Two cases of clinical Cushing`s disease caused by pituitary macroadenoma exhibiting Crooke`s hyaline changes and with immunoreactivity for ACTH and GH

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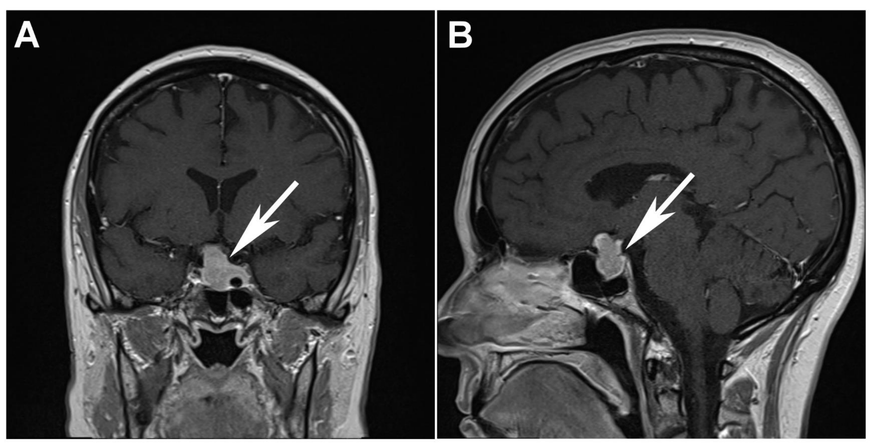
Introduction

Cushing`s disease is caused by functional corticotroph adenomas of the pituitary, mostly microadenomas (1). Crooke`s cell adenomas are rare, accounting for up to 4.4% of corticotroph adenomas and mostly present as aggressive macroadenomas (2). Pituitary adenomas showing immunoreactivity for both adrenocorticotropic hormone (ACTH) and growth hormone (GH) are also very uncommon (3) . We present two cases of clinical Cushing`s disease caused by pituitary macroadenomas that showed immunoreactivity for both ACTH and GH and exhibited variable degree of Crooke`s cell hyaline changes.

Case #1

A 51-year old woman presented to a neurologist with a self-limiting episode of visual loss in her right eye. Arterial hypertension, long-standing irregular periods with history of PCOS and 1-year history of tiredness were noted. MRI of the pituitary revealed a 21x19mm large macroadenoma with extension into the suprasellar cistern and left cavernous sinus which was abutting, but not compressing the optic chiasm. (**Fig. 1A and 1B**).

Figure 1



Laboratory investigations are summarised in **Table 1**.

Table 1

Test	Value (Ref. range)	Test	Value (Ref. range)
LH	8.0 IU/L (7.7 – 59)	**IGF-1**	120 µg/L (97 – 292)
FSH	10.7 IU/L (26 – 135)	**Short Synacthen Test**	0min: 262 nmol/L 30min 751 nmol/L (>430)
Estradiol	58 pmol/L (<183)	**1mg ONDST (48h value)**	Cortisol: **549 nmol/L** (<50) ACTH: **220 ng/L**
TSH	0.96 mIU/L (0.27 – 4.2)	**2x24h UFC; Urine Vol.**	**952 nmol/24h**; 1700 mls **401 nmol/24h**; 1130 mls, (0 – 165 nmol/24h)
fT4	13.5 pmol/L (12.0 – 22.0)	**48h low-dose DST (0h – 48h)**	Cortisol: 417 nmol/L – 1126 nmol/L ACTH: 148 ng/L – 177 nmol/L
Prolactin	**710 mIU/L** (102 – 496)	**100 µg CRH test**	Max change vs. baseline **Cortisol: +46%, ACTH: +18%**

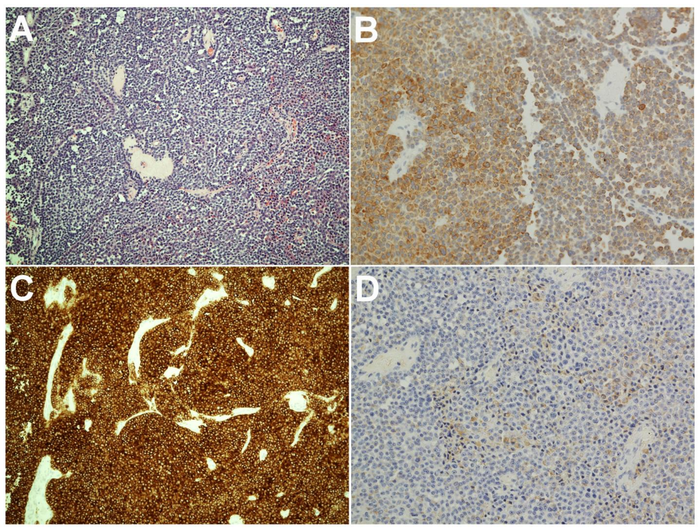
CT scan thorax/abdomen/pelvis: 2 small ground-glass laesions in the right upper lung lobe which have been stable on follow-up imaging and nodular adrenal glands with a 15 x 10 mm large right adrenal adenoma (density 0 HU).

Endoscopic transsphenoideal surgery (ETSS) in June 2016 with a day 2 post-surgery morning cortisol 60 nmol/L.

Post-surgery MRI scan: Residual adenoma tissue with max. diameter 8 mm.

Histology/mmunohistochemistry: Extensive areas of Crooke`s hyaline changes (**Fig. 2A**) with strong immunoreactivity for cytokeratin (CAM 5.2) (**Fig. 2B**). Moderate diffuse immunoreactivity for ACTH (**Fig. 2C**) and GH (**Fig. 2D**). The Ki67 labelling fraction was <3% with no evidence for P53 mutation.

Figure 2*

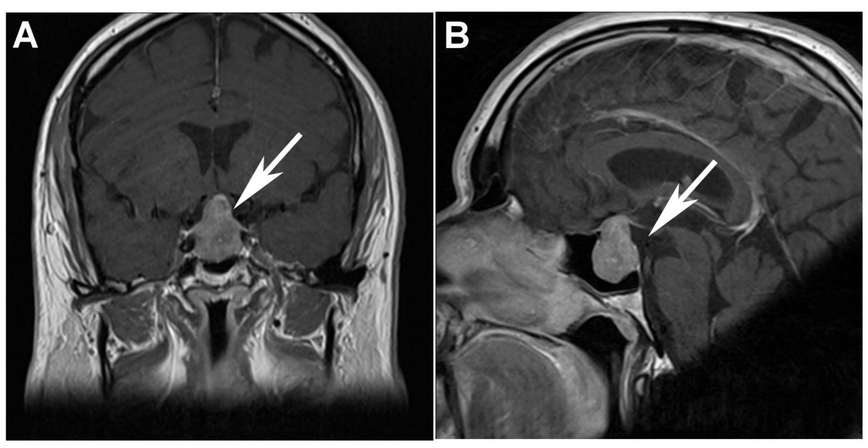


Follow-up: A 1-year post surgery MRI scan of the pituitary showed an increase of size of the residual tumour to 11.5 mm (1mg ONDST cortisol 67 nmol/L) indicating a progression of the disease. This lady is currently awaiting a repeated ETSS for tumour debulking with subsequent stereotactic radiosurgery.

Case #2

A 50-year old man presented with tiredness and erectile dysfunction and was found to have secondary hypogonadism and hypothyroidism. Arterial hypertension, obesity and obstructive sleep apnoea were noted. MRI of the pituitary revealed a 27x19x23mm large macroadenoma compressing the optic chiasm (**Fig. 3A and 3B**), but there was no visual disturbance reported by the patient.

Figure 3



Laboratory investigations are summarised in **Table 2**.

Table 2

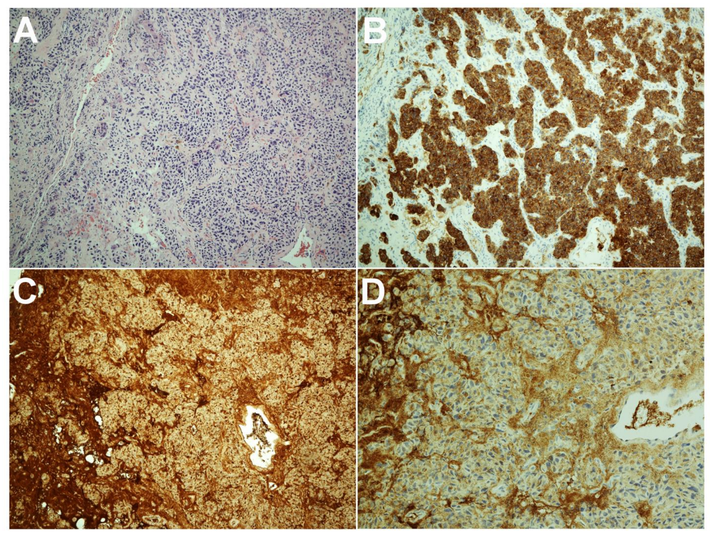
Test	Value (Ref range)	Test	Value (Ref range)
LH	3.9 IU/L (<9)	**IGF-1**	116 µg/L (97 – 292)
FSH	3.8 IU/L (<9)	**SST**	0min: 360 nmol/L 30min 712 nmol/L (>600)
Testosterone	**5.6 nmol/L** (8-27)	**1mg ONDST (48h value)**	Cortisol: **600 nmol/L** (<50)
TSH	0.56 mIU/L (0.4 – 5.5)	**2x24h UFC; Urine Vol.**	**351 nmol/24h**; 1400 mls **181 nmol/24h**; 1870 mls (10 – 147 nmol/24h)
fT4	**10.9 pmol/L** (11 – 26)	**48h low-dose DST (0h – 48h)**	Cortisol: 671 nmol/L – 340 nmol/L ACTH: 94.9 ng/L – 76.0 nmol/L
Prolactin	**469 mIU/L** (86 – 324)		

ETSS in April 2017 with day 2 post-surgery morning cortisol 98 nmol/L.

Post-surgery MRI scan: Complete resection of the adenoma.

Histology/ Immunohistochemistry: Extensive Crooke`s hyaline cell changes (**Fig. 3A**) with strong immunoreactivity for cytokeratin (CAM 5.2) (**Fig. 3B**). Strong immunoreactivity for ACTH (**Fig. 3C**) and widespread GH staining (**Fig. 3D**). The Ki67 labelling fraction was low with no evidence for P53 mutation.

Figure 4*



* Figures 2 and 4. Panels A, B and C – magnification x10, Panel D – magnification x20.

Follow-up: 6 months post surgery is the patient on hydrocortisone, laevothyroxine and testosterone replacement therapy.

Acknowledgements

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Conclusions/Discussion

- To our knowledge, this is the first report of clinical Cushing`s disease caused by pituitary macroadenomas with immunoreactivity for ACTH and GH and with areas of Crooke`s hyaline changes positive for cytokeratin (CAM 5.2).
- Similar to Crooke's cell pituitary adenomas that represent a rare cause of Cushing`s disease, the tumour in Case 1 has recurred and acted aggressively and needs strict surveillance (2).

References

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