

Synchronous Esthesioneuroblastoma and Growth-Hormone-Secreting Pituitary Macroadenoma: Combined Open and Endoscopic Management

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Abstract

Background Esthesioneuroblastoma is an uncommon malignant neoplasm that arises from the olfactory neuroepithelium. In this article we report a case of esthesioneuroblastoma presenting concomitantly with a growth-hormone (GH)-secreting pituitary macroadenoma.

Results A 52 year old woman underwent surgery for suspected nasal polyps. Intralesional debulking of an intranasal tumor disclosed a low-grade esthesioneuroblastoma. Magnetic resonance imaging (MRI) demonstrated a large nasal and intracranial tumor, in addition to a separate sellar and suprasellar tumor. The patient was frankly acromegalic. She underwent a first-stage gross total resection of the esthesioneuroblastoma via a combined extended subfrontal and extended endonasal approach, followed by focused radiation therapy. She then returned for endoscopic removal of the GH-secreting pituitary macroadenoma.

Conclusion The combined open and endoscopic management of this patient is described and a review of the literature presented. To our knowledge this is the first case of synchronous esthesioneuroblastoma and macroadenoma, in this case GH secreting, described in the literature.

Keywords

- ▶ esthesioneuroblastoma
- ▶ pituitary adenoma
- ▶ acromegaly
- ▶ endoscopic skull base surgery
- ▶ craniofacial resection

Introduction

Esthesioneuroblastoma is an uncommon malignant neoplasm that arises from the olfactory neuroepithelium¹ and is typically located in the upper nasal cavity and cribriform plate.² In this article we report a case of esthesioneuroblastoma presenting concomitantly with a growth-hormone (GH)-secreting pituitary macroadenoma. The combined open and endoscopic management of this patient is described, and a review of the literature presented.

Case Report

The patient is a 52-year-old woman who presented with a 9-month history of recurrent sinusitis refractory to a repeated course of antibiotics. She was seen by an outside ear nose and throat surgeon who operated on her for suspected nasal polyps. A partial debulking of an intranasal lesion disclosed a low-grade esthesioneuroblastoma. She complained of right orbital pain postoperatively and was

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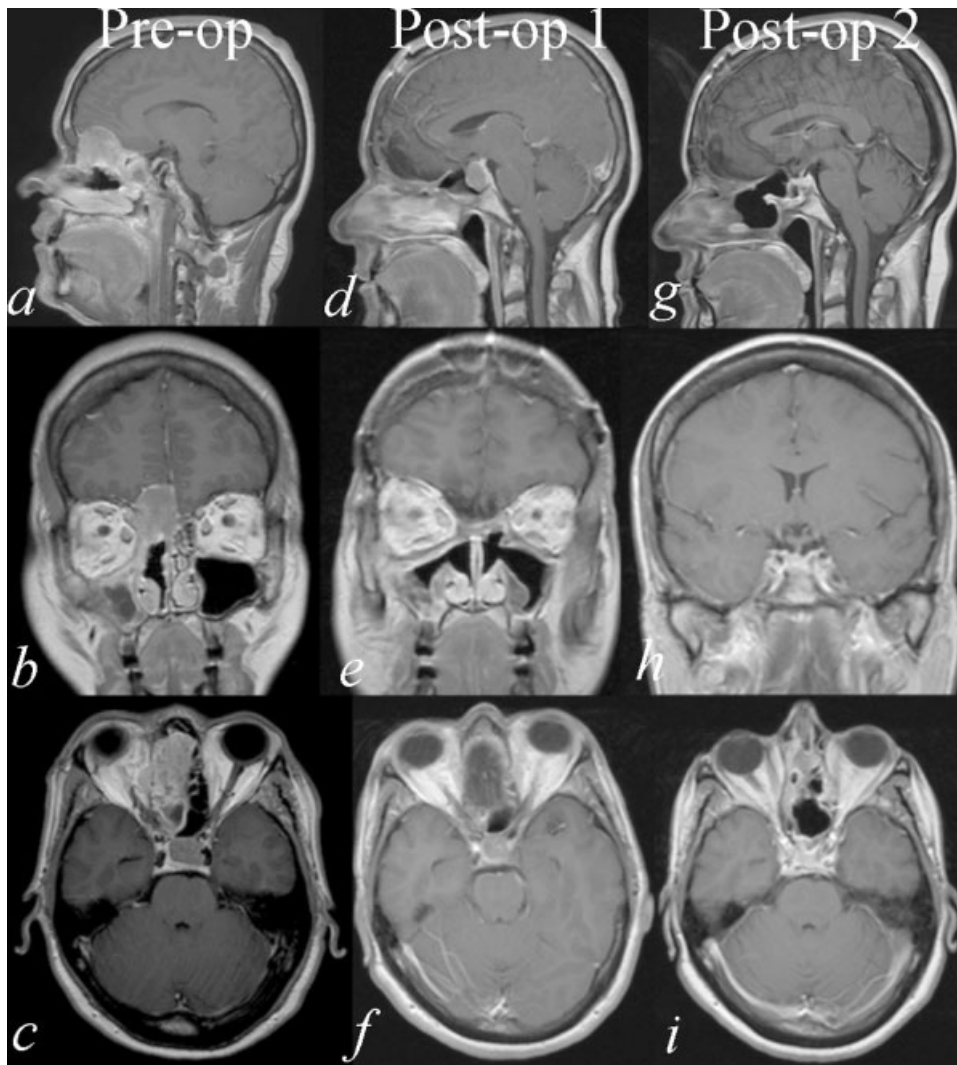


Fig. 1 (A) Sagittal, (B) coronal, and (C) axial T1 weighted magnetic resonance imaging (MRI) with gadolinium demonstrating anterior skull base esthesioneuroblastoma with involvement of the right lamina papyracea and extension through the cribriform plate and dura, and a noncontiguous pituitary macroadenoma. (D–F) MRI after initial gross total resection of esthesioneuroblastoma. (G–I) MRI after a second-stage endoscopic transsphenoidal resection of pituitary macroadenoma, with reconstitution of the normal residual pituitary gland.

also treated for a postoperative sinusitis. In retrospect, she admitted to a 4-month history of anosmia, although she denied any alteration of taste. Neurosurgical clinical evaluation revealed frank acromegalic features. Visual acuity was 20/30-1 in both eyes with a very mild bitemporal hemianopia. Her eye movements were full and facial sensation was normal. Subsequent computed tomography and magnetic resonance imaging (MRI) of the brain and sinuses demonstrated an enhancing mass along the anterior skull base with extension through the right cribriform plate, with a lobular component displacing the right gyrus rectus, along the right medial orbital wall and into the nasal cavity. Also seen was a large sellar and suprasellar unrelated macroadenoma (►Fig. 1). A preoperative cervical MRI was negative for metastatic disease.

Her preoperative insulinlike growth factor (IGF)-1 level was 154.00 nmol/L (normal: 7.60–25.20 nmol/L), and prolactin was mildly elevated at 36.2 µg/L (normal: 3.9–29.5 µg/L). In light of the tumor size, the right lamina papyracea destruction, and significant intradural involvement, the tumor stage

was classified as T4N0M0 based on the Dulguerov TNM system³ and Kadish stage C.⁴ A recommendation of staged resection of the esthesioneuroblastoma followed by the pituitary macroadenoma was made. For the first stage, a combined open and endoscopic resection was proposed, to facilitate a true en bloc resection and to harvest a generous pericranial flap for repair. Following this, the patient would undergo stereotactic radiation to the tumor bed, and she would return electively for endoscopic resection of the pituitary macroadenoma.

The first-stage operation was performed as follows. An extended subfrontal approach was completed first, consisting of a bicoronal incision, bifrontal craniotomy, and bilateral orbital osteotomy sparing the cribriform plate. The tumor was immediately identified violating the dura. A generous extracapsular dissection of the intradural portion of the tumor was completed as well as a wide dural incision around the tumor, including posteriorly at the posterior aspect of the planum sphenoidale. The endonasal endoscopic approach was then performed (►Fig. 2), consisting of

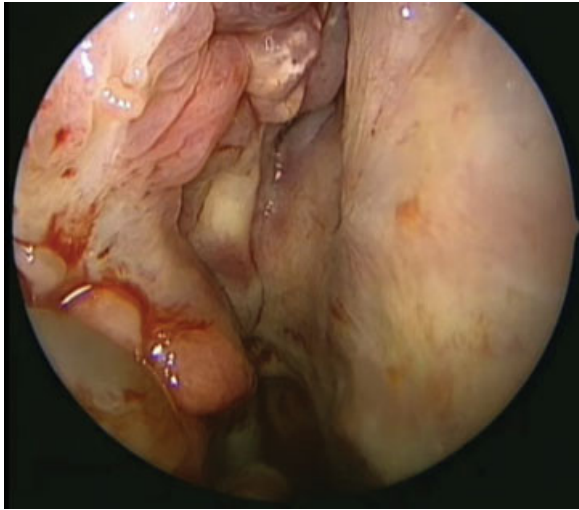


Fig. 2 Endonasal endoscopic view of esthesioneuroblastoma with exophytic growth in the right nasal cavity.

a right middle turbinectomy, complete sphenoidectomies, and a superior septectomy. The lamina papyracea component of tumor was resected with the aid of a handheld retractor protecting the periorbital from the orbitotomy above (►Video 1). The anterior and posterior ethmoidal arteries were cauterized and divided. The left side of the planum was drilled out as was the posterior planum, releasing the tumor as a single specimen. As such, an en bloc resection was completed without violation of the tumor. The dural defect was reconstructed with a free pericranial graft, and a second pedicled pericranial flap was mobilized over the dural closure prior to replacement of the orbital osteotomy and craniotomy flap. Postoperatively she developed symptomatic pneumocephalus that was thought to be secondary to lumbar drain placement. The pneumocephalus resolved with 100% oxygen and discontinuation of the lumbar drain. There were no other complications postoperatively, and the patient was discharged home on postoperative day 7. The rationale for staging was to avoid potential complications during the esthesioneuroblastoma resection, such as a separate cerebrospinal fluid (CSF) leak or hypopituitarism, and possibly delaying adjuvant radiation therapy. Following complete resection of the esthesioneuroblastoma and radiation therapy, the patient returned to electively manage the pituitary tumor.

Video 1

Combined open and endoscopic resection of esthesioneuroblastoma.
 Online content including video sequences viewable at:
www.thieme-connect.com/products/ejournals/html/10.1055/s-0034-1372472.

Pathologic examination (►Fig. 3) revealed a small blue cell tumor arranged in lobules and with mild nuclear pleomorphism. Rosettes were infrequent. There was positive staining for chromogranin A and synaptophysin. Sustentacular cells were present and stained positive for S-100 protein. The specimen was consistent with a Hyams grade 2 esthesioneuroblastoma.⁵ Postoperative MRI confirmed gross total resection of the esthesioneuroblastoma (►Fig. 1D–F). Postoperatively, the patient underwent fractionated intensity-modulated radiation therapy to the resection area. A total of 60 Gy over 30 fractions were administered, after which six cycles of carboplatin and paclitaxel were given.

As a second stage, 8 months following the first surgery, the patient underwent a complete endoscopic transsphenoidal removal of the pituitary macroadenoma (►Fig. 4). There was a mild intraoperative CSF leak at the end of the resection, and a right nasoseptal flap was harvested in this case to repair the sella as well as autologous fascia lata. The pericranial repair from the craniofacial resection site was pristine. She was discharged home on postoperative day 2 without complications. Pathology for the pituitary tumor was consistent with a pituitary adenoma, with both prolactin and GH positivity (►Fig. 3D). By 2-week follow-up, there was marked improvement in her acromegalic features, the patient's facial complexion had improved and the finger breadth diminished (►Fig. 5).

Postoperatively, her IGF-1 level normalized, from 154.00 to 22.00 nmol/L, consistent with endocrinologic cure.⁶ The remainder of her pituitary hormonal panel is otherwise normal. Her last ophthalmologic assessment revealed 20/20-1 visual acuity in both eyes with no evidence of optic neuropathy or visual field deficit. Her most recent MRI demonstrated complete resection of the pituitary macroadenoma with reconstitution of the normal residual pituitary gland (►Fig. 1G–I). The patient remains free from recurrence of esthesioneuroblastoma through 14 months thus far.

Discussion

To our knowledge this is the first case of synchronous esthesioneuroblastoma and macroadenoma, in this case GH secreting, described in the literature. Esthesioneuroblastoma has been described as a secondary tumor occurring many years after treatment for pituitary neoplasms,^{7,8} presumably from radiation therapy. Several cases of primary intrasellar esthesioneuroblastoma or neuroblastoma in the absence of pituitary adenoma have also been reported.^{9–17} Esthesioneuroblastoma can mimic pituitary adenomas in imaging appearance, and misdiagnoses of pituitary adenoma have been reported.¹⁸ Positive immunoreactivity for neuron-specific enolase and synaptophysin are distinguishing features.²

No etiologic basis or risk factors for esthesioneuroblastoma formation have been described, although several cases have been identified following radiation therapy or exposure^{19–21} including two cases following remote radiation for pituitary adenomas.^{7,8} One case of esthesioneuroblastoma was described followed kidney transplant and

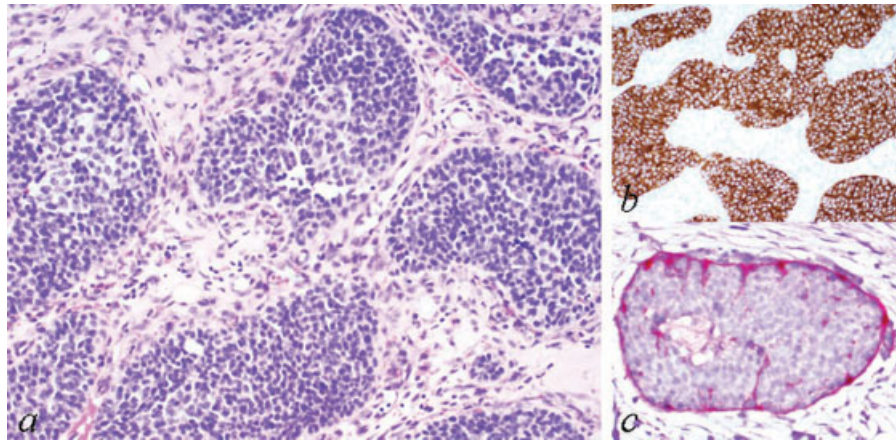


Fig. 3 (A) Hematoxylin and eosin preparation demonstrating a small blue cell tumor arranged in lobules and with mild nuclear pleomorphism. (B) There was positive staining for chromogranin A and synaptophysin. (C) Sustentacular cells were present and stained positive for S-100 protein. The specimen was consistent with a Hyams grade 2 esthesioneuroblastoma. (D) In a second stage, a typical pituitary macroadenoma was removed.

immunosuppression therapy.²² Very rarely esthesioneuroblastoma presents in association with ectopic adrenocorticotropic hormone secretion.²³

Patients with acromegaly have an increased risk of several neoplasms including colorectal and thyroid cancer and pos-

sibly breast, prostate, and hematologic malignancies.²⁴ Both GH and IGF-1 are known to promote cellular growth and proliferation, and they may also have mitogenic, proangiogenic, and antiapoptotic properties.^{25,26} Several authors have observed an association between high serum IGF-1

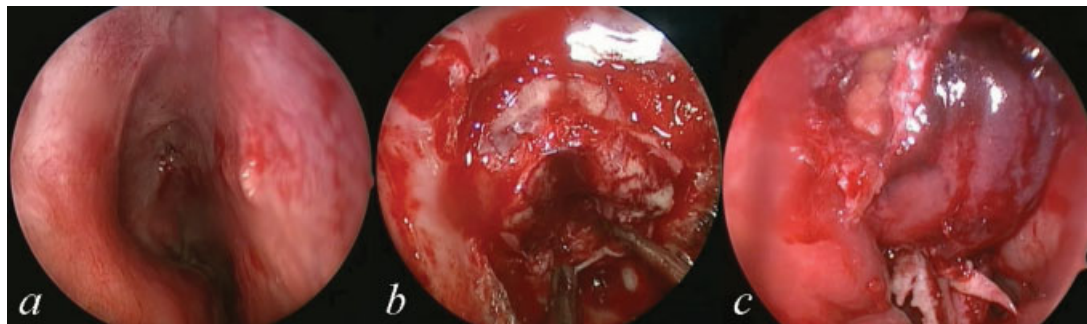


Fig. 4 Stage 2 resection of the pituitary macroadenoma. (A) Endoscopic view right nasal cavity demonstrating pristine pericranial repair of anterior skull base resection. (B) Transsphenoidal resection of pituitary macroadenoma with (C) nasoseptal flap reconstruction.



Fig. 5 (A) Patient postoperative day 2 combined open and endoscopic resection of esthesioneuroblastoma. (B) Patient 2 weeks after endoscopic resection of growth-hormone-secreting pituitary macroadenoma, demonstrating early resolution of acromegalic facies.

levels and colorectal malignancy in acromegalic patients.²⁷⁻²⁹ A meta-analysis of 21 studies and 3609 cases found associations between high IGF-1 levels and prostate and premenopausal breast cancer.³⁰ In a prospective study, fasting and 2-hour GH levels were also associated with increased mortality from combined malignancies among nonacromegalic cohorts.³¹ Other possible mechanisms of carcinogenesis include altered cellular immunity, related to an altered lymphocyte subset pattern. Colao et al found a significant reduction in cluster of differentiation (CD) 19 and 20, and an increase in CD3 from the lamina propria of polyps in patients with acromegaly.²⁸

Standard surgical management of anterior skull base malignancies including esthesioneuroblastomas is typically in the form of an open craniofacial resection. The management of malignant tumors of the anterior skull base has received considerable attention in the recent literature owing to increasing trends of purely endoscopic or combined open and endoscopic oncologic resection. In one meta-analysis of all sinonasal malignancies, no statistically significant difference in outcome between open and endoscopic resection was found for low-grade (T1-2 or Kadish A-B) malignancies.³² A second meta-analysis for esthesioneuroblastomas including 379 subjects did not demonstrate inferiority of purely endoscopic resection; however, the authors acknowledge significant sources of error from publication bias, limited follow-up duration, and more advanced tumor stage in the open craniofacial resection group.³³ In a multicenter study incorporating 23 patients, complete resection was achieved in this carefully selected cohort in 17 of 23 patients.³⁴ CSF leaks occurred in 4 of 23 patients. All patients were disease free at a mean follow-up of 45.2 months. In summary, it remains to be determined whether true en bloc resection of esthesioneuroblastomas is superior to endoscopic intrasellar resection, albeit with negative margins.

Purely endonasal resection of anterior skull base malignancies has been generally reserved for patients with relatively earlier disease stage and no or limited skull base invasion.³⁵ Significant invasion of the fovea ethmoidalis or the cribriform plate, significant dural involvement or transdural spread,³⁵ involvement of the soft tissues of the face,³⁶ lateral extension over the orbital roof, extensive frontal sinus involvement, and invasion through the lamina papyracea into the intraorbital space all increase the level of difficulty of achieving a gross total resection via an endoscopic approach.³⁷ In our case, endoscopic visualization of the inferior cuts facilitated a true en bloc resection of the esthesioneuroblastoma, without the use of facial incisions or intrasellar debulking.

It is generally accepted that complete resection followed by adjuvant radiation therapy reduces the rate of local recurrence in patients with esthesioneuroblastoma³⁸ and improves disease-free survival.^{39,40} Chemotherapy remains a matter of debate in upfront treatment, with typical indications being high-grade, recurrent, metastatic, or unresectable tumors.⁴¹ In some centers, neoadjuvant chemotherapy has been used with success prior to standard craniofacial resection.^{42,43}

Conclusion

In this patient, complete resection of an esthesioneuroblastoma was achieved using a combined open craniofacial and endoscopic approach, followed by a complete endoscopic resection of a GH-secreting pituitary macroadenoma, resulting in endocrinologic cure. The relative indications and advantages of the expanded endonasal approach for anterior skull base malignancies are illustrated.

Note

Salvatore Di Maio had full access to all the data in the study and final responsibility for the decision to submit for publication.

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