

Pituicytoma: A report of three cases and literature review

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Abstract. Pituicytoma is a rare tumor of the sellar and suprasellar regions, arising from the pituicytes, which are specialized glial cells in the neurohypophysis and infundibulum. Due to its rarity, ambiguity persists over the diagnosis, management and prognosis of pituicytoma. The current study presents a case series of three patients, each with a histopathological diagnosis of pituicytoma. A summary of the clinical manifestations, radiological characteristics, histopathological features, treatment strategies and prognoses are presented. In addition, 78 cases of pituicytoma, identified in a search of the published literature in Pubmed, are profiled. Pituicytoma typically presents with dysfunction of the optic nerve and pituitary. The radiological characteristics are nonspecific; diagnosis is typically made on the basis of histopathological results. The tumor is slow growing and benign and is amenable to surgical treatment by gross total resection; subsequent tumor recurrence is rare. A definitive assessment of prognosis requires an extended follow-up in a larger cohort.

Introduction

Pituicytoma (previously referred to as infundibuloma) is a rare tumor of the sellar and suprasellar regions, originating from specialized glial cells in the neurohypophysis and infundibulum (1). The tumor is slow growing and benign, and histologically corresponds to World Health Organization (WHO) grade I (2,3). Only 78 cases of pituicytoma have been reported since it was first described in 1955 (4). Due to its rarity, the clinical manifestations, radiological characteristics, histopathological features and prognoses have yet to be fully elucidated. Pituicytoma is typically challenging to distinguish from other sellar and suprasellar lesions, including granular cell tumor, pituitary adenoma, pilocytic astrocytoma and lymphocytic hypophysitis (2,3). Surgical treatment may be challenging, owing to the hyper vascularity of the tumor. The

present case study reports three cases of histopathologically diagnosed pituicytoma. Clinical presentations, surgical strategies and treatment outcomes are presented and the relevant published literature is discussed.

Case reports

Case 1. A 41-year-old male presented to the First Hospital of Jilin University (Changchun, China) in February 2015 with a 20-day history of headaches and dizziness. The physical examination revealed bitemporal hemianopsia. Brain magnetic resonance imaging (MRI) revealed a contrast-enhanced 3.7x2.2x2.5-cm mass compressing the pituitary stalk and optic chiasma (Fig. 1A and B). The mass appeared isointense on T1-weighted images (T1WI), and there was signal heterogeneity on T2-weighted images (T2WI); the central homogeneous enhancement was remarkable following gadolinium-diethylenetriamine pentaacetic acid (Gd-DTPA) administration. Subsequent investigation revealed normal endocrine hormone levels (including TSH, FT3, FT4, PRL, FSH, GH, LH, serum hydrocortisone, and urinary free cortisol). A preoperative diagnosis of craniopharyngioma was determined.

Examinations of the anterior segments of the eyes and fundus were normal. No dermatological abnormalities that are typically associated with neurofibromatosis were detected. A further ophthalmologic examination revealed binocular ametropia, whereas the binocular visual field was normal. Right eye proptosis and right sixth nerve palsy were clearly discernible. No further neurological abnormalities were identified.

A craniotomy was performed via a right frontal-temporal approach. Intraoperatively, a hard gray-white mass was observed, which exhibited solid and cystic components, hyper vascularity and was adhered to the optic nerve. The tumor was resected gradually and a diagnosis of pituicytoma was subsequently confirmed following histopathological examination (Fig. 2). Immunohistochemical staining (5) revealed that the tumor was positive for glial fibrillary acidic protein (GFAP), oligodendrocyte transcription factor 2 (Oligo-2), vimentin and S-100 protein, but negative for tumor protein 53 (p53), isocitrate dehydrogenase 1 R132H (IDH1R132H), myelin basic protein (MBP), epidermal growth factor receptor, synaptophysin (Syn), chromogranin A (CgA), neuronal nuclear antigen and epithelial membrane antigen (EMA). The positive expression rate for antigen Ki-67 was ~2%, and for O-6-methylguanine-DNA methyltransferase (MGMT) it was <5%.

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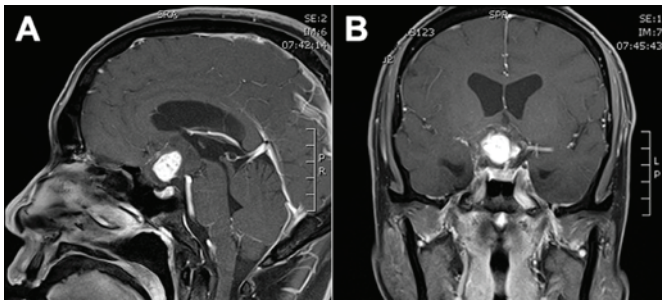


Figure 1. Magnetic resonance imaging of the brain in case 1 showing a contrast-enhanced mass compressing the pituitary stalk and optic chiasma in T1-weighted enhanced imaging (A and B). The central homogeneous enhancement is clear following Gd-DTPA administration, as shown on the T1-weighted enhanced images. Gd-DTPA, gadolinium-diethylenetriamine pentaacetic acid.

Postoperatively, the patient experienced nausea and vomiting, and his skin was abnormally dry. Investigation revealed a decreased serum sodium ion level (120-130 mmol/l; normal range, 136-146 mmol/l), a decreased free triiodothyronine level (1.73 pmol/l; normal range, 3.1-6.8 pmol/l), an elevated free thyroxine level (8.99 pmol/l; normal range, 3.1-6.8 pmol/l), a decreased adrenocorticotrophic hormone level (0 h level, 0.22 pmol/l; 16 h level, 0.28 pmol/l; normal range, 1.6-13.9 pmol/l) and decreased serum testosterone level (1.39 nmol/l; normal range, 6.07-27.1 nmol/l). Hypopituitarism was diagnosed and complete remission was achieved following treatment with hydrocortisone (Shanghai Sine Pharmaceutical Laboratories, Co., Ltd., Shanghai, China; 20 mg at 8 am and 2 pm for 2 weeks) and euthyrox (Merck KGaA, Darmstadt, Germany; 25 μ g once a day for one month following hydrocortisone treatment for a week). At the 17-month postsurgical follow-up, binocular vision was markedly improved. No recurrence of the tumor was noted, and all aforementioned hormone levels were observed to be within the normal ranges.

Case 2. A 44-year-old female presented with a 4-year history of irregular menstruation. The physical examination revealed no evident abnormalities. A brain MRI revealed a contrast-enhancing 2.2x2.2x2.1-cm mass in the sellar and suprasellar regions (Fig. 3A-F). The mass appeared hypointense on T1WI and exhibited heterogeneous hyper intensity on T2WI; the tumor demonstrated clear homogeneous enhancement following Gd-DTPA administration. The tumor was located adjacent to the bilateral internal carotid arteries; the pituitary stalk was displaced to the left, and the optic chiasma displaced antorsely. Endocrine hormone levels were observed to be within normal ranges: TSH, 0.465 μ IU/ml (normal range, 0.27-4.2 μ IU/ml); FT3, 3.2 pmol/l (normal range, 3.1-6.8 pmol/l); FT4, 12.4 pmol/l (normal range, 12-22 pmol/l); PRL, 61.11 mIU/l (normal range, 70.81-566.5 mIU/l); FSH, 21.46 mIU/l (normal range, 4.54-22.51 mIU/l); GH, 0.327 ng/ml (normal range, 0.01-3.607 ng/ml); LH, 9.74 mIU/ml (normal range, 2.12-10.89 mIU/ml); serum hydrocortisone (8 am, 292.07 nmol/l; 0 am, 513.54 nmol/l; normal range, 240-619 nmol/l; 4 pm, 523.7 nmol/l; normal range, <276.0); urinary free cortisol, 905 nmol/24 h (normal range, 108-961 nmol/24 h). The preoperative diagnosis was pituitary adenoma.

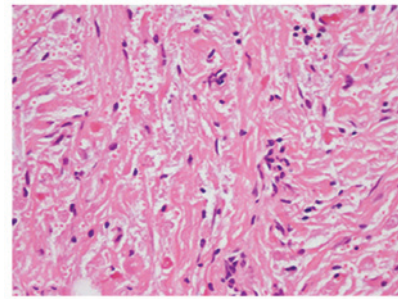


Figure 2. Histopathological examination of the pituitary tumor specimen in case 1, demonstrating round to spindle shaped cells with a fascicular or storiform growth pattern. Abundant eosinophilic cytoplasm and a rich capillary network are visible in the tumor cells. Nuclei are round to oval without evidence of cellular atypia or mitotic figures.

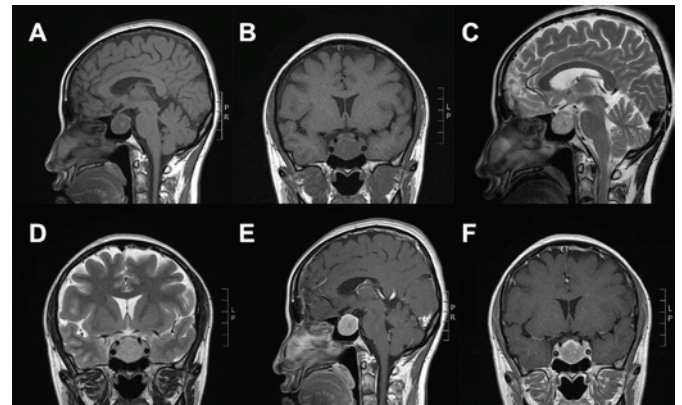


Figure 3. Magnetic resonance imaging of the brain in case 2 showing a contrast enhanced mass in the sellar and suprasellar regions. (A and B) The mass demonstrated hypointensity on T1WI and (C and D) heterogeneous hyper intensity on T2WI; (E and F) the tumor demonstrated clear homogeneous enhancement following Gd-DTPA administration. Gd-DTPA, gadolinium-diethylenetriamine pentaacetic acid; T1WI, T1 weighted image; T2WI, T2 weighted image.

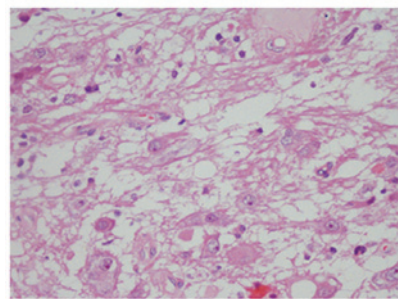


Figure 4. Histopathological examination of the pituitary tumor specimen in case 2, exhibiting round to spindle shaped cells with a fascicular or storiform growth pattern. Abundant eosinophilic cytoplasm and a rich capillary network are visible in the tumor cells. Nuclei are round to oval without evidence of cellular atypia or mitotic figures.

The tumor was completely resected via a transsphenoidal surgical approach. Intraoperatively, the gray-white mass was soft and hypovascular. Histopathological examination confirmed pituitary tumor (Fig. 4). Immunohistochemical staining revealed that the tumor was positive for Oligo-2, Syn, neural cell adhesion molecule (CD56), CgA and neuro-specific

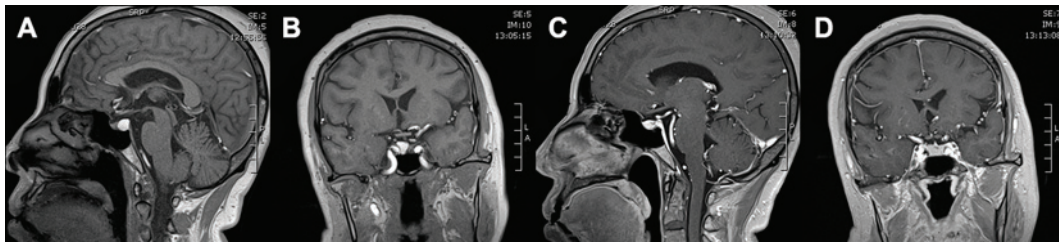


Figure 5. Magnetic resonance imaging of the brain in case 3 exhibiting a well-defined mass in the sellar region compressing the pituitary gland to the left. (A and B) The mass demonstrated hyper intensity on T1WI, with a cystic component in the central section of the pituitary; (C and D) the tumor demonstrated marked enhancement following Gd-DTPA administration. Gd-DTPA, gadolinium-diethylenetriamine pentaacetic acid; T1WI, T1 weighted image.

enolase but negative for GFAP, p53, MBP and S-100 protein. The positive expression rate for MGMT was 30-40%.

Postoperatively, the patient experienced transient diabetes insipidus that resolved following 6 IU hypophysin treatment (Tianjin Biochemical Pharmaceutical Co., Ltd., Tianjin, China). Repeat investigations revealed normal hormone levels (TSH, FT3, FT4, PRL, FSH, GH, LH, serum hydrocortisone and urinary free cortisol). Regular menstruation was restored during the 43-month follow-up period and no recurrence of the tumor was observed.

Case 3. A 61-year old female presented with a 6-month history of frequent headaches, nausea and vomiting. The physical examination revealed no discernable abnormalities. A brain MRI identified a well-defined 0.9x0.8x0.9-cm mass in the sellar region, compressing the pituitary gland to the left (Fig. 5). The mass exhibited hyperintensity on T1WI and isointensity on T2WI, with a cystic component in the central section of the pituitary; the tumor was markedly enhanced following Gd-DTPA administration. Subsequent investigation revealed an elevated serum thyroid stimulating hormone (TSH) level (5.73 μ IU/ml; normal range, 0.27-4.2 μ IU/ml). A preoperative diagnosis of pituitary adenoma was determined.

The tumor was completely removed using a transsphenoidal approach. Intraoperatively, the gray-white mass was soft and hypervascular. Histopathological examination confirmed pituicytoma (Fig. 6). Immunohistochemical staining indicated that the tumor was positive for GFAP, vimentin and S-100 protein, but negative for reticular fibers. The positive expression rate for antigen Ki-67 was <1%.

Postoperative recovery was satisfactory and subsequent examination revealed normal TSH levels (mean, 0.475 μ IU/ml). During the follow-up period of 45 months, no recurrence of the tumor was observed.

Discussion

Pituicytomas are rare, primary tumors originating from the so-called pituicytes in neurohypophysis and pituitary stalk (2). Pituicytes are glial cells that support the large axons of vasopressin- and oxytocin-producing hypothalamic neurons, and comprise major, dark, oncocyctic, ependymal and granular cell types; the majority of pituicytomas are considered to derive from the first two types (6). The first case of this type of glioma was identified in the posterior lobe of the pituitary gland and was described by Scothorne in 1955 (4). Brat *et al* (2) reported nine cases of low-grade glioma of the neurohypophysis in

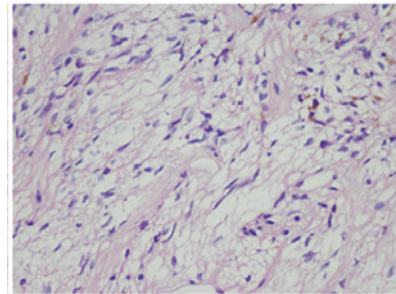


Figure 6. Histopathological examination of the pituicytoma specimen in case 3, exhibiting round to spindle shaped cells with fascicular or storiform growth patterns. An abundant eosinophilic cytoplasm and a rich network of capillaries are visible in the tumor cells. The nuclei are round to oval in appearance without evidence of cellular atypia or mitotic figures.

2000, for which the term pituicytoma was proposed. Pituicytoma was previously regarded as a condition with a wide clinical spectrum, including pituitary astrocytoma, posterior lobe glioma, choristoma and infundibuloma in the sellar and suprasellar regions. However, the tumor was named as a separate entity in the 2007 WHO classification of central nervous system tumors (3).

A total of 78 published case reports of pituicytoma were retrieved in a search of the published literature. A summary of these cases is presented below (Table I). Pituicytomas occur predominantly in adults, with a mean age of 46.9 years (range, 7-83 years) at the time of diagnosis. The current study indicated that the peak age was between the fourth and fifth decade, accounting for 50.6% of all patients. Out of 78 patients, only 3 were in the pediatric age group (age, 7-13 years) (7-9). A total of 44 male and 33 female subjects were included in the present study; the male: Female ratio was 1.3:1. The clinical details were not available in one case. The most common symptoms of pituicytoma were vision and visual field disorders (44 cases, 56.4%), headaches (34 cases, 43.6%), hypopituitarism (17 cases, 21.8%), hyposexuality (16 cases, 20.5%), sexual dysfunction (7 cases, 9.0%), menstrual disorder (7 cases, 9.0%), dizziness (6 cases, 7.7%), diabetes insipidus (3 cases, 3.8%) (10-12), epilepsy (3 cases, 3.8%) (13-15), gynecomastia (3 cases, 3.8%) (10,16,17) and spontaneous tumor hemorrhage (1 case, 1.3%) (18). There were also sporadic cases that presented with nausea (6), vomiting (9) or edema (9). In one case the pituicytoma was incidentally revealed at autopsy (19).

The clinical symptoms are typically attributable to the local effects of tumor, and therefore, depend on the tumor size and location. For instance, optic chiasm compression may

Table I. The summary of previous cases with pituitaryomas.

Characteristics	Case number (N)	Percentage
Gender	N=77 ^a	
Male	44	57.1%
Female	33	42.9%
Main clinical symptoms	N=78	
Vision and visual field disorders	44	56.4%
Headache	34	43.6%
Hypopituitarism	17	21.8%
Hyposexuality	16	20.5%
Sexual dysfunction	7	9.0%
Menstrual disorder	7	9.0%
Dizziness	6	7.7%
Diabetes insipidus	3	3.8%
Epilepsy	3	3.8%
Gynecomastia	3	3.8%
Spontaneous tumor hemorrhage	1	1.3%
Locations	N=77	
The sellar region	15	19.4%
The suprasellar region	34	44.2%
The sellar and suprasellar regions	28	36.4%
Operations	N=67	
Craniotomy	24	35.9%
Transsphenoidal operation	41	61.1%
Endoscopic endonasal transsphenoidal operation	2	3.0%

^aThe clinical profiles were not available in one case.

cause bitemporal hemianopsia; hypophysis compression may lead to headache and hypopituitarism; infundibular compression may result in hypothalamic dopamine delivery disorders, inducing hyperprolactinemia, amenorrhea, hyposexuality and sexual dysfunction. The three cases detailed in this study presented with combinations of bitemporal hemianopsia, headache, dizziness, amenorrhea, nausea and vomiting, which is consistent with the previous case reports. The duration of the symptoms prior to the diagnosis ranged from a few months to several years. One patient had acute symptomatic onset due to spontaneous tumor hemorrhage into the third ventricle (17). There was one case of accidental head trauma in which a diagnosis of pituitaryoma was made (20).

In various patients, there was a history of endocrine disorders prior to the onset of pituitaryoma. These included parathyroid adenomas and follicular carcinoma of the thyroid (21), strumectomy (16), amyotrophic lateral sclerosis (17), orchiectomy (22), orchidorrhaphy (18), diabetes (23) and Cushing's disease (24). Furthermore, a solitary case was reported that exhibited genomic copy-number imbalances, including losses on chromosome arms 1p, 14q and 22q, and gains on 5p (11).

The imaging characteristics of pituitaryoma are nonspecific. The radiological profiles were available in 77 cases; 15

of these 77 cases revealed pituitaryoma in the sellar region, 34 in the suprasellar region, and in 28 both the sellar and suprasellar regions were involved. In 12 cases, a computed tomography scan revealed a solid, isointense mass with homogenous enhancement and no accompanying evidence of calcification, necrosis, bony erosion or hyperostosis. On the MRI examination, pituitaryomas commonly presented as well-defined, solid, round or oval masses in the sellar region, with or without suprasellar extension. The tumors usually appeared hypointense-isointense on T1WI, low-moderately hyperintense on T2WI, and with homogenous or heterogeneous contrast enhancement (6,13,25). Only four cases had solid cystic pituitaryomas (2,7,26). In the present study, cases 1 and 3 exhibited solid cystic tumors. The differential diagnoses had included pituitary adenoma, meningioma, craniopharyngioma, hemangiopericytoma, pilocytic astrocytoma, granulocyte tumor, ganglioglioma, germinoma, hamartoma and metastatic tumors (6,27).

Surgical resection is the preferred treatment for pituitaryoma, with an extremely low recurrence rate (4.3%) following complete resection. Among all the reported cases treated with gross total resection, only one experienced tumor recurrence (28). In the literature, 67 surgeries, involving 60 patients, were described. Craniotomy was performed in 24 patients, of which gross total resection was achieved in 7 patients; complications were noted in 11 patients. Transsphenoidal surgery was performed on 41 patients, of which gross total resection was achieved in 14 patients; complications were noted in 8 patients. An endoscopic endonasal transsphenoidal approach was employed in 2 patients, and gross total resection was achieved in the 2 cases (29). Intraoperatively, the tumors were revealed to be pink and solid. The majority of pituitaryomas were well demarcated and of a benign nature. In a minority of cases, the tumor had a tight dural attachment at the diaphragma sellae (22). Pituitaryomas with a soft texture or a cystic component were infrequently observed (17,30). Hypervascularity is a common intraoperative challenge, as it can hinder the success of gross total resection. However, hypovascular entities have also been described in the literature (31). In certain cases, carotid angiography was helpful in surgical planning (17,23). To achieve complete tumor resection, a comprehensive preoperative assessment is essential.

Current mainstream surgical approaches include the aforementioned frontotemporal craniotomy and the transsphenoidal approach. Feng *et al* (29) reported complete resection of recurring pituitaryomas when the surgery was performed via an expanded endoscopic, endonasal, transsphenoidal and transplanum approach. However, the efficacy and safety of the expanded transsphenoidal procedure has yet to be fully established as there is currently insufficient clinical evidence (29). The most common postoperative complications included diabetes insipidus (9 cases), hypopituitarism (7 cases), visual impairment (6 cases) and hypothyroidism (3 cases). These complications were considered to be associated with the iatrogenic trauma to contiguous structures. Adjuvant radiotherapy was administered in 7 patients, however the respective follow-up data was not available. In the current case series, no adjuvant radiotherapy, or chemotherapy, was performed and there were no tumor recurrences observed during a maximal follow-up period of 45 months.

The accurate diagnosis of pituitary adenoma continues to depend on histopathological evidence. Microscopically, pituitary adenomas are composed of round to spindle-shaped cells with a fascicular or storiform growth pattern. The tumor cells have an abundant eosinophilic cytoplasm and a rich capillary network is visible. Tumor cell nuclei are round to oval, without evident atypia or mitotic figures. However, Zhi *et al* (28) reported a pituitary adenoma with atypical histological features, including sparse intercellular reticulin surrounding the tumor cells, absent Rosenthal fibers and eosinophilic granular bodies, which usually help to distinguish between pituitary adenomas and pilocytic astrocytomas (32). In previous studies, pituitary adenomas demonstrated positive immunofluorescence staining for S-100 and vimentin protein, negative or low-moderately positive staining for GFAP (2,10,21,31), and negative staining for EMA, Syn, chromogranin, cytokeratin and neurofilament protein (26). Using electron microscopy, cytoplasmic intermediate filaments and tumor vessel basal lamina were typically observed in pituitary adenomas, but desmosomes and pericellular basal lamina were absent (10,31). In the cases presented in this study, the immunohistochemical features are consistent with those reported previously. In addition, the low proliferation index is indicative that pituitary adenomas may be consistently benign.

The recurrence interval following subtotal tumor resection is usually long and no instances of malignant transformation or cerebrospinal dissemination have been reported. Since the radiological characteristics and clinical manifestations are nonspecific, pituitary adenomas are liable to be initially misdiagnosed. The definitive diagnosis still depends on pathological examination. The role and efficacy of adjuvant radiotherapy and chemotherapy is unclear at present and requires further study. Considering the local recurrence following subtotal resection, postoperative radiotherapy should be recommended in patients where gross total resection is not feasible. Even for those patients undergoing complete tumor resection, a close MRI follow-up is essential.

Pituitary adenomas are extremely rare entities. The surgical resection should be designed for optimal functional preservation, and an MRI may provide guidance in this respect. Furthermore, understanding of the surrounding anatomical structures is crucial in facilitating complete tumor resection and nerve preservation.

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