**Invasive fungal infections in endogenous Cushing’s syndrome**

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**Abstract**

Cushing’s syndrome is a condition characterized by elevated cortisol levels that can result from either augmented endogenous production or exogenous administration of corticosteroids. The predisposition to fungal infections among patients with hypercortisolism has been noted since Cushing’s original description of the disease. We describe here a patient with endogenous Cushing’s syndrome secondary to an adrenocortical carcinoma, who developed concomitant disseminated cryptococcosis and candidiasis in the course of his disease.

**Introduction**

Cushing’s syndrome is a condition characterized by supraphysiological cortisol levels that can occur because of either augmented endogenous production or exogenous administration of corticosteroids.1 The most common complications of Cushing’s syndrome are diabetes, hypertension, obesity, osteoporosis, and a predisposition to mucocutaneous and invasive fungal infections, bacterial infections, reactivation of tuberculosis, and postoperative wound infections. This state is characterized mainly by impaired cell-mediated immunity, augmented by deficient neutrophil and macrophage function.2

In this report, we describe a patient with Cushing’s syndrome secondary to an adrenocortical carcinoma, who developed concomitant disseminated cryptococcosis and candidiasis in the course of his disease.

**Case Report**

A 38-year-old man with a history of hypercortisolism was admitted because of hypokalemia and early onset diabetes. He had been attending our outpatient clinic since 2006 and was taking diuretics, beta-blockers, and calcium channel antagonists for his hypertension. In the past two months he presented with an episode of severe hypokalemia with potassium levels of 2.2 mg/dL and hyperglycemia, which required oral and intravenous potassium replacement and insulin therapy.

A physical examination showed a blood pressure of 170/100 mmHg, temperature 36.7°C, with normal cardiac and respiratory rates. The patient presented a typical moon face, truncal obesity, and edema of the legs with proximal muscular weakness. The values of the initial laboratory tests showed a normal blood count and renal function (creatinine 1.0 mg/dL, the midnight serum cortisol level was 89.8 µg/dL, and a 24-hour urine cortisol was 8360.59 µg/dL (normal value <137.0 µg/dL). Serum ACTH concentration was undetectable (<10 pg/mL). An abdominal CT scan showed a tumor of 12 cm by 10 cm with calcifications, an irregular shape, and heterogeneous contrast impregnation in the left adrenal gland. The patient underwent an open adrenalectomy with resection of the left adrenal gland and kidney. The histopathological examination confirmed an adrenocortical carcinoma.

Although hypercortisolism was controlled, in the postoperative period the patient developed septic shock that required hemodynamic and ventilatory support. He was started on broad-spectrum antibiotics, the patient was started on amphotericin B and 5′-flucytosine. He developed many surgical complications and recurrent upper gastrointestinal bleeding, and died 90 days after admission because of bacterial peritonitis and refractory septic shock.

**Table 1. Invasive mycoses described in patients with endogenous Cushing’s syndrome.**

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<thead>
<tr>
<th>Fungal Infection</th>
<th>Characteristics</th>
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<tbody>
<tr>
<td>Scedosporosis</td>
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<td>5</td>
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<tr>
<td></td>
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<tr>
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<td>Candidiasis</td>
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Key words: cryptococcosis, candidemia, pneumocystosis, scedosporiosis, histoplasmosis, aspergillosis, Cushing’s syndrome, Cushing’s disease, hypercortisolism, fungal infections, mycosis.

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**Discussion**

Compared with patients with iatrogenic Cushing’s syndrome, fewer invasive fungal infections arise in those with endogenous Cushing’s syndrome.1 ACTH-dependent hypercortisolism from a functioning pituitary adenoma, and also known as Cushing’s disease, makes up approximately 70% of cases of endogenous hypercortisolism. In contrast, ACTH-independent hypercortisolism contributes to approximately 15% of cases of endogenous Cushing’s syndrome. As observed in our patient, the most common cause is an autonomous overproduction of cortisol from an autonomous overproduction of cortisol from a adrenal adenoma. This case report highlights the importance of considering fungal infections in patients with endogenous hypercortisolism, particularly in those who present with atypical symptoms or have a history of previous fungal infections.

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The predisposition to fungal infections among patients with hypercortisolism has been noted since Cushing's original description of the disease. Hypercortisolism has been shown to impair neutrophil adherence to the endothelium, to decrease degranulation capacity and phagocytic action, to diminish maturation of macrophages, and to down-regulate multiple proinflammatory cytokines. As shown in Table 1, there are several reports describing invasive fungal infections such as histoplasmosis, aspergillosis, pneumocystosis, cryptococcosis, and candidiasis in patients with endogenous Cushing's syndrome.4-7

Our case is unusual as it describes a patient with an endogenous hypercortisolism that developed concomitant invasive candidiasis and cryptococcosis. In fact, higher levels of endogenous hypercortisolism increases the risk of infection, and with its anti-inflammatory properties contributes to the subclinical manifestations of these infections. Therefore, invasive fungal infections should be suspected by physicians in patients with endogenous hypercortisolism with early and minimal signs and symptoms of infection unresponsive to broad-spectrum antibiotics. Laboratory tests with a high degree of sensitivity and specificity such as the detection of serum cryptococcal capsular polysaccharide antigen, urinary histoplasmosis antigen in urine, serum galactomannan, serum β-D glucan, and PCR assays for fungi DNA detection are important diagnostic tools for screening invasive fungal infections in these patients. In addition to specific and aggressive antifungal therapy, pharmacological and surgical treatment for lowering plasma cortisol levels to physiological ranges appears to be a reasonable approach considering that extreme hypercortisolism is an immunological endocrine emergency.

References