Refractory Post-herpetic Neuralgia as an Initial Presentation of Olfactory Neuroblastoma-Related Ectopic ACTH Syndrome

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SUMMARY
We report a woman aged 64 years with ectopic adrenocorticotropic hormone (ACTH) syndrome caused by olfactory neuroblastoma as an initial presentation of refractory post-herpetic neuralgia. The manifestations such as cushingoid appearance and endocrine abnormalities are compatible with Cushing’s syndrome. Brain computed tomography revealed a sellar mass. A biopsy revealed olfactory neuroblastoma. Immunohistochemical staining further defined the tumor as an ACTH-secreting neuroblastoma. Subsequent opportunistic infections by Candida glabrata fungemia and multiple drug-resistant Acinetobacter baumannii pneumonia occurred during hospitalization as a complication of severe hypercortisolism. Before any therapy for Cushing’s syndrome and neuroblastoma could be initiated, the patient died from sepsis and multiorgan failure. We propose that Cushing’s syndrome is more complex than what clinicians thought, and that meticulous cerebral imaging studies are crucial. [International Journal of Gerontology 2009; 3(1): 81–84]

Key Words: Cushing’s syndrome, hypercortisolism, olfactory neuroblastoma, opportunistic infection

Introduction
Ectopic Cushing’s syndrome due to olfactory neuroblastoma is extremely rare. There have been only six cases of adults with pathologically proven ectopic adrenocorticotropic hormone (ACTH)-producing olfactory neuroblastoma in the literature¹–⁶. Most cases of ectopic ACTH-producing tumors have been shown to be malignant and systemically influential in nature, ranging from small cell lung carcinoma, bronchial carcinoid to medullary thyroid carcinoma and breast tumor⁵. Here, we present a Taiwanese woman aged 64 years with olfactory neuroblastoma linked to ectopic ACTH syndrome. Its mechanism and pathophysiology are closely delineated.

Case Report
A Taiwanese woman aged 64 years with fairly well-controlled non-insulin-dependent diabetes mellitus, dyslipidemia and essential hypertension had regular follow-ups to her personal primary physician clinic. Unfortunately, 4 months prior to admission, she started to complain of general weakness. An obtunded mental state was also observed by her family. She was thus brought to the neurology clinic for evaluation. Physical examination produced unremarkable findings except ulcerative herpes zoster patches over the right anterior chest wall. Neurologic examination revealed altered mental testing and disorientation to time, space and
person. Cerebral computed tomography and magnetic resonance imaging disclosed a mass involving the upper clivus and sphenoid sinus (Figure 1).

Electroencephalography elucidated a diffuse slow-wave pattern (Figure 2). Intractable herpetic neuralgia pain was managed by an anesthesiologist through potent pain killers with limited effects. She presented to the emergency department with a temperature reaching 39°C for 2 days in June 2008. Initial chest roentgenogram showed pneumonia patches in the bilateral lower lung fields. She was, therefore, admitted for advanced treatment. Physical examination showed a cushingoid appearance (moon face, prominent supraclavicular fat pads, truncal obesity, and easy bruising), high blood pressure and 2+ pitting edema of the lower extremities.

During hospitalization, a lumbar puncture showed insignificant findings. Laboratory results revealed a high ACTH and cortisol level (ACTH, 89.4 pg/mL; morning cortisol, 73.5 μg/dL; 24-hour urine cortisol, >600 μg/24-hour total volume), hypokalemia, metabolic alkalosis, and hyperglycemia alongside prominent leukocytosis. Endocrine tests revealed a nonsuppressible response to a low-dose dexamethasone suppression test (LDDST) (plasma cortisol level was 133 μg/dL after LDDST). These endocrinologic findings matched a diagnosis of ACTH-dependent Cushing’s syndrome.

A culture of the sputum yielded multiple drug-resistant Acinetobacter baumannii in three out of three sets. A culture of the blood yielded the presence of Corynebacterium species and Candida glabrata in one of two sets.

She was immediately treated with meropenem, colistimethate, vancomycin and caspofungin on account of her previously immunocompromised state. A biopsy over the sphenoid sinus was confirmed to be olfactory neuroblastoma (Figure 3A). Immunohistochemical staining further identified the tumor as an ACTH-secreting neuroblastoma (Figures 3B–D). Despite empirical antibiotic treatment, her clinical status still progressed to respiratory failure. An endotracheal tube was inserted with mechanical ventilation for respiratory support. Before any emergent therapy could be launched, the patient’s condition became aggravated because of severe sepsis, and she died shortly thereafter.

Discussion

Ectopic Cushing’s syndrome due to olfactory neuroblastoma is not often seen1,7. There have been only six cases in adults with pathologically proven ectopic ACTH-producing olfactory neuroblastoma recorded in the literature1–5,8. The elevated glucocorticoid levels often lead to immunosuppression, and infection is common. Ectopic ACTH syndrome with olfactory neuroblastomas shows increased susceptibility to infection by unusual organisms2,7,9. An opportunistic infection is less likely to occur in patients with pituitary Cushing’s disease than those with higher levels of cortisol overproduction from adrenal tumors or because of ectopic ACTH secretion9,10. In a 1998 review by Bakker and...
colleagues\textsuperscript{6}, only 36 patients were described during a 40-year period to have opportunistic infections secondary to endogenous Cushing’s syndrome. Fungi were the most commonly isolated pathogens; \textit{Aspergillus fumigatus}, \textit{Pneumocystis carinii}, and \textit{Cryptococcus neoformans} predominated\textsuperscript{6}. Other unusual infections included \textit{Toxoplasma}, \textit{Cryptosporidium}, the herpes viruses (\textit{Cytomegalovirus}, herpes simplex, and varicella-zoster), \textit{Mycobacterium tuberculosis}, \textit{Mycobacterium avium-intracellulare}, and \textit{Listeria monocytogenes}\textsuperscript{10}.

Patients with serum cortisol concentrations above 40 μg/dL (1,100 nmol/L), urinary cortisol excretion greater than 2,000 μg/day (5,500 nmol/L), or urinary 17-hydroxycorticosteroid excretion greater than 35 mg/g creatinine (96 μmol/g creatinine) are likely to suffer severe infections\textsuperscript{10}. Among the endogenous Cushing’s syndrome subtypes, invasive fungal infections are much more prevalent with ectopic ACTH production, probably because of extremely high plasma cortisol concentrations\textsuperscript{9}. Glucocorticoids enhance adhesion of \textit{Candida} species to epithelial cells. Studies in mice have shown that glucocorticoids increase both the \textit{Candida albicans} burden in the gastrointestinal tract and, indirectly, the frequency of \textit{C. albicans} translocation from the gastrointestinal tract to the bloodstream\textsuperscript{9}. Prompt correction of hypercortisolism with pharmacology, surgery, or both, and aggressive antifungal treatment, usually resolves infections and greatly reduces the risk of recurrence\textsuperscript{9}. Ectopic production of ACTH by a non-pituitary tumor accounts for 12% of all cases of Cushing’s syndrome and is usually caused by small-cell lung cancer or by bronchial carcinoid tumors\textsuperscript{3,5,7,10}. Olfactory neuroblastomas secrete plenty of neuroendocrine hormones, which may cause immunosuppression.

Olfactory neuroblastomas typically present with nasal congestion or obstruction, epistaxis, nasal discharge, or headache\textsuperscript{11}. In our case, none of these symptoms were noted, which could mislead medical doctors to diagnose either a common cold or sinusitis.
Our patient presented with symptom of mere herpes neuralgia, and we failed to track back its cause. Cushing’s syndrome was proven to beguile itself in a form of metabolic encephalopathy because of hypercortisolism from the olfactory neuroblastoma and exacerbated by an immunocompromised state. Ultimately, an upper respiratory tract infection led to systemic sepsis. Neither an anesthesiologist nor a neurologist could easily unravel this malady firsthand. This connection was not able to be found until cerebral imaging studies were arranged. The optimal therapy for the ectopic ACTH syndrome is surgical excision of the tumor\(^2,5,10\), but this action would not have occurred in time to stop the dramatic deterioration.

First-line clinicians should be alert and learn a lesson from this patient. Prompt evaluation of the cause of the hypercortisolism, initiation of cortisol lowering therapy and a search for concomitant infectious disease is vital.

References