INTRODUCTION

Esthesioneuroblastoma (olfactory neuroblastoma) is a rare sinonasal tumor originating from the olfactory neuroepithelium. Ectopic adrenocorticotropic hormone (ACTH) syndrome is defined as an abnormal elevation of plasma ACTH secreted from a source other than a pituitary or an adrenal gland. New technology that uses radiolabeled somatostatin analogs, such as 68Ga-DOTA-conjugated positron emission tomography (PET), is useful in detecting an unidentified ectopic ACTH-producing neuroendocrine tumor. Here, we report a case of esthesioneuroblastoma in which 68Ga-DOTA-conjugated PET was extremely useful.

CASE REPORT

History and examination

A 46-year-old man without significant medical history presented with general weakness and hyposmia, and underwent examination with serial endocrinological workup and brain imaging. 68Gallium-DOTA-TOC positron emission tomography scan was helpful where diagnosis of sellar MRI and inferior petrosal sinus sampling were discordant. Combined transcranial and endoscopic endonasal approach surgery was performed, and a diagnosis of esthesioneuroblastoma was given.

Key Words: Cushing’s disease; ectopic ACTH syndrome, esthesioneuroblastoma; positron emission tomography

Operation

Under the impression of an esthesioneuroblastoma causing...
Ectopic Cushing’s syndrome, the tumor was surgically resected. First, the intranasal portion of the tumor was removed by an endoscopic endonasal approach (Supplementary Video 1 only online). The tumor was very soft and hypervascular. We then performed transcranial tumor removal via a bifrontal craniotomy and an extradural approach. The tumor was radically removed together with surrounding dural layer and the anterior skull base. The galeal flap was harvested and used to cover the skull defect. From the nasal cavity, the skull defect was covered by a nasoseptal flap. Lumbar puncture was maintained until 13 days after surgery. After the surgery, the patient was closely monitored in the intensive care unit with regular measurement of serum ACTH, cortisol, and 24-h urinary free cortisol levels.

Histopathological findings
The histopathological diagnosis was that of an esthesioneuroblastoma with Hyams grade I (Fig. 2A). Immunohistochemical staining for ACTH was positive (Fig. 2B). The stains for neuron-specific enolase, synaptophysin, and chromogranin A, which are suggestive of neuroendocrine features, were positive (Fig. 2C and D). Anti T-Pit stain, a reliable corticotroph marker, was negative and disfavored an ectopic ACTH-secreting pituitary adenoma (Fig. 2E). Taken together, the histopathological findings were consistent with ACTH-secreting esthesioneuroblastoma.

Postoperative course
The serum levels of both cortisol and ACTH rapidly dropped to...
7.3 mcg/dL and 26.94 pg/mL at 12 hours after surgery and to 17.9 mcg/dL and less than 0.1 pg/mL on postoperative day 3. No remnant tumor was identified in 24-h postoperative brain MRI. After 1 month, the patient underwent adjuvant radiotherapy (total 55 Gy in 25 fractions). 12-month postoperative MRIs showed no recurrence (Fig. 1D). DMST results and 24-h urine free cortisol levels were all normal at 3 months after surgery. Serum cortisol and plasma ACTH levels were 8.4 mcg/dL and 40.00 pg/mL, respectively, at 12 months after surgery. To date, the patient is uneventful.

### Table 1. Preoperative endocrinological and radiological evaluation

| Study                             | Results                                                                 |
|-----------------------------------|-------------------------------------------------------------------------|
| **Basal hormone test**            | Serum cortisol 70.1 mcg/dL (reference: 6–23 mcg/dL)                     |
|                                   | Plasma ACTH 291.4 pg/mL (reference: 7.2–63.3 pg/mL)                     |
|                                   | 24 hr-urine cortisol 7665 mcg/day (reference: 58.00–403.00 mcg/day)     |
| **Low-dose DMST**                 | Serum cortisol 39.9 mcg/dL, Plasma ACTH 218.90 pg/mL                   |
| **High-dose DMST**                | Serum cortisol 34.8 mcg/dL, Plasma ACTH 159.10 pg/mL                   |
| **IPSS**                          | Left inferior petrosal sinus dominant                                   |
|                                   | Basal inferior petrosal sinus/peripheral 2.4 (Reference: >2.0)         |
| **Sellar dynamic MRI**            | No evidence of pituitary adenoma                                       |
|                                   | Tumor in the sinonasal cavity with intracranial and intraorbital extension|
| **68Gallium-DOTA-TOC PET**        | Suggesting neuroendocrine tumor in nasal cavity                        |
|                                   | Normal hot uptake of pituitary grand                                   |
| **Whole body bone scan**          | No distant metastasis                                                  |

ACTH, adrenocorticotropic hormone; DMST, dexamethasone suppression test; IPSS, inferior petrosal sinus sampling; MRI, magnetic resonance imaging; PET, positron emission tomography.

**Fig. 2.** High-power view of H&E staining shows small- to medium-sized neoplastic cells with lobulation. Necrosis and mitosis are not seen. Immunohistochemistry (IHC) staining for various cell markers revealed positive staining for adrenocorticotropic hormone (ACTH), neuron-specific enolase (NSE), and chromogranin A and negative staining for T-Pit. (A) H&E ×200, (B) ACTH-IHC ×200, (C) NSE-IHC ×200, (D) Chromogranin A-IHC ×200, and (E) T-Pit-IHC ×200.

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DISCUSSION

Esthesioneuroblastoma is a rare sinonasal tumor, that can extend to the paranasal sinuses, orbital cavity, and anterior cranial fossa. Ectopic ACTH syndrome comprises 5–20% of Cushing’s syndrome. Esthesioneuroblastoma as a hormone-secreting tissue was first identified in 1967 as a syndrome of inappropriate antidiuretic hormone presentation, and ACTH-secreting esthesioneuroblastoma was first described in 1987.

Endocrinological workup to diagnose Cushing’s disease includes low- and high-dose DMST, IPPSS, and corticotropin releasing hormone stimulation test. When IPPSS is suggestive of pituitary ACTH secretion and MRI fails to localize a tumor in a sellar region, a dilemma arises as to whether to seek an explorative operation or not. In our case, 68Ga-DOTA-conjugated PET greatly helped in localizing the source of ACTH secretion in the nasal cavity and not performing unnecessary pituitary surgery. In fact, if an ectopic ACTH source is located upstream of the nasal cavity and not performing unnecessary pituitary surgery. This is the first report to utilize 68Ga-DOTA-conjugated PET clearly demonstrated that the source of ACTH secretion was not the pituitary gland, but a tumor in the nasal cavity. This is the first report to utilize 68Ga-DOTA-conjugated PET to diagnosis undetected ACTH-secreting esthesioneuroblastoma.

The endoscopic endonasal approach provides great accessibility and visibility without extensive destruction of the craniofacial vault. However, in this case, because the tumor had invaded multiple paranasal sinuses and the anterior skull base, as well as part of the frontal lobe (Kadish stage C), we accessed the tumor with combined endonasal and transcranial approaches. A high likelihood of local recurrence in the Kadish stage C tumor necessitated adjuvant radiotherapy after the surgery. Some have advocated the usefulness of chemotheraphy, especially in the case of cervical metastasis or high histological grade (Hyams grade III or IV). Because the histological grade of the tumor in this case was Hyams grade I and radical tumor removal was achieved, the patient did not undergo chemotherapy.

Without question, careful surveillance is mandatory in advanced esthesioneuroblastoma. Not only regular MRI check-up, but also 68Ga-DOTA-conjugated PET is useful for surveillance. Furthermore, measuring serum cortisol and plasma ACTH directly provides helpful information. Kanno, et al. has proposed that measurement of tumor-associated hormones is important for surveillance. Despite the potential for some unforeseen difficulties, we emphasize that using 68Ga-DOTA-conjugated PET and monitoring ACTH and cortisol levels comprise a reliable and convenient way through which to check for recurrence in ectopic ACTH-secreting esthesioneuroblastoma.

SUPPLEMENTARY DATA

Video 1. Removal of intranasal part of the tumor under endoscopic endonasal approach. Intranasal part of the tumor was approached under endoscopic visualization. After identification of the tumor, en bloc resection was attempted rather than piecemeal resection. As the tumor showed high vascularity, meticulous coagulation and cutting was repeated along the attachment to the nasal roof antero-posteriorly. Finally, the tumor mass was separated from the nasal roof and the entire intranasal part of the tumor was removed in one piece.

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AUTHOR CONTRIBUTIONS

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