Metastasis of lung adenocarcinoma within a pituitaryneuroendocrine tumor: case report and review of the literature

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Case Report

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Abstract

Introduction:

Collision tumors in which malignant neoplasms metastasize to pituitary neuroendocrine tumors (PitNETs) are extremely rare. We report a case of PitNET with a history of colorectal and bladder cancers and a relatively rapid progression of neurological symptoms.

Case Report:

A 75-year-old man who underwent tumor resection for bladder cancer 36 years before and for colon cancer 18 years before without recurrence suffered from right-sided homonymous hemianopsia, ptosis and diplopia of the right eye. MRI revealed a tumor with a diameter of 3.2 cm, extending from the anterior pituitary gland to the suprasellar region. Gadolinium-enhanced MRI of the tumor showed heterogeneous contrast enhancement. Semi-emergency endoscopic endonasal transsphenoidal surgery was performed because of the relatively rapid progression of neurological symptoms. Histopathological examination revealed a group of thyroid transcription factor-1- and napsin A-positive papillary proliferating cells intermingled with α-subunit (α-SU)- and steroidogenic factor-1-positive PitNET cells. The patient was diagnosed with metastasis of lung adenocarcinoma within a PitNET (gonadotroph PitNET).

Results: Genetic testing revealed a positive EGFR (Ex-19del) mutation, and chemotherapy was initiated. Additional stereotactic radiotherapy was performed for the residual tumor in the sella turcica. Chemotherapy was continued, and 24 months later, both the primary and metastatic tumors were well controlled.

Conclusion: Cases of metastasis of a malignant neoplasm within a PitNET are difficult to diagnose. In the case of a sella turcica tumor with relatively rapid progression of neurological symptoms, early surgical intervention is recommended because of the possibility of a highly proliferative tumor and to obtain pathologic specimens.

Introduction

Although metastasis of malignant neoplasms to the normal pituitary gland is rare, reports of malignant neoplasms metastasizing to neoplasms in the sella turcica, resulting in collision tumors, are extremely rare [1, 2].

Collision tumors are defined as the presence of two or more histologically distinct tumors, benign or malignant, in the same anatomical location. In these sella turcica collision tumors, PitNETs, meningiomas, gliomas, schwannomas, and hemangioblastomas have been reported as recipient tumors in the sella turcica, and breast and lung cancers as the most common primary tumors [2].

There have only been 33 reports of collision tumors in which a malignant neoplasm metastasized within a PitNET, and the clinical symptoms and imaging findings have been similar to those of a solitary PitNET,

making preoperative diagnosis difficult.

Here, we report a case of PitNET with a history of colorectal and bladder cancers and a relatively rapid progression of neurological symptoms, in whom early surgical intervention revealed metastasis of a malignant neoplasm within the PitNET. Histopathological evaluation revealed the presence of a new lung adenocarcinoma.

Case Report

The patient was a 75-year-old man who had undergone total cystectomy and artificial cystostomy for bladder cancer 36 years before and tumor removal for colon cancer 18 years before the consultation, both of which were in remission, with no tumor recurrence.

He was referred to us because he had been suffering from right-sided homonymous hemianopsia for the past 4 months, in addition to ptosis and diplopia of the right eye for the past 2 months.

On initial presentation, the patient had inadequate oculomotor nerve palsy in the right eye, and visual function assessment revealed decreased visual acuity in both eyes and bilateral hemianopsia. There were no respiratory symptoms, such as cough and sputum, urinary symptoms, such as painful urination and hematuria, or gastrointestinal symptoms, such as anorexia and bloody stools.

Magnetic resonance imaging (MRI) of his head revealed a tumor with a maximum diameter of 3.2 cm, extending from the anterior pituitary gland to the suprasellar region (Fig. 1).

The suprasellar portion of the tumor drained the optic chiasm, and the normal pituitary gland was drained upwards. Gadolinium-enhanced magnetic resonance imaging of the patient's head showed heterogeneous contrast enhancement of the tumor.

Endocrinological evaluation showed a mild increase in prolactin (73.1 ng/mL, reference range 3.0–17.3 ng/mL), a mild decrease in thyroid stimulating hormone (0.708 ng/dL, reference range 0.5–5.0 ng/dL), and a decrease in free triiodothyronine (1.95 pg/mL, reference range 2.3–4.0 pg/mL). A preoperative growth hormone-releasing peptide-2 loading test showed a growth hormone (GH) peak level of 4.58 ng/mL, indicating severe GH deficiency.

The finding of high prolactin level was thought to be due to a stalk section effect, which is consistent with clinically nonfunctioning (NF) PitNET.

The relatively rapid progression of visual function loss and the appearance of oculomotor nerve palsy suggested the possibility of a highly proliferative tumor, such as a malignant neoplasm. Therefore, for diagnostic and therapeutic reasons we decided to operate early and perform semi-emergency endoscopic endonasal transsphenoidal surgery.

The intraoperative findings were consistent with PitNET with pituitary apoplexy, as the tumor was dark red, relatively soft, and suckable, with an internal hematoma noted after removal. However, when the arachnoid membrane was opened during tumor removal, the tumor attached to the pituitary stalk within the arachnoid membrane.

Postoperative visual function evaluation showed improvement of the bilateral hemianopsia and endocrinological improvement in thyroid stimulating hormone and GH hyposecretion, and the patient was discharged without postoperative complications.

Histopathological examination revealed a PitNET composed mainly of chromophobic cells, which were positive for α-subunit (α-SU) and steroidogenic factor-1 (SF-1), leading to the diagnosis of gonadotroph PitNET (Fig. 2).

In addition, a group of poorly differentiated cells with papillary growth pattern was found to be mixed with PitNET cells. The site was negative for various anterior pituitary hormones, but positive for epithelial membrane antigen, keratin (AE1/AE3), thyroid transcription factor-1, and Napsin A, with Ki-67 levels of 5–10% of positive nuclei, suggesting lung adenocarcinoma. Based on these results, a diagnosis of lung adenocarcinoma metastasis within a PitNET (gonadotroph PitNET) was made.

After histopathological evaluation, a postoperative computed tomography (CT) scan of the chest showed a 22 mm nodule in the middle lobe of the right lung, right hilar lymphadenopathy, and pleural dissemination (Fig. 3). Genetic testing of the removed tissue showed a positive *EGFR* (Ex-19del) mutation, which is an indication for molecular-targeted therapy, and hence chemotherapy (osimertinib) was started on postoperative day 51. In addition, an MRI scan of the sella turcica tumor immediately after surgery showed a residual contrast-enhancing lesion along the pituitary stalk.

After the start of chemotherapy, the residual lesion temporarily shrank, but 6 months after surgery, MRI revealed regrowth of the lesion, and additional stereotactic radiotherapy was performed in the same area. Chemotherapy was continued, and 24 months after surgery, both primary and metastatic tumors were well controlled.

Discussion

We report a case of PitNET with a history of colorectal and bladder cancers and a relatively rapid progression of neurological symptoms, in whom early surgical intervention revealed metastasis of a malignant neoplasm within the PitNET. Histopathological evaluation revealed the presence of a new lung adenocarcinoma.

It is estimated that PitNETs account for nearly 80% of the tumors of the sella turcica, and although the majority of neoplasms in the sella turcica are PitNETs, reports of collision tumors, in which a malignant neoplasm has metastasized to a PitNET, are extremely rare, with only 33 cases reported so far [2–29] (Table 1).

Including the present case, the average age of the previously reported patients was 66 years (44–87 years), with 16 men and 17 women. The breakdown of the primary malignant neoplasms was as follows: malignant neoplasms of the lung and trachea (n = 7), breast (n = 7), digestive organs (n = 5), kidney and urinary organs (n = 5), neuroendocrine tumors (n = 3), malignant melanoma (n = 2), and unknown (n = 4). The breakdown of primary malignant neoplasms was similar to that of pituitary metastases [1] (Fig. 4). The breakdown of recipient PitNETs was as follows: NF PitNET (n = 22), prolactinoma (n = 6), acromegaly (n = 4), and Cushing's disease (n = 1). This is similar to the incidence of PitNETs themselves, suggesting that there is no affinity between specific PitNETs and malignant neoplasms, and that they metastasize by the same mechanism as pituitary metastases of malignant neoplasms (Fig. 5).

In other words, in cases of pituitary metastases of malignant neoplasms, the malignant neoplasm tends to metastasize to the posterior lobe of the pituitary gland via the arterial blood flow of the neurohypophysis in the same way that the malignant neoplasm tends to metastasize into the tumor of the sella turcica via the abundant arterial blood flow that nourishes the pituitary gland, including branches of the capsular artery, inferior hypophysial artery, and superior hypophysial artery of the internal carotid artery [11].

In addition, previous reports have supported the hypothesis that PitNETs activate trophic vasculature and increase blood flow to the sella turcica via such trophic vessels [30]. Other possible mechanisms include direct invasion from adjacent bony structures or the meninges, or through the cerebrospinal fluid surrounding the sella turcica [31]. Of the patients with malignant neoplasm metastasized within a PitNET, only 60% (n = 20/33) had a known history of malignant neoplasm prior to definitive diagnosis, and only 15% (n = 5/33) had other intracranial metastases preoperatively.

As in previous reports, the present case had a history of malignant neoplasms of the bladder and colon but no other intracranial metastases. In the present case, there were no respiratory symptoms, and histopathological examination revealed the presence of adenocarcinoma of the lung within the PitNET, indicating a new malignant neoplasm of the lung, and thus, triple cancer.

As stated in previous reports, it is difficult to distinguish between a PitNET alone and a malignant neoplasm metastasizing within a PitNET preoperatively, based only on clinical and imaging findings. In many cases, metastatic lesions are too small to cause any clinical or imaging changes. If symptoms occur, they are often the same as those of PitNET alone and may include poor visual function due to optic chiasm drainage, headache, hypopituitarism, and slight hyperprolactinemia.

Considering the appearance of external ophthalmoplegia, it is more natural to consider PitNETs associated with pituitary apoplexy rather than collision tumors in the differential diagnosis. This is because 27% (n = 9/33) of patients with metastases of malignant neoplasms within PitNETs had external ophthalmoplegia, whereas 58.8% (n = 10/17) of patients with PitNETs alone had external ophthalmoplegia in the presence of pituitary apoplexy [32, 33].

Imaging evaluations, such as CT and MRI, are helpful in assessing the localization and extension of tumors of the sella turcica; however, it is still difficult to distinguish between a PitNET alone and a malignant neoplasm metastasizing within a PitNET.

However, as is the case with metastases of malignant neoplasms to the parasellar region, metastatic disease should be considered when there is invasive destruction of bony structures such as the sella turcica, anterior and posterior floor processes, dorsum sellae, and plateau; when there is rapid growth of the lesion on routine imaging evaluation; or when other intracranial lesions suggest metastases [34].

As a result, histopathological examination is essential for a definitive diagnosis, and it is important that the tumor is removed as much as possible. The entire removed tumor specimen is immunostained and histologically assessed to ensure that no malignant lesions are missed.

The prognosis of patients with metastases of malignant neoplasms within PitNETs is generally poor, as the malignancy is often already intracranially and systemically disseminated.

The literature indicates that 56% of patients have systemic metastases, 19% have intracranial metastases, and the median survival is reported to be 4 months [19, 25, 26] .

Recently, advances in diagnostic imaging have made early detection possible, and advances in chemotherapy, such as molecular-targeted drugs, have led to reports of good prognosis in cases of metastases of malignant neoplasms within PitNETs [2].

In the present case, with appropriate histopathological evaluation, chemotherapy with molecular-targeted agents, and additional stereotactic radiotherapy, both lung and sella turcica lesions progressed well with good tumor control and a relatively good outcome.

Endoscopic endonasal transsphenoidal surgery, which is relatively minimally invasive, may be an option not only for immediate decompression of the tumor and improvement of abnormal hormone secretion but also for diagnosis. Hence, the collection of a tumor specimen and the correct diagnosis of malignant neoplasm metastasizing to a lesion in the sella turcica, as in the present case, will allow to formulate a detailed treatment plan. Further, patients with advanced-stage malignant neoplasms can be spared invasive tests and unnecessary aggressive treatments.

Conclusion

In cases of sella turcica tumor with a relatively rapid progression of neurological symptoms, early surgical intervention is recommended because of the possibility of a highly proliferative tumor, such as a malignant neoplasm, and because it is important to obtain adequate pathologic specimens of the tumor.

Declarations

Competing interests

The authors have no competing interests to declare that are relevant to the content of this article.

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Tables

Table 1 is available in the Supplementary Files section.

Figures

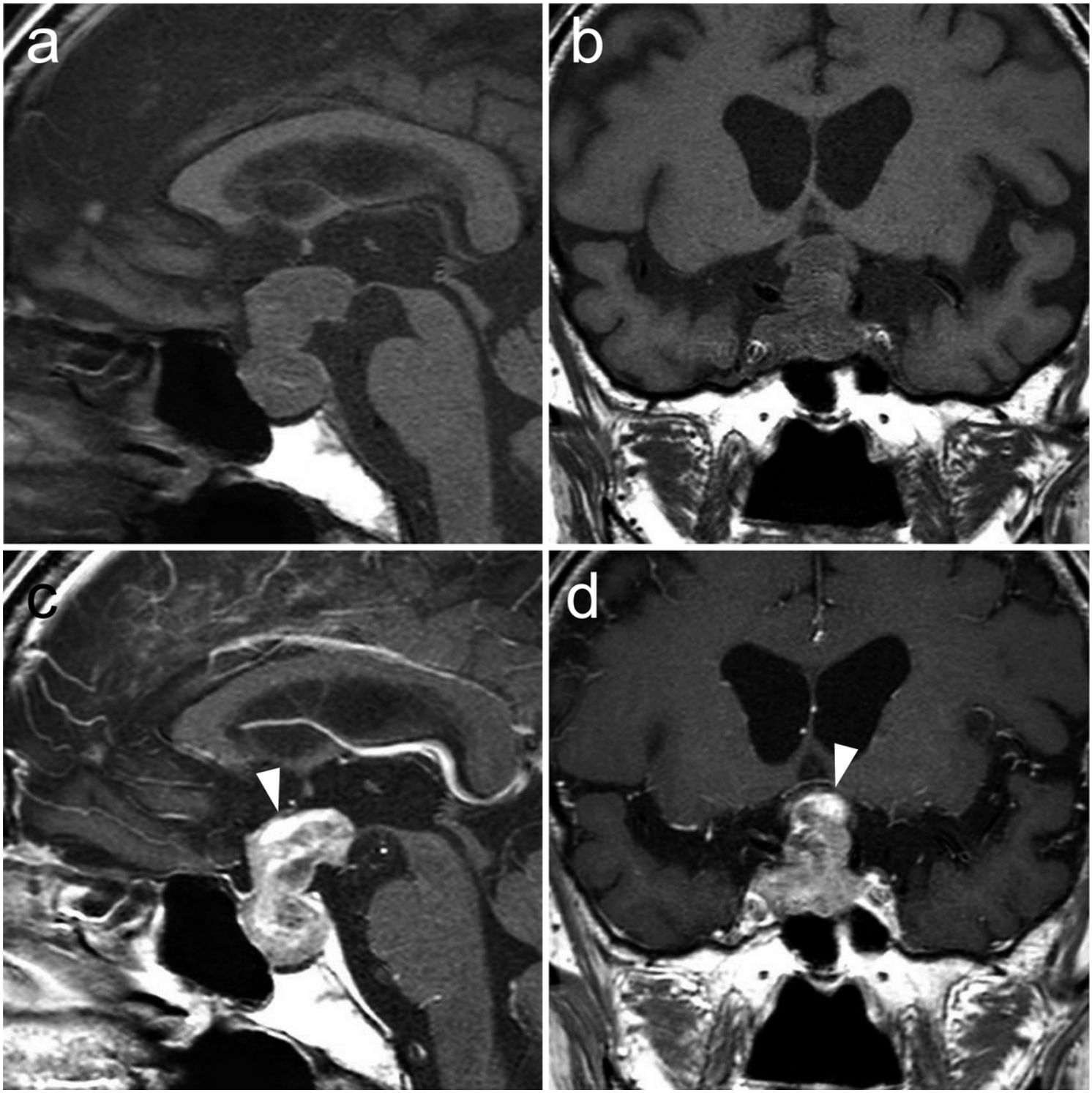

Figure 1

Preoperative MRI images of the brain

Sagittal T1-weighted image (a), coronal T1-weighted image (b), sagittal T1-weighted post-contrast image (c), and coronal T1-weighted post-contrast image (d) demonstrating a heterogeneously enhancing intrasellar and suprasellar mass and a normal pituitary gland (arrowhead).

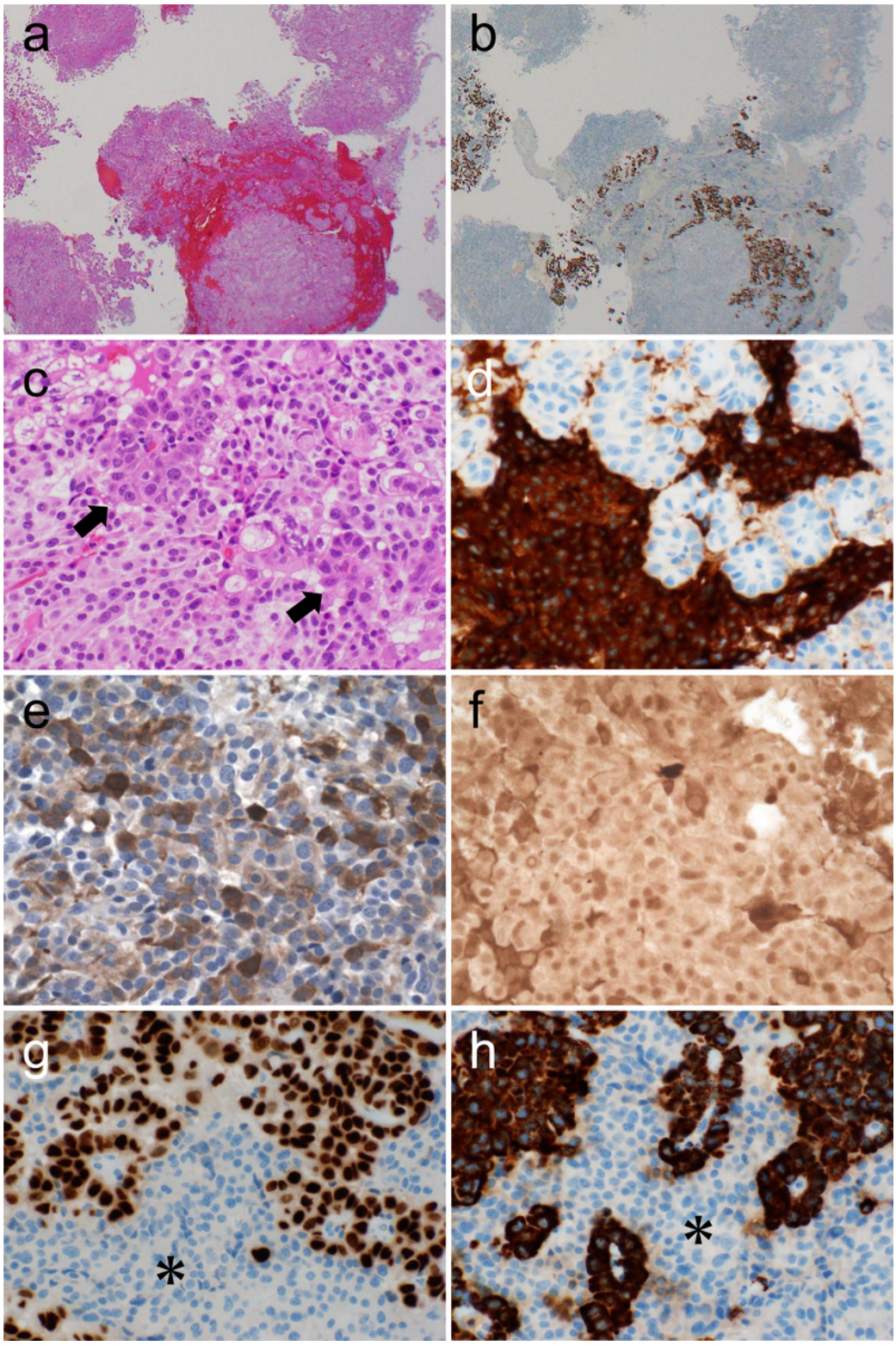

Figure 2

Pathological findings of the tumor

(a) & (b) –Low-power (x 40) image shows metastatic adenocarcinoma cells infiltrating pituitary neuroendocrine tumor (PitNET) cells. Hematoxylin and eosin (HE) staining. B–TTF-1 positive metastatic adenocarcinoma cells. (c) High power (x400)– monomorphous chromophobic PitNET cells in sheets

(lower left), intermixed with poorly differentiated cells that proliferate in a papillary pattern (arrow) (HE stain) (d) High power–Synaptophysin-positive PitNET cells (lower left). (e) & (f) - High-power-PitNET cells express α-SU (e) and SF-1 (f). (g) & (h) -High power – Adenocarcinoma cells in a papillary fashion express TTF-1 (g) and napsin A (h), whereas PitNET cells are negative (asterisk).

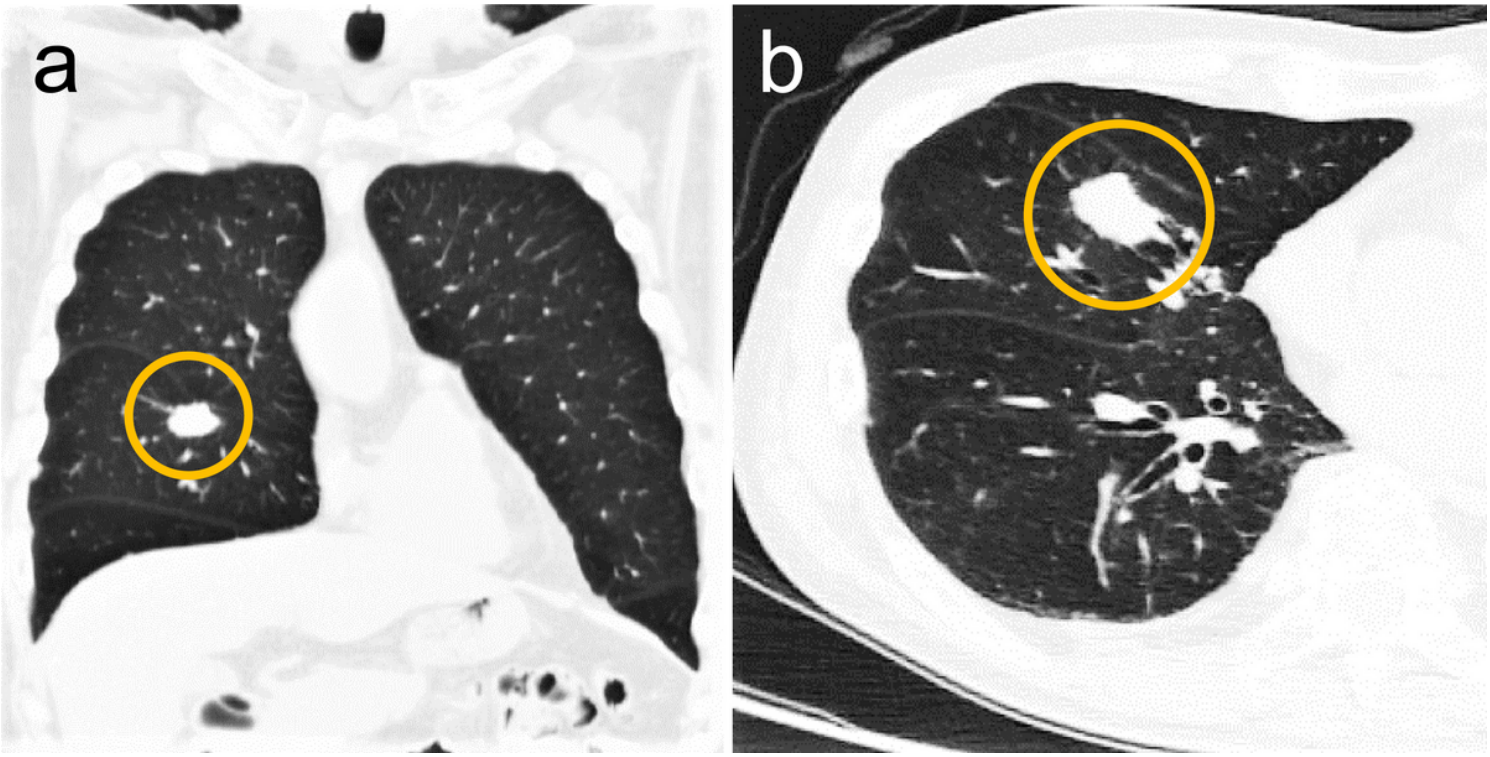

Figure 3

CT images of the chest

Contrast-enhanced chest computed tomography shows a 22-mm nodule in the middle lobe of the right lung (circle), right hilar lymphadenopathy, and pleural dissemination.

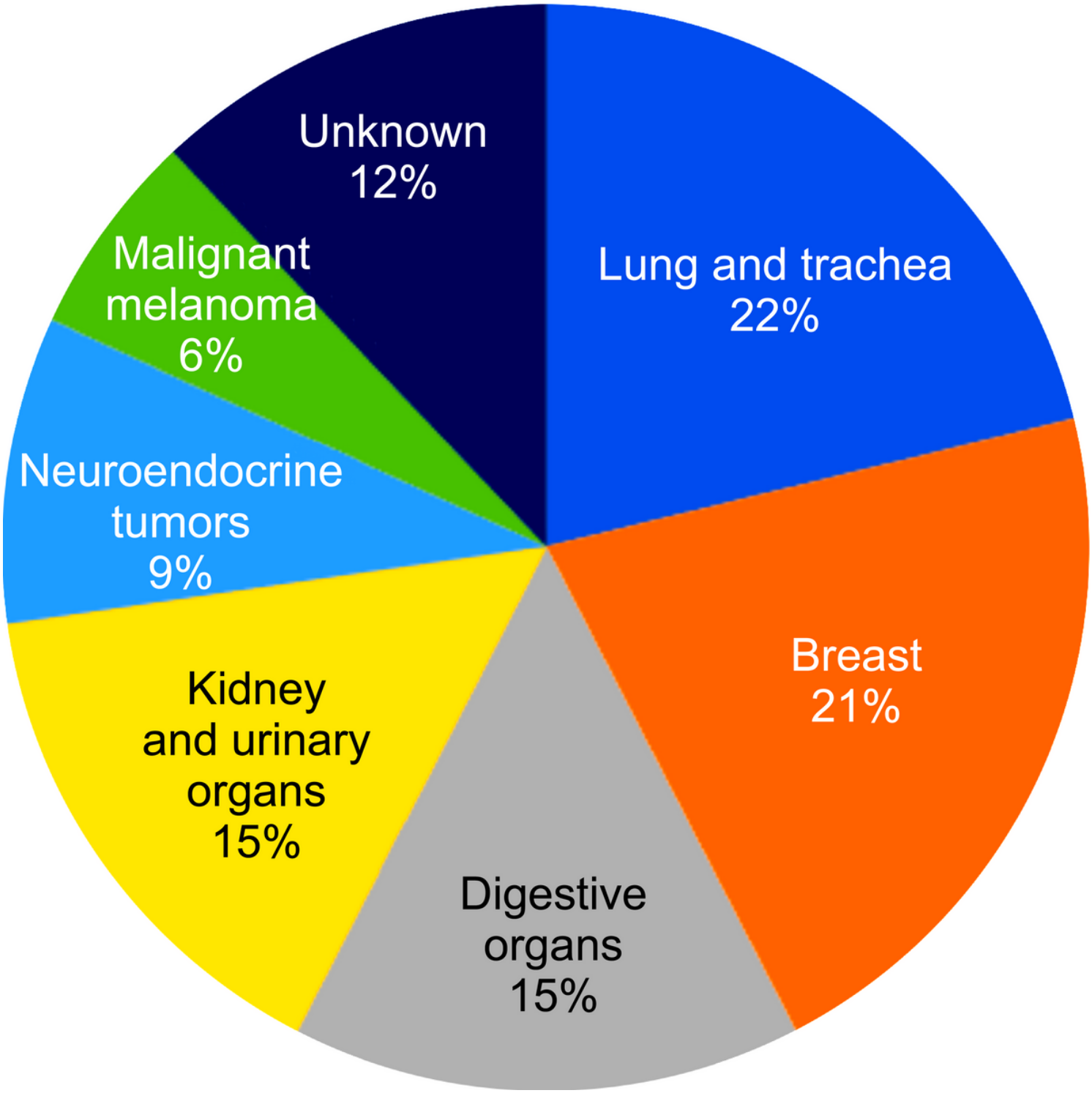

Figure 4

Primary site of a malignant neoplasm metastasized within a pituitary neuroendocrine tumor

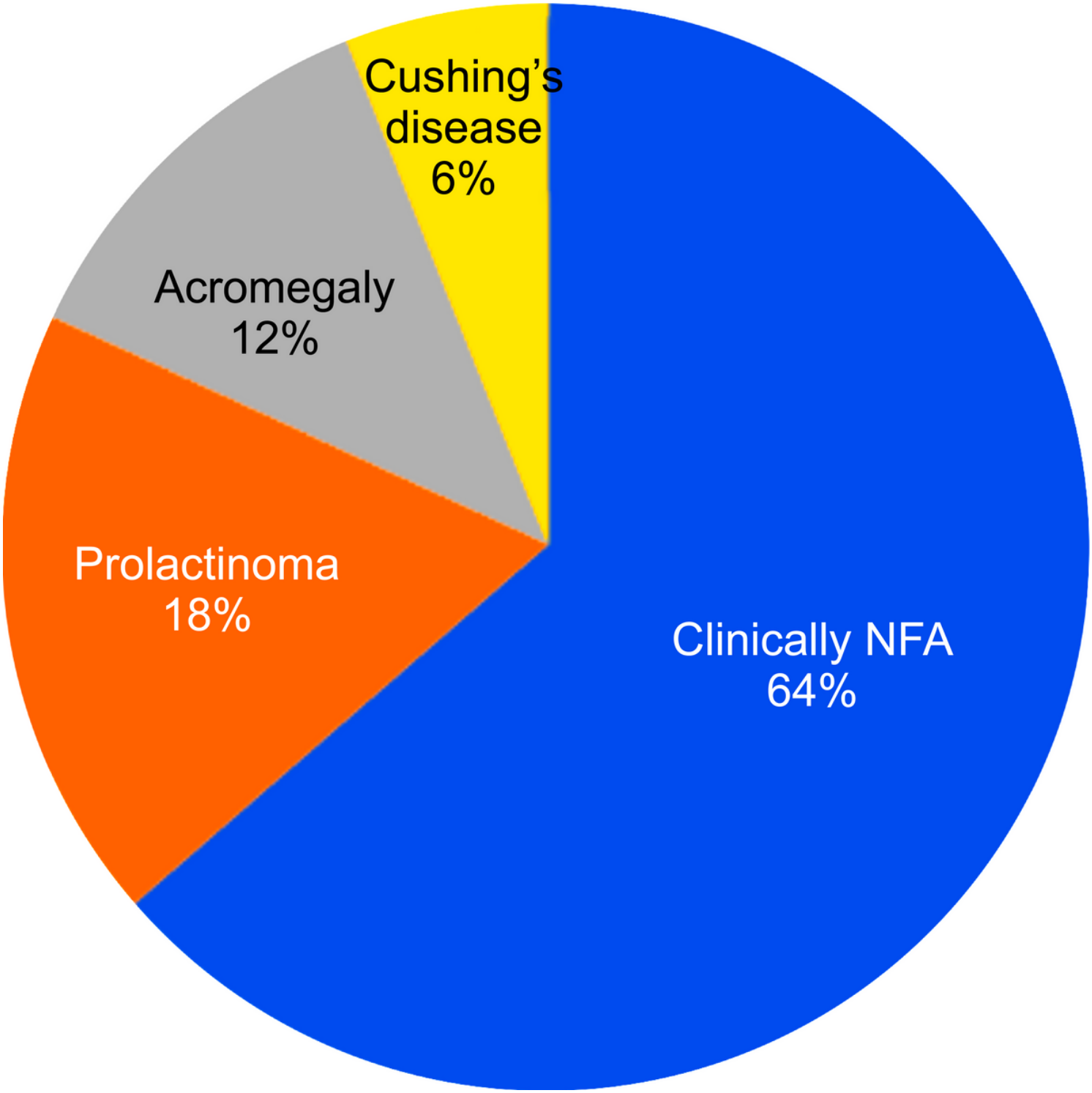

Figure 5

Pituitary neuroendocrine tumors with metastatic malignant neoplasms

Supplementary Files

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- Table1.xlsx