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Nonfunctioning Ectopic Pituitary Adenoma: A Rare Case Report from Southern Asia

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Abstract

Ectopic pituitary adenoma (EPA) is an extraordinarily rare condition characterized by the presence of a pituitary adenoma outside the intrasellar region. Although EPA may share similarities with typical pituitary adenomas in morphology, radiological findings, immunohistochemistry, and hormonal activity, it can present with either nonspecific or specific endocrine symptoms. A 37-year-old female school teacher with persistent and worsening headaches underwent neuroimaging, which revealed a sizable extra-axial solid mass in the right parasellar region, extending into the cavernous sinus, base of the skull, and sphenoid sinus. This mass was initially indicative of a cavernous sinus meningioma. Laboratory investigations, including a pituitary hormone profile, yielded normal results. Despite the lack of typical symptoms, the patient underwent an elective right temporal craniotomy and subtotal tumor resection, which exposed both extra-axial and intra-axial components. Immunohistochemistry analysis confirmed the presence of a pituitary adenoma with atypical features. Postoperatively, the patient recovered well, and adjuvant stereotactic radiosurgery was used to address the residual lesion. During the 1-year follow-up, the patient remained free of symptoms. This case highlights the diagnostic complexities associated with nonfunctioning EPAs and underscores the importance of a comprehensive approach to ensure accurate diagnosis, effective treatment, and sustained patient well-being.

Keywords

- ectopic pituitary adenoma
- pituitary adenomas
- inactive ectopic pituitary adenoma
- cavernous sinus meningioma

Introduction

Ectopic pituitary adenomas (EPAs) are rare tumors typically found in the sphenoid sinus or nasopharynx.[1] They are likely to arise from residual pituitary fragments within the craniopharyngeal duct and share similarities with typical pituitary adenomas in morphology, immunohistochemistry, and hormonal activity.[2,3] Identifying these tumors presents significant challenges, especially when they are located at the skull base, often leading to diagnostic ambiguities. Computed tomography (CT) scans and magnetic resonance imaging (MRI) are crucial for their detection.[4]

When diagnosing an EPA, differential diagnoses include schwannomas (especially oculomotor or trigeminal nerve

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types) in the cavernous sinus or parasellar region; meningioma (cavernous sinus meningioma), a common extra-axial tumor in the parasellar region; chordoma, a rare bone tumor extending into the sphenoid or cavernous sinus; craniopharyngioma, a nonpituitary tumor in the sellar or parasellar region; pituitary hyperplasia, involving diffuse enlargement of the pituitary gland; metastatic tumors that may affect the cavernous or sphenoid sinus; lymphoma (primary or secondary) in the cranial or sinonasal region; and primary neuroendocrine tumors in the sinonasal tract or skull base.[1–3]

Establishing a diagnosis requires tumor resection and a thorough pathological examination, including immunohistochemical studies targeting neuroendocrine markers.[1,4] This report presents a unique case of an ectopic, nonfunctioning pituitary adenoma located in the right cavernous sinus, extending into the base of the skull and sphenoid sinus, and causing intermittent headaches in a young female school teacher.[5]

Case Report

A 37-year-old woman presented to the emergency department with persistent and worsening headaches that were not responding to oral analgesics. Despite normal vital signs and neurological exams during prior outpatient visits, her ongoing symptoms necessitated neuroimaging. MRI revealed a large extra-axial solid mass in the right parasellar region, extending into the right cavernous sinus, the base of the skull, and the sphenoid sinus, resembling a cavernous sinus meningioma (►**Fig. 1A–C**). She had no visual complaints, raised intracranial pressure, or other neurological deficits. Preliminary laboratory tests, including pituitary hormone levels, were normal. Digital subtraction angiography showed increased vascularity but made embolization unfeasible due to difficulties in catheterizing the thin vessels (►**Fig. 2A, B**). Guided by our senior author, a right temporal craniotomy was performed with the goal of gross total tumor resection. After achieving a subtotal excision (> 70%), unexpected bleeding from the slender vessels complicated the procedure. Intraoperatively, the tumor was dark pink, highly vascular, and observed in the arachnoid, exerting slight pressure on the optic nerve and abutting the 4th segment of the middle cerebral artery, with no bony erosions. Options for addressing the residual tumor included redo surgery or adjuvant stereotactic radiosurgery.

The frozen section suggested some intra-axial features, but the exact etiology remained unclear. Postoperatively, the

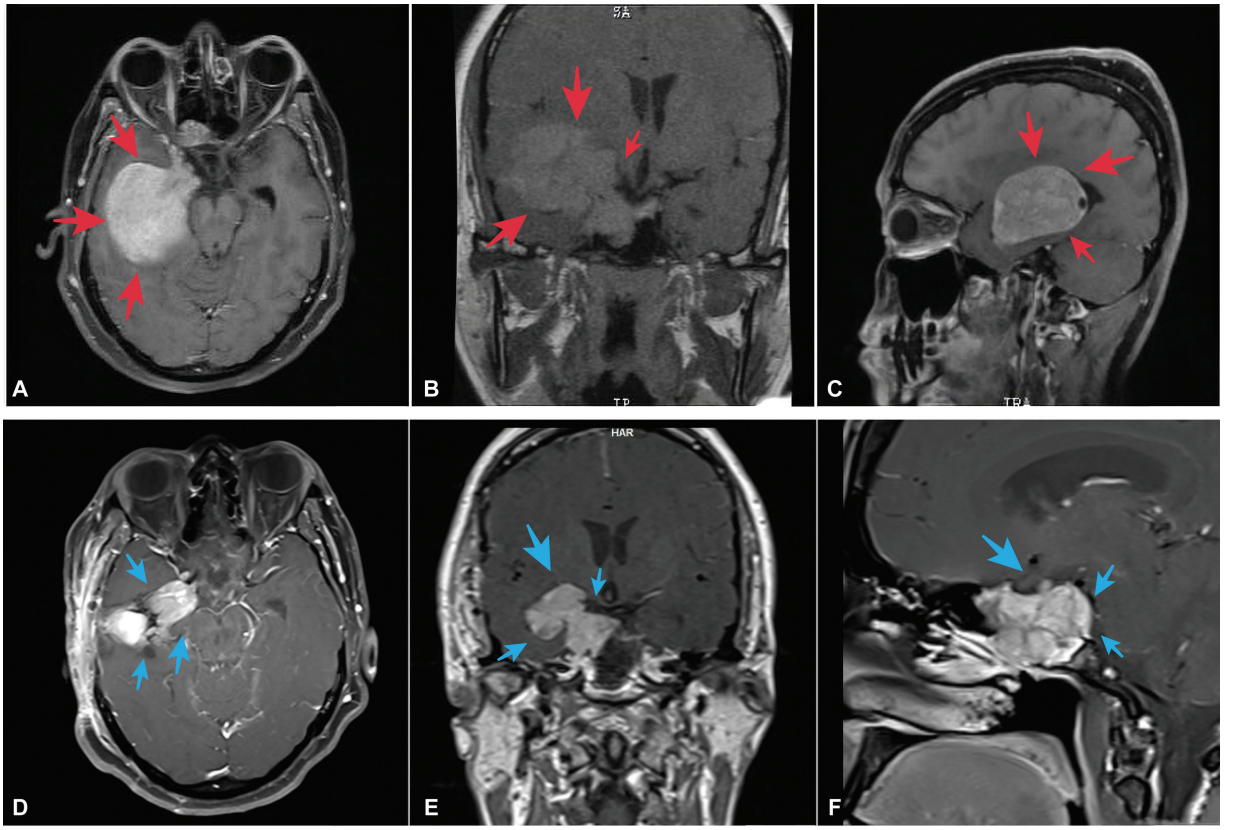

Fig. 1 (**A**–**F**) Preoperative (**A**: axial image, **B**: coronal image, **C**: sagittal image) and postoperative (**D**: axial image, **E**: coronal image, **F**: sagittal image). Magnetic resonance imaging (MRI) scans of the brain, allowing for comparison at similar levels. The preoperative transverse (axial) T1-weighted MRI scan of the brain showed a highly enhancing mass (5.4 × 4.5 × 4.5 cm) in the right parasellar region, indicative of aggressive tumor pathology, likely a cavernous sinus meningioma (**A**–**C**: red arrows). It extended into the right cavernous sinus, base of the skull, and sphenoid sinus, exerting pressure on adjacent structures. Compression and displacement of the left lateral ventricle were evident, with adjacent sulci showing signs of increased mass effect (**A**, **B**). Three and a half months after surgery, the postoperative MRI scan revealed a resection cavity surrounded by enhancement and gliosis, consistent with typical postsurgical findings (**D**–**F**: blue arrow). The sulci were more defined, and correction of the midline shift was observed, indicating successful lesion removal for symptomatic relief (**D**–**F**: blue arrow).

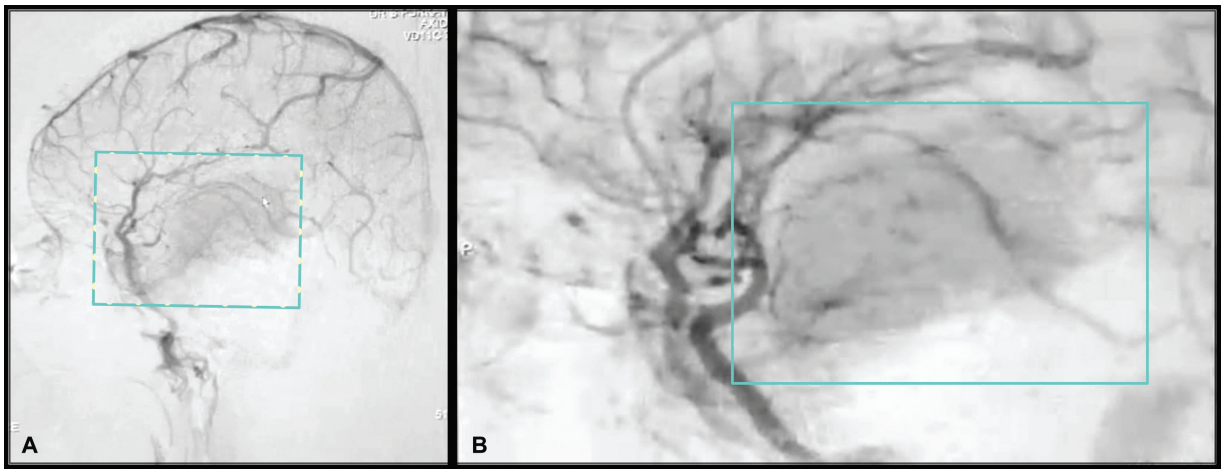

Fig. 2 (A, B) Preoperative findings from digital subtraction angiogram of the brain. A digital subtraction angiogram of the brain revealed a tumor blush (blue dotted box) from the right choroidal vessels. The right middle cerebral artery (MCA) Sylvian branches were shifted superolaterally, and the right carotid siphon was open. The remainder of the anterior and posterior circulation appeared normal in course, caliber, and branching pattern, with normal capillary and venous patterns.

patient had an uneventful recovery and was discharged on the 10th day in stable hemodynamic and neurological condition. Immunohistochemical examination showed diffuse positivity for synaptophysin and CD99, focal positivity for GATA binding protein 3 (GATA3), and positive pituitary-specific positive transcription factor 1, consistent with a pituitary adenoma (►**Fig. 3A, B**). Adjuvant stereotactic radiosurgery was performed for the residual lesion. Follow-up visits approximately every 3 months over the past year have shown that she is symptom-free with no new neurological complaints (►**Fig. 1D–F** and ►**Fig. 4**).

Discussion

EPAs are rare tumors located outside the sellar region, with approximately 1,000 cases reported since their first description in 1909.[1,3,6–8] Typically benign, EPAs lack a direct connection to normal pituitary tissue but can occasionally be malignant. They frequently occur in the sphenoid sinus or suprasellar regions and often present with nonspecific symptoms.[1–3,9] Although prolactinomas account for approximately 60% of pituitary adenomas, adrenocorticotropic hormone (ACTH)-secreting adenomas are less common but

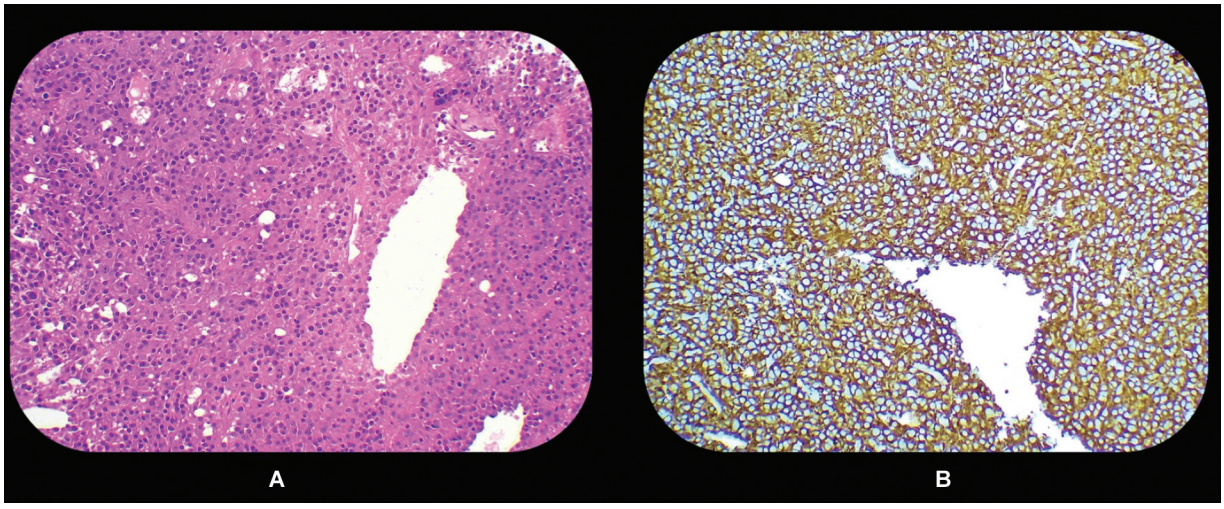

Fig. 3 Immunohistochemical slides (A), hematoxylin and eosin (H&E) stain, 100 × , and (B) immunoperoxidase stain, 200 × . Photomicrographs (A) show nests and trabeculae of monomorphic tumor cells with eosinophilic granular cytoplasm and uniform round nuclei (H&E stain, 100 ×). (B) Highlights diffuse strong synaptophysin positivity (immunoperoxidase stain, 200 ×), and CD99, focal positivity for GATA binding protein 3 (GATA3), and positive pituitary-specific positive transcription factor 1 (PIT1) consistent with a pituitary adenoma. The MIB-1 (Mindbomb homolog 1) labeling index indicated low proliferation (1–2% in the most proliferative areas), and tumor cells were positive for PIT1 but negative for TPIT (T-box pituitary transcription factor) and tyrosine hydroxylase. Additionally, tumor cells were negative for markers such as AE1/AE3 (cytokeratin antibodies), NeuN (neuronal nuclei), vimentin, GFAP (glial fibrillary acidic protein), Olig2 (oligodendrocyte transcription factor 2), EMA (epithelial membrane antigen), S100 (S100 proteins), STAT6 (signal transducer and activator of transcription 6), cytokeratin, LCA (leukocyte common antigen), CD68 (cluster of differentiation 68), CD138 (syndecan-1), and IDH1R132H (isocitrate dehydrogenase 1 R132H mutation).

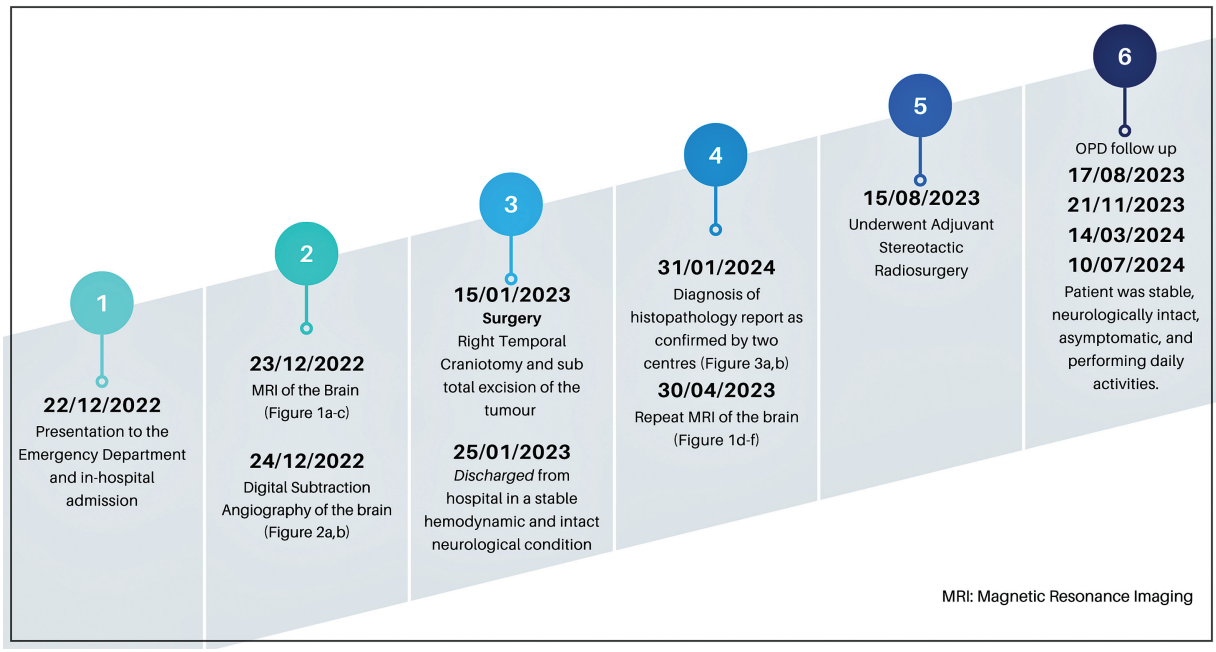

Fig. 4 A Memphis Design timeline graph illustrating the stages of treatment and overall impact.

are more frequent in EPAs.[1,7,8] EPAs are believed to arise from embryonic pituitary cell remnants that migrate along the path of Rathke's pouch.[1,2,8] The exact pathogenesis of EPAs remains unclear, with speculation that these remnants may have migrated to the sphenoid sinus and undergone neoplastic changes.

Diagnosis can be challenging due to the varied ways EPAs present. Isolated sphenoid sinus lesions can mimic EPAs, often presenting with symptoms such as headache and nasal obstruction.[3,9] Hormone-inactive EPAs, like the one observed in our case, may present with headaches, sinus fullness, nasal congestion, and cranial nerve paralysis. These tumors are often detected incidentally during routine imaging. Despite their potential for aggressive behavior, our case was detected early and did not exhibit aggressive features.

Endocrine evaluations and imaging studies, including MRI and CT, assist in differentiating EPAs, while endoscopic nasal examination is useful for detecting sphenoid sinus lesions.[2,10] An empty sella, commonly seen with EPAs, is indicative but not definitive.[7] Clival EPAs, which may present with mass effects or cranial nerve palsy, can be mistaken for other clival lesions such as chordomas, which have distinct imaging features.[6,11] Nasopharyngeal EPAs may also be misdiagnosed as chronic sinusitis due to their rarity. Accurate diagnosis requires ruling out primary hyperthyroidism and following standard procedures for inappropriate thyroid-stimulating hormone secretion.[7–9] Suprasellar and cavernous sinus EPAs may be confused with intrasellar pituitary adenomas, necessitating repeated MRI and careful review.[12]

ACTH-secreting EPAs, particularly in the suprasellar and cavernous areas, are more challenging to differentiate from intrasellar Cushing's disease. Nuclear medicine imaging, such as somatostatin receptor scintigraphy and 68 gallium-68 DOTATATE positron emission tomography/CT (PET/CT), can assist in detection, though its effectiveness varies.[13] Additionally, fluorine-18 fuorodeoxyglucose PET/CT is helpful in identifying recurrent or residual tumors.[13] Due to the rarity of EPAs, diagnosis is often confirmed postsurgery. Diagnostic features include a low mitotic count and specific immunohistochemical markers. Hormonally inactive EPAs typically show chromophobic, monomorphic cells with minimal nuclear atypia. The immunohistochemical profile often includes negativity for anterior pituitary hormones and positivity for neuron-specific enolase, synaptophysin, CD99, and occasionally GATA3.[1–3,14]

Treatment approaches for EPAs follow similar guidelines as those for intrasellar pituitary adenomas, depending on the tumor's clinical manifestations and characteristics. Management options include surgical intervention, radiotherapy, and drug therapy, depending on endocrine changes, local compression, and surgical feasibility.[2,3,8,12]

Conclusion

EPA is an extremely rare condition, often leading to diagnostic delays. Accurate diagnosis requires thorough hormone evaluation, detailed imaging, and a comprehensive preoperative assessment. Clinical symptoms, imaging, histology, and immunohistochemical markers must be integrated for an accurate diagnosis. Management should consider the tumor's clinical manifestations, size, location, extent of invasion, and hormone secretion profile. In our case, subtotal tumor resection followed by stereotactic radiosurgery was performed. The patient responded favorably to the treatment and is currently doing well.

Author's Contributions

D.H. was involved in concepts, design, definition of intellectual content, literature search, manuscript preparation, editing, and review. G.M.C. contributed to the definition of intellectual content, literature search, manuscript preparation, editing, and review. I.C. participated in concepts, definition of intellectual content, manuscript editing, and review, and served as a guarantor. A.G. contributed to concepts, definition of intellectual content, manuscript editing, review, and also served as a guarantor.

Patients' Consent

We confirm that we have secured written consent from the patient to share her clinical information in this journal report. The patient and her family are aware that while her name and initials will remain confidential, and every effort will be made to protect her identity, complete anonymity cannot be guaranteed.

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Conflict of Interest

None declared.

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