REVIEW

Adenohypophyseal hyperfunction syndromes and posterior pituitary tumors: prevalence, clinical characteristics, and pathophysiological mechanisms

Pedro Iglesias [1,2] · Fernando Guerrero-Pérez[3] · Carles Villabona[3] · Juan José Díez[1,2,4]

Abstract

Posterior pituitary tumors are rare nonneuroendocrine neoplasms originating in the neurohypophysis that lack hormonal secretory capacity. Surprisingly, these tumors are relatively frequently associated with adenohypophyseal syndromes of hormonal hypersecretion such as Cushing's disease and acromegaly. Fifteen cases of posterior pituitary tumor associated with hypercortisolism have been reported to date, 13 of them were pituicytomas (Pi) and 2 were granular cell tumors (GCT). Six patients with posterior pituitary tumor associated with acromegaly have been reported (4 Pi and 2 GCT). The main forms of clinical presentation and the possible pathophysiological mechanisms of this association are reviewed.

Keywords Cushing's disease · Acromegaly · Hyperprolactinemia · Posterior pituitary tumor · Pituicytoma · Granular cell tumor

Introduction

Posterior pituitary tumors (PPTs) are very rare neoplasms, with less than 300 cases reported to date [1, 2]. They are low-grade nonneuroendocrine sellar/suprasellar tumors originating from pituicytes, specialized glial cells of the neurohypophysis [3]. Four pathological types have been reported: pituicytoma (Pi), granular cell tumor (GCT), spindle cell oncocytoma (SCO), and sellar ependymoma (SE). These tumors are immunohistochemically characterized by expression of thyroid transcription factor-1 (TTF-1) as described in fetal and adult pituicytes but not in neurosecretory cells of the adenohypophysis [4]. As evidenced by a negative immunohistochemical staining for all adenohypophyseal hormones and ultrastructural microscopic characteristics, pituicytes do not have the ability to synthesize and secrete hormones.

PPTs are usually diagnosed in the 5th decade of life without sex predilection. Pi is the most common histological type (approximately half of the cases), followed by GCT (~25%), SCO (18%), and SE (3%) [1]. They usually manifest as visual disturbances, headaches with or without hypopituitarism. The prevalence of diabetes insipidus is very low at clinical presentation [1, 5]. However, a nonnegligible percentage of patients have been associated with hypercortisolism [5–17] or acromegaly [5, 11, 12, 17, 18]. This association is relatively high given the low incidence of both diseases [1].

The objective of this article is to review and describe in detail the cases of Cushing's disease (CD) and acromegaly associated with PPT until now. Selection criteria and data analysis were performed as previously published [1]. All cases that met WHO criteria for PPT diagnosis and clinical and hormonal data for CD and acromegaly were selected. In addition, cases reported in PubMed's database in the last 2 years until March 2020 were also included. Further, we analyze the possible different pathogenic mechanisms of this association.

✉ Pedro Iglesias
piglo65@gmail.com

[1] Departments of Endocrinology, Hospital Universitario Puerta de Hierro Majadahonda, Madrid, Spain

[2] Instituto de Investigación Sanitaria Puerta de Hierro Segovia de Arana (IDIPHISA), Majadahonda, Madrid, Spain

[3] Hospital Universitario Bellvitge l'Hospitalet de Llobregat, Barcelona, Spain

[4] Department of Medicine, Universidad Autónoma de Madrid, Madrid, Spain

Cushing's disease and posterior pituitary tumors

Only 15 cases of hypercortisolism associated with PPTs have been reported so far, all of them in the last 8 years [5–17] (Table 1). This figure indicates a prevalence of 5.6% of all PPTs [1]. Most of them ($n = 13$, 86.7%) were Pi and the rest GCT. To date, no clinical reports of CD associated with SCO or SE have been reported.

CD is a very rare disease with an incidence of 6.2–7.6 per million person years [19]. For this reason, a prevalence of CD of 5–6% in PPT patients is very high, allowing us to consider that their relationship is probably not just coincidental.

The first case was reported by Schmalisch et al. [6]. He was a 48-year-old man with CD and a 4 mm microadenoma image in pituitary magnetic resonance imaging (MRI). Pathological study after transsphenoidal surgery (TS) showed an incidental Pi. After surgery, hypercortisolism persisted and a right hemi-hypophysectomy was performed. The patient developed adrenal insufficiency, indicating the remission of CD. A corticotropic adenoma (CA) could not be demonstrated in the pathological study.

Between 2013 and 2018, another nine patients (eight women and one man) with clinical and biochemical characteristics of ACTH-dependent Cushing's syndrome (CS) were reported. Seven of which had pituitary adenoma (PA) on pituitary MRI [7–13]. In all cases, the pathological study showed an incidental Pi. Six of the nine patients achieved remission of CD after surgery, although only two of them presented histopathological findings compatible with CA. In the remaining three patients, hypercortisolism persisted after surgery, and were treated with radiotherapy ($n = 2$; one of them with corticotropic hyperplasia, CH) and surgery in another patient. In the latter, the presence of a CA could be demonstrated in the pathological specimen.

The association of GCT with CD was reported for the first time in 2018 by Zhang et al. [14] in a 32-year-old man with CD and normal pituitary MRI. Pathological study after TS showed an incidental GCT without evidence of PA or corticotroph hyperplasia (CH). After surgery, the patient showed a normal serum cortisol rhythm and urinary free cortisol levels without tumor recurrence.

In 2019, the remaining four patients (three women and one man) with CD associated with PPT were reported [5, 15–17]. Pituitary surgery demonstrated an incidental Pi in three of the patients and a GCT, also incidental, in the other patient. In the three patients with Pi, histopathological lesion of CA or CH was not demonstrated, while the patient with GCT showed CH. All patients with Pi went into CD remission after surgery. Whereas, GCT patient showed CD persistence and ketoconazole was began to control hypercortisolism.

A more detailed analysis of this series of 15 patients indicates that all PPT patients showed a hormonal study compatible with ACTH-dependent hypercortisolism (Table 1).

Histological lesions associated with ACTH hypersecretion could not be demonstrated in more than half of the patients ($n = 9$, 60%). However, five patients (33.3%) showed evident histological lesions [three CA [8, 11, 13], one was discovered in the second TS [8], and two CH [5, 9]]. Another patient (patient #1, Table 1) (6.7%) presented a nontumorous specimen of the adenohypophysis cells with signs of Crooke's hyalinization compatible with CD [6]. The majority of patients ($n = 9$, 60%) presented remission of CD or hypercortisolism symptoms after surgery, regardless of whether ($n = 2$) or not ($n = 8$) histological lesion was found. In the remaining five patients with CD persistence, two of them remitted (one after a second surgery and the other after pituitary radiotherapy), while in another two patients hypercortisolism was controlled with bilateral adrenalectomy in one of them and with ketoconazole in the other. The remaining patient was treated with radiosurgery without follow-up data.

Present data suggest that ACTH-dependent hypercortisolism due to CD, is associated with relative frequency to PPTs. As occurs with sporadic CD, it is more common in women, but in this case with a lower female:male ratio (2.5:1 vs 5–10:1). Mean age at diagnosis was 41.3 ± 15.1 year (range, 7–62 year). In this series men were slightly younger than women (35.2 ± 15.1 vs 43.5 ± 16.5 year, ns). No lesion related to CA or CH was detected on imaging in any of the PPT patients, which occurs in about 40% of sporadic CD [20]. After the first surgery, no histological lesion was observed in more than half of the cases. When present, the most common demonstrated histological lesion is CA, followed by CH. The absence of histological lesion in the surgical specimen is relatively frequent in patients undergoing CD surgery. In fact, negative histology for PA has been reported in 12.5% of patients with CD that underwent TS, those of which 69.4% were in remission after surgery [21]. CD remission in the cases of negative histological study could be explained by a suction of the ACTH-secreting pituitary microadenoma during the surgical procedure.

There are some distinguishing features between PPTs associated with or without CD. In contrast to sporadic PPTs (22 ± 14.2 mm) [1], those associated with CD are usually micro-tumors (<10 mm), all of which have been incidentally discovered in the histological study. Moreover, sporadic PPTs have a higher Ki67 index (1–7% vs 1–2%) [5]. The reason for these differences is unknown, and therefore needs further investigation. Lastly, all PPTs associated with CD went into remission after surgery without recurrence, differently to sporadic PPTs in which the recurrence rate is around 5% [1]. Clinical features of PPT associated with CD are shown in Table 2.

Table 1 Summary of reported clinical cases of ACTH-dependent hypercortisolism and Cushing's disease associated with posterior pituitary tumors

#Patient author/ year (Ref.)	Age/sex	Clinical presentation	Endocrine evaluation	Tumor size (mm)	Surgery approach	Resection	Pathology	Postop. course	Re-operation/ radiotherapy	Pathology	CD Postop. course
#1 Schmalisch et al. 2012 [6]	48/M	Severe CS	Increased serum cortisol and plasma ACTH / 24 h UFC 1467 µg/24 h / Nugent test: serum cortisol 80 nmol/l / High dose (8 mg) DXM suppression test >50% suppression of serum cortisol / CD + central hypogonadism	4	TS	Total	Incidental Pi (Ki67 1%) Negative IHC against pituitary hormones / No CA or CH	Pi cure + CD persistence	TS with right Hemi-hypophysectomy	CA not found; cells showing signs of Crooke's hyalinization	CD remission
#2 Chakraborti et al. 2013 [7]	24/M	Facial swelling pedal edema m, cushingoid features and HTA	Serum cortisol at 8.00 a.m. (20.72 µg/dl) and 6:00 p.m. (13.4 µg/dl) / ACTH 70.4 pg/dl / Hypercortisolemia, hypercorticotropinemia and altered cortisol rhythm	6 × 4	EETS	Total	Incidental Pi (Ki67 1–2%) IHC data for pituitary hormones NA / No CA or CH	Pi cure + remission symptoms of hypercortisolism + normocortisolemia			
#3 Cambiaso et al. 2015 [8]	7/F	Signs and symptoms of CS	Midnight serum cortisol and ACT were 24.3 µg/dl and 33.7 pg/ml, respectively / 24 h UFC 897.6 µg/24 h / Nugent test and low dose (2 mg) DXM suppression test positive for CD	NA	MTS	Total	Incidental Pi (Ki67 < 1%) IHC data for pituitary hormones NA / No CA or CH	Pi cure + CD persistence	EETS	ACTH-secreting pituitary adenoma	Persistent CD / bilateral laparoscopic adrenalectomy; adrenocortical hyperplasia
#4 Guo et al. 2016 [9]	46/F	Signs and symptoms of CS	Serum cortisol 23.8 µg/dl / Plasma ACTH 72.6 pg/ml / 24 h UFC 538.1 µg/24 h / 48-h 2 mg DXM suppression test, serum cortisol decreased by 62% / CD	15 × 10 × 7	MTS	Total	Incidental Pi (Ki67 1%) IHC for ACTH was strongly positive / CH	Pi cure + CD persistence	Radiotherapy		CD remission
#5 Barresi et al. 2017 [10]	53/F	Hirsutism, central obesity and asthenia	Serum cortisol 19.5 µg/dl / Plasma ACTH 35.3 pg/ml / Nocturnal cortisol 10.37 µg/dl / Nugent test: cortisol 9.4 µg/dl / Exaggerated responsiveness of plasmatic ACTH and serum cortisol to CRH / CD	5 × 6 × 7	EETS	Total	Incidental Pi (Ki67 < 1%) Negative IHC against pituitary hormones / No CA or CH	Pi cure + CD remission			
#6, #7, and #8 Chang et al. 2018 [11]	51/F	CS	Serum cortisol 30.2 µg/dl / Rest of study not reported by authors / CD	6.5 × 6.5 × 7.6	TS	Total	Incidental Pi IHC data for pituitary hormones NA / No CA or CH	Pi cure + CD persistence	Radiosurgery		NA
	53/F	CS	Serum cortisol 44.4 µg/dl / Rest of study not reported by authors / CD	5.7 × 5.8 × 4.5	TS	Total	Incidental Pi IHC data for pituitary hormones NA / No CA or CH	Pi cure + CD remission			
	57/F	CS	Serum cortisol 22.5 µg/dl / Plasma ACTH 37.5 pg/ml / Rest of study not reported by authors / CD	5.1 × 2.2 × 3.3	TS	Total	Incidental Pi IHC data for pituitary hormones NA / CA	Pi cure + CD remission			
#9 Feng et al. 2018 [12]	29/F	Signs and symptoms of CS	Serum cortisol 27.6 µg/dl / Plasma ACTH 11.9 pg/ml / 24-h UFC 296.9 µg/24 h / Low-dose DXM suppression test: cortisol 19.7 µg/dl and 24 h UFC 186.3 µg/24 h / High-dose DXM suppression test: cortisol 3.4 µg/dl and 24 h UFC < 0.8 µg/24 h / CD	4	TS	Total	Incidental Pi IHC positive for all pituitary hormones in normal pituitary tissue / No CA or CH	Pi cure + CD remission			

Table 1 (continued)

#Patient author/year (Ref.)	Age/sex	Clinical presentation	Endocrine evaluation	Tumor size (mm)	Surgery approach	Resection	Pathology	Postop. course	Re-operation/radiotherapy	Pathology	CD Postop. course
#10 Lefèvre et al. 2018 [13]	56/F	Weight gain, HTA, hirsutism, glucose intolerance and depression	Hormonal data NA. Cavernous sinus sampling confirmed asymmetrical secretion of ACTH in the right part of the sella CD	Normal	TS	Total	Incidental Pi IHC data for pituitary hormones NA ACTH-secreting pituitary adenoma	Pi cure + CD remission			
#11 Zhang et al. 2018 [14]	32/M	Central obesity, fat accumulations over the neck, moon face, and buffalo hump	24 h UFC after low- and high-dose DXM suppression test were 888.7 and 677.1 µg/24 h, respectively. IPSS: ACTH of the inferior petrosal sinus on the right and left, and the peripheral vein were 318, >1250, and 136.0 pg/mL, respectively CD	Normal	TS	Total	Incidental IHC data for pituitary hormones NA GCT (Ki67 5%) No CA or CH	GCT cure + CD remission			
#12 Gezer et al. 2019 [15]	37/M	Signs and symptoms of CS	Serum cortisol 16 µg/dl. Plasma ACTH 32 pg/ml. Midnight cortisol 13.5 µg/dl. 24-h UFC 425 µg/24 h. Low-dose DXM suppression test: cortisol 9.7 µg/dl. High-dose DXM suppression test: cortisol 1.97 µg/dl CD	Infundibular lesion 6 × 6.5	EETS	Total	Incidental Pi IHC data for pituitary hormones NA No CA or CH	Pi cure + CD remission + hypopituitarism			
#13 Li et al. 2019 [16]	32/F	Severe CS	Serum cortisol 1122 nmol/l. Normal plasma ACTH. Low-dose DXM suppression test failed to suppress serum cortisol	7.6 × 5.7	TS	Total	Incidental Pi (Ki67 < 1%). The tumor cells were negative for pituitary hormones (ACTH, GH and PRL). No CA or CH	Pi cure + CD remission			
#14 Del Pont et al. 2019 [17]	33/F	Central obesity, muscular Weakness and arterial hypertension	Serum cortisol 32.6 µg/dl. Plasma ACTH 50 pg/ml. Nocturnal salivary cortisol 21 nmol/l. 24-h UFC 797 µg/24 h. 1 mg DXM suppression test: cortisol 3.3 µg/dl CD	<10	TS	Total	Incidental Pi IHC data for pituitary hormones NA No CA or CH	Pi cure + CD remission			
#15 Guerrero-Pérez et al. 2019 [5]	62/F	CS	Serum cortisol 35.1 µg/dl. Plasma ACTH 57 pg/ml. Low-dose DXM suppression test: cortisol 30.5 µg/dl. High-dose DXM suppression test: cortisol 3.8 µg/dl. CRH plus desmopressin test: ACTH increase from 19 to 91 pg/ml and cortisol increase from 14 to 37 µg/dl. IPSS: ACTH of the inferior petrosal sinus on the right and the peripheral vein were 127 and 35 pg/mL, respectively CD	Normal	TS	Total	Incidental GCT IHC positive for ACTH CH	GCT cure + CD persistence	No		Ketoconazole

CA corticotroph adenoma, CH corticotroph hyperplasia, CS Cushing's syndrome, CD Cushing's disease, CRH corticotropin releasing hormone, DXM dexamethasone, EETS endoscopic endonasal transsphenoidal surgery, F female, GCT granular cell tumor, HTA hypertension, IHC immunohistochemistry, IPSS inferior petrosal sinus sampling, M male, MTS microscopic transsphenoidal surgery, NA not available, Pi pituicytoma, TS transsphenoidal surgery, 24 h UFC 24 h urinary free cortisol

Table 2 Clinical features of posterior pituitary tumors (PPT) associated with Cushing's disease (CD) or acromegaly

	Cushing's disease	Acromegaly
Number of patients	15	6
Sex, F (%)	11 (73.3)	5 (83.3)
Age (year), mean ± SD (range)	41.3 ± 15.1 (7–62)	51.3 ± 15.3 (29–79)
Pituicytoma, n (%)	13 (86.7)	4 (66.7)
Granular cell tumor, n (%)	2 (13.3)	2 (33.3)
Maximal tumor diameter (mm) (mean ± SD)	7.2 ± 3.2	14.4 ± 3.5
Total resection, n (%)	15 (100)	3 (50)
Subtotal resection, n (%)	0 (0)	3 (50)
Incidental, n (%)	15 (100)	6 (100)
PPT cure after first surgery, n (%)	15 (100)	5 (83.3)
PPT persistence, n (%)	0 (0)	1 (16.7)
Recurrence, n (%)	0 (0)	0 (0)
CD persistence after PPT surgery, n (%)	5 (33.3)	–
CD remission after PPT surgery, n (%)	10 (66.6)	–
Acromegaly persistence after PPT surgery, n (%)	–	4 (66.6)
Acromegaly remission after PPT surgery, n (%)	–	2 (33.3)

Acromegaly and posterior pituitary tumors

Although less frequently observed than with CD, acromegaly has also been described in association with PPTs (Table 3). Until now, only six acromegalic patients have been reported, all of them in the last 10 years [5, 11, 12, 17, 18]. Therefore, and according to the published series, the estimated prevalence of acromegaly associated with PPT is 2.3% [1]. Most of them (n = 4, 66.7%) were Pi and the rest GCT. To date, there is no report of acromegaly associated with SCO or SE. Although this prevalence may appear to be low, as it occurred with CD, the low prevalence of acromegaly in the general population (2.8–13.7 cases per 100,000 people) [22], together with the small number of patients described with PPT (<300 cases) [1] lead us to consider it as a nonincidental association. The cases described to date are summarized below (Table 3).

The first clinical case was reported by Losa et al. [18]. She was a 48-year-old woman with 10 years of GH excess symptoms. Endocrinological evaluation confirmed the diagnosis of acromegaly and MRI revealed an 11 × 11 × 9 mm pituitary lesion. She underwent TS, achieving a subtotal resection. The histological study showed a GCT without somatotroph adenoma (SA) or somatotroph hyperplasia (SH). After surgery, acromegaly persisted and she

underwent TS reoperation obtaining the same histological result as previous surgery. At follow-up, remission of acromegaly was demonstrated.

Eighteen years later, Chang et al. [11] reported a 46-year-old male patient who complained of acromegaly symptoms. The diagnosis was confirmed after hormonal study. The MRI revealed an 8.7 × 11.9 × 7.5 mm pituitary lesion. He was operated via TE approach with total resection of the lesion. The histological study showed a Pi with no evidence of SA or SH, achieving the Pi cure and acromegaly remission.

In that same year, Feng et al. [12] reported two other women (56 and 65 years of age), diagnosed with acromegaly and macroadenoma on the pituitary MRI. Both underwent TS. In the first patient, the histological study was Pi without lesions compatible with PA or SH, and acromegaly persisted after surgery. In the second patient, a subtotal resection of the lesion was performed by TS. The histological result was a GCT without SA or SH data. After surgery, acromegaly persisted and a somatostatin analog (SSA) was prescribed.

The last two patients were reported in 2019 [5, 17]. The first of them was a 29-year-old acromegalic woman with pituitary macroadenoma undergoing endoscopic endonasal transsphenoidal surgery with subtotal resection. The pathological result was Pi and SA. After surgery, acromegaly persisted, and patient was treated with radiosurgery [17]. The second patient was a 70-year-old acromegalic woman with a pituitary MRI compatible with SA. She underwent TS with complete tumor resection. Pathological study showed an incidental Pi without SA or SH. Post-operative course revealed acromegaly remission.

This series of acromegalic patients with PPT suggests that this association is more frequent in women (female: male ratio, 5:1), unlike what occurs in cases of sporadic acromegaly, in which the distribution by sex is similar [22]. Mean age at diagnosis was 51.3 ± 15.3 year (range, 29–79) similar to sporadic cases [22]. All but one of the six patients showed macroadenomas (≥10 mm) in pituitary MRI. However, these lesions corresponded histologically with PPTs and not with SA. Only one patient (#5, Table 3) of the six cases showed a PA in the histological study. There was no case described as SH. Acromegaly persisted in four patients (#1, #3, #4, and #5) after the first surgery. One of whom (#1) was cured after a second surgery, although the histological study did not show SA or SH. Another patient (#4) was controlled with SSA. Surprisingly, two of the six patients (#2 and #6) without histological lesions compatible with SA or SH, remitted after the first surgery. This indicates a possible pathogenic role of PPT in the development or maintenance of GH hypersecretion.

Interestingly, and as it occurs with CD, PPTs associated with acromegaly are smaller (14.4 ± 3.5 mm) than sporadic PPTs (22.0 ± 14.2 mm) all of which were incidentally

Table 3 Summary of reported clinical cases of acromegaly associated with posterior pituitary tumors

# Patient author/year (Ref.)	Age/sex	Clinical presentation	Endocrine evaluation	Tumor size (mm)	Surgery approach	Resection	Pathology	Postop. course	Re-operation/radiotherapy	Pathology	Acromegaly Postop. course
#1 Losa et al. 2000 [18]	42/F	Acral enlargement, headache, and menstrual abnormalities	Acromegaly (IGF-1 462 ng/ml)	11 × 11 × 9	TS	Subtotal	Incidental GCT IHC studies for pituitary hormones and GHRH were all undetected No SA or SH	CGT + acromegaly persistence	TS	GCT No PA or SH	Acromegaly remission
#2 Chang et al. 2018 [11]	46/M	Acromegalic symptoms	Acromegaly (IGF-1 617 ng/ml)	8.7 × 11.9 × 7.5	TS	Total	Incidental Pi IHC studies for pituitary hormones in glandular cells were strongly positive for PRL, LH, and ACTH, and faintly positive for FSH, GH, and TSH No SA or SH	Pi cure + acromegaly remission			
#3 and #4 Feng et al. 2018 [12]	56/F	Acral enlargement, macroglossia and thickened, coarse skin	Acromegaly (IGF-1 891 ng/ml) and mild hyperprolactinemia (PRL 51.8 ng/ml)	18 × 14 × 10	TS	Total	Incidental Pi IHC staining revealed that anterior pituitary hormones were not detectable No SA or SH	Pi cure + acromegaly persistence	NA	NA	NA
	65/F	Macroglossia, thickened, coarse skin, and large, spade-like hands and feet	Acromegaly (IGF-1 537 ng/ml)	Macroadenoma	TS	Subtotal	Incidental GCT IHC staining negative for ACTH, GH, TSH, PRL, FSH, and LH No SA or SH	CGT + acromegaly persistence			SSA
#5 Del Pont et al. 2019 [17]	29/F	Acromegalic symptoms	Acromegaly (IGF-1 > 1000 ng/ml)	15 × 17 × 12	EETS	Subtotal	Incidental Pi IHC data for pituitary hormones NA SA	Pi cure + acromegaly persistence	Radiosurgery		NA
#6 Guerrero-Pérez et al. 2019 [5]	70/F	Acral and facial changes	Acromegaly (IGF-1 33.2 nmol/l; N: 4.8–21.6)	4 × 5	TS	Total	Incidental Pi IHC staining negative for ACTH, GH, TSH, PRL, FSH, and LH No SA or SH	Pi cure + acromegaly remission			

CD Cushing's disease, EETS endoscopic endonasal transsphenoidal surgery, F female, GCT granular cell tumor, IHC Immunohistochemical, M male, NA not available, Pi pituicytoma, TS transsphenoidal surgery, SA somatotropic adenoma, SH somatotroph hyperplasia, SSA somatostatin analogs

discovered [5]. The most common PPT associated to acromegaly was Pi. However, GCT was higher in patients with acromegaly (33.3%) compared to sporadic PPT group (25.6%). In this population, all patients with PPT were cured after the first surgery, except for one patient who required second TS. Clinical features of PPT associated with acromegaly are shown in Table 2.

Hyperprolactinemia and posterior pituitary tumor

Hyperprolactinemia is the most frequently anterior pituitary hormone disorder associated to PPTs. Hyperprolactinemia appears in about 40% of patients. It is generally mild but some cases with galactorrhea have been reported [1, 5].

To our knowledge, no histologically proven cases of prolactinoma associated with PPT have been reported so far. In 2015, a case of a giant prolactinoma was described in a 25-year-old woman who underwent surgery. Pathological study revealed a prolactin-secreting PA with atypical spindle cell morphology. However, the immunohistochemical study was positive for prolactin, chromogranin A, synaptophysin; and negative for glial fibrillary acidic protein, S-100 protein, epithelial membrane antigen, and vimentin [23].

The lack of prolactinoma associated with PPT may be related to the fact that surgery is rarely performed in mild cases of hyperprolactinemia and PA, as these patients are easily controlled with dopamine agonists.

Pathophysiological mechanisms

Different mechanisms might explain the association of adenohypophyseal hypersecretion syndromes with PPTs.

In relation to hyperprolactinemia, the responsible mechanism seems to be the compression of the pituitary stalk and the consequent reduction of inhibitory dopaminergic tone on anterior pituitary lactotroph cells.

Regarding the association of CD and acromegaly with PPT the explanation is more difficult and complex. The association of PPTs with CD is more common than with acromegaly. However, in the general population the incidence and prevalence of CD is lower than acromegaly. Different pathogenic mechanisms could be considered (Table 4).

PPT cells may have hormonal secretory capacity acting as neuroendocrine cells with hypersecretion of ACTH or GH in some patients. This hypothesis should be completely ruled out since it has been recently shown that PPTs derive from pituicytes, specialized cells of the glia of the posterior pituitary gland [3]. Although morphological features of

Table 4 Possible pathogenic mechanisms related to the development of adenohypophyseal hyperfunction syndromes in posterior pituitary tumors

Induction of hypersecretion of ACTH or GH by PPT tumor cells
Induction of local signals and cell proliferation (cytokines, growth factors, etc.) on adjacent adenohypophyseal neurosecretory cells (hyperplasia and/or tumorigenesis)
Induction of hypothalamic releasing hormones
Induction of ACTH- or GH-releasing factors
Common cellular origin of both tumors
Ectopic functioning pituitary adenoma located in the posterior pituitary
Stimulation of the corticotroph cells of the intermediate lobe by PPTs
Not related (coincidental)

endocrine differentiation (secretory granules) have been reported in a case of Pi [24], the expression of adenohypophyseal hormones in cells from PPTs have not been demonstrated [1, 4, 6, 10–12, 16, 18].

Cells from PPTs might induce stimulation signals (cytokines and/or growth factors) and cell proliferation on adjacent adenohypophyseal neurosecretory cells facilitating the development of hypersecretion syndromes with [8, 13, 17] or without PA [1, 6, 7, 10–12, 14–18]. In support of this argument, some patients with PPT hypersecretion syndromes, PPT were found in the location where the different neuroendocrine neurohypophyseal cells (ACTH- or GH-secreting cell region) are commonly placed [11]. This action could be due to a permissive effect of hypothalamic adenohypophyseal hormone-releasing hormones or through proliferative paracrine signals that could change the microenvironment of the anterior pituitary (local irritation) facilitating the development of hyperactivity adenohypophyseal cells [18]. If this hypothesis was to be true, the glia cells of the posterior pituitary lobe might play an important role in the development of adenohypophyseal hyperplasia [9] or oncogenic differentiation of the anterior pituitary gland [8, 12, 13, 17]. However, to date, no potential stimulatory signal or factors for adenohypophyseal hormone secretion from PPT cells have been identified.

Other authors suggest that Pi can regulate hypothalamic releasing hormones (CRH or GHRH) or different ACTH- or GH-releasing factors [18, 25, 26]. In this setting, some studies have reported that most PPTs patients with neuroendocrine secretion show immunohistochemical (IHC) staining findings that indicate specific hormone change in their normal pituitary glands [11]. This would explain, at least in part, the remission of CD and acromegaly after PPT removal in which no PA was detected. On the other hand, the IHC study for GHRH performed in a patient with acromegaly and GCT was negative [18], indicating that the pathogenic role of hypothalamic releasing hormone

hypersecretion in PPT-associated adenohypophyseal hypersecretion syndromes is not clearly defined.

Another possibility could be the coexistence of a functioning PA with PPT. As discussed above, given the rarity of the association of both tumors, it seems unlikely to be coincidental [8]. Therefore, it could be possible that the glia cells of the posterior pituitary might play a pathogenic role in the tumorigenesis of the anterior pituitary. However, there is no clear explanation that supports that PPT can develop a functioning PA, although this possibility cannot be totally ruled out. The explanation of a possible common origin of both tumors from the same precursor cell has been suggested by some authors [8]. Other authors have described ultrastructural features intermediate between a Pi and a PA, suggesting that Pi might also arise from the specialized stromal folliculo-stellate cells (FSCs) of the adenohypophysis, which would be able to differentiate into endocrine cells [24]. FSCs could act as stem cells, by differentiating into endocrine cells and expressing the oncoprotein B-cell lymphoma-2 that could contribute to the progression of various tumor types, including adenomas and PPTs [27]. However, this explanation seems to be unlikely due to the different biomolecular profile recently reported in both tumors [10, 28]. In fact, TTF-1 expression is a feature of PPTs and not FSCc [4, 29, 30]. Lastly, we should consider, in cases of PPT and adenohypophyseal hyperfunction syndrome that remits after PPT surgery without histological demonstration of PA, the possibility that the PA can be aspirated during surgery, a situation that frequently happens in the EC.

Another possible explanation could be the development of an ectopic functioning PA located in the posterior pituitary, as it has been occasionally reported [31]. However, this situation is not plausible in the cases reported here, because PPT was confirmed histologically in all of them.

Lastly, a stimulation of the corticotroph cells of the intermediate lobe by PPTs could explain the development of CD in some PPT patients [32].

Interestingly, unlike Pi and GCT, SCO have never been associated with CD or acromegaly. The reason for this lack of association is unclear given the common origin with the other PPTs. It is true that the number of SCOs published until now is very low ($n = 47$; 17%) [1]. We cannot rule out that with an increasing number of SCO, new cases of CD or acromegaly could emerge, although this is merely speculative.

Conclusions and future perspectives

In summary, PPTs are rare neoplasms originating from the glia cells of the neurohypophysis. Although cases reported to date have been few, the association of these tumors with

hormone hypersecretion syndromes is higher than what would be expected by coincidence. Furthermore, in reported associations some peculiarities stand out, such as the preference for the female gender, the predominance of Pi, the smaller size of PPTs compared to sporadic ones, and the incidental nature of all PPTs. Cure rates of PPTs after surgery has been reported to be high, although no pathological imaging of PA was found in most patients. Nonetheless, hormone hypersecretion remission was not always achieved, especially in the cases of patients with acromegaly.

The structural and functional relationship of pituicytes with adenohypophysis cells and the intermediate pituitary lobe should be further studied. In this context, it would be helpful to carry out cytological and IHC studies in cells from PPT to analyze the presence of substances such as cytokines, different growth factors, ACTH- or GH-releasing factors that could stimulate the secretion and growth of corticotropic and somatotropic cells. This could demonstrate that neoplastic glial cells of the neurohypophysis play a role in hormonal secretion and oncogenic differentiation of some types of adenohypophyseal cells. Therefore, the focus should be on investigating the effect of neurohypophyseal glial cells on the secretory and proliferative function of anterior pituitary cells.

Our current knowledge is limited and further molecular, translational and clinical investigation on PPTs is warranted.

Compliance with ethical standards

References

1. F. Guerrero-Perez, A.P. Marengo, N. Vidal, P. Iglesias, C. Villabona, Primary tumors of the posterior pituitary: a systematic review. Rev. Endocr. Metab. Disord. **20**, 219–238 (2019)

2. F.J. Salge-Arrieta, R. Carrasco-Moro, V. Rodriguez-Berrocal, H. Pian, J.S. Martinez-San Millan, P. Iglesias, L. Ley-Urzaiz, Clinical features, diagnosis and therapy of pituicytoma: an update. J. Endocrinol. Investig. **42**, 371–384 (2019)

3. O. Mete, M.B.S. Lopes, F. Roncaroli, T. Tihan, S. Yamada, in *Tumors of the posterior pituitary*, ed. by R.V. Lloyd, R.Y. Osamura, G. Klöppel, J. Rosai. WHO Classification of Tumours of Endocrine Organs. International Agency for Reseach on Cancer, Lyon (France), pp. 52–54 (2017)

4. E.B. Lee, T. Tihan, B.W. Scheithauer, P.J. Zhang, N.K. Gonatas, Thyroid transcription factor 1 expression in sellar tumors: a histogenetic marker? J. Neuropathol. Exp. Neurol. **68**, 482–488 (2009)

5. F. Guerrero-Perez, N. Vidal, A.P. Marengo, C.D. Pozo, C. Blanco, D. Rivero-Celada, J.J. Diez, P. Iglesias, A. Pico, C. Villabona,

Posterior pituitary tumours: the spectrum of a unique entity. A clinical and histological study of a large case series. Endocrine **63**, 36–43 (2019)

6. K. Schmalisch, J. Schittenhelm, F.H. Ebner, F. Beuschlein, J. Honegger, R. Beschorner, Pituicytoma in a patient with Cushing's disease: case report and review of the literature. Pituitary **15**(Suppl 1), S10–S16 (2012)

7. S. Chakraborti, A. Mahadevan, A. Govindan, K. Sridhar, N.V. Mohan, I.R. Satish, S. Rudrappa, S. Mangshetty, S.K. Shankar, Pituicytoma: report of three cases with review of literature. Pathol. Res. Pract. **209**, 52–58 (2013)

8. P. Cambiaso, D. Amodio, E. Procaccini, D. Longo, S. Galassi, F. D. Camassei, M. Cappa, Pituicytoma and Cushing's disease in a 7-year-old girl: a mere coincidence? Pediatrics **136**, e1632–e1636 (2015)

9. X. Guo, H. Fu, X. Kong, L. Gao, W. Wang, W. Ma, Y. Yao, R. Wang, B. Xing, Pituicytoma coexisting with corticotroph hyperplasia: literature review with one case report. Medicine **95**, e3062 (2016)

10. V. Barresi, S. Lionti, E. Messina, F. Esposito, F.F. Angileri, S. Cannavo, A 53-year-old woman with Cushing's disease and a pituitary tumor. Neuropathology **37**, 86–90 (2017)

11. T.W. Chang, C.Y. Lee, S.M. Jung, H.Y. Lai, C.T. Chen, M.C. Yeap, C.C. Chuang, P.W. Hsu, C.N. Chang, P.H. Tu, S.T. Lee, Correlations between clinical hormone change and pathological features of pituicytoma. Br. J. Neurosurg. **32**, 501–508 (2018)

12. Z. Feng, Z. Mao, Z. Wang, B. Liao, Y. Zhu, H. Wang, Non-adenomatous pituitary tumours mimicking functioning pituitary adenomas. Br. J. Neurosurg. 1–5 (2018). https://doi.org/10.1080/02688697.2018.1464121

13. E. Lefevre, S. Bouazza, F. Bielle, A.L. Boch, Management of pituicytomas: a multicenter series of eight cases. Pituitary **21**, 507–514 (2018)

14. Y. Zhang, Y. Teng, H. Zhu, L. Lu, K. Deng, H. Pan, Y. Yao, Granular cell tumor of the neurohypophysis: 3 cases and a systematic literature review of 98 cases. World Neurosurg. **118**, e621–e630 (2018)

15. E. Gezer, A. Selek, B. Cetinarslan, Z. Canturk, I. Tarkun, S. Ceylan, The coexistence of infundibular pituicytoma and Cushing's disease due to pituitary adenoma: a case report. Endocr. Regul. **53**, 263–267 (2019)

16. X. Li, Y. Liu, Y. Miao, J. Wang, L. Wang, E.H. Wang, A rare case of pituicytoma presenting with severe Cushing disease: a case report and review of literature. Medicine **98**, e17772 (2019)

17. F. Marco Del Pont, J.F. Villalonga, T. Ries-Centeno, N. Arakaki, D. Katz, A. Cervio, Pituicytoma associated with acromegaly and cushing disease. World Neurosurg. **136**, 78–82 (2019)

18. M. Losa, W. Saeger, P. Mortini, C. Pandolfi, M.R. Terreni, G. Taccagni, M. Giovanelli, Acromegaly associated with a granular cell tumor of the neurohypophysis: a clinical and histological study. Case report. J. Neurosurg. **93**, 121–126 (2000)

19. M.S. Broder, M.P. Neary, E. Chang, D. Cherepanov, W.H. Ludlam, Incidence of Cushing's syndrome and Cushing's disease in commercially-insured patients <65 years old in the United States. Pituitary **18**, 283–289 (2015)

20. S. Melmed, Pituitary-tumor endocrinopathies. N. Engl. J. Med. **382**, 937–950 (2020)

21. G.D. Hammer, J.B. Tyrrell, K.R. Lamborn, C.B. Applebury, E.T. Hannegan, S. Bell, R. Rahl, A. Lu, C.B. Wilson, Transsphenoidal microsurgery for Cushing's disease: initial outcome and long-term results. J. Clin. Endocrinol. Metab. **89**, 6348–6357 (2004)

22. A. Lavrentaki, A. Paluzzi, J.A. Wass, N. Karavitaki, Epidemiology of acromegaly: review of population studies. Pituitary **20**, 4–9 (2017)

23. R. Inoue, M. Aoki, Y. Matsumoto, S. Haraoka, K. Kazekawa, K. Nabeshima, Prolactin-producing pituitary adenoma with atypical spindle cell morphology: a case report. World J. Surg. Oncol. **13**, https://doi.org/10.1186/s12957-015-0655-x (2015)

24. G. Cenacchi, P. Giovenali, C. Castrioto, F. Giangaspero, Pituicytoma: ultrastructural evidence of a possible origin from folliculo-stellate cells of the adenohypophysis. Ultrastruct. Pathol. **25**, 309–312 (2001)

25. Y. Nakasu, S. Nakasu, A. Saito, S. Horiguchi, T. Kameya, Pituicytoma. Two case reports. Neurol. Med. Chir. **46**, 152–156 (2006)

26. G.I. Hatton, Pituicytes, glia and control of terminal secretion. J. Exp. Biol. **139**, 67–79 (1988)

27. A.J. Ulm, A.T. Yachnis, D.J. Brat, A.L. Rhoton Jr, Pituicytoma: report of two cases and clues regarding histogenesis. Neurosurgery **54**, 753–757 (2004)

28. M.C. Neidert, H. Leske, J.K. Burkhardt, S.S. Kollias, D. Capper, D. Schrimpf, L. Regli, E.J. Rushing, Synchronous pituitary adenoma and pituicytoma. Hum. Pathol. **47**, 138–143 (2016)

29. G. Singh, S. Agarwal, M.C. Sharma, V. Suri, C. Sarkar, A. Garg, S.S. Kale, Spindle cell oncocytoma of the adenohypophysis: report of a rare case and review of literature. Clin. Neurol. Neurosurg. **114**, 267–271 (2012)

30. T. Yoshimoto, J. Takahashi-Fujigasaki, N. Inoshita, N. Fukuhara, H. Nishioka, S. Yamada, TTF-1-positive oncocytic sellar tumor with follicle formation/ependymal differentiation: non-adenomatous tumor capable of two different interpretations as a pituicytoma or a spindle cell oncocytoma. Brain Tumor Pathol. **32**, 221–227 (2015)

31. M.F. Azevedo, P. Xekouki, M.F. Keil, E. Lange, N. Patronas, C. A. Stratakis, An unusual presentation of pediatric Cushing disease: recurrent corticotropinoma of the posterior pituitary lobe. J. Pediatr. Endocrinol. Metab. **23**, 607–612 (2010)

32. R.V. Lloyd, C.J. D'Amato, M.T. Thiny, L. Jin, S.P. Hicks, W.F. Chandler, Corticotroph (Basophil) invasion of the pars nervosa in the human pituitary: localization of proopiomelanocortin peptides, galanin and peptidylglycine alpha-amidating monooxygenase-like immunoreactivities. Endocr. Pathol. **4**, 86–94 (1993)