# CASE REPORT

# Pituicytoma: Four cases with unusual imaging features and a literature review

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### **Abstract**

**OBJECTIVE:** Pituicytomas (PTs) are rare and benign neoplasms. The variable imaging and clinical features of PTs, which overlap with other sellar pathologies, can make preoperative diagnosis challenging. In the interest of a more comprehensive understanding of the diagnostic aspects of PTs, it is necessary to report and synthesize the variable imaging and clinical features of PTs.

**METHODS:** We retrospectively included and analysed four pathologically proven PTs with unusual imaging and/or clinical features. Additionally, we reviewed the literature on PT between 2007 and 2019 in the PubMed database to provide context for the individual patient data described herein.

**RESULTS:** Our series included three female and one male adult patient (mean age: 44.75, age range: 20–56 y). Based on clinical symptoms, we noticed that case 1 had Cushing's syndrome, case 2 had increased prolactin, case 3 had extremity enlargement but with a normal level of human growth factor, and case 4 presented with tinnitus and dizziness. On radiograph, inconsistent with the main imaging findings of PTs in the literature, there was one case in the pituitary anterior lobe, three cases with hypointensity on T2-weighted images, two patients with reduced homogeneous contrast enhancement, and one case demonstrating invasion potential. In addition, one of our patients underwent PET-CT examination, and the lesion had a slight increase in glucose uptake and no significant decrease in ammonia uptake. Postoperative follow-up monitoring revealed no tumour recurrence. **CONCLUSION:** Our cases highlight the unusual imaging manifestations of PTs.

Recognizing these imaging features plays an important role in the preoperative diagnosis, treatment, and postsurgery monitoring of PTs.

### **Abbreviations & units:**

PT - Pituicytoma EMA - epithelial membrane antigen
T1WI - T1-weighted images COR - corticosteroid hormone
T2WI - T2-weighted images ACTH - adrenocorticotropic hormone

TTF-1 - thyroid transcription factor-1

### INTRODUCTION

Pituicytomas (PTs) are rare and benign neoplasms arising from the glial cells of the neurohypophysis and infundibulum. The first case of PT was reported by Scothorne in 1955, who described PT as a glioma in the posterior lobe of the pituitary (Scothorne 1955). In 2000, Brat *et al.* proposed a modern depiction of the histopathological features of PT (Brat *et al.* 2000). In 2007, PT was named a distinct entity according to the World Health Organization classification of central nervous system tumours (Brat *et al.* 2007). The estimated incidence of PT was 0.07% of all seller lesions (Chang *et al.* 2018). The diagnostic and therapeutic approach of PT has not been established with clarity due to its low frequency as well as the scarcity of scientific literature, represented mainly by case reports.

Several papers have reviewed the clinical and radiological manifestations of PT (Salge-Arrieta et al. 2018; Yang et al. 2016; Tian et al. 2013). These studies found that PT had a higher prevalence in the fifth and sixth decades of life, with a slight male predominance and the main symptoms of visual field defects and pituitary-hypothalamic dysfunctions, all of which tended to be progressive. MRI was superior to CT in evaluating PT. Most PTs were homogeneously isointense on T1-weighted images (T1WI), hyperintense on T2-weighted images (T2WI), and homogeneously enhanced after injection of contrast agent. However, due to the rare prevalence of PT, the reported clinical and radiological features of PT might only represent part of its clinical and imaging manifestations. The

diagnosis of PT mainly relies on histopathological and immunohistochemical examinations. To comprehensively understand the clinical, diagnostic, and therapeutic aspects of PT, it is necessary to report and evaluate the variable clinical and imaging features of PT, which could shed light on the early preoperative diagnosis of PT.

Hereby, a retrospective analysis of four primary cases of PT with variable clinical and radiologic features in our institution was conducted. Case 1 was a young female with a pathologically proven PT in the anterior lobe of the pituitary. Case 2 was a middle-aged female with a hypointense lesion of the pituitary. Case 3 was a PET- and MRI-confirmed case with clivus invasion. Case 4 was a middle-aged man who presented with unusual clinical symptoms (tinnitus and dizziness). In addition, we performed a literature search of the PubMed database with the word 'pituicytoma' from 2007.01 to 2019.10. All the studies were limited to publications in English or Chinese. In total, 100 published articles were identified. After screening the title and/or abstract, we excluded 38 papers without PT in the paper. For the remaining articles (n=62), we carefully examined the full text and further excluded review studies (n=4). Finally, 58 articles with 142 PT cases were reviewed in this study.

### **METHODS**

### **Ethics**

This study was approved by the Ethics Committee of the First Affiliated Hospital of Sun Yat-sen University

Tab. 1. The clinical and laboratory presentations of our reported four cases of pituicytoma

	Case No.			
	01	02	03	04
Age (y)	29	47	56	47
Sex	Female	Female	Female	Male
Headache	no	No	no	no
Visual defect	yes	No	no	no
Other presentations	Cushing's syndrome	amenorrhea	progressing enlargement of the extremities	tinnitus and dizziness
Human Growth hormone (hGH)	N	N	N	<0.05
Adrenocorticotrophic hormone (ACTH)	11.91	N	N	12.8↑
Thyroid stimulating hormone (TSH)	N	N	N	0.01↓
Free T3	N	N	N	6.071
Free T4	N	N	N	19.01
Cortisol, 0 AM	18.2	-	-	1.1
Cortisol, 8 AM	17.3	-	-	14.7
Sex hormone	N	Hyperprolactinemia	N	-

<sup>\*</sup>N: normal; -: lack of this specific examination; normal range of hormones: hGH 0-10 μg/L, ACTH 0.0-10.2 pmol/L, TSH 0.035-4.94 mIU/L, Free T3 2.63-5.70 pmol/L, Free T4 9.01-19.05 pmol/L, Cortisol, 0 AM 2.9-19.4 μg/dL, Cortisol, 8 AM 2.9-19.4 μg/dL.

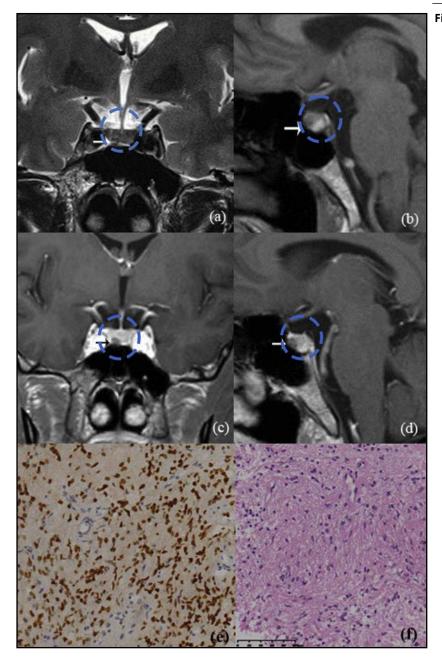


Fig. 1. A 29-year-old female presented with a 16-month history of unexplained rapid weight gain and menstrual disorders. Preoperative coronal T1WI (a), sagittal T2WI (b), and contrast-enhanced T1WI MR images (c and d) revealed a small and well-circumstanced nodule (arrow) located on the right side of the frontal pituitary lobe. Significant hypointensity on T2WI (arrow) and reduced enhancement (arrow) were noted. A histopathological exam (f) found focal spindle cells, which were arranged in a spiral pattern among the normal pituitary anterior lobe tissue. Immunohistochemical staining (e) revealed that the tumour was diffusely immunopositive for thyroid transcription factor-1 (TTF-1). No obvious atypia or mitotic figures were observed in the tumour cells.

and The First Affiliated Hospital, Zhejiang University school of medicine. This was a retrospective observational study, and informed consent was waived.

### Case reports

Case 1: A 29-year-old female presented a 16-month history of unexplained rapid weight gain and menstrual disorders. The patient started to have irregular menstruation and menorrhagia 16 months prior (after abortion). In the last two months, she presented with amenorrhea and experienced increased thirst, urination, and anxiety. A physical examination revealed that she had a moon face, trunk obesity, striae, and "buffalo hump". Visual examination showed that the patient had decreased visual sensation and partial visual field defects in both eyes, and a physiologic blind spot

enlargement was observed in the left eye. Furthermore, laboratory examinations (Table 1) revealed that the high-dose dexamethasone suppression test was positive, while the low-dose dexamethasone suppression test was negative, which suggested Cushing's syndrome. These laboratory findings were in line with the physical examination abnormalities. No other pituitary function abnormality was noticed.

Conventional MRI revealed a lesion of 3 mm×4 mm, with an unclear boundary in the anterior lobe of the pituitary. Compared with the brain grey matter, the lesion had homogenously lower T1-weighted (T1W) and T2-weighted (T2W) MRI intensities. The lesion showed reduced enhancement compared with the rest of the pituitary gland, and the lesion boundary became more discernible after enhancement (Fig. 1).

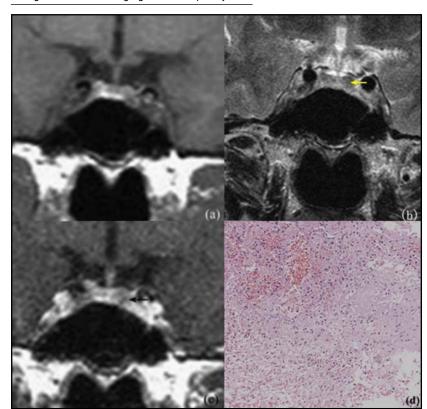


Fig. 2. A 47-year-old female presented with a nine-year history of hyperprolactinemia and two years of secondary amenorrhea. Non- and enhanced coronal MR images (a, b, and c) demonstrated a small and well- circumscribed nodule (arrow), which is located on the left side of the pituitary. The nodule was poorly detected on T1WI and T2WI MR images, and the lesion with reduced homogeneous enhancement was noticed after injection of contrast agent. A histopathological exam (d) proved the diagnosis, the cells had no obvious atypia, and no mitotic figures were observed.

In addition, a noncontrast abdominal CT scan showed that the bilateral adrenal glands were diffusely enlarged.

Under a suspicious diagnosis of pituitary adenoma, the patient underwent a transsphenoidal operation. The intraoperative view depicted that the lesion was soft and hypervascular. The histopathologic analysis did not provide any distinct adenomatous evidence. Focal fusiform cells that were distinguished from the surrounding pituitary tissue were noticed. Under light microscopy, the tumour cell density was significantly increased, whereas tumour cell nuclear atypia was not obvious. Mitoses were extremely rare, and <1% of nuclei were MIB1-positive. Furthermore, immunohistochemistry demonstrated partial positivity for the S-100 protein, strong positivity for thyroid transcription factor-1 (TTF-1), and negativity for epithelial membrane antigen (EMA), which supported the diagnosis of PT (Fig. 1).

The patient was followed up for four years, and no tumour recurrence was detected by MRI. Laboratory examinations showed that corticosteroid hormone (COR) and adrenocorticotropic hormone (ACTH) were all within normal ranges.

Case 2: A 47-year-old female presented a nine-year history of hyperprolactinemia and two years of secondary amenorrhea. Neurological examination revealed no impairment of visual acuity or visual fields. An endocrine investigation revealed elevated prolactin (PRL) levels (110  $\mu$ g/l), which might be secondary to the pituitary stalk effect. Other endocrine hormone levels were within normal ranges (Table 1).

Subsequently, pituitary CT and MRI scans were performed. No abnormalities were found in the pituitary CT scan. Further MRI scans identified a small nodule (4 mm×4 mm) in the left pituitary and a bright spot in the posterior pituitary. The small nodule was poorly detected on T1WI (isointensity) and T2WI (slight hypointensity), with a reduced homogeneous enhancement after injection of contrast agent. The tumour was followed up for one year, and MRI found that the lesion was stable (without changes in size or MRI signal) (Fig. 2). However, the serum PRL level continued to rise.

Hereby, under suspicion of pituitary adenoma, the tumour was completely resected via a transsphenoidal surgical approach. Intraoperatively, the grey–white nodule was soft. Histopathological examination confirmed PT, and the tumour section showed spindle cells arranged in fascicles or whorl patterns. Immunohistochemical staining revealed that the tumour had diffuse immunopositivity for TTF-1, thyroid EMA, S-100, and neuron-specific enolase and was partly positive for Ki-67 (<1%).

To date, this patient has been followed for five years, but her menstrual cycle has not returned to normal. Endocrine investigation revealed that PRL levels gradually decreased (from 219.84  $\mu$ g/l to 144.27  $\mu$ g/l) but were still above the normal range. No signs of residual tumour or recurrence were found during the follow-up MRI scans.

Case 3: A 56-year-old female mainly complained of a one-year history of progressive enlargement of the

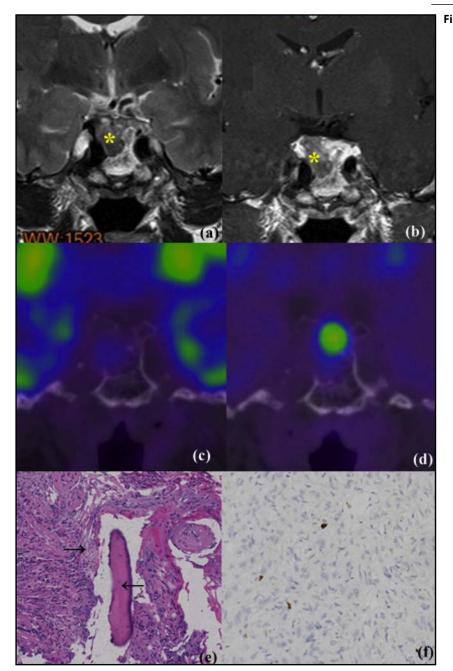


Fig. 3. A 56-year-old female mainly complained of a one-year history of progressing enlargement of the extremities. The lesion was hypointense on T2WI (1). T1WI-enhanced MR imaging (b) showed that the lesion had heterogeneous contrast enhancement (asterisk). A PET/CT scan with 18F-FDG and 13N-NH3 demonstrated the lesion with slightly increased uptake of glucose (c) but no significant decrease in uptake of ammonia (d). The PET-CT image clearly showed that the lesion had invaded the sella turcica and clivus. By light microscopy (e), it was observed that the tumour had invaded the bone tissue (←). Part of the tumour tissue was deformed owing to electrotome burn (→). Unexpectedly, immunohistochemical imaging (f) showed that the proliferation index of Ki-67 was <1%.

extremities. Neurological examination revealed no impairment of visual acuity or visual fields. During hospitalization, her hGH was slightly higher but still within normal ranges (Table 1).

Initial MR images of the sellar region demonstrated an irregular and poorly delineated lesion, which measured 20 mm×14 mm. The lesion was indistinct from the pituitary parenchyma and had invaded the clivus and the right cavernous sinus. The lesion was isointense on T1WI and mainly hypointense on T2WI with heterogeneous enhancement (Fig. 3). Preoperative MRI presumed this lesion to be an invasive PA. Additional PET-CT with <sup>18</sup>F-FDG and <sup>13</sup>N-NH3 was performed. PET-CT showed that the lesion had a higher uptake of glucose (SUVmax=1.8) and had no significant

decrease in ammonia uptake, which suggested that the lesion was an invasive PA (Fig. 3).

Thus, under the presumptive diagnosis of invasive PA, the patient underwent subtotal resection (because of clivus invasion) of the tumour. Intraoperative observation showed that the tumour was reddish and soft in texture. Under light microscopy, the tumour was comprised of spindle and short spindle cells. Tumour cell atypia was insignificant, and no mitosis or necrosis was found. Immunohistochemistry demonstrated the following: TTF-1(+), S-100 (+), routine synaptophysin (Syn) (+), CD56 (+), vimentin (+), GFPA (-), EMA (-), cytokeratin (CK) (-), luteinizing hormone (LH) (-), follicle-stimulating hormone (FSH) (-), thyroid stimulating hormone (TSH) (-), ACTH (-), hGH (-), PRL (-),

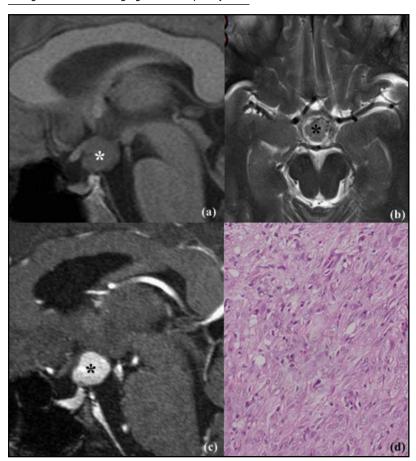


Fig. 4. A 47-year-old male presented with a sixmonth history of nonprogressing tinnitus and dizziness. An MRI scan demonstrated a round suprasellar mass (asterisk). The MRI signal of the tumour was homogeneous. It had hyperintensity on T2WI MR images (b), slight hypointensity on T1WI MRI images (a) and homogenous enhancement after injection of contrast agent (c). Histology (d) proved that this tumour was a pituocytoma, and haematoxylin and eosin (HE) staining revealed that tumour cells were arranged in vaguely fascicular or storiform patterns.

and partly positive for Ki-67 (<1%), which supported the diagnosis of PT.

Endocrine investigations have been performed annually. To date, no abnormalities have been detected, and no sign of residual tumour progression has been observed during follow-up MRI.

Case 4: A 47-year-old male presented a six-month history of nonprogressive tinnitus and dizziness. Neurological physical exams were normal. The endocrine evaluation showed a slightly elevated ACTH level (12.8 pmol/L), and other hormones were within normal ranges (Table 1). MRIs of the ears and pituitary were performed. There were no abnormalities in the bilateral middle or inner ears. However, an occult round solid nodule measuring 15 mm×14 mm was detected in the suprasellar region. The lesion involved the infundibular stalk (Fig. 4). The lesion was isointense on T1WI and hyperintense on T2WI with avid homogenous enhancement. Hereby, the mass was presumed to be a solid craniopharyngioma.

After exclusion of surgery contraindications, a craniotomy was performed via a right frontal-temporal approach. A total mass excision was achieved. Intraoperatively, a reddish and hypervascular solid mass was observed in the middle of the pituitary stalk. A diagnosis of PT was subsequently confirmed following histopathological examination. The tumour was composed of bipolar spindle and oval cells, which

were arranged in vaguely fascicular or storiform patterns. No significant mitotic activity was observed. No anterior pituitary tissue was present, and routine immunohistochemistry was negative for GFAP, partially positive for Syn, strongly positive for TTF-1, and Ki-67 <1%.

After surgery, the patient underwent low-dose hydrocortisone replacement therapy (5 mg/d), and he was followed for five years. His serum COR and ACTH levels were decreased to normal levels, and there was no evidence of tumour recurrence.

### DISCUSSION AND CONCLUSION

PTs are commonly found in middle-aged (between 40 and 60) adults. PT rarely occurs in children; thus far, only six cases (6/142) under 18 years old have been reported (Tian et al. 2013; Cambiaso et al. 2015; Kim & Park 2015; Feng et al. 2014; Yilmaz et al. 2012; Brandao et al. 2010). No significant gender bias is observed (male:female=1.12) among PTs. Our review found that visual defects (54%, n=127), headache (32%, n=127), hypopituitarism (40%, n=127) and hyperprolactinemia (16%, n=127) are the most common symptoms among PT patients. However, case 1 presented with Cushing's syndrome, and case 4 presented with tinnitus and dizziness, which are seldom found as the main complaints of PT patients. To our knowledge, including case 1,

only eight cases have been reported with Cushing's syndrome [4; Feng et al. 2018; Lefevre et al. 2018; Guo et al. 2016; Chakraborti et al. 2013). This might suggest that PT is associated with endocrinopathy. In the meantime, it should be noted that Cushing syndrome might also be caused by the coexistence of PT and PA (Guo et al. 2016). Whether PT and PA tend to occur simultaneously or if their coexistence is coincidental remains a mystery. In addition, we should not neglect that the assessment of minute adenomas for histopathological examination was not always feasible, and pituitary microadenoma was more in favour of an endocrinological diagnosis (Schmalisch et al. 2012).

PT mainly manifests as a solid lesion in the suprasellar/sellar-suprasellar (43%, n=105) region, and it is seldom found in the pituitary frontal lobe, as in case 1. Cenacchi et al. (2001) found that PT and PA share a transitional feature, which suggests that PT possibly originates from the folliculostellate cells (FSCs) of the anterior pituitary lobe. PT often has a regular shape and a distinct boundary. Erosion of adjacent structures by PT is very rare. To date, including our case 3, three cases have been reported to exhibit skull base bone invasion [13 (Wang et al. 2016; Wolfe et al. 2008). Hence, early intervention of PT lesions might be recommended. Furthermore, most PTs share similar MRI manifestations (isointense on T1WI (59%, n=39), hyperintense on T2WI (83%, n=35), and homogeneous contrast enhancement (79%, n=63) after injection of contrast agent. Our case 4 followed the typical MRI features of PTs. However, the other three cases had atypical imaging manifestations since they shared rather low T2WI signal intensity (especially case 1), with reduced enhancement. The T2WI hypointensity of PT was difficult to explain, but it was definitely not caused by calcification. No PT with calcification has been reported in the literature (Salge-Arrieta et al. 2018; Yang et al. 2016; Tian et al. 2013). The imaging manifestations of PTs are shown in Table 2.

Advanced MRI sequences have seldom been used to evaluate PT. Only perfusion has been analysed, and compared with the normal pituitary parenchyma, significant hyperperfusion was noted in the tumoral area due to the hypervascular features of PT (Salge-Arrieta et al. 2018). However, PA is also hypervascular, making the differential diagnosis between PA and PT by perfusion challenging. <sup>18</sup>F-FDG PET has been found to have a high sensitivity in detecting PA (Wang et al. 2018). However, the utility of PET-CT in the diagnosis and differential diagnosis of PT has not yet been reported. In our case series, we reported the first PET-CTevaluated PT case. In recent years, several papers have illustrated that the uptake of <sup>18</sup>F-FDG by PA is usually higher than that in the normal pituitary parenchyma (Wang et al. 2018: Bergström et al. 1991). Furthermore, Wang Z et al. (2019) showed that PAs demonstrated a delayed uptake peak of <sup>18</sup>F-FDG. <sup>13</sup>N-NH3 PET is mainly used to evaluate hypopituitarism, and it has not

**Tab. 2.** The summary of MRI manifestations in previously reported cases

Charactersitics	Case number	Percentage
Location	105	
Sellar	25	23.8%
Sellar/Suprasellar	45	42.9%
Suprasellar	35	33.3%
T1WI	39	
Hyper	3	7.7%
Iso	23	59.0%
Нуро	13	33.3%
T2WI	35	
Hyper	29	82.9%
Iso	4	11.4%
Нуро	2	5.7%
Enhancement	63	
Homogeneous	52	82.5%
Heterogenous	11	17.5%

<sup>\*</sup> Cases without corresponding imaging findings are not included in this statistic.

been fully evaluated in pituitary tumours. Case 3 had a slightly increased uptake of <sup>18</sup>F-FDG and no significant decrease in the uptake of <sup>13</sup>N-NH3. Based on this case, quantitative analysis of <sup>18</sup>F-FDG uptake might be a promising method to distinguish PT from PA (PA is presumed to have higher <sup>18</sup>F-FDG uptake than PT), but more cases are needed to confirm this hypothesis.

Gross total removal appears to be the mainstream treatment of PT, but the hypervascularity nature of PT and its potential infiltration can make total resection difficult (Vellutini *et al.* 2018). Usually, there is no recurrence after resection in PT patients. However, from 2007 to 2019, 14 cases (14/100) with tumour recurrence were reported, and all of them underwent subtotal resection owing to the hypervascularity nature. Thus, we cautiously recommend that all PT patients with subtotal resection require regular MRI follow-up. Due to the low recurrence rate, low tumour growth, and proliferation rate, pituitary MRI with or without enhancement should be recommended annually.

PT was mainly located in the suprasellar/sellar-suprasellar region, with isointensity on T1WI, hyper-intensity on T2WI, and homogeneous contrast enhancement after injection of contrast agent. Most PTs had clear boundaries after enhancement, and they seldom invaded adjacent structures. However, our cases highlight the unusual imaging manifestations of PT. PT can be located in the anterior lobe of the pituitary or the infundibulum, it may demonstrate hypointensity on T2WI and reduced homogeneous enhancement, and it can also invade the bone structure of the skull

base. Additionally, we illustrated that the first PT patient underwent PET-CT examination with slight glucose uptake and no significant decrease in ammonia uptake. Knowing these unusual imaging features is very important for expanding the imaging spectrum of PT and monitoring PT. Moreover, pituitary MRI with or without enhancement should be recommended annually for partially resected cases.

### **ACKNOWLEDGMENTS**

Not applicable.

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