Case Report

Intracranial seeding of pituitary neuroendocrine tumor: a case report

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Background: Pituitary neuroendocrine tumors (PitNETs) are predominantly benign, though a minority may exhibit invasive tendencies. A diagnosis of metastatic PitNETs, in the absence of malignant histology, hinges on the identification of craniospinal and/or systemic metastases. Only a minority of PitNETs exhibit intracranial seeding. Notably, craniotomy for PitNETs excision is a prominent catalyst for iatrogenic seeding.

Case Description: This article presented a compelling case that 15 years following craniotomy for the resection of a somatotroph PitNET, a lesion emerged at the left frontal base within the ethmoid sinus. Subsequent post-operative pathology unveiled a mature plurihormonal pituitary specific transcription factor 1 (PIT-1)-lineage PitNET. Growth hormone (GH) levels decreased significantly from 22.8 ng/mL pre-operation to 2 ng/mL post-operative, and concurrently, prolactin (PRL) levels decreased from 26.7 ng/mL pre-operation to 4.5 ng/mL post-operation. Furthermore, in the follow-up examination conducted 5 months after the operation, both GH and PRL levels were found to be within the normal range for the patient. This robustly suggested that the initial surgical procedure played a key role in the development of the lesion.

Conclusions: This underscores the paramount significance of strictly adhering to the non-tumor removal during craniotomy for PitNETs excision. Regardless of apparent complete resection on imaging, it remains imperative to conduct routine follow-up evaluations, encompassing both imaging studies and hormone level assessments.

Keywords: Pituitary neuroendocrine tumors (PitNETs); metastatic seeding; growth hormone (GH); prolactin (PRL); case report

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Introduction

Background

Pituitary neuroendocrine tumors (PitNETs) are derived from the endocrine cells of the anterior pituitary gland and present in approximately 10% of persons in the general population (1). While these neoplasms are typically considered benign (2), a subset may exhibit aggressive characteristics, including local tissue invasion and encroachment upon adjacent structures (3). However, it is crucial to note that, despite such aggressive characteristics, these tumors often remain localized to the sellar region and are not classified as metastatic PitNETs (3). Metastatic PitNETs are very uncommon, and their identification relies mostly on the existence of a primary PitNET located in the sellar region, accompanied by the development of

metastases in distant organs, including the brain, spinal cord, or locations beyond the sellar area (3). The metastatic seeding commonly occurs in some malignant tumors (4), whereas metastatic seeding of PitNETs is less frequently reported.

Objective

This article documented a compelling case whereby a patient, 15 years following the initial transcranial resection of a PitNET using the left subfrontal approach, exhibited with a lesion in the area of the left subfrontal-ethmoid sinus. It was hypothesized that this lesion had its origins in the seeding of neoplastic cells during the first surgical procedure. This case served as a painful reminder that, despite the prevailing perception of PitNETs as generally benign, surgical interventions must rigorously adhere to the basic concept of excising the tumor without causing harm to surrounding tissues. We present this case in accordance with the CARE reporting checklist (available at https://gs.amegroups.com/article/view/10.21037/gs-24-36/rc).

Case presentation

A 33-year-old Chinese male presented with a persistent 1-month history of recurrent headaches dating back to 2008, with no identifiable triggering factors. Physical examination revealed distinctive clinical features, including nasal enlargement, prominent cheekbones, and hypertrophy of the fingers and toes, which were notably pronounced in comparison to individuals of his age group.

Highlight box

Key findings

- Intracranial seeding of lesions is observed in pituitary neuroendocrine tumors (PitNETs).

What is known and what is new?

- PitNETs are predominantly benign, though a minority may exhibit invasive tendencies.
- Craniotomy for PitNET excision is a prominent catalyst for seeding.

What is the implication, and what should change now?

- Adherence to strict non-tumor resection protocols is paramount during craniotomy for PitNETs excision.
- Strictly adhering to the non-tumor removal during craniotomy for PitNETs excision.

Laboratory investigations demonstrated elevated levels of growth hormone (GH). The patient had an unremarkable medical history, devoid of any familial predisposition to neoplastic conditions or hereditary disorders. A provisional diagnosis of acromegaly was established. Subsequently, brain and pituitary magnetic resonance imaging (MRI) with gadolinium-based contrast agents (GBCAs) was performed, revealing the presence of a lesion within the sellar region. Seeking therapeutic resolution, the patient underwent transcranial resection of the sellar region lesion. Postoperative pathological analysis conclusively identified a somatotroph PitNET. After the procedure, due to residual tumor, γ-Knife therapy was administered as an adjunct treatment. Following these interventions, the patient reported a marked improvement with his headache symptoms. Regrettably, the medical records pertaining to this case are no longer available.

The patient did not adhere to a regular schedule of follow-up brain and pituitary MRI and monitoring of GH levels after γ-knife therapy. During this interval, the patient displayed remarkable clinical changes, including an increase in height from 189 to 196 cm, a weight gain of approximately 15 kg over 3 years (from 100 to 115 kg), an expansion in shoe size from 48 to 53, further enlargement of the cheekbones and frontal bones, thickening, and hypertrophy of finger and toe joints, along with the onset of hip joint arthritis. In January 2023, the patient experienced recurrent intermittent headaches, prompting a follow-up brain and pituitary MRI with GBCAs performed in April 2023. The MRI revealed a discrete nodular abnormal signal in the left aspect of the sellar region measuring approximately 7 mm in diameter. Additionally, a soft tissue mass was detected in the left sphenoid sinus-floor/ethmoid sinus region with a maximum diameter of approximately 30 mm (*Figure 1*). Concurrent laboratory assessments indicated elevated GH levels at 22.8 ng/mL (normal range, <2.0 ng/mL) and elevated prolactin (PRL) levels at 26.7 ng/mL (normal range, <15.0 ng/mL). Given the recurrence of a somatotroph PitNET within the sellar region and the nature of the soft tissue mass in the left sphenoid sinus-floor/ethmoid sinus region, further diagnostic evaluation became imperative. Consequently, on June 15, 2023, the patient underwent a neuro-navigation-assisted transcranial approach for the resection of the sellar region lesion, an endoscopic transnasal approach to explore the sellar region, and reconstruction of the sellar floor. Intraoperatively, the tumor presented as a grayish-white, solid mass with partial cystic changes, limited vascularity,

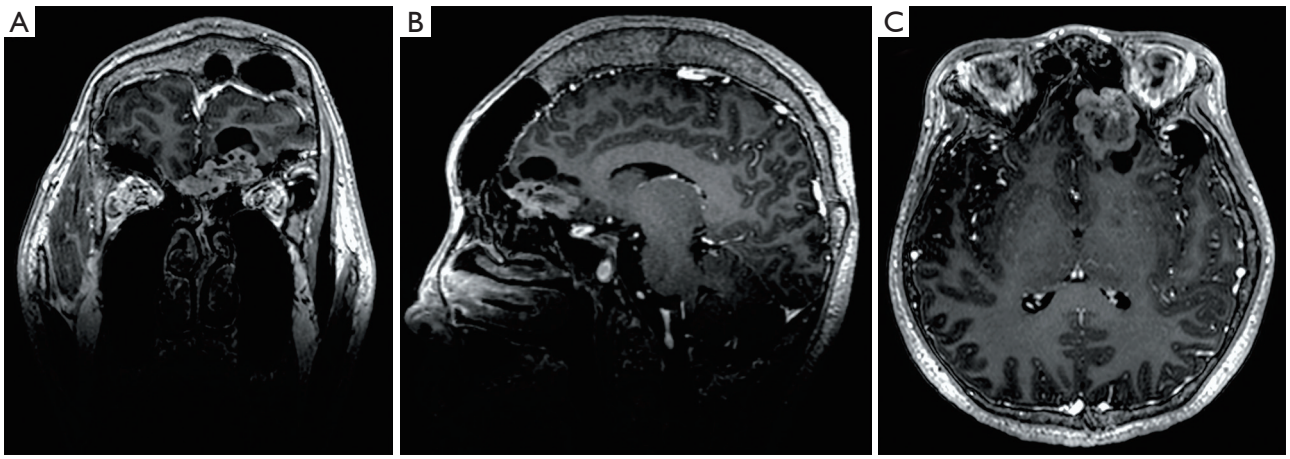

Figure 1 The coronal (A), sagittal (B), and axial (C) planes of pre-operative brain and pituitary MRI with GBCAs. It showing a small nodular abnormal signal on the left side of the pituitary, approximately 7 mm in diameter, and a cystic-solid mixed soft tissue mass in the left sphenoid sinus and anterior cranial fossa, with a maximum diameter of approximately 3 cm. MRI, magnetic resonance imaging; GBCAs, gadolinium-based contrast agents.

a relatively soft texture, and local toughness. The superior aspect of the tumor abutted the left olfactory nerve, which had been subject to infiltration and structural compromise due to the tumor. Initially, bipolar electrocoagulation was employed to meticulously coagulate and disengage the tumor from its attachment to the anterior skull base. Following this, a debulking procedure was undertaken, accompanied by frozen section for pathological assessment, which indicated the likelihood of a PitNET. While the tumor's interface with the skull base was distinctly delineated, there was a notable degree of close adhesion. The tumor exhibited infiltration into the ethmoid sinus, extending into the nasal cavity and resulting in localized bone destruction, although complete skull base erosion was not observed. The excision of the left-sided tumor was conducted in segments, with partial incision of the brain falx facilitating the separation and removal of the right-sided tumor. Notably, an exploration of the sellar region unveiled a suspicious lesion within the first inter-cavernous sinus, which was meticulously dissected and completely excised. Subsequently, nasal disinfection was carried out, followed by endoscopic exploration of the right sphenoid sinus opening, executed via a single nostril approach. Selective incision of the nasal septal mucosa, along with drilling was performed to remove the lateral wall of the sphenoid sinus, exposing the sellar floor. Navigation confirmed the presence of a suspicious lesion on the left side of the pituitary, leading to the exposure of the sellar floor dura. Multiple puncture aspirations of cerebrospinal fluid were performed, indicating an empty sellar space, and further dural incision was avoided to prevent cerebrospinal fluid leakage.

Postoperative immunohistochemical analysis corroborated the anterior cranial fossa floor region lesion as a mature plurihormonal pituitary specific transcription factor 1 (PIT-1)-lineage tumor. Immunohistochemistry results indicated the following: luteinizing hormone (LH) (–), adrenocorticotropic hormone (ACTH) (–), GH (+), Ki-67 (index 2%), P53 (–), PRL (partially +), thyroid-stimulating hormone (TSH) (intermittently +), follicle-stimulating hormone (FSH) (–), T-box transcription factor 19 (T-PIT) (–), PIT-1 (+), cytokeratin (CAM5.2) (sporadically +), estrogen receptor (ER) (–), somatostatin receptor 2 (SSTR2) (3+), steroidogenic factor-1 (SF-1) (–), O^6-methylguanine-DNA methyltransferase (MGMT) (+), chromogranin A (CgA) (+) (*Figure 2*). The diagnosis of a mature plurihormonal PIT-1-lineage PitNET was duly confirmed.

Following meticulous postoperative monitoring, the patient achieved substantial alleviation of headache symptoms. Subsequent reassessment through brain and pituitary MRI with GBCAs revealed the postoperative change of the PitNET, with no evidence of discernible tumor residue (*Figure 3*). Furthermore, GH levels significantly decreased to 2.0 ng/mL (normal range, <2.0 ng/mL), insulin-like growth factor 1 (IGF-1) levels significantly decreased to 293.0 mg/L (normal range, 71–234 mg/L), and PRL also decreased to 4.5 ng/mL (normal range, <15 ng/mL).

Following the postoperative period, a reassessment was

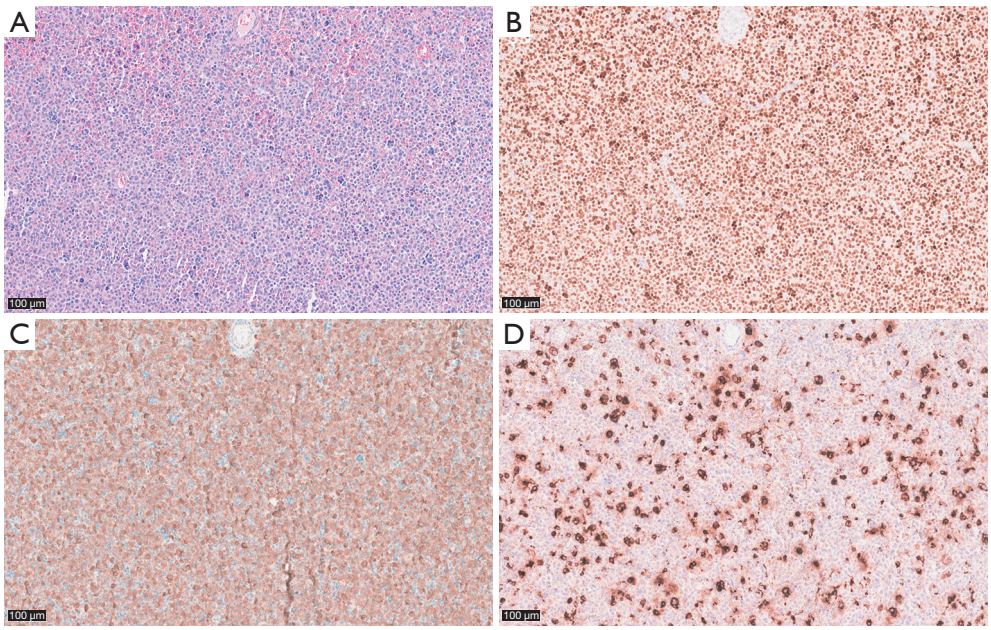

Figure 2 Histopathological and immunohistochemical staining of the lesion at the anterior skull base. (A) HE staining; (B) PIT-1 staining; (C) GH staining; (D) PRL staining. Scale bar =100 μm. The pathological images were obtained from the Department of Pathology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences. HE, hematoxylin and eosin; PIT-1, pituitary specific transcription factor 1; GH, growth hormone; PRL, prolactin.

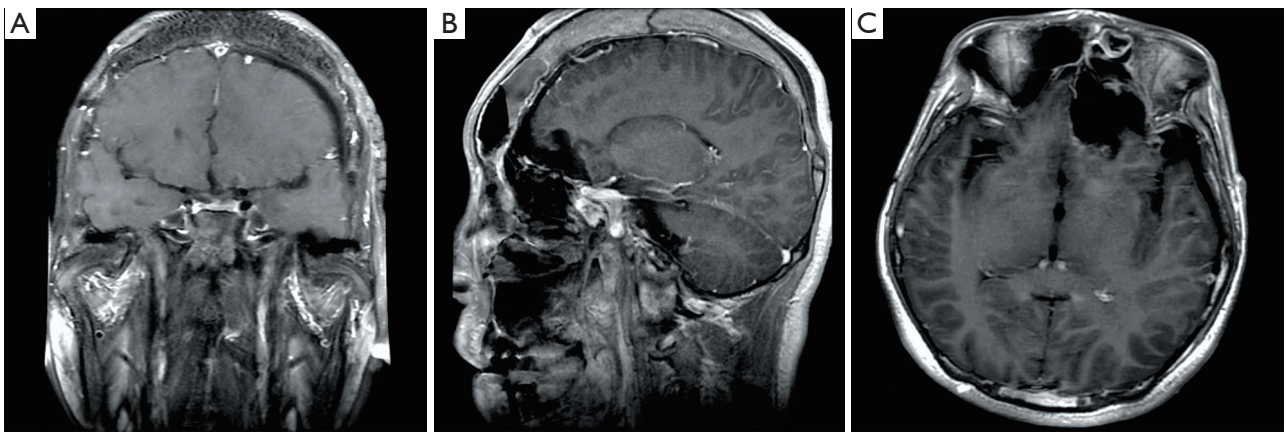

Figure 3 The coronal (A), sagittal (B), and axial (C) planes of post-operative brain and pituitary MRI with GBCAs. It showing the lesions in the anterior cranial fossa and the left side of the pituitary have resolved. MRI, magnetic resonance imaging; GBCAs, gadolinium-based contrast agents.

conducted on November 13, 2023. The comprehensive pituitary hormone examination revealed the following values: GH 1.0 ng/mL, IGF-1 269 ng/mL, and PRL 4.6 ng/mL (*Figure 4*). The brain and pituitary MRI with GBCAs 4 months postoperatively showed a reduction in the residual cavity in the surgical area, accompanied by a patchy softening lesion in the left frontal lobe (*Figure 5*). Collectively, these findings suggested an absence of residual tumor. However, ongoing monitoring of the patient's GH and PRL levels, coupled with regular imaging studies, is necessary. If there is an increase in hormone levels, consideration should be given to initiating somatostatin therapy.

Ethical consideration

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for the publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Discussion

Key findings

This article presents a case of which a patient, 15 years post-somatotroph PitNET resection, exhibited with a new space-occupying lesion in the anterior cranial fossa during an MRI reassessment for headache. Laboratory tests revealed notable elevations in GH and PRL levels. Subsequently, we employed a combined transcranial and transnasal surgical approach. The final pathology results confirmed the lesion in the anterior cranial fossa as a mature plurihormonal PIT-1-lineage PitNET. Postoperatively, hormone levels normalized, and the headache symptoms resolved. In the 5-month follow-up, the patient reported no discomfort, and both GH and PRL levels remained within normal ranges. Imaging studies also showed no apparent residual tumor. Consequently, we conclude that the lesion in the anterior cranial fossa is the result of sellar lesions seeding (*Figure 6*).

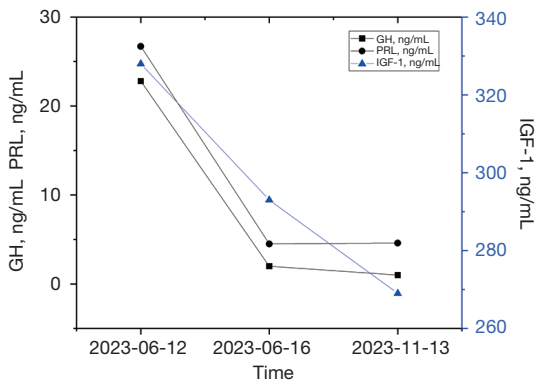

Figure 4 Trends in the levels of GH, IGF-1, and PRL. GH, growth hormone; PRL, prolactin; IGF-1, insulin-like growth factor 1.

Explanations of findings

The identification of metastatic PitNETs typically hinges upon the detection of craniospinal and/or systemic metastases, particularly in the absence of malignant histological features (5). Among cases of metastatic PitNETs, the majority are associated with corticotroph and lactotroph metastatic PitNETs (6-8). While a single biomarker alone may not suffice to predict tumor behavior, studies have shown the usefulness of at least one marker in the majority of instance involving metastatic PitNETs. Notably, a Ki-67 index exceeding 3% emerges as the most frequently observed positive marker in metastatic PitNETs. Additionally, P53 positivity and a mitotic count exceeding two mitoses per 10 high-power fields (HPFs) are

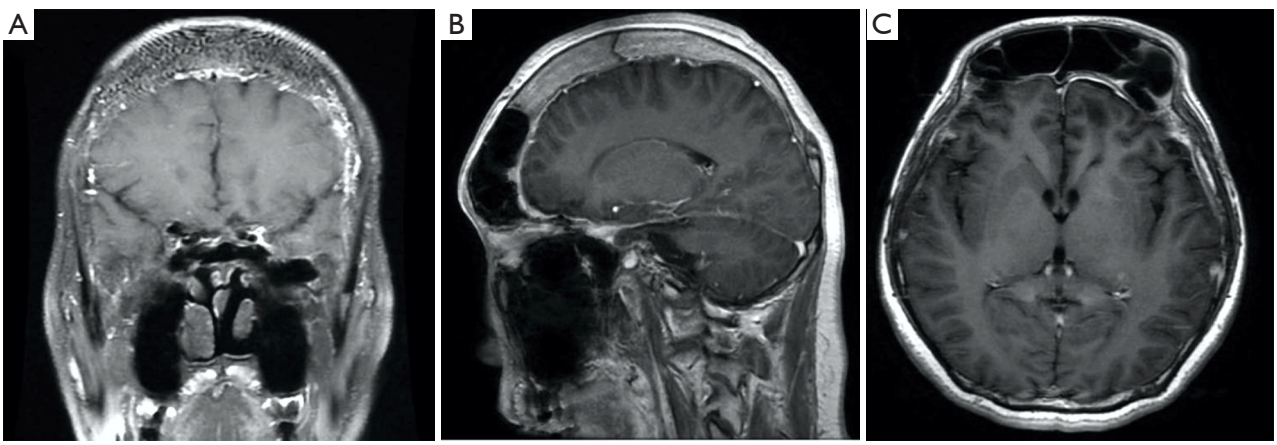

Figure 5 The coronal (A), sagittal (B), and axial (C) planes of postoperative brain and pituitary MRI with GBCAs at 4 months. It showing a reduction in the residual cavity in the surgical area, accompanied by a patchy softening lesion in the left frontal lobe. MRI, magnetic resonance imaging; GBCAs, gadolinium-based contrast agents.

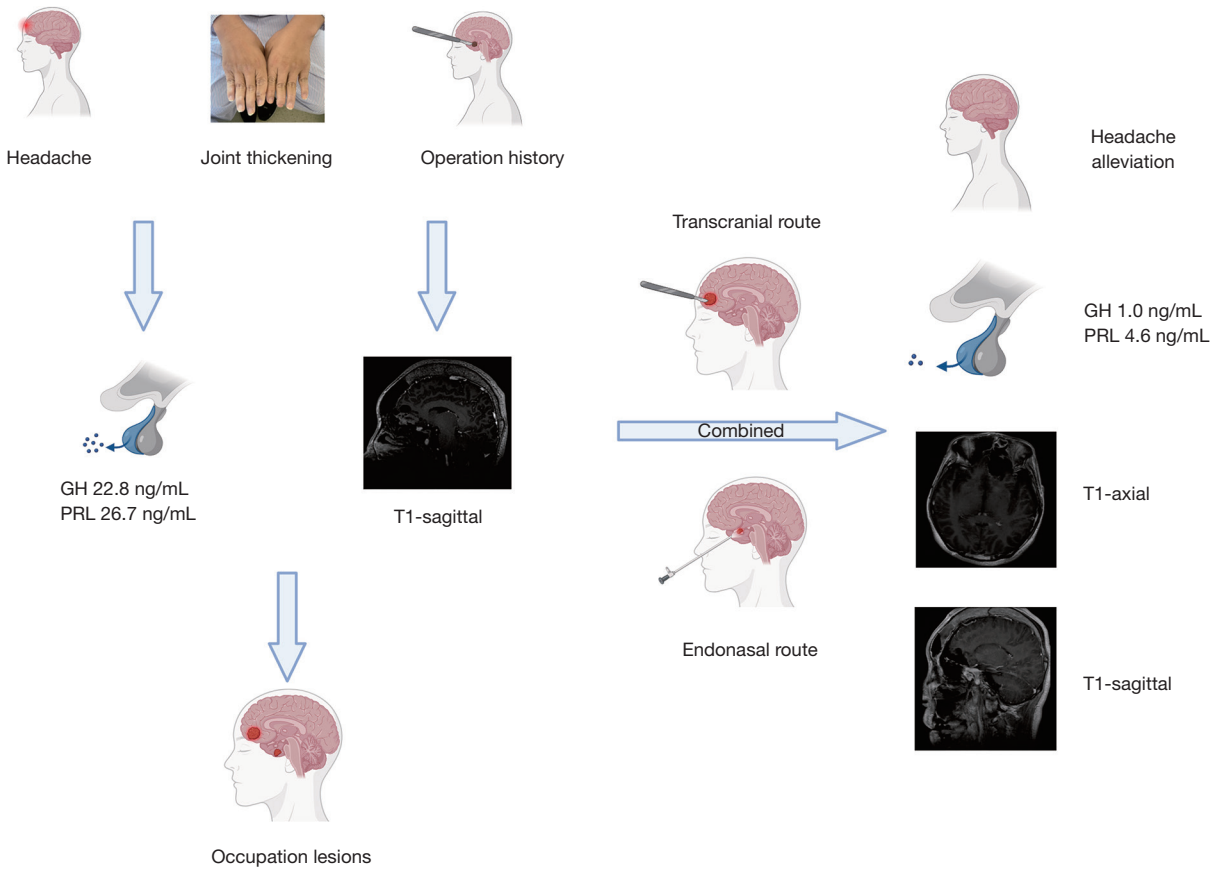

Figure 6 An overview of the patient's clinical course. The patient presented with headache on this occasion. Previously, he had undergone transcranial surgery via the anterior cranial fossa route for the resection of a GH PitNET. Physical examination revealed characteristic features of acromegaly, such as coarse facial features and joint thickening. Laboratory tests indicated significantly elevated levels of GH and PRL. Subsequent imaging revealed new lesions in the anterior cranial fossa and on the left side of the pituitary. The patient underwent combined transcranial anterior cranial fossa and endoscopic endonasal surgery for tumor removal. Postoperative imaging showed no residual tumor, and the patient experienced significant improvement in headache symptoms. Hormone levels returned to normal. GH, growth hormone; PRL, prolactin; PitNET, pituitary neuroendocrine tumor.

recurrently documented features in metastatic PitNETs (3). Besides, only a minority of PitNETs exhibit a tumor cell seeding, including circulation via the cerebrospinal fluid or the operation (8).

The precise etiology of the lesion discovered in the left frontal base-ethmoid sinus area in this case remains enigmatic. Given the patient's pathological findings pointing toward a mature plurihormonal PIT-1-lineage PitNET, we do not ascribe it to a spontaneous ectopic adenoma. Consequently, we postulate that the emergence of this tumor can be elucidated through several potential mechanisms. Primarily, it is plausible that viable tumor cells were inadvertently introduced along the surgical trajectory during the initial procedure, a scenario we deem the most plausible for explaining the lesion in the left frontal base-ethmoid sinus area. A second hypothesis pertains to the possibility that following tumor resection, the entire surgical path was infiltrated with cerebrospinal fluid, potentially facilitating metastasis through cerebrospinal fluid seeding. As the patient underwent the initial surgery employing a transcranial left sub-frontal approach for the resection of the sellar region lesion, the lesion's site coincides with the prior surgical path. Surgery, in addition to potentially causing tumor capsule rupture, might have inflicted damage to the normal arachnoid membrane, thus fostering conducive conditions for tumor cell seeding along

the subarachnoid space (9).

Comparison with similar researches

Notably, Tanaka *et al.* reported a 70% incidence of metastasis following surgery among 30 cases of primary PitNETs (10). Other modes of metastasis such as hematogenous spread were not considered in our case, because the patient's Ki-67 index, at a mere 2%, and the negative P53 status collectively suggest a low proliferative rate and a diminished metastatic propensity. Moreover, an analogous case of PitNETs seeding along the surgical trajectory has been documented by Krueger and colleagues (11). Shah *et al.* reported three cases of meningeal tumor seeding along the surgical path (12).

Implications and actions needed

Studies have suggested that the likelihood of tumor seeding following transsphenoidal surgery for sellar region lesions is relatively low, which may be attributed to the lower occurrence of cerebrospinal fluid leakage associated with this surgical approach (9,13). Therefore, postoperative seeding of PitNETs may be closely related to the surgical method employed. However, the above discussions lack support from large-scale randomized controlled studies (9). Additionally, the number of case samples with postoperative seeding of PitNETs is relatively small. Therefore, the analysis is a clinical inference, and further validation of how to prevent tumor seeding along the surgical path is crucial. It remains unclear whether extensive irrigation with saline during the surgery after tumor resection is beneficial in preventing recurrence. Nevertheless, there is a possibility that tumor cells could seed through surgical instruments or irrigation fluid (9). Alternatively, it is uncertain how to effectively seal the resected tumor cavity after tumor removal to prevent the seeding or spread of cerebrospinal fluid, blood, or tumor cells (12). Even in the case of PitNETs, long-term imaging follow-up is recommended to monitor for recurrence.

Limitations

The present case report is limited primarily due to the absence of initial presentation data, as all records from the patient's first visit have been lost. Information regarding the initial encounter and data are solely based on the patient's recollection. Efforts have been made to retrieve the initial medical records from the hospital where the patient was initially seen; however, regrettably, they were not found.

Conclusions

The seeding of PitNETs may be affected by the tumor's intrinsic biological properties, including its invasiveness, as well as factors related to the surgical approach employed. In the context of transcranial surgery for PitNET resection, it is imperative to strictly adhere to the fundamental principle of achieving non-tumor excision, with the overarching objective of mitigating lesions seeding risk. Irrespective of the radiological evaluation of achieving tumor resection, we propose the adoption of routine postoperative imaging and periodic monitoring of hormone levels as a cautious approach to vigilantly scrutinize for any potential indications of tumor recurrence or seeding.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://gs.amegroups.com/article/view/10.21037/gs-24-36/rc

Peer Review File: Available at https://gs.amegroups.com/article/view/10.21037/gs-24-36/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://gs.amegroups.com/article/view/10.21037/gs-24-36/coif). All authors report receiving support from the National Natural Science Foundation of China (No. 82170799). The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research

committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for the publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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