotics coverage (trimetoprim-sulfametoxazole and meropenem). Waiting for resolution of the bacteremia to do further investigations, the patient was started on ketoconazole 200 mg BID, increased to TID. As his repeated cortisol was still high after 1 week of a daily dose of 600 mg/day, mitotane 500 mg TID was added. He was planned to do PET scan, and if negative, bilateral inferior petrosal sinus sampling (BIPSS) after resolution of the bacteremia, but he went back to Iraq and was lost of follow-up since then.

Discussion

We presented a case of ectopic ACTH secretion in a 60-year-old patient presenting with hypokalemia, lower limb edema and multilobar consolidations with left apical and right lower lobe lung masses with normal bronchoscopy and a bronchoalveolar lavage that was negative for malignancy, but grew Nocardia species. To our knowledge, ectopic ACTH secretion presenting as isolated lower lib edema was reported only once, and cases reporting association with Nocardia infection are scarce.

Hypercortisolemia and infection

The increased susceptibility to infections was noted since Cushing's original description of the disease, with a predisposition to opportunistic infections. The risk of infection is influenced by the underlying cause of hypercortisolemia, and seems to be correlated with higher general levels of ambient steroid. This risk is highest with exogenous steroids, followed by ectopic ACTH secretion, then other causes of endogenous hypercortisolism [6, 7].

Deficits in cell-mediated immunity as well as alterations in neutrophils and macrophages functions predispose patients with Cushing syndrome to fungal infections. For example, Candida infections can be superficial, or it can cause bloodstream infections with septicemia. Aspergillus causes most of the invasive fungal infections in patients treated with glucocorticoids. *Pneumocystis jiroveci* is well known to cause pneumonia in patients treated with glucocorticoids [8].

Elevated cortisol levels predispose patients to more severe, disseminated and prolonged viral infections, including, as examples, infections with herpes simplex viruses, varicella zoster, and cytomegalovirus. Both Gram-positive bacteria such as Staphylococci, streptococci and listeria, and Gram-negative organisms including enterobacteriacae and Legionella are seen in increased frequency in patients with hypercortisolemia [8].

Nocardia asteroides, an uncommon filamentous Gram-positive organism, has been previously reported in few cases of hypercortisolemia.

Rizwan et al described three cases of ectopic Cushing syndrome presenting with uncontrolled hypertension, elevated blood sugar and hypokalemia. CT chest of these subjects demonstrated cavitatory lung lesions. Microscopic analysis of respiratory samples was suggestive of infection with Nocardia species; however, histopathology of bronchoscopic-guided biopsy revealed no malignancy. Antihypertensives, insulin, potassium replacement, ketoconazole and trimethoprim-sulphamethoxazole were initiated. The patients' symptomatology improved and cavitatory lesions resolved with treatment; however, the primary source for the ectopic Cushing remained unknown [9].

Dohchin et al reported a 54-year-old male patient who presented for further investigation of multiple nodules disclosed by a chest roentgenogram. Investigations revealed an occult ectopic ACTH syndrome. Bronchial secretion samples obtained by bronchoscopy contained Nocardia asteroides bacteria. After treatment with sulfamethoxazole-trimethoprim, the nodules gradually disappeared, leaving only scars. However, pulmonary nocardiosis relapsed following the termination of sulfamethoxazole-trimethoprim therapy despite mitotane therapy to suppress hypercortisolemia [10].

Huang et al reported a 25-year-old man diagnosed with ectopic Cushing syndrome due to an ACTH producing small cell lung carcinoma who had a rapidly progressive course of pulmonary nocardiosis and died 3 days after the initiation of antibiotics and ketoconazole [11].

Sutton et al presented the case of a 42-year-old woman who had Cushing syndrome due to a carcinoid tumor in the lung secreting ACTH. Her course was complicated by the appearance of multiple pulmonary nodules, which were shown by fine needle aspiration to be infectious in nature. A Gram stain revealed numerous Gram-positive branching organisms, and culture of the specimen grew Nocardia asteroides. Her pulmonary infection was treated with antibiotics and she underwent successful ablation of the carcinoid tumor [12].

Hypercortisolemia and lower limbs edema

Few cases have reported the presentation of Cushing syndrome as only lower limbs edema. Of note, Lin et al described a 43-year-old patient presenting for bilateral lower limbs edema, hyperpigmentation and easy bruisability who was found to have ectopic Cushing syndrome due to a small cell lung cancer. His endocrinologic workup was relevant for hypogonadism and hypothyroidism [5].

This is the second case reported to describe the presentation of hypercortisolemia as lower extremities edema. It is noted that our patient had also central hypogonadism and labo-

ratory findings suggestive of central hypothyroidism.

Hypercortisolemia and hypokalemia

ACTH level in our patient at presentation was 312 pg/mL. Plasma ACTH levels tend to be higher in the ectopic ACTH syndrome (EAS) than in Cushing's disease, but there is a large overlap between values and no cut-off limit was found for the definite and clear distinction. ACTH levels were elevated more than 200 ng/L in 50-64% of subjects with ectopic ACTH secretion. No correlation could be established with the tumor size, as ACTH levels did not differ in patients with occult and overt ectopic ACTH syndrome [13-16].

Hypokalemic alkalosis is found in 10-15% of patients with Cushing's disease, but in more than 95% of patients with ectopic ACTH syndrome. High concentrations of cortisol can either saturate the 11β-hydroxysteroid dehydrogenase type II enzyme in the kidney or decrease its expression, allowing cortisol to act even more as a mineralocorticoid causing potassium losses. Hypokalemia reflects the prevailing levels of cortisol rather than the specific etiology. It has a high sensitivity for the ectopic ACTH syndrome, but a specificity that only approaches the pretest likelihood [17, 18].

Conclusion

Ectopic ACTH secretion that is complicated by severe Cushing syndrome is often a devastating disease. It is associated with many opportunistic infections notably with Nocardia species. Its presentation as bilateral lower extremities edema has been rarely reported. Aggressive therapy for hypercortisolemia should be instituted. If ipatients cannot undergo curative or palliative surgery, medical therapy should be applied with mifepristone or combination therapy with inhibitors of steroidogenesis according to individual patient characteristics. In selected cases, somatostatin analogs may be effective [19].

Conflicts of Interest

The authors have no conflicts of interest to declare.

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