Endocrine (2019) 63:36–43
https://doi.org/10.1007/s12020-018-1774-2

ENDOCRINE SURGERY

Posterior pituitary tumours: the spectrum of a unique entity. A clinical and histological study of a large case series

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Received: 23 July 2018 / Accepted: 24 September 2018 / Published online: 1 October 2018

Abstract

Purpose In 2017, the WHO established that pituicytoma, granular cell tumour (GCT) and spindle cell oncocytoma (SCO) are posterior pituitary tumours (PPT). Recent data suggests that these tumours probably arise from the pituicytes and may constitute a spectrum of a unique histopathological entity. Our aim is to report the clinical findings and surgical outcomes of 16 patients with PPT. We also evaluated the tissue specimens available in light of current knowledge.

Method Cross-sectional study with retrospective data.

Results PPT were 7 pituicytomas, 3 GCT and 6 SCO. Patients mean age was 55 years old and 75% were female. Basal hormonal study showed hyperprolactinemia (43.7%) and hypopituitarism (37.5%). There was no case of diabetes insipidus (DI). MRI showed sellar/suprasellar masses with mean size of 19.7mm. PPT was not suspected in any patient. Fifteen patients underwent surgery and complications were common: 20% had perioperative bleeding (one patient died because of a massive haemorrhage), 57.1% hypopituitarism, 35.7% permanent DI and 21.4% underwent a second surgery. Pathological findings shown positivity for thyroid transcription factor 1, vimentin and negativity for cytokeratin and chromogranin A in all specimens evaluated. S100 protein was positive in 88.8% of tumours. Ki67 was ≥ 3% in 66.6% and ranged from 4-7% in SCO.

Conclusion PPT have similar histology, clinical features and are frequently misdiagnosed as nonfunctioning pituitary tumours. However, post-surgical complications including haemorrhage are common. A high clinical suspicion is needed to presume the diagnosis prior surgery and diminish the high morbidity of these tumours.

Keywords Posterior pituitary tumours · Pituicytoma · Granular cell tumours of the neurohypophysis · Spindle cell oncocytoma

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Introduction

The posterior lobe of the pituitary gland is an extremely rare place for the development of symptomatic primary tumours. Until recently, it was not clear as to what type of tumours actually originated in the neurohypophysis [1, 2]. In 2017, the World Health Organization (WHO) established that pituicytoma, granular cell tumour of the sella (GCT), spindle cell oncocytoma (SCO) and sellar ependymoma (SE) are the tumours derived from the posterior pituitary gland [3]. Furthermore, recent data suggest that these tumours could be the spectrum of a single neurological entity and they probably arise from pituicytes, the glial cell of the neurohypophysis [4–6].

Primary posterior pituitary tumours (PPT) are by far rarer than pituitary adenomas and nonadenomatous tumours and are not usually considered by clinicians in the differential

Table 1 Clinical features and surgical outcomes

Patient	Type of tumour	Gender/Age	Presenting symptoms	MRI appearance	Surgical approach	Resection	Complications
1	Pituicytoma	M/40	Incidental	Suprasellar	TC	Total	Haemorrhage, hypopituitarism, DI
2	Pituicytoma	F/30	Visual impairment	Sellar	TS	Total	Hypopituitarism, DI
3	Pituicytoma	F/45	Amenorrhoea, galactorrhea	Sellar	TS	Subtotal	Hypopituitarism
4	Pituicytoma	F/37	Incidental	Sellar	TS	Subtotal	No
5	Pituicytoma	F/45	Amenorrhoea	Sellar/suprasellar	TS	Total	No
6	Pituicytoma	F/31	Amenorrhoea	Suprasellar	TC	Total	Haemorrhage, hypopituitarism, DI
7	Pituicytoma	F/70	Acral and facial changes	Sellar	TS	Total	No
8	GCT	F/58	Visual impairment	Sellar	TS	Subtotal	Hypopituitarism, DI
9	GCT	M/66	Headache	Suprasellar	TC	—	Mortal haemorrhage
10	GCT	F/62	Hypercortisolism	Normal	TS	Total	No
11	SCO	F/74	Visual impairment	Sellar	None	—	—
12	SCO	F/69	Weakness[a]	Sellar/suprasellar	TS	Total	Hypopituitarism
13	SCO	F/74	Nausea, vomiting, confusion[a]	Sellar/suprasellar	TS	Subtotal	Hypopituitarism
14	SCO	M/60	Visual impairment	Sellar/suprasellar	TC	Subtotal	Hypopituitarism, DI
15	SCO	M/60	Visual impairment	Sellar/suprasellar	TS	Subtotal	No
16	SCO	F/62	Visual impairment	Sellar	TS	Total	No

GCT granular cell tumour, *SCO* spindle cell oncocytoma, *F* female, *M* male, *TC* transcranial, *TS* transsphenoidal, *DI* diabetes insipidus

[a]Pituitary disease was suspected due to a secondary hypothyroidism in lab test

diagnosis of the sellar masses. The small number of cases reported means that these tumours have been poorly understood. These lesions are non-neuroendocrine tumours presenting with clinical symptoms, hormonal profile and radiological findings resembling non-functioning pituitary adenomas [7] and for this reason, clinical suspicion of PPT prior surgery is a real challenge. In the present study we report the clinical findings and surgical outcomes of a large cohort of patients with PPT. We also provide some relevant features that can help to suspect these tumours before surgery and lastly, we analyse some data pointing out the pathological similarities of these tumours.

Materials and methods

A retrospective multicentre study was carried out to analyse the clinical characteristics and surgical outcome of 16 patients with histological diagnosis of PPT (pituicytoma, GCT and SCO). The patients were diagnosed and treated in six tertiary Spanish hospitals (Hospital Universitari de Bellvitge, Barcelona; Hospital General Universitario de Alicante, Alicante; Hospital Universitario Ramón y Cajal, Madrid; Hospital Universitario Príncipe de Asturias, Madrid; Hospital Universitari Mutua Terrassa, Barcelona and Hospital Universitario Miguel Servet, Zaragoza). The variables evaluated were sex, age at diagnosis, clinical symptoms, basal pituitary function, radiological findings, surgical approaches, histopathology and post-treatment complications. This is a retrospective analysis of our usual everyday work. The patient's data were obtained under the standard medical care conditions. The patient's confidential information was protected according to national normative. This manuscript has been revised for its publication by the Clinical Research Ethics Committee of Bellvitge University Hospital.

Secondary hypothyroidism was diagnosed in patients with low free thyroxin (fT4) serum levels and normal/low serum thyroid stimulating hormone. Secondary adrenal insufficiency was established in patients with low morning serum cortisol (<5 μg/dl) or insufficient response (<18 μg/dl) to 250 μg cosyntropin stimulation test or insulin tolerance test and normal/low plasma adrenocorticotropic hormone (ACTH). Hypogonadotropic hypogonadism in men was established in cases of serum testosterone levels below the lower limit of the reference range and in women with low serum estradiol levels. In both, low/normal serum gonadotropins levels were necessary. A diagnosis of diabetes insipidus (DI) was made based on hypotonic polyuria (urine output >3.5 liters per day associated with urinary osmolality <100 mOsm/kg) with elevated plasma osmolality and

polydipsia. Cushing's disease was diagnosed in presence of appropriate clinical findings when morning plasma ACTH was normal/elevated and there was a lack of serum cortisol suppression after low dexamethasone tests. Cushing's disease was distinguished from ectopic ACTH syndrome when basal ACTH gradient of inferior petrosal sinus to peripheral was greater than 2.0.

Magnetic resonance imaging (MRI) focused on the pituitary was obtained in all cases and the images were evaluated by neuroradiologists. The intervention was performed by expert pituitary surgeons and surgical specimens were evaluated by neuropathologists. Clinical, endocrinological and neuroradiological assessment was completed in the first 6 months after surgery in all operated patients. Diagnosis of pituicytoma, GCT and SCO was made using the WHO criteria [6]. Immunohistochemistry with primary antibodies was performed using 4-μm-thick sections of formalin-fixed and paraffin-embedded tissue. To evaluate the immunohistochemical similarities among the different types of PPT as well as the differences with pituitary neuroendocrine tumours in the light or current knowledge, we used the following antibodies: TTF-1 (clone 8G7G31, Dako), vimentin (clone V9, Dako), S100 protein (Dako), GFAP (clone 6F2, Dako), CD56 (clone MRQ-42), cytokeratin (clone AE1/AE3, DAKO), chromogranin A (Cg A) (clone DAK-A3, Dako) and Ki67 (clone MIB-1, DAKO).

Results

Sixteen patients with PPT were evaluated: seven pituicytomas, three GCT and six SCO. Clinical data and surgical outcome are summarized in Table 1. Three of these patients (cases 6, 15 and 16) were previously described [8, 9]. Mean age at diagnosis was 55 ± 25 (range 30−74) and 12 patients (75%) were female. Patients 11 and 12, both with SCO diagnosis, were sisters. Visual disorder was the first symptom in six patients (37.5%) and amenorrhoea in three cases (18.7%). Other main symptoms were headache and weakness and case 13 was diagnosed after detection of hyponatremia secondary to central hypothyroidism. Case 10 complained of hypercortisolism symptoms (centripetal obesity, moon-like facies, proximal muscles weakness and atrophy, minimal trauma bruises and pathological rib fractures). In two patients (cases 1 and 4) the diagnosis was incidental.

Preoperative hormone profile showed hyperprolactinemia (less than twice the upper limit of normal range) in seven patients (43.7%); five cases (31.2%) had anterior pituitary deficiency and one patient isolated hypogonadotropic hypogonadism. There was no case of DI prior surgery. Hormonal study in patient 10 revealed an elevated morning serum and 24-h urine cortisol with inappropriate normal plasma ACTH. Morning serum cortisol and 24-h urine cortisol showed lack of suppression with a low-dose dexamethasone test, and were suppressed with a high-dose test. MRI in this patient revealed no sellar lesion. Therefore, a selective venous catheterization to obtain an inferior petrosal sample was performed. The peak ratio of ACTH concentration in the inferior petrosal sinus and that in simultaneously peripheral venous blood after CRH 100 μg intravenous injection was 3.62 and interpetrosal ACTH ratio showed a left lateralization before and after CRH administration. In the remaining 15 patients, MRI showed sellar/suprasellar masses with mean size of 19.7 ± 11.6 mm, chiasmatic compression in seven cases (43.7%), and cavernous sinuses infiltration in two patients (Fig. 1). A previous known concomitant meningioma was present in two patients (right frontal meningioma in case 10 and left occipital meningioma in case 14).

PPT was not clinically suspected and pituitary macroadenoma was the presumptive diagnosis in all patients. One patient (case 11) died at home before surgery. In this patient, diagnosis of SCO was previously made by pituitary biopsy carried out in another institution. A tissue sample was reviewed and the prior pathological diagnosis was validated. Fifteen patients underwent surgery; transphenoidal approach was the first intervention in 11 patients (68.7%) and craniotomy in 4 cases. A transphenoidal left hypophysectomy was performed in the patient with Cushing's disease (case 10). During surgical exploration, behind the pituitary gland, a small, firm and fusiform tumour was removed. Pathological evaluation showed a tumour composed of epithelioid and fusiform cells with abundant granular eosinophilic cytoplasm and nodular disposition. Immunohistochemistry for TTF-1, vimentin and S100 protein was positive. Adjacent to this tumour, the pituitary tissue showed corticotroph hyperplasia strongly positive for ACTH. These findings were congruent with GCT coexisting with ACTH secreting pituitary hyperplasia.

Complications after surgery were common. Serious bleeding during surgical procedure developed in three patients (20%). In patient 9, a massive haemorrhage with brainstem compression and ventricular dilation occurred and the patient died in early postsurgical period. In patient 1, resection could not be completed as a consequence of a profuse haemorrhage and a second intervention was needed. A total of eight patients (57.1%) required permanent hormone replacement. Three of them developed hypopituitarism after intervention and in five patients (31.2%) with previously detected hypopituitarism the hormone deficiency persisted. Permanent DI appeared in five patients (35.7%). After first intervention, complete resection was achieved in eight patients (57.1%) and subtotal in six cases (42.8%). Three patients (21.4%) underwent a second surgery, one case managed to complete resection and in two patients a

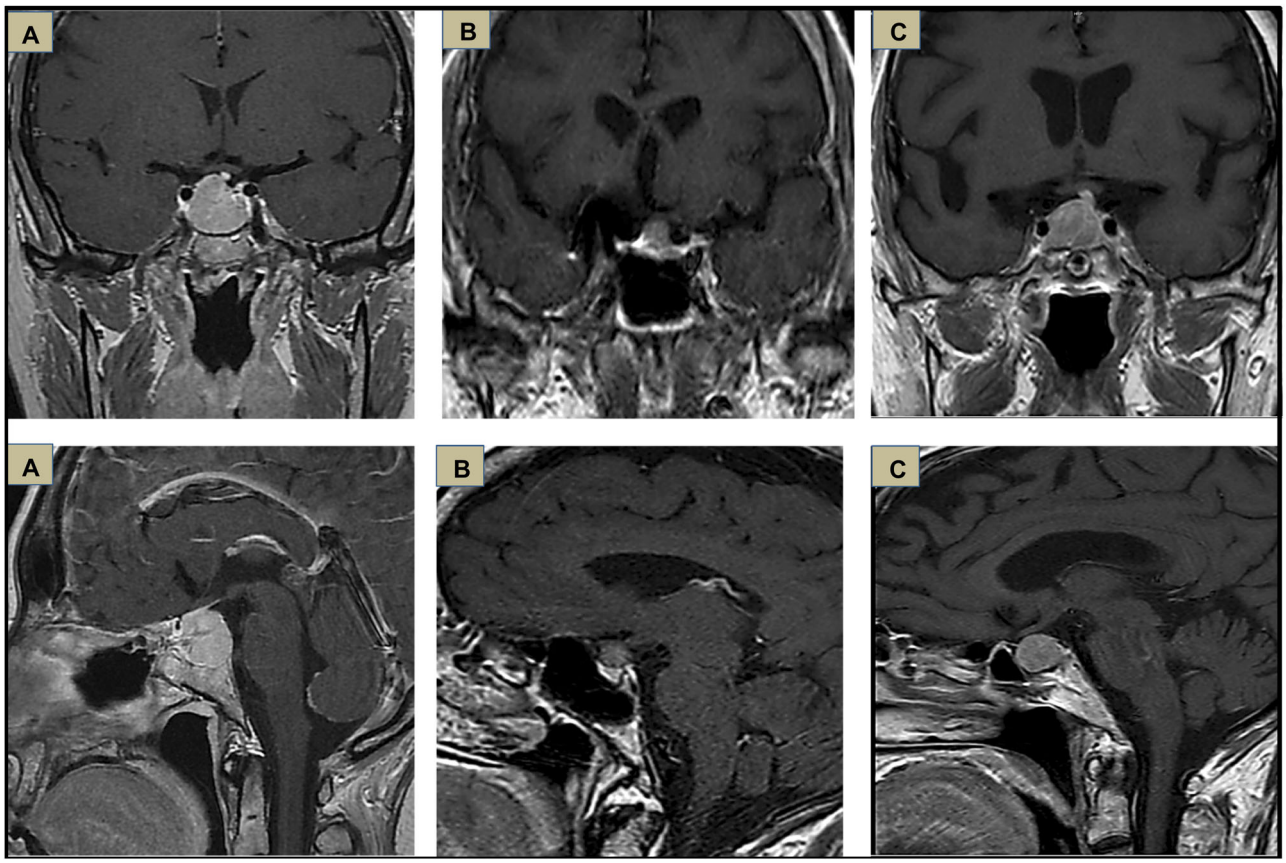

Fig. 1 Coronal (top) and sagittal (bottom) T1-weighted gadolinium-enhanced MRI. **a** Pituicytoma (case 3); **b** Granular cell tumour (case 9); **c** Spindle cell oncocytoma (case 13)

Table 2 Immunohistochemical findings in specimen evaluated

Patient	Type of tumour	TTF1	VIM	S100	GFAP	CD56	CK	CgA	Ki67 (%)
2	Pituicytoma	+	+	+	+	+	−	−	4
3	Pituicytoma	+	+	+	−	+	−	−	5
4	Pituicytoma	+	+	+	−	+	−	−	1−2
7	Pituicytoma	+	+	+	+	+	−	−	1−2
8	GCT	+	+	−	−	−	−	−	3
9	GCT	+	+	+	+	+	−	−	1−2
11	SCO	+	+	+	−	−	−	−	5
12	SCO	+	+	+	−	+	−	−	7
13	SCO	+	+	+	+	−	−	−	4

GCT granular cell tumours, *SCO* spindle cell oncocytoma, *TTF-1* thyroid transcription factor 1, *VIM* vimentin, *S100* S100 protein, *GFAP* glial fibrillary acidic protein, *CD56* neural cell adhesion molecule (NCAM), also called CD56, *CK* cytokeratin, *CgA* chromogranin A, + positive, − negative

residual tumour persisted, even after three surgeries, as in case 14. In this patient, stereotactic radiosurgery was performed, obtaining the tumour stabilization after 1 year of follow-up. In patient 10, postsurgical hormonal evaluation showed persistency of Cushing's disease and ketoconazole treatment was prescribed to control the hypercortisolism.

We re-evaluated the tissue specimens available (four pituicytomas, two GCT and three SCO), confirming the previous histological diagnosis and also performed a wide immunohistochemistry study (Table 2). Tumour was positive for TTF-1 and vimentin and negative for cytokeratin and CgA in all the specimens evaluated (Fig. 2). S100 protein was positive in all, except one case with GCT. Expression was variable for GFAP (55% negative) and CD56 (66% positive). Ki67 was ≥3% in six of these tumours, particularly in SCO that ranged from 4 to 7%.

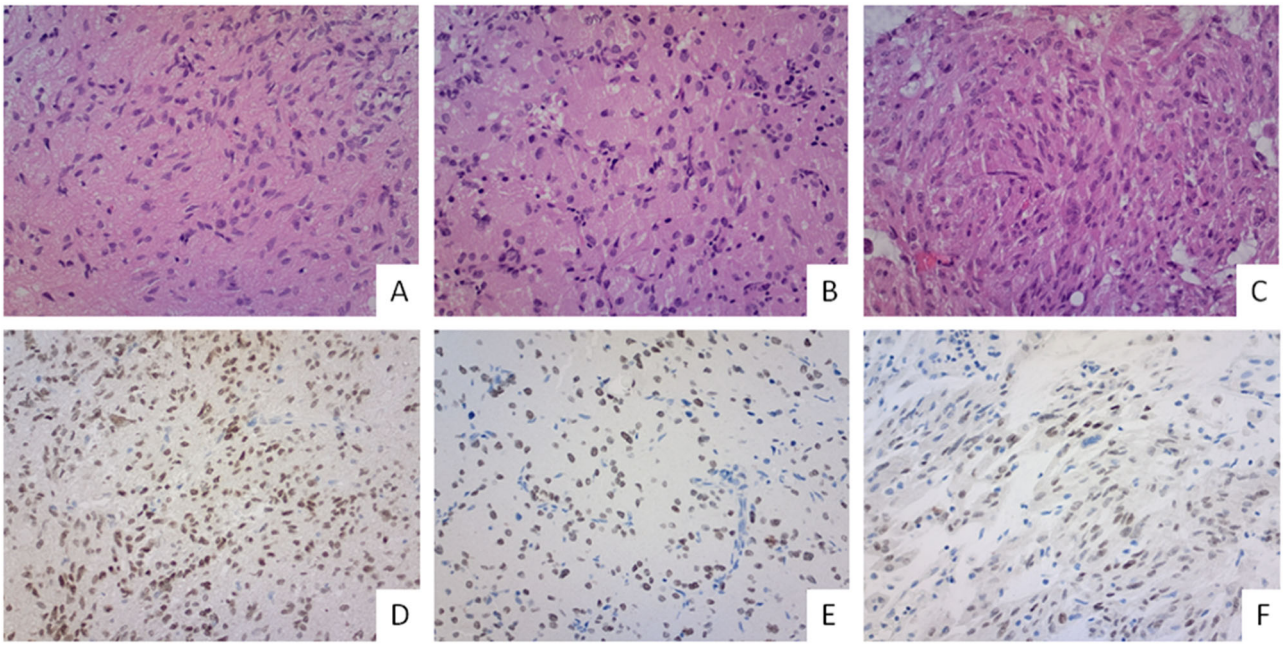

Fig. 2 **a**, **d** Pituicytoma (case 4); **b**, **e** Granular cell tumour (case 8); **c**, **f** Spindle cell oncocytoma (case 12). **a–c** *Hematoxylin* and *eosin* staining of tissue sections (×200). **a**, **c** show fusocellular proliferation; in **b** the cytoplasm is larger and granular. **d–f** TTF1 immunohistochemistry (×200). The three subtypes of posterior pituitary tumours show TTF1 nuclear positivity

Discussion

The posterior pituitary gland consists mainly of the hypothalamic magnocellular neurons distal axons. Pituicytes are specialized glial cells with sustentacular function of which five types can be differentiated. The major pituicytes are the most common and other types are dark, oncocytic, granular and ependymal pituicytes. All of them are considered different functional forms of a unique cell line derived from the ependymal [10].

Pituicytoma and GCT of the neurohypophysis have classically been considered to derive from posterior pituitary gland. In addition, SCO was originally considered to arise from adenohypophysis folliculostellate cells [11, 12]. However, recently different authors have found positivity for TTF-1 in patients with SCO [4, 13]. TTF-1 is positive for pituicytes and negative in folliculostellate cells. Additional evidence came from other reported mixed tumours composed of oncocytic and ependymal cells also positive for TTF-1 protein, all of which contribute to reinforce the unique origin of PPT [14–16]. Finally, the 2017 WHO classification of pituitary tumours considered that although pituicytoma, GCT and SCO are individual entities, they may constitute a spectrum of a unique histopathological disease probably derived from pituicytes [17]. Regarding SE, only four cases in humans had been reported in literature before the patient published by Scheithauer et al. in 2009 and they speculated that this tumour is probably a variant of pituicytoma [18].

Microscopically, PPT mirrors the five variants of pituicytes described by Takei et al. [10]. Similar to most light and dark pituicytes, pituicytoma tumour cells have a non-granular and nonvacuolated eosinophilic cytoplasm with oval to elongated nuclei and mitotic figures are rare. The tumour shows a solid structure with bipolar spindle cells arranged in a fascicular or storiform pattern [10, 19]. Like granular pituicytes, GCT contains densely packed polygonal cells with abundant granular eosinophilic cytoplasm due to a high content of lysosomes which are periodic acid-Schiff-positive and diastase-resistant [19]. Moreover, similar to oncocytic pituicytes, SCO cells are characteristically composed of interlacing fascicles and ill-defined lobules of spindle or epithelioid cells with eosinophilic and variable oncocytic cytoplasm [19]. PPT have nuclear TTF-1 expression, they are negative for Cg A or adenohypophyseal hormones and have variable immunoreactivity for vimentin, S100 protein and GFAP [4, 19]. Almost identical to histological data found by Hagel et al. in 27 patients with PPT [5], our cases evaluated showed positivity for TTF-1, vimentin, S100 protein and negativity for Cg A and cytokeratin. Our findings support the histological similarities of different types of PPT, reinforcing the hypothesis that these tumours may constitute a morphological spectrum of a single entity. In addition, positivity for TTF-1 and negativity for Cg A also support the common neurohypophysis origin of the three types of PPT. The Ki-67 proliferation index is generally low in PPT; however, in our series 66%

were ≥3%. Similar to our findings, a higher index could be found in some SCO tumours [3].

PPT are commonly diagnosed between the fourth and sixth decade of life, with a slight female preponderance [20–22]. In our series, the mean age of diagnosis was 55.1 years and notably 75% were female. Typical clinical manifestations of PPT are hypopituitarism, symptoms related to hyperprolactinemia such as amenorrhoea or galactorrhea and visual field defects. It is important to note that even though these tumours arise from the neurohypophysis, the prevalence of DI prior surgery is less than 5% (pituicytoma, GCT) and there is no case reported for SCO [21, 23, 24]. In our series, the most common symptoms were visual defects (37.5%) and amenorrhoea (18.7%). Interestingly, the two women who were sisters complained of fatigue and weakness and pituitary disease was suspected due to a secondary hypothyroidism presented in lab tests. Remarkable was also patient 10 who was diagnosed with Cushing's disease. In contrary to the case reported by Losa et al. [25] with PPT and pituitary hyperfunction (acromegaly associated with GCT) where only one tumour was demonstrated in the histological analysis, in our patient two distinct and independent lesions (hyperplasia with ACTH-positive cells and GCT) were found. To our best knowledge, this is the first case reported with Cushing's disease secondary to pituitary hyperplasia associated with GCT of the neurohypophysis. Although PPT have classically been considered nonfunctioning tumours [3], recently some cases with clinical symptoms of anterior pituitary hormones hypersecretion have been reported. It has also been speculated that the possibility of some substances such as cytokines or hypophysiotropic hormone-related factors produced by PPT might stimulate the adenohypophysis [26, 27]. This issue could be plausible in our case, considering both pathological findings and that pituitary hyperplasia is an uncommon cause of ACTH-dependent hypercortisolism.

Imaging features of PPT are nonspecific and it is very difficult to distinguish these tumours from pituitary adenomas and other sellar/suprasellar lesions. On MRI, they appear usually as a solid and well-delimited both sellar and suprasellar mass, or exclusively limited to sellar or suprasellar region [28–31]. In our patients, MRI showed sellar/suprasellar masses with mean size of 19.7 ± 11.6 mm and the tumour was sellar in seven patients (43.7%), both sellar/suprasellar in five cases (31.2%) and exclusively suprasellar in three patients (18.7%). PPT are frequently masses centred in the middle line without cyst component or calcification and the normal posterior lobe hyperintensity cannot be recognized in some cases. On MRI they are commonly hypo/isointense in T1-weighted, hyperintense in T2-weighted and they show a uniform and variable enhancement after gadolinium (strongly in some cases). The rapid enhancement in dynamic MRI may indicate a well-developed capillary network [31–34]. The presence of multiple hypointense millimetric foci and linear signal void areas on T1-weighted (probably hemosiderin deposits and vascular structures respectively) has been proposed as a distinctive radiological finding of SCO [34]. The diagnosis of PPT is always made after surgery and unfortunately, only in few cases an angiography has been performed [28, 35, 36].

Surgery is the gold standard treatment for PPT. The complete tumour resection gives a good prognosis of curation; however, in most cases it is difficult because of the high vascularity and firmness of the tumour. For this reason partial resection is suggested when there is a high risk of bleeding or vital structure damages [37]. Both transphenoidal and transcranial access have been used in PPT management. Craniotomy has been associated with higher risk of visual damage and transphenoidal approach with subtotal resection [32]. Transcranial access is preferred in patients with important suprasellar and parasellar extensions or when transphenoidal intervention was not successful [38]. In our series, 11 patients underwent transphenoidal surgery (73.3%) and craniotomy was performed in 4 cases. Complete resection was achieved in eight cases and residual tumour persisted in the remaining six patients, even after a second (case 3) or third intervention (case 14).

Perioperative complications are very common in patients with PPT. Hypopituitarism, DI, visual defects, cranial nerve palsies and even death has been reported. Intraoperative haemorrhage is a serious and relatively frequent complication [35, 37–40]. In our series, critical bleeding occurred in three patients (20%) and one of them died for this reason. After surgery, eight patients had hypopituitarism (57.1%) and five patients (35.7%) developed DI.

Although PPT are considered as grade I neoplasms in the WHO 2016 classification of tumour of central nervous system [19], recurrences have been reported in some patients with SCOs, even in cases with previous total resection [41, 42]. Especially notable is the patient recently reported by Kong et al. with several recurrences after three interventions and progressive increase of tumour Ki-67 index from 6 to 45% [43]. However, no evidence of recurrent SCO has been reported in many other patients [44–47]. The usefulness and indication of radiotherapy is not well established in patients with PPT. It has been used in some patients with incomplete resection without clear results [34, 48–51]. In our patients, case 14 received stereotactic radiosurgery obtaining tumour stabilization after a year of follow-up.

In summary, PPT should be taken into account in the differential diagnosis of patients with sellar and suprasellar masses. Given that PPT resembles nonfunctioning pituitary tumours, clinician judgment is essential for suspicion. Although it is not possible to make a definitive diagnosis by

neuroimaging, there are many radiological clues that help in making the presumptive diagnosis. This is a critical point because if the possibility of PPT is considered previous to intervention, neurosurgeons can have an improved surgical plan and even consider performing a diagnostic or therapeutic angiography. PPT are frequently firm, very attached to surrounding structures and vascular tumours; and for this reason complications such as intraoperative bleeding, permanent anterior and posterior hypopituitarism and subtotal resection are common. No large systematic studies have been conducted in patients with PPT and natural history is not well known but surgical treatment is at present the only curative option in these patients. An adequate preparation for surgery could be of benefit in the surgical result for patients with these tumours.

Acknowledgements The authors thank Georgina Petropoulos Nouna for the language review of the paper.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with animals performed by any of the authors. The patient's confidential information was protected according to national normative. All patients or relatives gave consent regarding participation in the study. This manuscript has been revised for its publication by the Clinical Research Ethics Committee of Bellvitge University Hospital.

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