

## Collision of Two Tumors: A Case Report of a Lung Adenocarcinoma With Metastasis to a Pituitary Adenoma

Marisa Khatijah Borhan,<sup>1</sup> Florence Hui Sieng Tan,<sup>1</sup> Nur Shazwaniza Awang Basry<sup>2</sup>

<sup>1</sup>Endocrinology Unit, Sarawak General Hospital, Sarawak, Malaysia

<sup>2</sup>Pathology Department, Sarawak General Hospital, Sarawak, Malaysia

### Abstract

A collision tumor involving metastasis to a pituitary adenoma is rare. We describe a case of a 68-year-old Bidayuh woman with underlying treatment-responsive lung adenocarcinoma, who presented with mass effect, panhypopituitarism and polyuria. Her initial imaging study reported pituitary macroadenoma, and she was treated with hormone replacement therapy. She then underwent transsphenoidal tumor debulking surgery with subsequent histopathological findings of a collision tumor of an adenocarcinoma with metastasis to a non-functioning pituitary adenoma.

**Key words:** collision tumor, pituitary adenoma, pituitary metastasis

### INTRODUCTION

Metastatic lesions in the pituitary gland are uncommon, reported to account for <1% of intracranial metastases in a surgical series.<sup>1</sup> Lung and breast cancer are the most common primary malignancies, accounting for 60% of pituitary metastases.<sup>1</sup> Tumor-to-tumor metastasis, also known as a collision tumor, involving metastasis to a pituitary adenoma is rare, with only 35 cases being reported in literature to date.<sup>2</sup> The definitive diagnosis of a collision tumor is determined by histopathological examination, but the clinical presentation, a history of malignancy and imaging findings may provide clues to support the diagnosis. We present a rare case of a lung adenocarcinoma with metastasis to a non-functioning pituitary adenoma, diagnosed after post-operative histopathological and immunohistochemical examination of the excised tissue.

### CASE

A 68-year-old Bidayuh woman presented at the emergency department with a 3-week history of confusion, lethargy, blurred vision and polydipsia. Her symptoms deteriorated 2 days before admission. She had been diagnosed with stage 4 epidermal growth factor receptor (EGFR)-positive lung adenocarcinoma 1 year before, with findings of a 1.5 cm x 2.0 cm right perihilar mass and bilateral adrenal masses. She has been receiving the tyrosine kinase inhibitor, gefitinib, as oral chemotherapy. Three months prior to current presentation, a repeat chest computed tomography (CT) performed after six months of oral gefitinib treatment

showed a reduction in the size of the right perihilar mass to 1.1 cm x 1.4 cm, suggestive of treatment response.

At the emergency room, the patient appeared confused, with blood pressure ranging from 95 to 100/50 to 60 mmHg. She did not exhibit Cushingoid features, acromegalic appearance or galactorrhea. Eye examination demonstrated reduced visual acuity (VA) limited to finger counting with bitemporal hemianopia. Polyuria was also observed.

The patient had hypernatremia [155 mmol/L, normal value (NV): 135 to 145 mmol/L], low urine osmolality (108 mOsm/kg, NV: 300 to 900 mOsm/kg) and high serum osmolality (331 mOsm/kg), suggestive of diabetes insipidus. Hormonal assays revealed hyperprolactinemia (3665  $\mu$ IU/mL), with evidence of central hypothyroidism [thyroid stimulating hormone (TSH) 2.62 mIU/L, NV: 0.3 to 3.94 mIU/L; free thyroxine (FT4) 9.24 pmol/L, NV: 12.3 to 20.2 pmol/L], hypogonadism [follicle stimulating hormone (FSH) 2.66 mIU/mL, luteinizing hormone (LH) <0.3 mIU/mL] and hypocortisolism (morning cortisol 19.4 nmol/L). IGF-1 was within normal (57.9 ng/mL, NV: 42.0 to 179.0 ng/mL).

Pituitary magnetic resonance imaging (MRI) revealed a large, solid sellar lesion with suprasellar extension measuring 2.8 cm x 3.6 cm x 3.8 cm, compressing the optic chiasm and abutting the cavernous sinuses (Figure 1). The pituitary gland, pituitary stalk and posterior bright spot were not visualized. There was a blooming artifact at the periphery of the mass with T1 hyperintensity, suggestive of hemorrhage. However, no abnormal meningeal

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Corresponding author: Marisa Khatijah Borhan, MRCP

Endocrinology Unit, Sarawak General Hospital

Jalan Tun Ahmad Zaidi Adruce, 93586

Kuching, Sarawak, Malaysia

Tel. No.: +6082-276666

Fax No.: +6082-242751

E-mail: [mkborhan@gmail.com](mailto:mkborhan@gmail.com)

ORCID: <https://orcid.org/0000-0003-4053-0930>

enhancement, dural thickening, bony erosion or other suspicious brain parenchymal lesions were present.

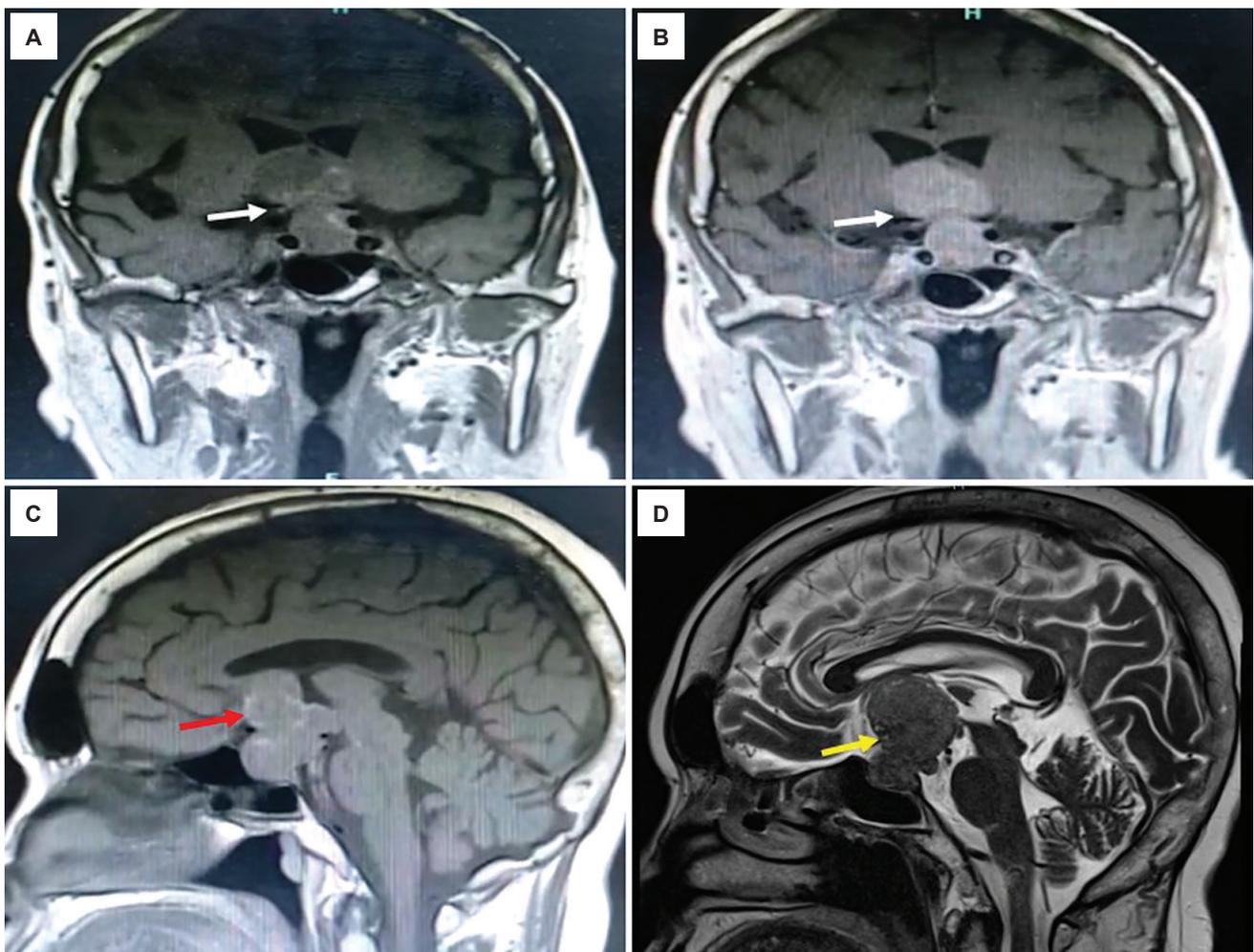
Based on the imaging findings and laboratory investigations, the patient was diagnosed with pituitary macroadenoma, complicated by pituitary apoplexy, panhypopituitarism and central diabetes insipidus (CDI). Hydrocortisone and levothyroxine replacement were initiated. Oral desmopressin was also started for CDI. Her blood pressure, urine output and serum sodium levels normalized after hormone replacement and supportive care.

Due to progressive visual decline, she underwent transphenoidal tumor debulking surgery. There was a residual suprasellar mass which was deemed unresectable due to its extension into the third ventricle. Histopathologic examination of the specimen showed fragments of tumor tissue arranged in papillary architecture and some solid clusters. The tumor cells display pleomorphic hyperchromatic to vesicular nuclei with moderate amount of eosinophilic to vacuolated cytoplasm and increased mitosis. These tumor cells stained positive for cytokeratin 7

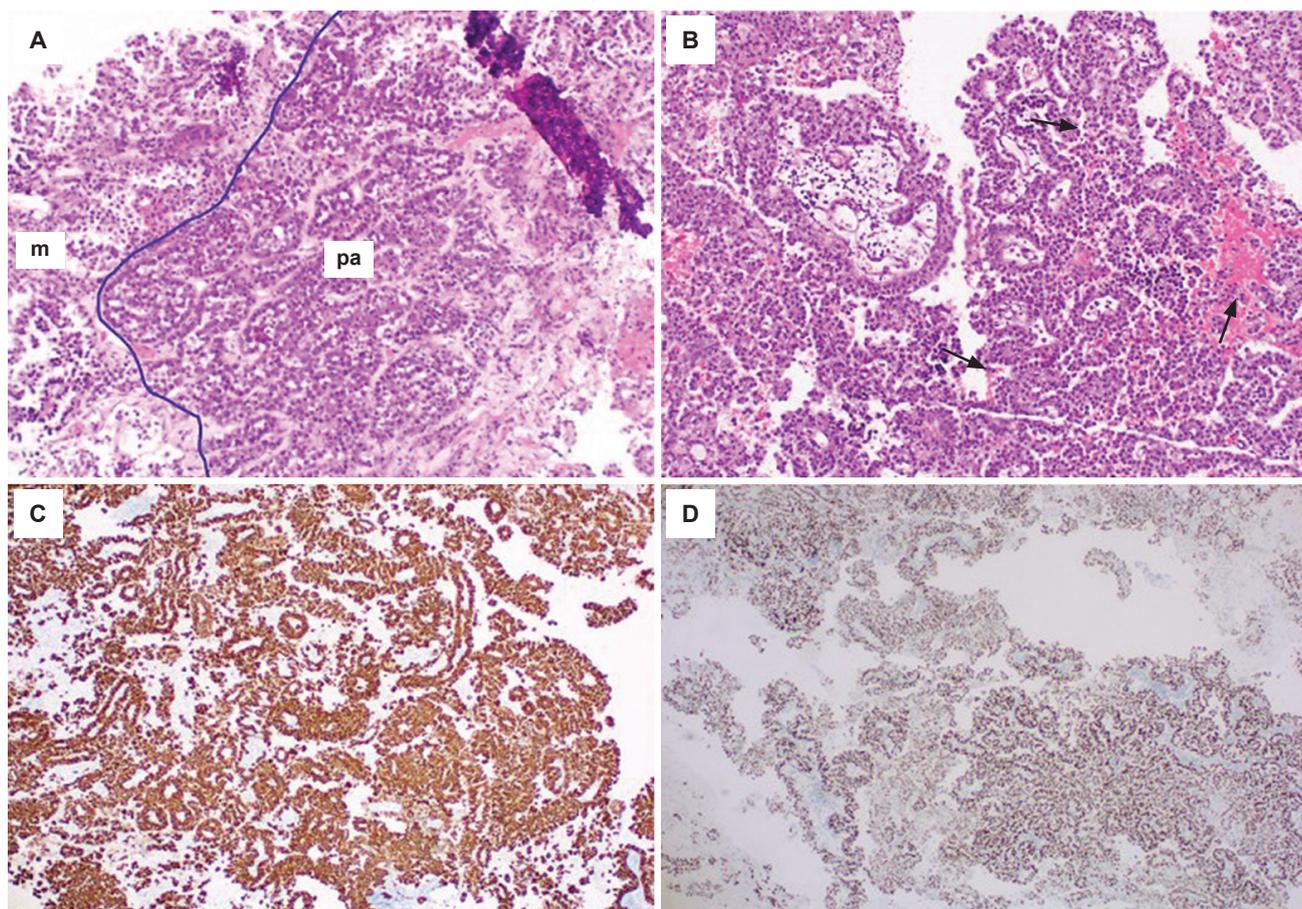
(CK7) and thyroid transcription factor-1 (TTF-1), suggestive of metastatic lung adenocarcinoma (Figure 2).

In adjacent foci, there were neoplastic pituitary cells with small nucleoli and moderate amounts of granular eosinophilic cytoplasm, with no significant mitotic activity. These neoplastic pituitary cells stained positive for synaptophysin, growth hormone (GH), adrenocorticotropic hormone (ACTH) and prolactin, suggestive of pituitary adenoma (Figure 3). Based on these histopathologic and immunohistochemical findings, the patient was diagnosed with a collision tumor involving a pituitary adenoma and metastatic lung adenocarcinoma.

Postoperatively, the patient was more alert, with improved general well-being. Her VA improved from counting fingers to 6/18 on the right eye and 6/24 on the left. A CT scan of the chest, abdomen and pelvis for further metastatic workup showed a new right upper lung lobe mass measuring 2.4 cm x 1.5 cm, an enlarged right perihilar mass measuring 4.0 cm x 3.1 cm x 2.1 cm, and bilateral adrenal masses which were unchanged in terms of size (Figure 4).



**Figure 1.** Coronal T1-weighted (A) pre-contrast and (B) post-contrast magnetic resonance imaging of the pituitary showing a homogeneously enhancing dumbbell-shaped sellar mass measuring 2.8 cm x 3.6 cm x 3.8 cm. On non-contrast sagittal view, it is (C) T1-hypointense with heterogenous intensity on (D) T2. There is T1 hyperintensity (red arrow) and T2 hypointensity (yellow arrow) at the peripheral aspect of the mass suggestive of hemorrhage. The posterior bright spot is absent.



**Figure 2.** (A) Histopathology of the collision tumor showing a focus of metastatic adenocarcinoma (m) adjacent to pituitary adenoma (pa) (H&E, 10x). (B) The metastatic adenocarcinoma displayed pleomorphic cells arranged in papillary architecture (H&E, 10x). Immunohistochemical staining revealed positive staining for (C) cytokeratin 7 (CK7) and (D) thyroid transcription factor-1 (TTF-1).

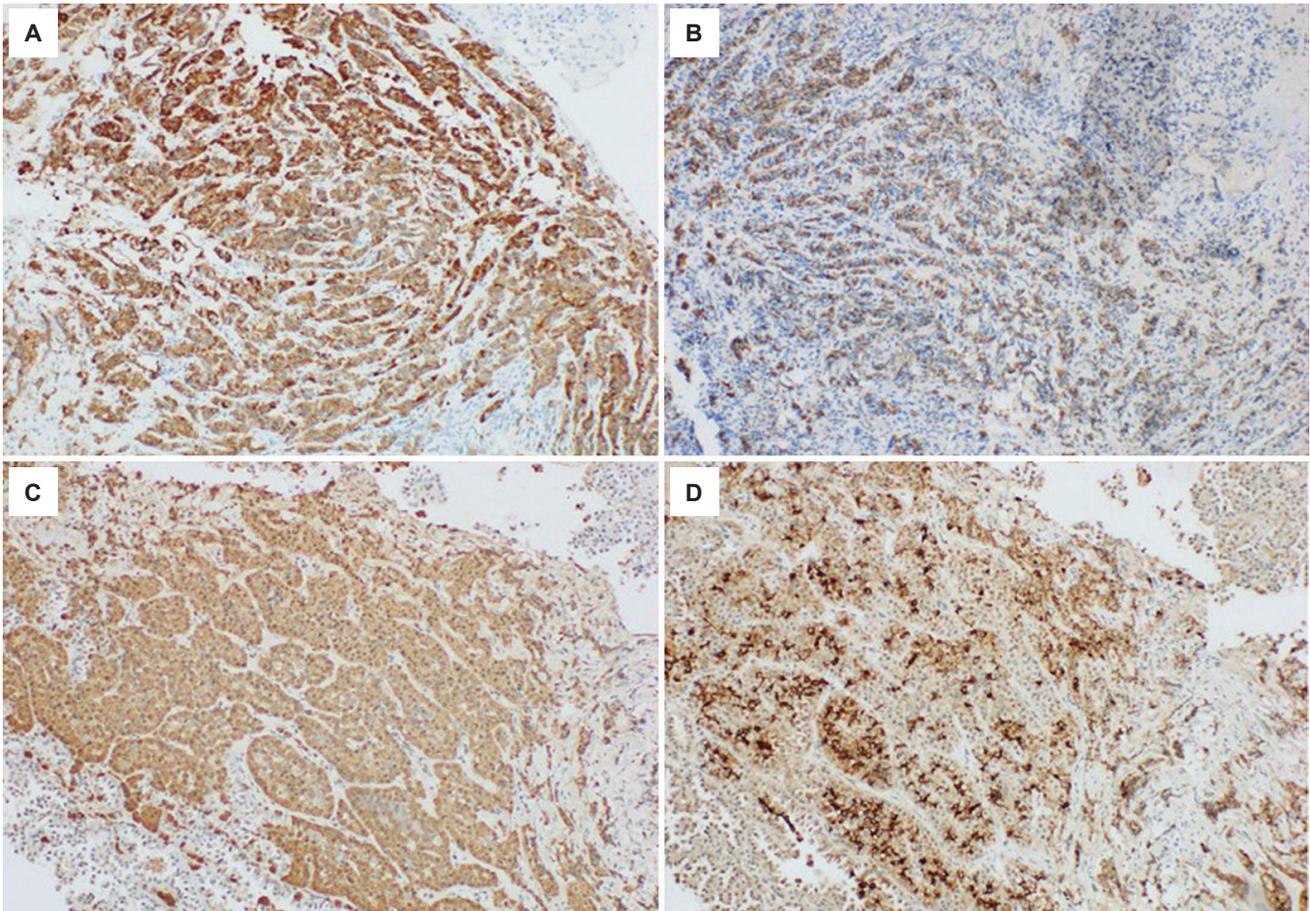
Bone scintigraphy revealed right scapular bone metastasis, indicating progression of the carcinoma. The patient was counseled for radiotherapy by the oncology team; however, the patient refused and opted for palliative care instead.

She was discharged with oral hydrocortisone 10 mg twice a day, oral levothyroxine 75 µg once a day and oral desmopressin 0.05 mg twice a day. On follow-up at the endocrine clinic, she remained well with hormone replacement and reported stable visual acuity. Unfortunately, the patient was subsequently lost to follow-up.

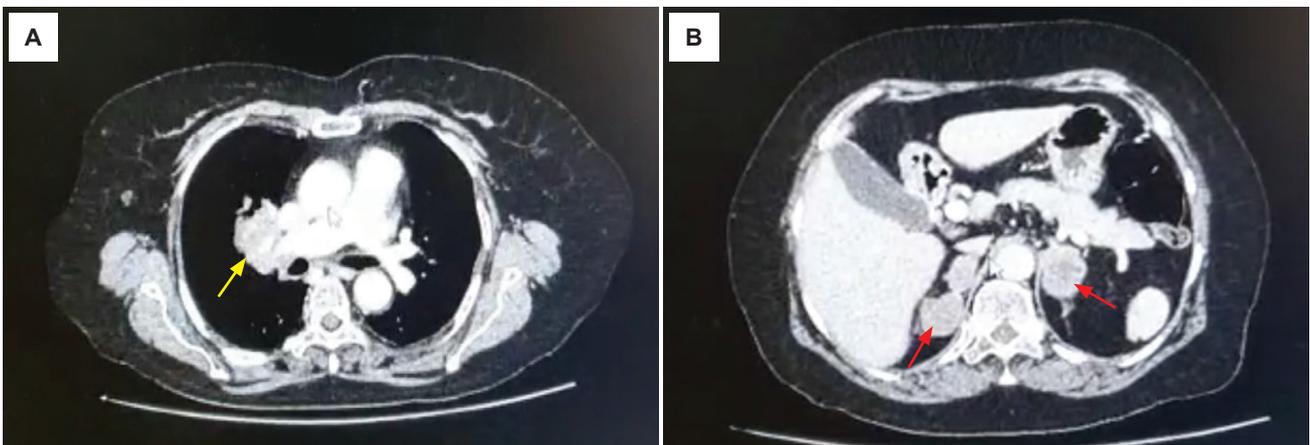
## DISCUSSION

Collision tumors represent the coexistence of two morphologically and immunohistochemically distinct tumors within a single organ, that may include neoplastic, vascular, congenital, infectious or inflammatory lesions.<sup>1</sup> Among collision tumors that involve carcinoma metastasizing to sellar tumors, the reported recipient tumors include pituitary adenomas, meningiomas, gliomas, schwannomas and hemangioblastomas, with meningiomas being a more common type of sellar recipient tumor than pituitary adenomas.<sup>1,2</sup> Although pituitary adenomas are the most common sellar lesions comprising 10 to 15% of

all intracranial tumors, metastasis to a pituitary adenoma occurs in only 1 to 5% of patients with malignancies.<sup>1</sup> In the 36 reported cases of pituitary adenoma with metastatic carcinoma (including our case), lung cancer was the most common primary malignancy (n=9), with the majority being non-small cell lung carcinoma.<sup>1,3,4</sup> Other primary malignancy sites reported in these case series were the kidney (n=5), breast (n=5), melanoma (n=4), colorectum (n=3), stomach (n=1), pancreas (n=1), mediastinum (n=1) and prostate (n=1); the remaining 5 cases had unknown primary sites.<sup>1-4</sup> With the majority of the reported recipient pituitary tumors as non-functioning pituitary adenomas, most of the patients presented with symptoms of mass effect such as headache, cranial nerve palsies, visual disturbances and anterior pituitary hormone deficiency.<sup>3,4</sup> Compression of the pituitary stalk disrupts delivery of dopamine, the major inhibitory regulator of prolactin secretion, to the pituitary gland. The ensuing hyperprolactinemia is usually less than ten times the upper limit of normal as seen in our case, in contrast to very high levels associated with macroprolactinomas. Patients with metastasis to a pituitary adenoma also had more rapid tumor growth and a higher rate of optic chiasmal compression than patients with pituitary adenoma alone. These differences in clinical presentation are believed to arise from increased



**Figure 3.** Immunohistochemical staining of the pituitary adenoma at 10x magnification, with positive staining for (A) synaptophysin, (B) growth hormone (GH), (C) adrenocorticotropic hormone (ACTH) and (D) prolactin.



**Figure 4.** Computed tomography scan with contrast on axial view of the (A) thorax and (B) abdomen revealing a lobulated lesion at right perihilar area encasing the right pulmonary veins (*yellow arrow*), bilateral adrenal masses (*red arrows*) and bilobed right adrenal mass.

neoplastic metastatic growth within a pre-existing, benign pituitary adenoma.<sup>4</sup> In our case, the rapid onset of visual disturbances and symptoms of pituitary hypofunction may also be due to pituitary apoplexy. A rare finding in pituitary metastasis, pituitary apoplexy is also attributed to rapid tumor growth that exceeds its own blood supply, as well as underlying vasculopathy causing tumor infarction and hemorrhage.<sup>5</sup>

In addition to the high incidence of visual disturbances and hypopituitarism, central diabetes insipidus is the most common symptom in patients with pituitary metastasis due to the predilection for hematogenous metastatic spread to the posterior pituitary lobe via the neurohypophyseal vessels.<sup>6</sup> Up to 30% of patients with pituitary metastases present with CDI, which rarely occurs with pituitary adenoma alone, as pituitary adenomas typically arise from

the anterior lobe of the gland, which receives systemic arterial blood supply mainly from the capsular and inferior hypophyseal arteries.<sup>2,7</sup> Metastasis to a pituitary adenoma can rarely occur either via the arterial supply of the adenoma itself, via direct extension of an adjacent bone metastasis or via meningeal spread through the suprasellar cistern.<sup>1</sup> Hence, the presence of CDI in our patient should dissuade the diagnosis of pituitary adenoma as the sole cause of the sellar mass.

In our case, differentiating a pituitary adenoma from a collision tumor based on imaging studies alone was challenging: intratumoral hemorrhage and loss of the posterior bright spot on pituitary MRI are also observed in pituitary adenomas and are not specific to pituitary metastases.<sup>8,9</sup> However, metastasis to the pituitary gland should be suspected in the presence of aggressive bony destruction, rapid growth with a relatively normal pituitary fossa, involvement of the infundibulum, the appearance of a dumbbell-shaped tumor with a clear indentation at the level of the diaphragma sellae, or the presence of additional intracerebral metastatic lesions.<sup>10</sup>

The definitive diagnosis of collision tumors, therefore, is made through histopathologic examination of the sellar mass, mostly from tumors resected during pituitary surgery or rarely, from postmortem examination.<sup>1,3,4</sup> The treatment approaches to pituitary adenoma and metastasis differ due to poorer prognosis of the latter. Surgery has no impact on overall survival in patients with pituitary metastasis, but only aims to relieve the mass effect and optic chiasmal compression in patients with cranial nerve palsies and visual disturbances.<sup>11,12</sup>

The prognosis of patients with metastasis to a pituitary adenoma is poor, mainly due to the advanced stage of the primary malignancies at the time of diagnosis of the collision tumor. In a systematic review of 657 patients with pituitary metastases, the median survival rate was 14 months; patients with primary lung cancer (31% of the cohort) had a shorter median survival of 9 months compared to patients with breast and renal cancer.<sup>11</sup> In a review of patients with collision tumors, Hoellig et al., determined the median survival time was 9.8 weeks, but also commented that it was uncertain if the short lifespan was due to concomitant peripheral metastases or additional intracerebral metastases, as the exact cause of death was not mentioned in most cases.<sup>4</sup> In the same review, 56.3% of the patients had multiple peripheral metastases, while 18.8% had coexisting intracerebral metastases, suggestive of advanced stages of malignancy at the time of the presentation of the collision tumor.<sup>4</sup> Due to advanced cancer stage, treatment modalities such as pituitary surgery or sellar radiotherapy are mainly palliative and are unable to improve survival.

The management of collision tumors includes the alleviation of mass effects, replacement of hormone deficiencies, treatment of hormone hypersecretion by functioning

adenomas and targeted therapy for metastasis. In recent years, a multimodal treatment approach targeting both the primary malignancy and the metastasis to the pituitary gland, with pituitary surgery, sellar radiotherapy, hormonal replacement and chemotherapy, has been found to improve patient prognosis and extend the median survival time to 16 months.<sup>6</sup> Targeted radiotherapy to the pituitary gland, particularly stereotactic radiotherapy, is associated with a significant improvement in survival time (16 months) compared to that of untreated patients (6 months).<sup>8</sup> Nevertheless, unless effective targeted treatment is available for the primary malignancy, the prognosis is still poor, as survival is determined by the primary malignancy itself rather than the pituitary lesion.

## CONCLUSION

Collision tumors are rare and can only be accurately diagnosed by histopathologic examination of the tumor. Although uncommon, the differential diagnosis of collision tumors should be considered in patients with sellar lesions and underlying malignancies, especially when there is rapid tumor growth causing mass effects, apoplexy and/or concurrent diabetes insipidus. Atypical imaging features may also help establish the diagnosis. The management of collision tumors involves treatment of both the pituitary adenoma and associated pituitary dysfunction, as well as the underlying primary malignancy and its metastatic disease. As life expectancy is often limited in patients with advanced primary malignancy, a multidisciplinary approach aimed at palliative care with careful consideration of the risks and benefits of each different therapeutic modality is pragmatic for the improvement of patient care.

### Ethical Consideration

Patient consent was obtained before submission of the manuscript.

### Statement of Authorship

All authors certified fulfillment of ICMJE authorship criteria.

### Author Contributions Statement

MKB conceived and wrote the original draft preparation; reviewed and edited the manuscript; created and presented the data of the published work. FHS reviewed and edited the manuscript and supervised the research activity planning and execution. NSAB created and presented the data of the published work.

### Author Disclosure

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