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DOI: https://doi.org/10.1016/j.pathol.2022.08.003

Co-existence of pituicytoma and corticotroph adenoma in a patient with Cushing's disease

To the Editor,

Pituicytomas are rare neoplasms derived from pituicytes of the neurohypophysis. The co-existence of pituicytomas and other functional pituitary neuroendocrine tumours (PitNET) may pose a diagnostic dilemma. We present the evaluation and management of a novel case presenting with Cushing's syndrome subsequently diagnosed with co-existent pituicytoma and corticotroph adenoma. To our knowledge, this is the first reported case in the English literature of co-existent pituicytoma and corticotroph adenoma in adults.

A 71-year-old Chinese male presented with 4-month history of facial swelling, easy bruising, proximal muscle weakness, as well as frequent falls. Additional significant medical history included stable ischaemic heart disease for which he was on aspirin, hypertension, hyperlipidaemia, and a 2-year history of pre-diabetes. He had sustained a T7 vertebral fracture after a fall 1 month prior to presentation. He reported no family history of pituitary neuroendocrine tumours or endocrinological disorders.

Physical examination revealed pertinent findings of rounded facies, facial plethora and prominent dorsocervical fat pad. There was evidence of central obesity as well as reduced proximal lower limb power. Endocrinological evaluation confirmed Cushing's syndrome (CS) as evident by an elevated 24 h urinary free cortisol of 3780 nmol/day [reference range (RR) 59−413 nmol/day] which was confirmed on two separate readings and an unsuppressed serum cortisol 960 nmol/L (RR <50 nmol/L) following 1 mg overnight dexamethasone suppression test. Plasma adrenocorticotropic hormone (ACTH) levels were elevated (226.9 ng/L, RR 10.0−60.0 ng/L). Magnetic resonance imaging (MRI) scan of the pituitary revealed two focal lesions (Fig. 1): the first a 0.6×0.4 cm lesion with T2 hyper-intensity and early hyper-enhancement in the left lateral wing, and the second a 1.0×0.6 cm lesion with T2 iso-intensity and delayed enhancement in the right lateral wing. There was no evidence of cavernous sinus invasion or suprasellar extension. Additional laboratory investigations revealed secondary hypogonadism. The thyroid hormone axis, growth hormone axis and prolactin levels were normal. We proceeded with bilateral inferior petrosal sinus sampling (IPSS) which confirmed Cushing's disease (CD) and suggested lateralisation of the source of hypercortisolism to the right. The patient underwent transsphenoidal surgery with peri-operative glucocorticoid cover. The operative findings were that of a soft, pale, flaky lesion in the right side of the gland that had a clear plane between the lesion and the medial wall of the right cavernous sinus; the lesion in the left half of the gland contained firm, gritty tissue with different characteristics to that of the right-sided lesion. Both pituitary lesions were resected without complications. Morning serum cortisol was 119 nmol/L on day 3 post-surgery which suggested remission of CD. He remained well post-surgery and was discharged on physiological dosing of hydrocortisone while awaiting recovery of his hypothalamic-pituitary-adrenal axis function. An MRI scan of the pituitary 3 months after surgery did not show any residual tumour. One year post-surgery, he is well and remains on sick day hydrocortisone, with no signs of recurrence of Cushing's disease. A 1 mg overnight dexamethasone suppression test performed 18 months after resection of the tumours suppressed the cortisol to 19 nmol/L (RR <50 nmol/L).

The histopathology findings (Fig. 2A−C) of the right pituitary lateral wing lesion returned as densely granulated corticotroph adenoma measuring 1×1×0.2 cm. The lesional cells showed strong diffuse staining for ACTH. Few scattered Crooke cells were seen predominantly within the entrapped native anterior pituitary lobules. Histology of the left pituitary lateral wing lesion (Fig. 2D−F) was consistent with a pituicytoma, with bland spindle cells within a fibrillary and haemorrhagic background without granular cytoplasm, multinucleated giant cells or mitotic figures. Immunohistochemical stains showed the lesional cells diffusely positive for thyroid transcription factor-1 (TTF-1) (diffuse nuclear staining), S100, and synaptophysin with some peripheral glial fibrillary acidic protein (GFAP) staining. ACTH and epithelial membrane antigen (EMA) were negative.

This case presents a previously unreported phenomenon of co-existent pituicytoma and corticotroph adenomas in adults. Pituicytomas are rare tumours derived from pituicytes, which are specialised glia of the posterior pituitary,[1] and are characterised by fibrillary cells with elongated nuclei arranged in fascicles.[2] These are solid, low grade (WHO Grade 1) glial neoplasia with spindle cell morphology that originate in the

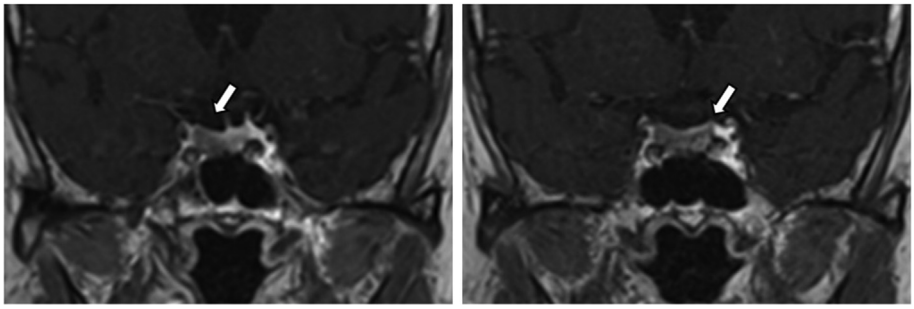

Fig. 1 Magnetic resonance imaging of the pituitary showing two focal lesions in the right and left lateral wing of the pituitary.

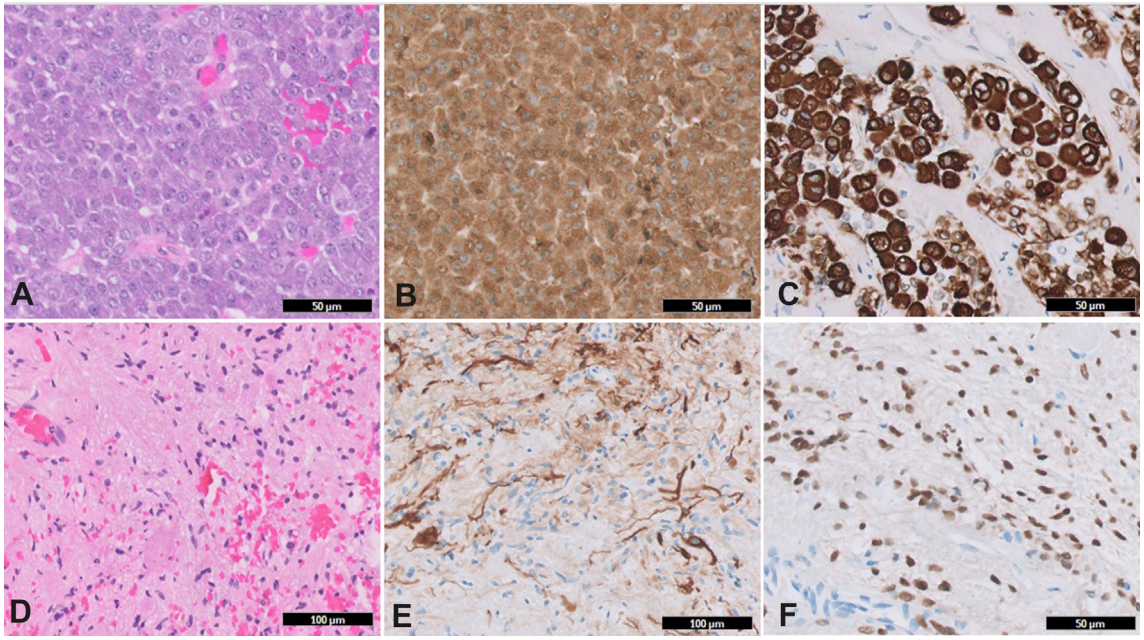

Fig. 2 Histopathology. (A–C) Right pituitary lateral wing lesion revealed features of (A) an adenoma with (B) strong diffuse staining for ACTH. (C) Few scattered Crooke cells are seen within the entrapped native anterior pituitary lobules, as identified by the Cam5.2 stain. (D–F) Left pituitary wing lesion shows (D) spindle cells within a fibrillary background on H&E stain that was (E) positive on staining for GFAP and (F) diffusely positive for TTF-1.

neurohypophysis or infundibulum.[3] A recent review[4] of the 117 reported cases of pitucytoma in the literature shows that the most frequent clinical complaint was visual field impairment followed by endocrinological disturbances from anterior pituitary hormonal hypofunction. The diagnosis of pituicytoma relies on histological and immunohistochemical analysis, with TTF-1 the most reliable immunostain for diagnosis, given the variability in staining for other markers including GFAP, EMA, S100 and synaptophysin.[5] In the 2021 WHO Classification of Tumors of the Central Nervous System,[6] pituicytomas are grouped together with granular cell tumour and spindle cell oncocytoma. These tumours share expression of TTF-1,[7] suggesting a common histogenesis.[8] Chromosomal imbalances may predict poorer patient outcomes in terms of poorer progression free survival.[9] Pituicytomas are rare with most of the literature existing as small case series or case reports.[5] The clinical manifestations can be varied and typically present with symptoms of mass effect rather than hormonal hyperfunction.[10] Surgical resection is the preferred treatment for pituicytomas with low reported recurrence rates (4.3%) following complete resection.[11] Post-operative radiotherapy has been attempted in cases of tumour remnant or regrowth, but there is a distinct lack of data regarding its effectiveness with respect to tumour control,[10] and the usefulness, indication or type of radiotherapy in the management of posterior pituitary tumour management is not well established.[12]

Final histopathological analysis of our patient with biochemically proven CD revealed co-existence of a pituicytoma with a corticotroph adenoma. A recent review by Iglesias *et al.*[13] reported a prevalence of 5.6% of hypercortisolism in posterior pituitary tumours, with the majority being associated with pituicytoma. This relatively high prevalence adds fuel to the notion that this relationship may not be coincidental. To our knowledge, there are no previous cases reported in the English literature of co-existent pituicytoma and corticotroph adenomas in adults. Pituicytoma on its own without a co-existing corticotroph adenoma has been reported in the setting of CD. Schmalisch *et al.* (Table 1) reported a case of CD in a 48-year-old man who underwent initial transsphenoidal surgery with removal of a posterior pituitary 4 mm microadenoma with a subsequent histopathological diagnosis of pituicytoma made. There was no post-operative decrease of ACTH or cortisol levels and the patient underwent a second transsphenoidal surgery, this time a right hemihypophysectomy. The non-tumourous specimen of the adeno-hypophysis from the re-operation showed signs of Crooke's hyalinisation consistent with CD. Post-operative hypocortisolism confirmed successful resection of the underlying ACTH source during re-operation. Case reports have also been published where patients diagnosed with CS underwent transsphenoidal surgery with final histological diagnoses of pituicytoma being made (summarised in Table 1). Of note, the case by Chakraborti *et al.* (Table 1) reported a patient with Cushingoid features but did not report formal biochemical confirmation of CS. In the majority of these cases (Table 1), the authors report removal of the culprit lesion responsible for CS as evidenced by subsequent biochemical remission, yet pituitary corticotroph adenoma was not confirmed histologically in these cases with evidence of pituicytoma being found. One case report of pituicytoma coexisting with corticotroph hyperplasia was reported by Guo and colleagues (Table 1). Cambiaso and colleagues (Table 1) reported the only previous case in the literature with confirmed co-existence of pituicytoma with corticotropin-secreting adenoma in a 7-year-old patient, where initial transsphenoidal surgery provided unequivocal evidence of pituicytoma. In view of persistent hypercortisolism, the patient underwent repeat transsphenoidal surgery with removal of two lesions, later confirmed on immunohistological examination to be corticotropin-secreting adenoma. This co-existence raises questions on a potential pathogenetic mechanism linking the two. Whether glia cells of the posterior pituitary play a pathogenic role through the release of

Table 1 Review of cases in the literature of co-existent pituicytoma and Cushing's syndrome

Author	Age/Sex	Clinical presentation	Imaging	Surgery	Pathology	Post-operative outcome
Schmalisch *et al. Pituitary* 2012; 15 (Suppl 1): S10−16	48/Male	Cushing's syndrome, hypertension, diabetes mellitus, pathological fractures	4 mm PitNET	1. Transsphenoidal resection 2. Right hemi-hypophysectomy	1. Pituicytoma 2. Signs of Crooke's hyalinisation; no definite adenoma	Persistent hypercortisolism remained after first surgery; CD remission after second surgery
Chakraborti *et al. Pathol Res Pract* 2013; 209: 52−8	24/Male	Facial puffiness, Cushingoid features, hypertension	6 mm PitNET	Transsphenoidal resection	Pituicytoma	Remission of symptoms
Cambiaso *et al.* Pediatrics 2015; 136: e1632−6	7/Female	Precocious pubarche, Cushing's syndrome	Enlarged gland with no distinct adenoma	1. Transsphenoidal resection 2. Repeat transsphenoidal resection	1. Pituicytoma 2. Corticotroph adenoma	Persistent hypercortisolism even after two surgeries with eventual bilateral adrenalectomy
Barresi *et al. Neuropathology* 2017; 37: 86−90	53/Female	Cushing's syndrome, hirsutism	7 mm PitNET	Transsphenoidal resection	Pituicytoma	CD remission
Guo *et al. Medicine (Baltimore)* 2016; 95: e3062	46/Female	Cushing's syndrome, menstrual disorder, hypertension	15 mm left PitNET	Transsphenoidal resection	Pituicytoma with adjacent ACTH-secreting pituitary hyperplasia	Initial residual disease; follow on radiotherapy (56Gy) achieved CD remission
Feng *et al. Br J Neurosurg* 2020; 34: 487−91	29/Female	Cushing's syndrome, menstrual disorder	4 mm PitNET	Transsphenoidal resection	Pituicytoma	CD remission
Gezer *et al. Endocr Regul* 2019; 53: 263−7	37/Male	Cushing's syndrome	6 mm infundibular lesion	Transsphenoidal resection	Pituicytoma	CD remission
Li *et al. Medicine* 2019; 98: e17772	32/Female	Cushing's syndrome, hypertension, diabetes mellitus, fragility fractures	7 mm PitNET	Transsphenoidal resection	Pituicytoma	CD remission
Rumeh *et al. J Surg Case Rep* 2020; 2020: rjaa104	47/Female	Cushing's syndrome, hypertension, diabetes mellitus	5 mm left PitNET	Transsphenoidal resection	Pituicytoma	Not available
Del Pont *et al. World Neurosurg* 2020; 136: 78−82	33/Female	Cushing's syndrome; hypertension	Right pituitary PitNET	Transsphenoidal resection	Pituicytoma	CD remission

ACTH, adrenocorticotropic hormone; CD, Cushing's disease; PiNET, pituitary neuroendocrine tumours.

local signals, growth factors, hypothalamic releasing factors thereby leading to tumourigenesis of the anterior pituitary[13] still remains an area of uncertainty and one that would benefit from further studies.

The presence of two distinct pituitary lesions added a layer of diagnostic complexity to our case, especially when considering targets for resection during transsphenoidal surgery. Based on initial biochemical investigations we were confident that the culprit corticotroph adenoma was the lesion in the right pituitary, whilst acknowledging the limitations of IPSS in predicting intra-pituitary tumour location. The decision for resection of both lesions was made intra-operatively by an experienced neurosurgeon, striking a fine balance of optimising surgical outcomes vis-à-vis complete tumour resection in one setting against that of preserving normal pituitary hormonal function. Post-operative hypocortisolism confirmed successful resection of the corticotroph adenoma without compromise of any other hypothalamo-pituitary hormonal axes.

In summary, pituicytomas are rare neoplasms derived from pituicytes of the neurohypophysis. The co-existence of pituicytomas and other functional PitNET may pose a diagnostic dilemma. This case adds to the body of evidence supporting the association of pituicytomas with that of CD, with the prevalence of this occurrence higher than can be attributable to coincidence alone.

Conflicts of interest and sources of funding: The authors state that there are no conflicts of interest to disclose.

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