Occult ectopic adrenocorticotropic hormone secretion: diagnostic dilemma and infective consequence

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Abstract

A 42-year-old male presented with polyuria, polydipsia and weight loss. His initial physical exam showed a paucity of cushingoid features. Diagnostic work up was consistent with an ectopic adrenocorticotropic hormone (ACTH) secretion. Imaging studies showed a small anterior mediastinal lesion without additional metabolically active tumors. Fine needle aspiration was consistent with a thymic neuroendocrine tumor. Following radical thymectomy, plasma ACTH and cortisol levels remained elevated. Despite medical management, he died within 2 months of presentation of disseminated intracranial aspergillosis. This case underscores the diagnostic dilemma of occult ectopic ACTH-secreting tumors and the fatal consequence of opportunistic infections.

Introduction

Cushing's syndrome is most commonly caused by exogenous glucocorticoid administration. The most common non-iatrogenic cause is Cushing's disease, an adrenocorticotropic hormone (ACTH) secreting pituitary adenoma. Very rarely, an ectopic ACTH secreting tumor is the cause of Cushing's syndrome. Thymic neuroendocrine carcinoma is a known ectopic source.[1] These carcinomas are often difficult to cure and localizing sites of metastasis can be challenging.[2] Treatment of opportunistic infections, in particular aspergillosis, in the context of uncontrolled hypercortisolism can be futile.[3] We present a case of Cushing's syndrome due to thymic neuroendocrine carcinoma (thymic carcinoid carcinoma).

Case Report

42-year-old male presented to the emergency department with a 7-week history of polyuria, polydipsia, mild muscle weakness and weight loss. Physical exam was significant for an elevated blood pressure of 180/100 mmHg and mild central obesity. Laboratory investigations showed low potassium of 2.8 mEq/L, an elevated blood sugar of 347 mg/dL, high serum ACTH level of 1013 pg/mL (normal, 7-50 pg/mL) and a 24 h urine cortisol of 21,469 mL mcg/24 h (normal <100 mL mcg/24 h). An elevated plasma cortisol of 130 mg/dL (normal 4 - 22 mcg/dL) was not suppressed following an overnight high dose of 8 mg dexamethasone. A computed tomography (CT) scan of the abdomen showed prominent bilateral adrenal gland hyperplasia without any discrete nodule. Magnetic resonance imaging (MRI) of the brain and pituitary was normal. Inferior petrosal sinus sampling is known to provide very good specificity and sensivity in patients without an obvious lesion on MRI. However, the above findings in our patient along with the rapid onset of symptoms and high degree of elevation of cortisol were consistent with an ectopic ACTH source. Consequently, a bilateral inferior petrosal sinus sampling was not pursued. A CT chest showed a single 1.4 cm hypervascular mediastinal lesion (Figure 1). A cavitary lesion in the right lower lobe was also observed. Microbiologic investigation of the cavitary lesion following a bronchoscopy revealed methicillin sensitive *Staphylococcus aureus*, Nocardiosis and Pneumocystosis. The patient had a negative HIV test. An octreotide scan was negative. A positron emission tomography – computed tomography (PET-CT) showed a 1.4 cm lesion noted in the anterior mediastinum by CT which was positive for metabolic activity on the PET. The PET-CT also revealed uptake in the pulmonary cavitary lesion consistent with active infection as well as both adrenals due to metabolic activity of the hypertrophic adrenals.

CT-guided fine needle aspiration of the anterior mediastinal lesion revealed a low-grade thymic neuroendocrine carcinoma. Bone marrow biopsy was negative for metastatic disease. The patient was treated with ketoconazole to inhibit cortisol synthesis and trimethoprim-sulfamethoxazole for his cavitary lung infections. He underwent a radical thymectomy and mediastinectomy with excision of a 2.5 cm anterior mediastinal thymic neuroendocrine tumor with noted lymphovascular involvement (Figures 2 and 3) and one metastatic lymph node. The patient was started on hydrocortisone on the day of surgery as it was expected that patient's ACTH would fall rapidly and adrenal insufficiency would ensue. Ketoconazole was discontinued. One day following surgery, plasma ACTH and 24 h urine free cortisol remained elevated (655 pg/mL and 8, 390 mL mcg/24 h respectively). Hydrocortisone therapy was discontinued. Ketoconazole was restarted and later octreotide was added but the serum cortisol levels remained >60 mg/dL over the ensuing days. Repeat PET-CT showed a new 1.5 cm lesion in the left temporal lobe. An MRI showed abnormal enhancement with surrounding edema and mass effect within the left medial temporal lobe. Due to the rapidity of appearance of the brain lesion, it was believed to be an infectious process, possibly a metastasis from the lung infection and the patient was continued indefinitely on trimethoprim-sulfamethoxazole. However, within a few days, his mental status deteriorated. A repeat MRI a week later showed similar lesions in multiple areas of the brain bilaterally (Figure 4). A brain biopsy of the lesions and culture demonstrated aspergillosis. The patient was started on voriconazole. However, he died several days later. A post-mortem autopsy showed disseminated aspergillosis in the brain, on the pericardial surface and in both lungs. The autopsy did not identify any other neuroendocrine primary or metastatic site.

Discussion

Thymic neuroendocrine carcinomas are rare and have been reported to account for only 0.06% of all thymic neoplasms.[4] Since the report by Scholz and Bahn, the association between thymic carcinoids and Cushing's syndrome has become well established.[5] Thymic carcinoids are neuroendocrine tumors of the thymus.[6] Cushing's syndrome associated with an ectopic ACTH-secreting (EAS) thymic neuroendocrine tumor is suspected when an anterior mediastinal mass is found in the context of hypercortisolism and non-suppressibility with high-dose dexamethasone. Localization of ectopic ACTH producing tumors or its metastasis can be difficult.[2] When the source

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of an ectopic ACTH secretion is not found, it is called an occult EAS tumor. Between 12 and 19% of tumors may not be localized on initial evaluation.[2] Imaging studies such as CT or MRI of the chest and abdomen, PET scans and somatostatin receptor scintigraphy are the most effective diagnostic studies to localize ectopic ACTH tumors.[7-9] Intraoperative ultrasonography has been used to localize ectopic sites within the abdomen.[2] In our case, initial work up identified a mediastinal tumor. However, excision of the identified thymic carcinoid carcinoma did not result in normalization of serum ACTH or cortisol concentrations, indicating residual metastatic disease. Repeat imaging did not identify any residual disease. Surgical resection remains the best therapeutic modality for curing thymic neuroendocrine tumors. In cases of unidentified ACTH source, control of hypercortisolism with octreotide therapy can be successful in both somatostatin receptor positive and somatostatin receptor negative tumors.[10-12] However some tumors are unresponsive.[13] Our case failed to respond to octreotide. Mifepristone was recently approved for the treatment of hyperglycemia associated with endogenous Cushing's syndrome and has been shown to improve some of the metabolic abnormalities.[14] This was not an approved treatment at the time of this case and it is unclear if this would have affected the outcome. In cases of occult EAS, metastatic disease or failure of medical control of hypercortisolism, bilateral adrenalectomy with subsequent steroid replacement is an effective alternative for control of hypercortisolism.[15,16]

Endogenous hypercortisolism especially when associated with ectopic ACTH secretion predisposes to fatal opportunistic infections. The most common infections were pneumocystosis, cryptococcidiosis, nocardiosis and aspergillosis. Staphylococcus aureus infections have also been reported.[17] In Graham's comparative analysis and Murry's case report, patients with aspergillosis uniformly died.[17,18]

In the context of hypercortisolism, antifungal treatment may not be sufficient therapy because of the ongoing immunodeficiency state.[3] Medical therapy has been shown to be sometimes effective in controlling hypercortisolism. However, in cases of indolent tumors or severe aspergillosis, bilateral adrenalectomy may be a reasonable treatment for prompt control of hypercortisolism.[19,20] Successful treatment of aspergillosis was reported in a patient following bilateral adrenalectomy and normalization of the serum cortisol concentrations despite diffuse cerebral involvement and severe pulmonary compromise.[19]

Bilateral adrenalectomy was considered in our case following failure of radical thymectomy to cure the disease. However the rapidity of decline of his clinical course did not afford the opportunity for another surgery. The report by Joubert would suggest that even a late intervention with bilateral adrenalectomy may be of value. In retrospect, prompt control of hypercortisolism by bilateral adrenalectomy may have given our patient's immune system a chance to recover and respond to antifungal therapy.

EAS tumors can be very difficult to localize and cure. The tumors are often fatal especially when complicated by fungal infections such as aspergillosis. The inability to achieve normal cortisol following excision of an apparent primary lesion resulted in the rapid demise of our patient. This case underscores the diagnostic challenges of occult EAS and the deadly opportunistic infection(s) that can occur as a result unchecked hypercortisolism.

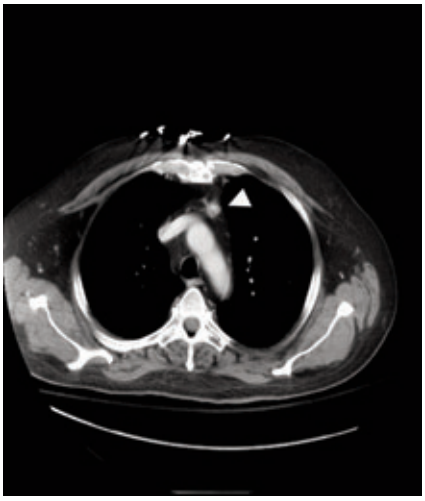

Figure 1. Computed tomography scan of chest showing an anterior mediastinal thymic mass (white arrow).

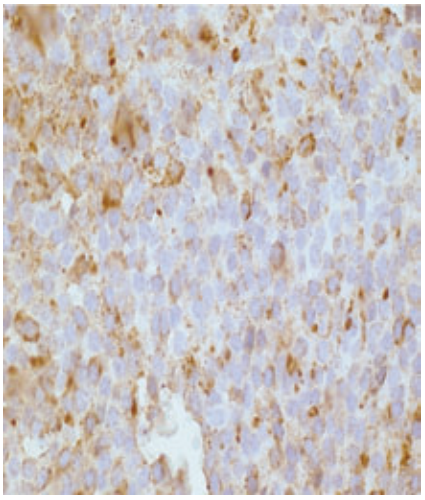

Figure 3. Immunostain for adrenocorticotropic hormone of thymic neuroendocrine tumor.

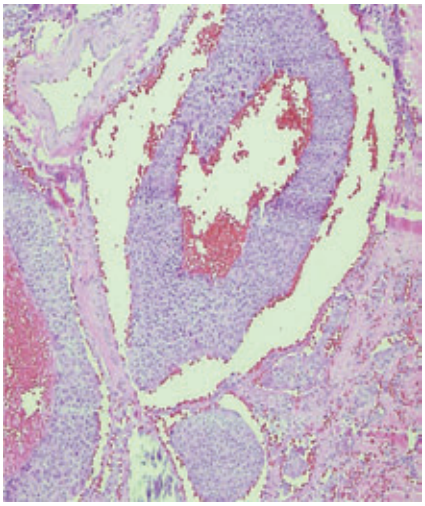

Figure 2. Hematoxylin and eosin stain showing low-grade neuroendocrine tumor with vascular invasion (magnification 100x).

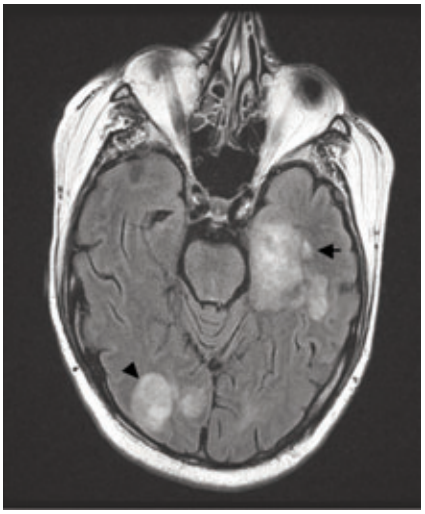

Figure 4. Computed tomography scan of head showing brain lesion consistent with disseminated intracranial aspergillosis (black arrows).

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