Two rare cases of Cushing's Disease in functional pleurihormonal pituitary adenomas tumors positive for T-PIT, ACTH, and FSH

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Introduction

- The World Health Organization (WHO) classification for pituitary adenomas (PA) expanded in 2017 to include pituitary transcription factors (PTF) PIT-1, T-PIT, and SF-1, which delineate PAs into 3 distinct lineages[1].
- This novel paradigm has led to changes in PA diagnosis and has promise to provide additional prognostic value based on subtype.
- Although PAs typically express one PTF, rarely they express multiple PTFs or hormone markers from multiple lineages (pleurihormonal tumors [PHT]).
- Most PHT are clinically silent; when functional, they most often secrete growth hormone or prolactin (PIT-1) lineage[2].
- We report two cases of functional pleurihormonal tumors arising from T-PIT and SF-1 lineages in patients presenting with Cushing's disease.

Example Patient Presentation

- 39-year-old male presented with 27 lbs weight gain over several months.
- Physical examination revealed truncal obesity with abdominal striae, dorsocervical & supraclavicular fat pads, facial adiposity (**Figure 1 A-C**).
- Magnetic resonance imaging demonstrating an approximately 1.7 x 1.4 x 0.7 cm (0.8 cm^3) enhancing sellar mass (**Figure 2 A-B**).
- Endocrinological workup was notable for elevated midnight salivary cortisol (4900 ng/dL; ref <100), 24 hour urine cortisol (1193 mcg; ref 3.5-45 mcg), and low-dose dexamethasone suppression test (90 mcg/dL, ref<10), as well as elevated ACTH and 8:00 A.M. cortisol on several occasions.
- Hemoglobin A1c was elevated at 6.4.
- He underwent a multidisciplinary endoscopic endonasal transsphenoidal approach for resection.
- Waiver of Institutional Review Board approval for case reports and consent from patients for participation and sharing of identifying information including images were obtained.

Postoperative Course

- Cortisol downtrended to a nadir of 3 before he sustained a brief hypotensive episode when out of bed on postoperative day 1 (**Figure 2C**).
- Hydrocortisone replacement began and slowly tapered to physiologic dosing.
- Histopathology was positive for TPIT and ACTH with abundant Crooke cell change. Pathology was also positive for FSH. It was negative for SF1, PIT1 and other pituitary hormones (**Figure 2**).
- The patient recovered very well without complication and was discharged on postoperative day 4.

Discussion

We present two rare cases of individuals who presented with clinical and biochemical hypercortisolism and was found to have a pleurihormonal tumor co-expressing TPIT, ACTH, and FSH with Crooke cell change.

- PHT are a rare subset of PitNETs whose diagnosis has expanded with the 2017 WHO update to include tumors of multiple transcription factor lineages.
- Previous literature has shown ACTH-secreting PHTs to be exceedingly rare, and even less common to include an SF1 lineage hormone marker
  - Several large case series[3-5] showed no cases of Cushing disease from a PitNET with TPIT/SF1 co-lineage.
- As ACTH-secreting PHTs have a demonstrated a higher recurrence risk than other PHTs[6], and are associated with a morbid clinical syndrome, this rare subclass of PHT warrants careful attention, biochemical workup, and close follow up.

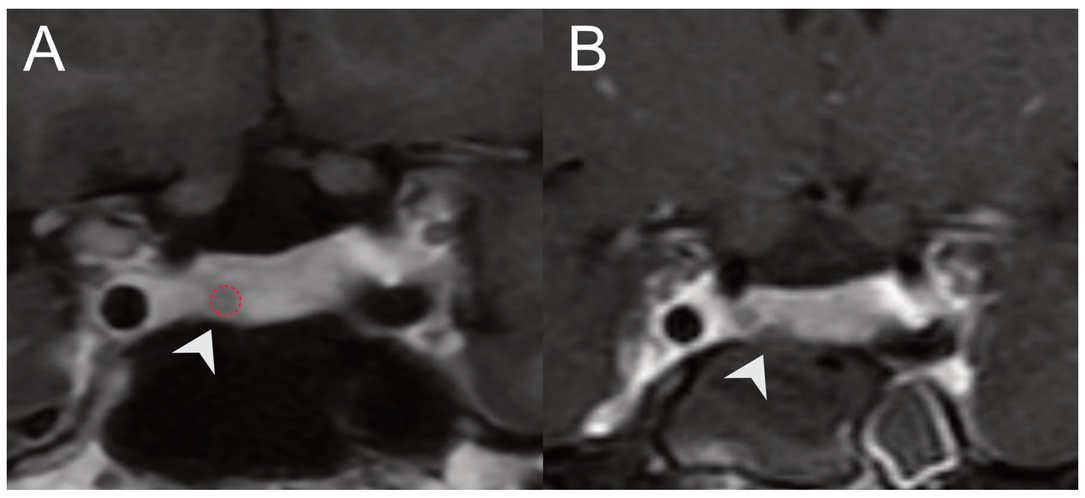

Figure 3. Preoperative (A) and postoperative (B) T1-weighted post-contrast sellar MRI shown of the second patient. There is a 0.22 x 0.23 x 0.28 mm microadenoma located in the right side of the pituitary gland preoperatively. Postoperatively, there is radiographic gross total resection of the lesion.

Figure 1. Preoperatively (A-C), classical physical examination findings of Cushing's syndrome including (A) truncal obesity, (B) facial adiposity, (C) dorsocervical fat pad. Postoperatively (D-F), photograph shows significant reduction in Cushingoid features. Written consent for identifying information including photograph and video was provided by patient.

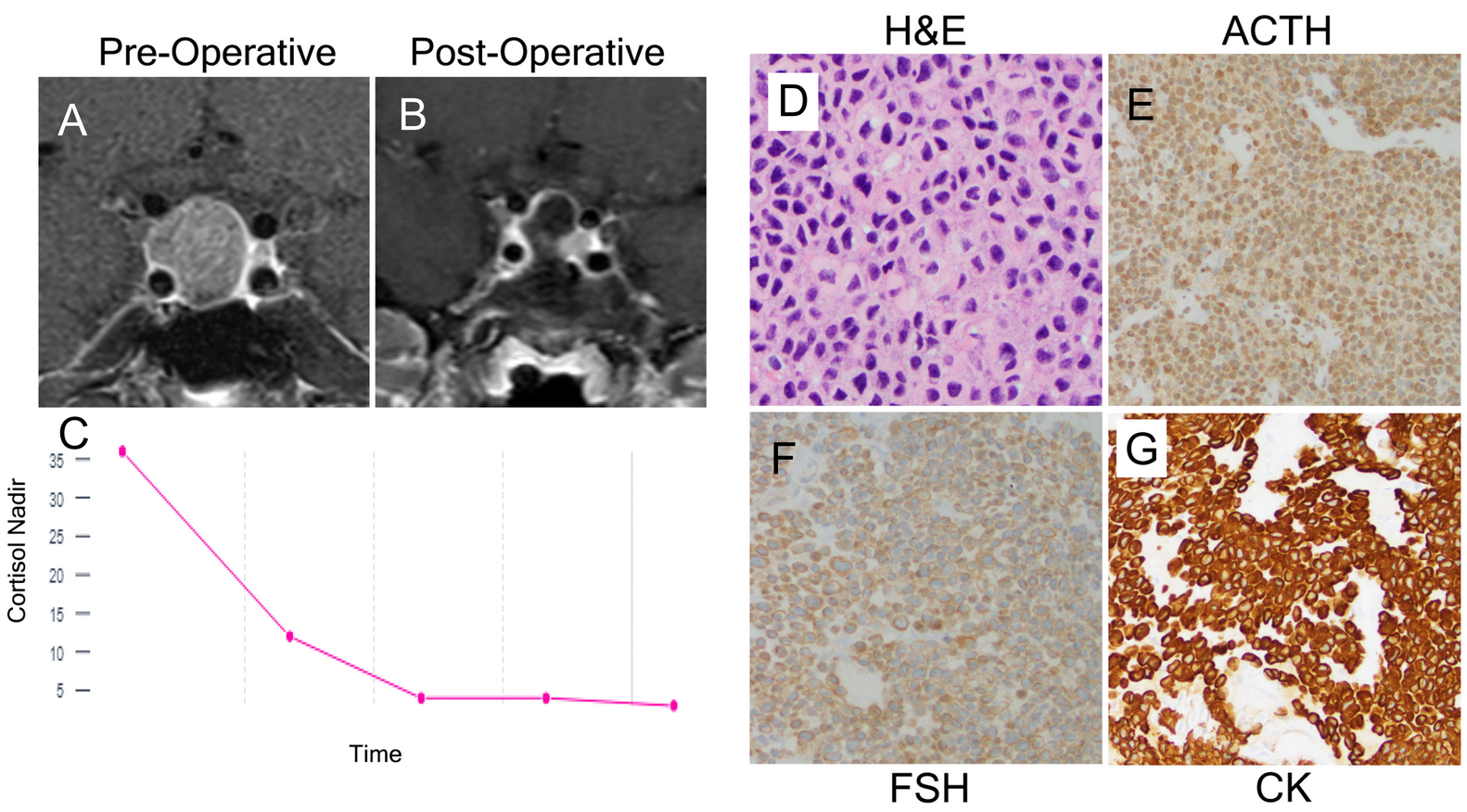

Figure 2. Coronal (A) preoperative vs. (B) postoperative T1-post contrast MRI showing gross total resection. (C) Postoperative cortisol nadir. Histopathology showing (D & G) abundant Crooke cell change, (E) diffuse ACTH and (F) FSH staining.

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