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Case Series

Rare TTF-1 Posterior Pituitary Tumors with Distinctive Morphologic and Immunohistochemical Features: Mini-Series - Two Cases

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Abstract

Two patients admitted to the hospital were to have sellar masses with similar locations and neuroradiological features but dispatched dissimilar morphologic and immunohistochemical features. Presumptive diagnoses were meningioma of the first case, and pituitary adenoma for the latter. Pathologic examination of these cases revealed a common TTF-1 positivity but divergent morphology, and immunohistochemistry other than TTF-1 reactivity. Although they are known as TTF-1 positive tumors of the posterior pituitary due to their morphological and immunohistochemical differences, pituicytoma and spindle cell oncocytoma are not similar. The fact that it was shown in this study that pituicytoma is especially rich in reticulum is a histopathological finding that should be kept in mind. TTF-1 positive tumors, thought to originate from posterior pituitary pituicytes, do not resemble each other due to their morphological and immunohistochemical properties. In the differential diagnosis of sellar and parasellar masses, posterior pituitary tumors other than pituitary adenoma, chordoma, and meningioma are among the differential diagnoses.

Keywords: Granular Cell Tumor; Pituicytoma; Posterior Pituitary; TTF-1 Positive Tumors

Introduction

Pituicytoma, granular cell tumor (GCT), and spindle cell oncocytoma are low-grade, benign neoplasms that express thyroid transcription factor-1 (TTF1) and originate from pituicytes in the posterior pituitary or infundibulum [1].

Pituicytomas are tumors composed of elongated, spindle-shaped cells organized into solid sheets or short bundles, often displaying a storiform pattern. Immunohistochemistry reveals negative staining for cytokeratins, pituitary hormones, chromogranin A, synaptophysin, and neurofilaments. They exhibit strong reactivity for vimentin and S100, but show variable levels of GFAP staining. The tumors also show varying expression of EMA, CD56, galectin-3, CD68, and BCL2 [2]. Pituicytoma is a slow-growing lesion mainly accompanied with visual defect, hypopituitarism and headache symptoms [3]. Pituicytomas show distinctive radiographic features. These solid intra- or suprasellar tumors are usually well-defined, isointense on T1-weighted images, and hyperintense on T2-weighted images. This is different from the variable appearance

of granular cell tumors. Preoperatively, pituicytomas are most commonly mistaken for pituitary adenomas, but they can also resemble meningiomas [4]. Most pituicytomas can be effectively treated with a simple excision via a transsphenoidal approach, typically without the need for radiation or chemotherapy, and generally do not recur following complete removal [5].

GCTs consist of densely packed polygonal cells with granular eosinophilic cytoplasm. The tumor cells are variably PAS, and immunoreactive for S100, CD68, vimentin but negative for NFPs cytokeratins, chromogranin A, synaptophysin, desmin, SMA, and the pituitary hormone expression [2]. Typically, GCTs are benign, slow-growing, and non-secreting tumors, and they do not exhibit space-occupying effects when they are small. However, symptoms such as visual defects and headache are common in larger tumors due to mass effect [6]. Preoperative diagnosis of GCT is difficult because it closely resembles other sellar lesions, such as adenoma, meningioma, chordoma, and teratoma [7]. Radiologic findings are usually nonspecific [8]. The primary treatment of choice is complete surgical resection. However, surgical removal of this tumor is often challenging, with only subtotal resection typically achievable in many cases due to its high vascularization and close proximity to the optic chiasm [6].

Case 1

A 63-year-old man with a 1-year history of headache was admitted to the Department of Neurology in another hospital. An intracranial mass was detected in the brain MRI and the patient was referred to our center. Medical history showed that he had type 2 diabetes mellitus for 5 years and he was on oral diabetic agents. His diabetes was poorly regulated and HbA1c was 13.5%. He had also hyperlipidemia. On physical examination body mass index (BMI) was 27,45 kg/m^2. Blood pressure was 120/80 mmHg and heart rate was 72/min. Baseline hormonal, and biochemical investigation, complete blood count, liver function tests, kidney function tests and electrolytes were unremarkable.

Neuroradiology

Pituitary MRI imaging revealed a well-circumscribed mass lesion, localized to the anterior part of the third ventricle and measuring 25 mm in the largest sagittal plane. The mass lesion was isointense with the cerebral cortex on T1, T2-weighted images, and showed intense contrast enhancement after IVCM. Diffusion MRI showed no restriction in diffusion (Figure 1). No findings consistent with micro-calcification or micro-bleeding were detected in susceptibility-weighted sections. The mass lesion was bulging into the suprasellar cistern. The mass lesion compresses the optic chiasm and displaces it anteriorly. Minimal edema was observed in the optic chiasm. Significant increase in perfusion was detected in perfusion MR examination. MRI findings were consistent with the tumoral lesion. In the differential diagnosis, meningioma can be considered in the first place.

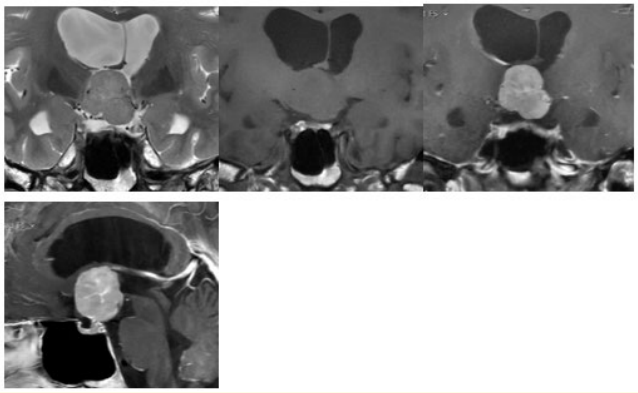

Figure 1: a. H&E, x200 b. S100, x200 c.TTF-1, x200, d. Reticulin stain, x200.

(Left to right): Coronal T2 and T1 non-enhanced T1 weighted images reveal a well-circumscribed mass lesion, localized to the anterior part of the third ventricle and is isointense with the cerebral cortex. Coronal and sagittal T1 weighted images shows intense contrast enhancement.

Surgical intervention

He was operated and the lesion was removed totally with right frontoparietal parasagittal craniotomy anterior interhemispheric transcallosal transforaminal approach. Total removal of the lesion was confirmed with intraoperative MRI performed during surgery. The postoperative period was uneventful and postoperative the hormonal investigation revealed central diabetes insipidus, central hypothyroidism and hypogonadotropic hypogonadism. Appropriate hormone replacement therapy was started.

Pathologic findings

The lesion composed of nodular and fascicular pattern. It consisted of spindle cells with hyperchromatic nucleus and abundant cytoplasm. Herring body, Rosenthal fibers, eosinophilic granular body, cytoplasmic vacuoles were not observed. There was no necrosis. An expanded immunohistochemical panel was used (Table 1). Tumor showed diffuse nuclear TTF-1 expression. Additionally, it was immunoexpressing or S100, CD56, SYN, BCL2, and Ki76: 4% (Figure 2). In contrary, tumor was negative for neuroendocrine (GH, PRL, ACTH, FSH, LH, TSH) and transcription (TPIT, PIT-1, SF1) markers. Conclusively, it was consistent with TTF-1 reactive posterior pituitary neoplasm, pituicytoma. It was consistent with pituicytoma.

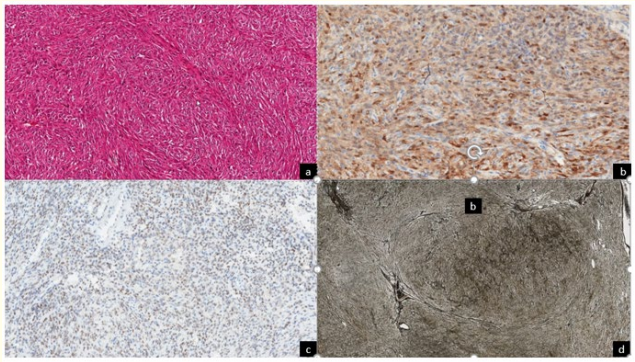

Figure 2: a. HE, x200; b. S100, x200, c. TTF-1, x200, d. Reticulin stain, x100.

Antibodies	Expressivity***				Target	Tissue site	Company	Clone	Code
Immunohistochemistry									
BCL-2	-				Endothelium	Present	DAKO	124	IR61461-2
CD34				+++	Endothelium	Present	DAKO	QBEnd10	GA63261-2
CD45				+++	Lymphocyte	Dispersed in cortex	DAKO	2B11+PD7/26	GA75161-2
CD56				+++	Neuroendocrine cells	Present	DAKO	123C3	IR62861-2
CD68		++			Macrophage	Present	DAKO	KP1 or PG-M1	GA60961-2
EMA	-				Pituitary cell	Absent	DAKO	E29	GA62961-2
GAL-3	-				Pituitary cell	Absent	DAKO	B2C10	MC0132
GFAP		++			Glial cells	Present	DAKO	Polyclonal	GA52461-2
H3 K27m	-				Glial cells	Absent	DAKO	RM192	RM0106
Ki-67		+			Proliferating cells	Low %4	DAKO	MIB-1	GA62661-2
NEUN	-				Neuron	Absent	DAKO	A60	MC0557
NFP	-				Endocrine cell, neuron	Absent	DAKO	2F11	GA60761-2
P53	-				TSG oncogene expressing cells	Absent	DAKO	DO-7	GA61661-2
PANCK	-				Endocrine cells	Absent	DAKO	AE1/AE3	GA05361-2
PROGESTERON	-				Endocrine cells, epithelial cells	Present	DAKO	PgR 1294	GA09061-2
S-100				+++	Glial cells, neuropil	Present	DAKO	Polyclonal	GA50461-2
SYN	-	++			Endocrine cells, glial cells	Present	DAKO	DAK-SYNAP	GA66061-2
TTF1		++			Thyroid cells, endocrine cells	Present	DAKO	8G7G3/1	IR05661-2
VİMENTİN				+++	All cells	Present	DAKO	V9	IR63061-2

Table 1: IHC* of various antibodies in diagnosing pituicytoma.

Abbreviations: *IHC: immunohistochemistry; **Expressivity: +++: strong reactivity; ++: mild reactivity; -: no reactivity

Case 2

A 56-year-old male patient was presented to our clinic with complaints of progressive bilateral visual loss. He was diagnosed with large suprasellar lesion suggesting pituitary macroadenoma 17 years ago after complaints of sensitivity to light. He was operated transsphenoidally in 2007 and 2019 in other clinic. He had no history of chemoradiotherapy. During his regular follow-ups, cranial MRI showed progressive enlargement of the tumor and compressing the optic nerves and displacing the chiasm anteriorly. Normal pituitary gland and stalk cannot be distinguished from adenoma. Surgical removal of the residual adenoma was suggested. MR elastography showed it is highly stiff and firm lesion for resection. Department of Endocrinology also evaluated the patient preoperatively and necessary hormonal replacements were initiated. Bilateral major deficits were found in visual field test and opthalmological examination performed preoperatively. The lesion resection was performed with two different surgeries by right and left pterional craniotomies performed 10-days interval.

Neuroradiology

Contrasted MRI imaging revealed residual relapsing macroadenoma extending to the suprasellar cistern and measuring 50 mm in the largest in coronal plane (Figure 3). The mass lesion compressed the optic chiasm and displaces it anteriorly. Normal pituitary gland and stalk cannot be clearly distinguished from adenoma. The macroadenoma was in close proximity to the supraclinoid segment of bilateral internal carotid arteries, A1 segment of bilateral anterior cerebral arteries, basilar artery, posterior cerebral arteries and superior cerebellar arteries. The 3rd cranial nerve was not clearly distinguishable from the mass. Elastography examination suggests that the macroadenoma had a firm consistency. Microhemorrhages were present within the adenoma.

Pathologic findings

The material was a granular cell tumor with focal lymphocyte infiltrates. Perilesional adenomatous anterior posterior and pituitary tissue was absent. The lesion composed of diffuse granular cell pattern without reticulin framework. Granular cells contain eccentric hyperchromatic nucleus and granular cytoplasm without pigment. Focal lymphocytic cell infiltrations were observed. There was no pleomorphism, necrosis, apoptosis, karyopyknosis, fibrosis and cystic degeneration within the tumor. PAS staining was positive for the cytoplasm.

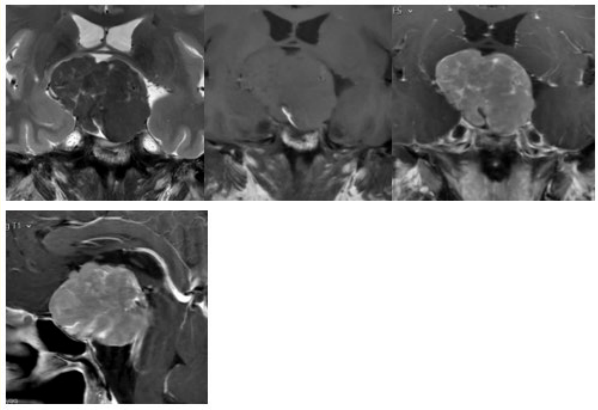

Figure 3: (Left to right) Coronal T2 and T1 non-enhanced T1 weighted images reveal a well-circumscribed mass lesion, localized to the sellar and suprasellar region, extending to the anterior part of the third ventricle and is hypointense on T2 W image and isointense with the cerebral cortex on T1 W image. Coronal and sagittal T1 weighted images shows intense contrast enhancement.

The tumor was immunoexpressing S100, TTF1, CD68, EMA, Galectin-3, GFAP, vimentin and Ki67: 1% (Figure 4). In contrary, it was negative for CD56, SYN, BCL2, neuroendocrine (GH, PRL, ACTH, FSH, LH, TSH) and transcription (TPIT, PIT-1, SF1) markers. Tumor didn't show reticular framework (Table 2). Morphologic and immunohistochemical features were consisted with granular cell oncocytoma.

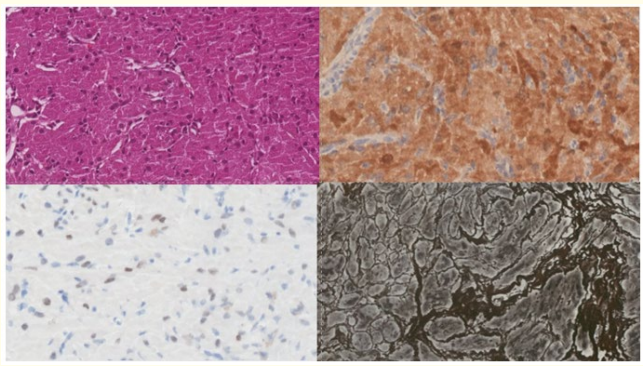

Figure 4: a. H&E, x200 b. S100, x200 c. TTF-1, x200 d. Reticulin stain, x200.

Antibodies	Expressivity**				Target	Tissue site	Company	Clone	Code
Immunohistochemistry									
BCL-2	-				Endothelium	Present	DAKO	124	IR61461-2
CD56				+++	Neuroendocrine cells	Present	DAKO	123C3	IR62861-2
CD68		++			Macrophage	Present	DAKO	KP1 or PG-M1	GA60961-2
EMA	-				Pituitary cell	Absent	DAKO	E29	GA62961-2
GFAP		++			Glial cells	Present	DAKO	Polyclonal	GA52461-2
Ki-67		+			Proliferating cells (low, 4%)	Present	DAKO	MIB-1	GA62661-2
P53	-				TSG oncogen expressing cells	Absent	DAKO	DO-7	GA61661-2
PANCK	-				Endocrine cells	Absent	DAKO	AE1/AE3	GA05361-2
Progesteron	-				Endocrine cells, epithelial cells	Present	DAKO	PgR 1294	GA09061-2
S-100				+++	Glial cells, neuropil	Present	DAKO	Polyclonal	GA50461-2
SYN	-	++			Endocrine cells, glial cells	Present	DAKO	SYNAP	GA60661-2
TTF-1		++			Thyroid cells, endocrine cells	Present	DAKO	8G7G3/1	IR05661-2
Vimentin				+++	All cells	Present	DAKO	V9	IR63061-2

Table 2: IHC* of various antibodies in diagnosing granular cell tumor.

Abbreviations: *IHC: immunohistochemistry; **Expressivity: +++: strong reactivity; ++: mild reactivity; -: no reactivity

Discussion

Pituicytoma, granular cell tumor and spindle cell oncocytoma are TTF-1 positive tumors of the sellar region and it is important to distinguish between them to make an accurate diagnosis [5]. Here, we describe 2 cases of sellar region tumors: the first one is a 63-year-old male with pituicytoma and the second one is a 56-year-old male with granular cell tumor.

The pituicytoma, is a rare tumor of the sellar region that has a spindle cell morphology, fascicular pattern, and variable glial fibrillary acidic protein (GFAP) immunoreactivity [9]. The posterior pituitary develops from the periventricular zone in the embryo, and TTF-1 is expressed in this area. TTF-1 is a specific marker for the posterior pituitary [10]**.** Pituicytomas usually presents in adults between the ages 40 and 60 years. The most frequent initial symptoms are vision problems caused by pressure on the optic chiasm and headaches. Symptoms of hypopituitarism, such as fatigue, menstrual irregularities, and decreased sexual drive, have also been observed. Hyperprolactinemia may be present in some cases due to compression of infundibulum. In rare cases, diabetes insipidus may also occur [5,11]**.** In our case, patient was presented with a 1-year history of headache and visual disturbance. Due

to neuroimaging; meningioma, craniopharyngioma, metastatic tumors were considered as differential diagnosis. However, absence of TTF-1 immunoreactivity distinguishes craniopharyngioma and meningioma from pituicytoma and other TTF-1 expressing tumors [12].

GCTs in the infundibulum are believed to originate from pituicytes, based on the detection of thyroid transcription factor 1 (TTF1) in immunohistochemical studies [13]. It consists of clusters of large cells with granular, eosinophilic cytoplasm due to abundant intracytoplasmic lysosomes [14]. GCT occurs more commonly in women, and most commonly presents between the ages 40 and 50 years [15]. The infundibular region contains key structures such as the optic chiasm and both the anterior and posterior pituitary glands, all of which can be affected by this neoplasm. Patients may experience symptoms such as headaches, vision problems, and hormonal imbalances due to the tumor's pressure, much like other tumors in the same area [13]**.** Visual deficits are quite common presenting complaint of GCT as it is seen in our case and other reported cases [16]. In the beginning, our differential diagnosis was a pituitary adenoma. However, adenomas typically have a higher nuclear-to-cytoplasmic ratio, and their cells can be organized in sheets, papillary, or tubular patterns. Moreover, the absence of neuroendocrine markers like chromogranin and pituitary peptide hormones in immunohistochemical stains led us to exclude adenoma from differential diagnosis [14].

When it comes to TTF-1 expressing neoplasms, pituicytoma, granular cell tumor and spindle cell oncocytoma are often compared. Spindle cell oncocytomas are composed of spindled or epithelioid tumor with eosinophilic, granular cytoplasm. The expression of EMA, anti-human mitochondrial antigen antibody MU213-UC, Galectin-3 and annexin A1 in spindle cell oncocytoma, distinguish it from pituicytoma [2]. Granular cell tumors are made up of tightly organized polygonal to spindled cells that have a high lysosomal content and eosinophilic granular cytoplasm. They are PAS positive and diastase resistant. The cells are positive for TTF-1, S100 protein and CD68 [5]. Pituicytomas are composed of elongated, bipolar spindle cells, typically organized into solid sheets and short fascicles, and may display a storiform pattern. According to WHO Classification of Central Nervous System 2021, absence of interspersed reticulin fibers is a desirable criterion for diagnosis of pituicytoma. However, in our case reticulin fibers were distinctly present. This finding raised questions regarding classification of pituicytoma. Moreover, there are studies suggesting redefining classification of these three tumors as diffuse TTF-1 expression in non-neoplastic pituicytes, pituicytomas, spindle cell oncocytomas, and granular cell tumors indicates a common pituicyte lineage [17]. Considering this information, it is evident that more studies should be conducted to clarify the classification and definition of TTF-1expressing posterior pituitary tumors.

Bibliography

1. Sassi F., *et al.* "Supra-sellar granular cell tumor: Report of a case with literature review". *International Journal of Surgery Case Reports* 112 (2013): 108977.

2. WHO Classification of Tumours, Central Nervous System, 5th edition, WHO Classification of Editor Board, Lyon IARC (2021).

3. Chen B., *et al.* "Pituicytoma: Report of three cases and a systematic literature review". *Clinical Neurology and Neurosurgery* (2021).

4. Wolfe SQ., *et al.* "Pituicytoma: case report". *Neurosurgery* 63.1 (2008): E173-E174.

5. El Hussein S and Vincentelli C. "Pituicytoma: Review of commonalities and distinguishing features among TTF-1 positive tumors of the central nervous system". *Annals of Diagnostic Pathology* 29 (2017): 57-61.

6. Gregoire A., *et al.* "Granular Cell Tumor of the Pituitary Stalk: A Rare and Benign Entity". *Journal of the Belgian Society of Radiology* 99.1 (2015): 79-81.

7. Bello CT., *et al.* "Granular cell tumour of the neurohypophysis: an unusual cause of hypopituitarism". *Endocrinology, Diabetes and Metabolism Case Reports* 2018 (2018): 17-0178.

8. Iglesias A., *et al.* "MR imaging findings in granular cell tumor of the neurohypophysis: a difficult preoperative diagnosis". *European Radiology* 10.12 (2000): 1871-1873.

9. Phillips JJ., *et al.* "Pituicytoma: characterization of a unique neoplasm by histology, immunohistochemistry, ultrastructure, and array-based comparative genomic hybridization". *Archives of Pathology and Laboratory Medicine* 134.7 (2010): 1063-1069.

10. Ozisik H., *et al.* "Two challenging cases of pituicytoma". *Hormones (Athens)* 20.4 (2021): 813-818.

11. Zygourakis CC., *et al.* "Pituicytomas and spindle cell oncocytomas: modern case series from the University of California, San Francisco". *Pituitary* 18.1 (2015): 150-158.

12. Kleinschmidt-DeMasters BK., *et al.* "An algorithmic approach to sellar region masses". *Archives of Pathology and Laboratory Medicine* 139.3 (2015): 356-372.

13. Polasek JB., *et al.* "Granular cell tumor of the infundibulum: a systematic review of MR-radiography, pathology, and clinical findings". *Journal of Neuro-Oncology* 140.2 (2018): 181-198.

14. Policarpio-Nicolas ML., *et al.* "Granular cell tumor of the neurohypophysis: report of a case with intraoperative cytologic diagnosis". *Diagnostic Cytopathology* 36.1 (2008): 58-63.

15. Ahmed AK., *et al.* "Surgical resection of granular cell tumor of the sellar region: three indications". *Pituitary* 22.6 (2019): 633-639.

16. Cohen-Gadol AA., *et al.* "Granular cell tumor of the sellar and suprasellar region: clinicopathologic study of 11 cases and literature review". *Mayo Clinic Proceedings* 78.5 (2003): 567-573.

17. Mete O., *et al.* "Spindle cell oncocytomas and granular cell tumors of the pituitary are variants of pituicytoma". *The American Journal of Surgical Pathology* 37.11 (2013): 1694-1699.