An ACTH-secreting Pituitary Adenoma Within the Sphenoid Sinus

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Abstract

A 68-year-old woman developed Cushingoid features three months prior to admission. She was found to have a markedly elevated plasma ACTH-cortisol level. Magnetic resonance imaging (MRI) revealed a mass in the left sphenoidal sinus, which had become enlarged to a point where it could not be removed by transsphenoidal surgery. We decided to proceed with radiation therapy to shrink the tumor. However, it was ineffective. Despite a reduction in serum cortisol levels using metyrapone, she died of septic shock. We describe a rare case of an ACTH-secreting pituitary adenoma within the sphenoid sinus.

Key words: Cushing’s disease, pituitary adenoma in the sphenoid sinus, ectopic ACTH syndrome


Introduction

Cushing’s disease can be life-threatening due to the hypersecretion of endogenous cortisol. Ectopic production of adrenocorticotropic hormone (ACTH) is a rare cause of Cushing’s syndrome. Elevated cortisol levels can impair cell-mediated immunity and trigger severe infections and sepsis (1). Whenever an ACTH-secreting adenoma is identified within the pituitary, adenectomy is the first-line treatment of an ACTH-secreting pituitary adenoma.

In this report, we describe a rare case of an ectopic ACTH-secreting pituitary adenoma within the sphenoid sinus that could not be surgically removed; therefore, we decided to perform radiotherapy, which was ineffective. Examination of the pathological specimen obtained after her death confirmed the presence of an ectopic ACTH-producing pituitary adenoma within the sphenoid sinus.

Case Report

A 68-year-old woman with a three year history of hypertension was admitted to our hospital with proximal muscle weakness of her lower limbs, Cushingoid features, hepatic impairment and hypokalemia. She did not have any significant past medical history, apart from hypertension, and her family history was unremarkable. She had gained 8 kg in body weight over the previous year. At the time of admission, her height was 144.9 cm and her body weight was 63 kg (body mass index 30.0 kg/m²). Her blood pressure was 166/104 mmHg and her pulse rate was regular at 92 bpm. The typical features of Cushing’s syndrome, including moon face, central obesity, proximal muscle weakness, and skin pigmentation were noted. Thus, Cushing’s syndrome was immediately suspected. Her laboratory data revealed a high WBC count, neutrophilia, hypokalemia, impaired liver function, metabolic alkalosis, and impaired glucose tolerance (Table 1). A urinalysis showed microalbuminuria. Pituitary hormone levels, apart from ACTH (TSH, GH, FSH, LH, and PRL), and thyroid hormone were normal (Table 1).

Plasma ACTH and cortisol levels were markedly elevated and failed to demonstrate circadian variation (Table 2). Plasma cortisol levels were not suppressed by low-dose (2 mg) or high-dose (8 mg) dexamethasone suppression tests. Plasma ACTH and cortisol levels did not demonstrate a significant response to stimulation with 100 μg of corticotropin-releasing hormone (CRH). Following oral administration of 1,500 mg metyrapone, plasma cortisol levels decreased. Conversely, after subcutaneous injections of 100 μg octreotide, plasma ACTH and cortisol levels did not de-
Cranial magnetic resonance imaging (MRI) revealed a mass (2.5 cm in diameter) occupying the sphenoid sinus. The mass demonstrated an intermediate T1 signal intensity and was not enhanced by gadolinium. The mass was distinct from the pituitary and morphological changes were not observed in the septum (Fig. 1A). To detect other ACTH-secreting tumors, we performed chest and abdominal computed tomography (CT), upper gastrointestinal endoscopy, which failed to reveal findings suggesting of an ACTH-secreting tumor. To make a definitive diagnosis, the patient underwent a fine needle aspiration biopsy, which revealed an ectopic ACTH-producing pituitary adenoma within the sphenoid sinus. Unfortunately, she became seriously ill one month after her admission, developing sepsis caused by methicillin-resistant Staphylococcus aureus (MRSA). Endotoxin (<5.0 pg/mL) and β-D glucan (9.2 pg/mL) concentrations were under the detectable limits. We had to take into account the general condition and that her adenoma was invasive to the left internal carotid artery. Surgical resection could not be performed. Therefore, we decided to perform radiotherapy (a total of 50 Gy), which was ineffective (Fig. 1B). We were able to reduce her cortisol levels by oral administration of metyrapone, but unfortunately, she died of septic shock. In order to further investigate the cause of her death, the adenoma and pituitary gland were obtained post-mortem for pathological analysis. A final detailed histological examination revealed that the pituitary was normal, while the intra-sphenoid mass was positive for ACTH proven by immunohistochemical staining (Fig. 2). It suggested invasive pituitary adenoma, same findings as a fine needle aspiration biopsy revealed earlier. We did not find metastatic disease in other organs.

**Discussion**

In Cushing’s syndrome, approximately 80% of the cases are due to excessive secretion of ACTH. This is usually from a pituitary corticotroph adenoma (Cushing’s disease), and less often a non-pituitary tumor. Ectopic ACTH production accounts for approximately 5-10% of all patients with ACTH-dependent hypercortisolism (2, 3). In Japan, however, ACTH-independent Cushing’s syndrome is increasing at a
greater rate than ACTH-dependent Cushing’s syndrome.

Here, we report a 68-year-old woman who had an ectopic ACTH-producing pituitary adenoma in the sphenoid sinus. The first case of an ectopic ACTH-producing pituitary adenoma was reported in 1975 (4). Several possibilities have been proposed regarding the origin of ectopic pituitary tumors (5), which have been reported to occur in various parts of the cranial cavity. In the present case, the adenoma was distinct from the normal pituitary gland revealed by MRI or pathological analysis. It is generally accepted that the most effective treatment for ACTH-secreting adenomas is surgical resection, which can be beneficial, however, this is not always possible (6). Surgical removal of the adenoma was our preference for treatment in this patient, however, her adenoma had become significantly enlarged during a one month period of treatment. Furthermore, she was seriously ill due to severe pneumonia. Therefore, we chose fractionated external beam radiotherapy, which has been shown to achieve control of hypercortisolemia in approximately 50-60% of patients within 3-5 years of their initial pituitary surgery (7-9). In the case of ectopic ACTH syndrome, tumor-directed therapy can include somatostatin analogs, systemic chemotherapy, interferon-α, chemoembolization, radiofrequency ablation, and radiation therapy (10-13). Ectopic ACTH-pituitary adenoma does not generally express somatostatin receptors, however, ectopic ACTH-secreting tumors often express somatostatin receptors (14). Thus, octreotide therapy can produce a rapid and sustained reduction of ACTH and cortisol levels in patients with ectopic ACTH-secreting tumors.

According to previously reported subcutaneous injections of 100 μg octreotide, this case was rare since octreotide failed to improve hypercortisolism (15).

Cushing’s syndrome can be life-threatening when plasma cortisol levels are extraordinarily high. Bakker et al. (16) described a case of Cushing’s syndrome with severe hypercortisolism that was complicated by simultaneous infections with multiple opportunistic pathogens, such as Staphylococcus aureus. In the present case, similarly, it was notable that severe sepsis and pneumonia caused by MRSA were related to severe hypercortisolism. The high level of plasma cortisol may interfere with the clearance of bacteria, as indicated by the number of events associated with aberrant host defense system, such as abscess, pneumonia, and osteomyelitis.

Since the present patient failed to respond to primary radiation therapy, we administered metyrapone as a medical therapy to reduce cortisol levels. Metyrapone has been reported to cause an acute reduction in serum cortisol levels within several hours in all types of Cushing’s syndrome. Furthermore, escape is rare after achieving successful con-
control of cortisol levels (17). Although metyrapone success-
fully reduced serum cortisol levels in our case, the patient’s
condition deteriorated and she died of septic shock three
months after the initial admission. Thus, care must be taken
to prevent infection prior to the initiation of metyrapone to
reduce cortisol levels in markedly hypercortisolemic pa-
tients.

In summary, we report a case of Cushing’s syndrome due
to the presence of an ectopic ACTH-producing pituitary ade-
noma within the sphenoid sinus. The risk of severe infection
is known to increase with serum cortisol levels of greater
than 40 μg/dL (1). Regardless of the ultimate treatment plan,
marked hypercortisolemia should first be treated to prevent
the development of severe infection, regardless of the loca-
tion of the ACTH-producing tumor.

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