

## Case Report

# Apoplexy in sellar metastasis from papillary thyroid cancer: A case report and literature review

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## ABSTRACT

**Background:** Pituitary metastasis from papillary thyroid cancer (PTC) is rare and only a few cases have been reported.

**Case Description:** We report the case of a patient who presented with visual dysfunction and panhypopituitarism. Magnetic resonance imaging revealed a pituitary tumor and hydrocephalus. Transsphenoidal surgery had been indicated, but his surgery had been postponed due to COVID-19 pandemic. During that waiting period, he showed pituitary apoplexy with consciousness disturbance, resulting in acute adrenal insufficiency and diabetes insipidus. He was urgently hospitalized and underwent transsphenoidal surgery. Rapid and permanent pathological examinations have confirmed metastasis of PTC to the pituitary. The patient also underwent serial thyroidectomy. He was also suspected to have secondary hydrocephalus and underwent lumboperitoneal shunting after excluding cerebrospinal fluid metastasis. Thereafter, his cognitive dysfunction and performance status improved dramatically.

**Conclusion:** To the best of our knowledge, this is the first patient with PTC who developed pituitary apoplexy secondary to metastasis.

**Keywords:** Case report, Papillary thyroid cancer, Pituitary apoplexy, Pituitary metastasis, Transsphenoidal surgery

## INTRODUCTION

Thyroid carcinoma accounts for only 2–4.1% of primary tumors.<sup>[10,14,23]</sup> Recently, the number of patients with cancer metastasis has been increasing due to prolonged survival time after diagnosis.<sup>[10]</sup> Papillary thyroid cancer (PTC) metastasizes in 8% of cases,<sup>[37]</sup> but metastasis to pituitary gland is extremely rare. Such patients develop symptoms such as pituitary insufficiency, visual impairment, cranial nerve palsy, or diabetes insipidus (DI). However, to the best of our knowledge, there have been no reports that metastatic pituitary tumor of PTC is associated with apoplexy. We present a case of pituitary metastasis from PTC whose course was unusual as it caused apoplexy and hydrocephalus during the period when surgery was postponed due to COVID-19.

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## CASE REPORT

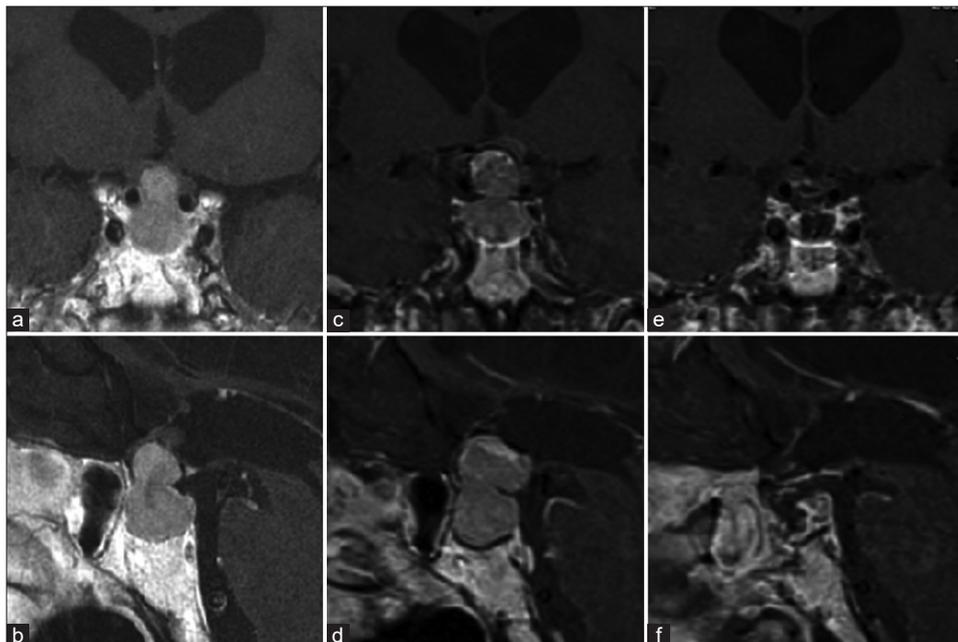
A 74-year-old man without notable medical history and family history who noticed a visual disturbance 3 years prior had extreme tiredness and sought medical care at a different hospital. After a detailed examination, bitemporal hemianopia and panhypopituitarism without DI were noted. Magnetic resonance imaging (MRI) revealed a dumbbell-shaped tumor ( $22 \times 17 \times 11$  mm) pushing the optic chiasm upward and unobstructed hydrocephalus [Figures 1a and b]. He was referred to our hospital and scheduled to undergo surgery, but it was postponed due to the COVID-19 pandemic under appropriate hormone replacement treatment. Four months later, he developed persistent fever, headache, and vomiting and he was transferred to a nearby medical center. His Glasgow Coma Scale (GCS) score was 12 (E3V3M6) and he became somnolent. Computed tomography (CT) showed a high-density area on the pituitary gland and MRI showed enlargement of the upper part of the tumor ( $24 \times 18 \times 18$  mm) [Figures 1c and d]. A previous doctor suspected pituitary apoplexy. The patient was treated with steroids and transferred to our hospital. He developed DI and was administered cortisol, thyroid hormones, and vasopressin. CT scan on admission for COVID-19 screening showed an enlarged thyroid gland. His consciousness gradually recovered after hormone treatment and correction of hyponatremia. Then, his GCS score improved to 14 (E4V4M6) and fever subsided. At the time, pituitary function tests were typical for hypopituitarism (growth hormone:  $0.16\text{ng/mL}$ ; prolactin:  $4.37\text{ng/mL}$ ; thyroid-stimulating hormone:

$<0.005$  mIU/mL; free T4:  $1.13$  ng/dL; adrenocorticotropic hormone:  $<1.5$  pg/mL; cortisol:  $<0.3$  mIU/mL; luteinizing hormone:  $<0.3$  mIU/mL; follicle-stimulating hormone:  $<0.3$  mIU/mL; and testosterone:  $<0.003$  ng/mL).

We performed an extended transsphenoidal surgery. The pituitary gland was thin and located in front of the tumor. The upper part of the tumor showed hemorrhagic changes consistent with apoplexy. The tumor was highly vascularized, unlike pituitary adenoma, and adhered tightly to the ventral part of the optic chiasm. The floor of the third ventricle was torn and the contents had leaked. Rapid diagnosis during surgery was suspicious of PTC, and due to the position of the tumor, we decided to retain the tumor capsule. MRI after surgery showed satisfactory decompression [Figures 1e and f].

After surgery, his visual symptoms improved. He underwent whole-body CT scan screening, which detected small lesions in the lung other than the thyroid mass. His serum thyroglobulin was abnormally high ( $1540$  ng/mL) before surgery and decreased to  $36.3$  ng/mL after surgery. He then developed meningitis and hyponatremia due to cerebral salt-wasting syndrome, which was medically treated.

Histological examination of the resected tumor confirmed PTC. An immunohistochemical test reported positive TTF1 and 25% MIB-1 [Figures 2a and b]. Part of the lesion showed hemorrhagic changes. Since the cell block of cerebrospinal fluid (CSF) was negative for TTF1 and thyroglobulin, we concluded that there was no dissemination of the tumor to the CSF.



**Figure 1:** Gadolinium-enhanced T1-weighted MR images (a and b) before apoplexy, (c and d) after pituitary apoplexy, and (e and f) after surgery.

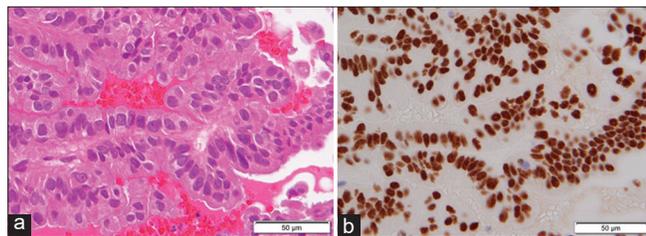
He was transferred to another hospital for further treatment of thyroid cancer. He underwent left-sided thyroidectomy and lymphadenectomy, and near-total resection was achieved. The pathological diagnosis was PTC (31 × 22 mm) that had invaded the surrounding muscle (pEx1, pT3b, and pN1b).

<sup>123</sup>I-iodoamphetamine single-photon emission computed tomography (IMP-SPECT) was performed for further evaluation of his cognitive dysfunction, which showed decreased signal mainly in the frontal lobe and was suspicious of hypothyroidism, hyponatremia, or other metabolic dysfunction disorders and not typical for hydrocephalus or Alzheimer’s disease.

The patient returned to our hospital with prolonged cognitive dysfunction. The tap test was performed. The CSF opening pressure was 19 cm H<sub>2</sub>O and he showed mild cognitive improvement the following day. The patient underwent lumboperitoneal (LP) shunt placement. Thereafter, his cognitive function recovered dramatically [Table 1]. He visited the outpatient clinic after 18 months without complications (modified Rankin scale 1).

**DISCUSSION**

Thyroid cancer is the most common endocrine malignancy; PTC accounts for 80% and is known for its good prognosis. Distant metastasis occurs in about 8% of PTC cases, but pituitary metastasis is extremely rare. Patients exhibit symptoms due to mass effects, such as visual impairment



**Figure 2:** Carcinoma cells from pituitary tumor (a) Tumor tissue with papillary structures, intranuclear inclusions, and nuclear grooving are observed. HE. (b) Tumor cells showed strong immunopositivities to TTF-1.

**Table 1:** Results of tests before and after shunting.

	On admission	Pretap test	Posttap test	Postshunting
Mini-Metal State Examination	11/30	15/30	20/30	27/30
Frontal assessment battery	-	-	9/18	12/18
Timed up and go	-	-	26 s	17 s

from compression of the optic nerve, ophthalmoplegia of the oculomotor nerve, trochlear nerve, abducens nerve invasion, anterior pituitary insufficiency, and DI.<sup>[14]</sup> The posterior lobe of the pituitary gland is more susceptible to hematogenous spread,<sup>[32]</sup> as the blood supply differs between the anterior and posterior lobes, which are mainly supplied by the portal vessels and the inferior hypophyseal arteries, respectively.

The reported poor prognostic factors of distant metastatic PTC are advanced age, distant metastasis from areas other than the lung, and degree of extrathyroidal invasion of the primary neoplasm.<sup>[37]</sup> To the best of our knowledge, 15 cases of pituitary metastasis from PTC have been reported. Excluding postmortem cases, 50% of these patients died within 13 months of the first presentation [Table 2].

Treatment options for pituitary metastasis from PTC include transcranial surgery, transsphenoidal surgery, radiotherapy, and iodotherapy, usually for local symptom management because there is no evidence of improvement in life expectancy.<sup>[26]</sup> Gross total resection for metastatic pituitary tumors is difficult to achieve because of their highly vascularized structure.

Preoperative diagnosis of metastatic tumors is challenging. Imaging can support the diagnosis of pituitary tumors. Dutta *et al.* reported that metastatic lesions tend to destroy the sellar floor and are less likely to destroy the sellar diaphragm.<sup>[8,16]</sup> Habu *et al.* reported that the upward extension of pituitary metastases was longer than that of nonfunctioning adenomas, although the difference was not statistically significant. In contrast, the downward extension of pituitary metastasis is significantly shorter than that of nonfunctioning adenoma.<sup>[10]</sup> In the report, the rate of constriction tumors in the diaphragmatic hiatus in pituitary metastatic cases was 44.7%. In our case, a dumbbell-shaped tumor was also observed.

DI is a rare manifestation of benign pituitary gland tumors. DI occurs in 3–23% of patients with pituitary apoplexy<sup>[9,25,34]</sup> and was previously reported as a common manifestation in patients with pituitary metastasis, as approximately 70% of metastatic patients were affected.<sup>[20,22]</sup> However, since the 2000s, several reports indicated the rate of DI from metastatic pituitary lesions ranged from 26% to 45%,<sup>[10,11,14,33]</sup> much lower than the previous reports.

Verrees *et al.* postulated that DI occurred as a result of impingement of the inferior hypophyseal artery, which caused diminished perfusion to the posterior lobe, or kinking or pressure on the infundibulum by edematous, hemorrhagic material that impeded transit of antidiuretic hormones from the hypothalamus to the posterior lobe.<sup>[39]</sup> Interestingly, our patient developed DI only after experiencing apoplexy. Based on the images obtained before and after apoplexy, the size of the upper part of the tumor increased and expanded backward to the ventral hypothalamus. In addition to

**Table 2:** Review of reported cases of sellar metastases of the PIC including the presented case.

References	Age, Sex	VI	CN Palsy	AI	DI	PA	Other symptoms	Prior diagnosis years	Other metastasis	Treatment	Outcome
McCarthy and Karsner, 1912 <sup>[21]</sup>	57, M	-	-	-	-	-	-	0	Lungs	None	Postmortem
Johnson and Atkins, 1965 <sup>[12]</sup>	56, F	-	o	-	-	-	-	7	None	RT, IT	Alive at 20 months f/u
Kistler and Pribram, 1975 <sup>[13]</sup>	69, F	-	o	-	-	-	-	9	Unknown	TCS	Died 1 year a/p
Pelosi <i>et al.</i> , 1977 <sup>[30]</sup>	32, M	-	o	o	o	x	-	0	Unknown	TCS	Died 1 month a/p
Ozanne <i>et al.</i> , 1982 <sup>[28]</sup>	66, M	o	o	x	x	x	-	2	Unknown	None	Died 2 months a/p
Sziklas <i>et al.</i> , 1985 <sup>[38]</sup>	44, M	-	-	o	x	x	-	25	Mediastinum, skull, chest wall	TSS, IT	Died 13 months a/p
Masiukiewicz <i>et al.</i> , 1999 <sup>[18]</sup>	56, M	x	x	o	x	x	-	5	Lungs, bone	IT	Alive at the time of reporting
	55, F	-	o	x	x	x	-	20	Lungs	RT, surgery, IT	Died 7 months a/p
Bell <i>et al.</i> , 2001 <sup>[2]</sup>	35, F	o	-	o	o	x	-	25	Lungs	TSS	Alive at the time of reporting
Simmons <i>et al.</i> , 2010 <sup>[35]</sup>	48, M	-	o	x	x	x	Seizure	0	None	IT	Alive at 3 years f/u
Xia and Wang, 2010 <sup>[41]</sup>	56, F	o	o	o	x	x	-	7	N.A.	TSS	Alive at 12 months f/u
Madronio and Frances, 2011 <sup>[17]</sup>	53, F	o	-	-	-	-	Headache	0	None	TSS	Alive at 12 months f/u
Stojanović <i>et al.</i> , 2012 <sup>[36]</sup>	67, F	o	-	o	o	x	-	0	Possible: intracerebral, bone	TSS	Alive at 13 months f/u
Chikani and Lambie, 2013 <sup>[6]</sup>	70, F	x	x	o	x	x	Nausea	3	Manubrium	TSS, RT, IT	Died 5 years a/p
Ardhaoui <i>et al.</i> , 2020 <sup>[1]</sup>	70, F	o	o	-	-	x	Headache	1	Sphenoid sinus	TSS	Alive at 6 months f/u
Popławska-Kita, 2020 <sup>[31]</sup>	68, F	o	o	x	x	x	Headache	2	None	TSS, IT	Died 3 years a/p
Present case	74, M	o	x	o	o	o	Headache, confusion	0	Lung	TSS, Surgery	Alive at 18 months f/u

VI: Visual impairment, CN: Cranial nerve, AI: Anterior pituitary insufficiency, DI: Diabetes insipidus, PA: Pituitary apoplexy, RT: Radiotherapy, IT: Iodotherapy, TSS: Transsphenoidal surgery, TCS: Transcranial surgery, f/u: Follow-up, a/p: After presentation

impingement of the inferior hypophyseal artery and effects on the infundibulum, direct damage to the hypothalamus due to the tumor mass effect may be contributed to development of DI. DI frequency due to PTC is lower than that of other types of metastases. Based on the reported 16 cases of pituitary metastasis from PTC, only two other cases besides ours developed DI.<sup>[1,2,6,12,13,17,18,21,28,30,31,35,36,38,41]</sup>

Pituitary apoplexy is a life-threatening event resulting from an acute hemorrhagic or ischemic event.<sup>[29]</sup> Four theories regarding the precipitants of pituitary apoplexy are proposed: rapid tumor growth exceeding arterial supply, acute increase in blood flow, endocrine stimulation of the pituitary gland, and coagulation disturbance.<sup>[3,21]</sup> Considering pituitary

apoplexy from pituitary metastasis, intratumoral hemorrhage due to vasculopathy would be an additional factor. Pituitary apoplexy typically occurs in macroadenomas and rarely in metastatic lesions; 14 cases have been reported.<sup>[4,5,15,19]</sup> Reports on the incidence of symptomatic pituitary apoplexy in the pituitary adenoma vary from 0.6% to 9.1%.<sup>[24,40]</sup> Komninos *et al.* reported that pituitary apoplexy can be seen about 5% of patients with pituitary metastasis.<sup>[14]</sup> To the best of our knowledge, this is the first reported case of metastatic PTC with pituitary apoplexy.

The patient's hydrocephalus was evident before apoplexy. IMP-SPECT can support the diagnosis of idiopathic normal-pressure hydrocephalus (iNPH). Ohmichi *et al.* reported in

80% of cases, IMP-SPECT for a typical iNPH patient shows convexity apparent hyperperfusion (CAPPAH) sign.<sup>[27]</sup> In our case, IMP-SPECT did not reveal a typical CAPPAH sign. We concluded his hydrocephalus was likely secondary NPH (sNPH). Daou *et al.* reported that intracranial malignancy is the third main etiology of sNPH, for which shunting is effective in 86.4% of patients.<sup>[7]</sup>

After the tap test, the patient's cognitive decline became milder. We implanted an LP shunt. Before surgery, CSF tests showed no signs of metastasis. Considering his cognitive improvement and performance status after LP shunt placement, CSF production or absorption seemed to be affected. Mitsuya *et al.* reported palliative CSF shunting for leptomeningeal metastasis-related hydrocephalus. In the study, CSF shunt surgery yielded rapid improvement in the performance status of 90.3% of patients.<sup>[23]</sup> Considering these results, CSF shunting is a good choice for improving the quality of life of end-stage patients regardless of CSF metastasis.

## CONCLUSION

We present the case of a patient with pituitary metastases from papillary thyroid carcinoma, who did not have a prior diagnosis of and developed pituitary apoplexy. To the best of our knowledge, this is the 16<sup>th</sup> case of pituitary metastasis from PTC, and the first case of apoplexy reported in the literature. His performance status improved dramatically after extended transsphenoidal surgery, hormonal treatment, and shunting. Finally, it should be noted that this pituitary apoplexy occurred during the period when surgery was postponed due to COVID-19 pandemic.

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## Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Nil.

## Conflicts of interest

There are no conflicts of interest.

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