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Case Report

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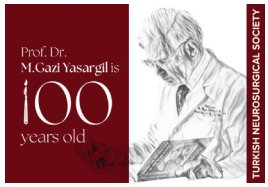


# Functional Transformation of a Corticotroph Pituitary Neuroendocrine Tumor 128 Months Following Primary Excision – A Case Report

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## ABSTRACT

Silent corticotroph pituitary neuroendocrine tumours (PitNETs) are rare, aggressive tumours that exhibit clinical and biochemical silence, despite their expression of adrenocorticotrophic hormone (ACTH) and the transcription factor Tpit. They exist on a spectrum of functionality between true silent adenomas and ACTH-secreting adenomas and rarely transform into functioning corticotroph adenomas. In this report, we describe an aggressive silent corticotroph PitNET, which recurred twice following complete excision and displayed functional transformation 128 months after primary excision, with clinical and biochemical profiles suggestive of Cushing's disease. The patient underwent re-operation followed by hypofractionated stereotactic radiotherapy. This case report demonstrates the importance of long-term clinical and biochemical follow-up in patients with silent corticotroph PitNETs, and highlights the aggressive nature of these tumours that warrants early adjuvant radiation.

**KEYWORDS:** Corticotroph, Adenoma, PitNET, Functional, Transformation

**ABBREVIATIONS: PitNET:** Pituitary neuroendocrine tumours, **ACTH:** Adrenocorticotrophic hormone, **SCA:** Silent corticotroph adenomas, **MRI:** Magnetic resonance imaging, **HPA:** Hypothalamic-pituitary-adrenal axis, **CT:** Computerised tomography, **CSF:** Cerebrospinal fluid, **PC1/3:** Prohormone convertase 1/3, **POMC:** Proopiomelanocortin

## INTRODUCTION

Corticotroph pituitary neuroendocrine tumours (PitNET) that exhibit clinical and biochemical silence, despite their expression of adrenocorticotrophic hormone (ACTH) and the transcription factor Tpit, previously referred to as silent corticotroph adenomas (SCAs), are considered 'high-risk'/aggressive tumours (10). They are said to exist on a spectrum of functionality between true silent adenomas and ACTH-secreting adenomas, termed by some authors as "whispering adenomas" (2). They have been shown to rarely transform into functioning corticotroph tumours/adenomas several months after initial diagnosis, however, this period usually ranges between 30-60 months (12,13). In this report, we describe the functional transformation of a recurrent Corticotroph PitNET 128 months after complete excision, the longest recorded interval for transformation to date.

## CASE REPORT

A 25-year-old male presented to our outpatient clinic in August 2010 with holocranial headache and decreased vision to perception of light in the left eye for a month. Magnetic resonance imaging (MRI) of the brain showed a sellar and

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suprasellar mass, most consistent with a pituitary macroadenoma, measuring 3.7 cm in maximum diameter and causing distortion of the floor of the third ventricle (Hardy grade C, Knosp grade 2). There was evidence of apoplexy in the posterosuperior aspect of the tumour, and it displayed multiple <2 mm-sized cysts, occupying more than a quarter of the tumour on T2-weighted coronal images (Figure 1A). Clinical and biochemical assessment did not suggest dysfunction of the hypothalamic-pituitary-adrenal axis (HPA); thyroid function testing and serum testosterone levels were also normal. He underwent endonasal endoscopic excision of the tumour, following which his visual acuity improved from perception of light to 6/36 in the left eye. Computerised tomography (CT) of the brain performed on the 5$^{th}$ postoperative day did not show any obvious tumour residue (Figure 1B). His postoperative period was uneventful, and the biopsy was reported as a silent corticotroph adenoma, since immunohistochemistry was positive for ACTH. The MIB-1 labelling index was 4%. Serial MRI brain imaging at 6 months and 14 months following surgery showed no tumor recurrence (Figure 1C & 1D). However, at his next review in January 2014, 41 months after surgery, he complained of decreased vision in his left eye, which was noted to have worsened to 6/60 with temporal hemianopia. While we were unable to identify any obvious recurrent tumour on MRI, there was a CSF-intensity cyst measuring 2.8 cm in maximum diameter in the sellar and suprasellar region, causing compression of the optic chiasm (Figure 1E). Pituitary hormonal functions were once again tested and found to be normal. On re-exploration, we found that the arachnoid had reached the sellar floor and that there was a small area of tumour overlying the neurohypophysis, which we removed. This tumour was also noted to be immunopositive for ACTH with a MIB-1 index of 6%. While his visual field defect remained unchanged, his visual acuity improved to 6/24 in the left eye, and he did not develop hypopituitarism postoperatively.

His hormonal axes remained normal a year after the second surgery, and a brain MRI once again, did not show any obvious residue (Figure 1F). He did not review in our outpatient clinic until 68 months later, in March 2021, with a mild headache. He also reported a weight gain of almost 12 kilograms in 6 months and, on examination, had Cushingoid features such as a moon face, a prominent supraclavicular pad of fat, acne and skin hyperpigmentation. He had elevated morning serum cortisol (8 AM) of 16.4 ug/dL, which failed to suppress following the overnight dexamethasone suppression test, along with elevated late-night salivary cortisol (0.245 µg/dl) and increased 24-hour urinary cortisol excretion (455 µg/day). His plasma ACTH value was elevated - 69.5 ug/dL, and serum cortisol was suppressed to 38% of the baseline value following high dose dexamethasone suppression, confirming ACTH-dependent Cushing's disease. This time, he was also found to have central hypothyroidism and hypogonadism, for which he was started on supplementation. His MRI revealed a recurrent pituitary tumour, measuring 2 cm in maximum diameter, with bilateral cavernous sinus invasion (Knosp

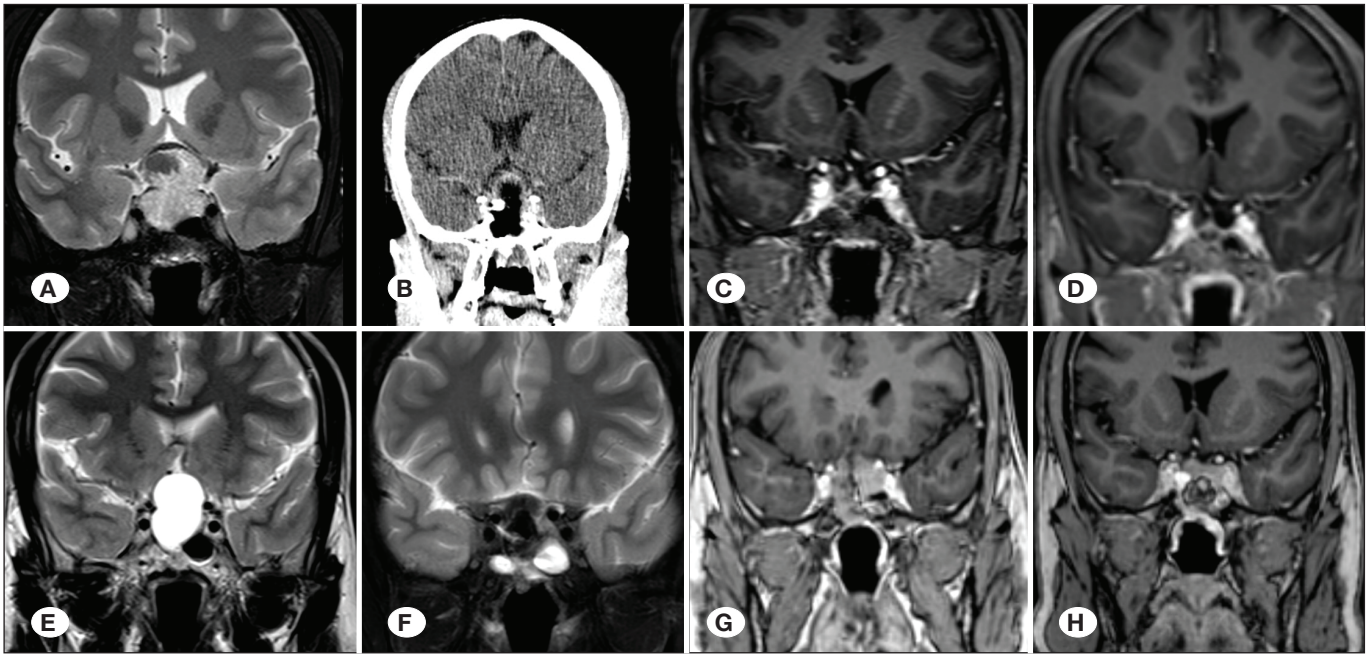


**Figure 1:** Coronal T2-weighted MRI showing a 3.7 cm pituitary macroadenoma displaying microcystic changes and evidence of haemorrhage in the superior aspect of the tumour **(A)**. No obvious residual tumour was seen on the first postoperative contrast-enhanced CT done 5 days after surgery **(B)**; The tumour did not recur at 6 months **(C)**, and 14 months **(D)** after surgery, however a 2.8 cm large, CSF-intensity cyst in the sellar and suprasellar region causing compression of the optic chiasm was seen at the 40-month follow-up **(E)**, for which he was reoperated and remained free of recurrence a year later **(F)**. However, he presented 68 months later with a large recurrence **(G)**, and features of Cushing disease. He underwent a repeat transsphenoidal resection followed by stereotactic radiation therapy for the residue **(H)**.

grade 3A) (Figure 1G). We approached the tumour once again via the endoscopic transsphenoidal route. The tumour in the Sella was removed, leaving behind the component within the cavernous sinuses (Figure 1H). The tumour was analysed for transcription factor expression, which revealed that it expressed Tpit and was negative for SF1, confirming that it was a corticotroph PitNET (Figure 2). He was administered hypo-fractionated stereotactic radiotherapy - 2500 cGy in 5 fractions for the residual tumour.

Written informed consent was obtained from the individual (and/or legal representative) for the publication of the case.

## DISCUSSION

We describe a case of a corticotroph PitNET/adenoma that was silent at initial presentation and manifested as Cushing's disease 128 months after tumour excision. The initial MRI showed micro-cystic changes within the tumour, now recognised to predict silent corticotroph histology (1,7). The tumour exhibited an aggressive course and recurred twice following complete excision. Finally, it underwent phenotypic transformation to a functional corticotroph adenoma, at which point we partially excised the tumour and administered radiation therapy. To the best of our knowledge, this report documents the longest period between the initial presentation of a clinically silent corticotroph PitNET/adenoma and its functional transformation.

### Phenotypic Transformation Among Corticotroph Adenomas

Corticotroph PitNETs/adenomas have been found to transition between silent and functional phenotypes in up to 4% of cases, with multiple interconversions during treatment of the same adenoma having been reported (13). On average, the duration to detection of conversion appears to be around 30 months (12,13), and most common in the first 12-24 months following initial presentation. An isolated case was reported, in which the transformation occurred after 120 months (12). As demonstrated in our case, the tumor gained functionality after 128 months, highlighting the importance of long-term follow-up in detecting the recurrence. The onset of subtle clinical features of hypercortisolism, such as weight gain may portend a recurrence with phenotypic transformation and must be assessed at serial follow-up visits in patients with SCA.

It is interesting to note that a large proportion of corticotroph PitNETs/adenomas that demonstrated phenotypic conversion required multiple surgeries, recurred after radiation therapy, and failed to achieve remission with the use of temozolomide (12). It therefore appears reasonable to initiate early adjuvant therapy in corticotroph PitNETs/adenomas that display phenotypic transformation, although the data available in the literature is sparse.

### Molecular Basis of Transforming Corticotroph Adenomas

The most widely accepted hypothesis explaining the "silence" of Corticotroph PitNETs is their inherent lack of prohormone convertase 1/3 (PC1/3), an enzyme along the path of cleavage of proopiomelanocortin (POMC) to adrenocorticotropic hormone (ACTH) (6,11). In its absence, tumour cells are unable to produce ACTH in sufficient amounts to cause hypercortisolism. It has been demonstrated that corticotroph PitNETs

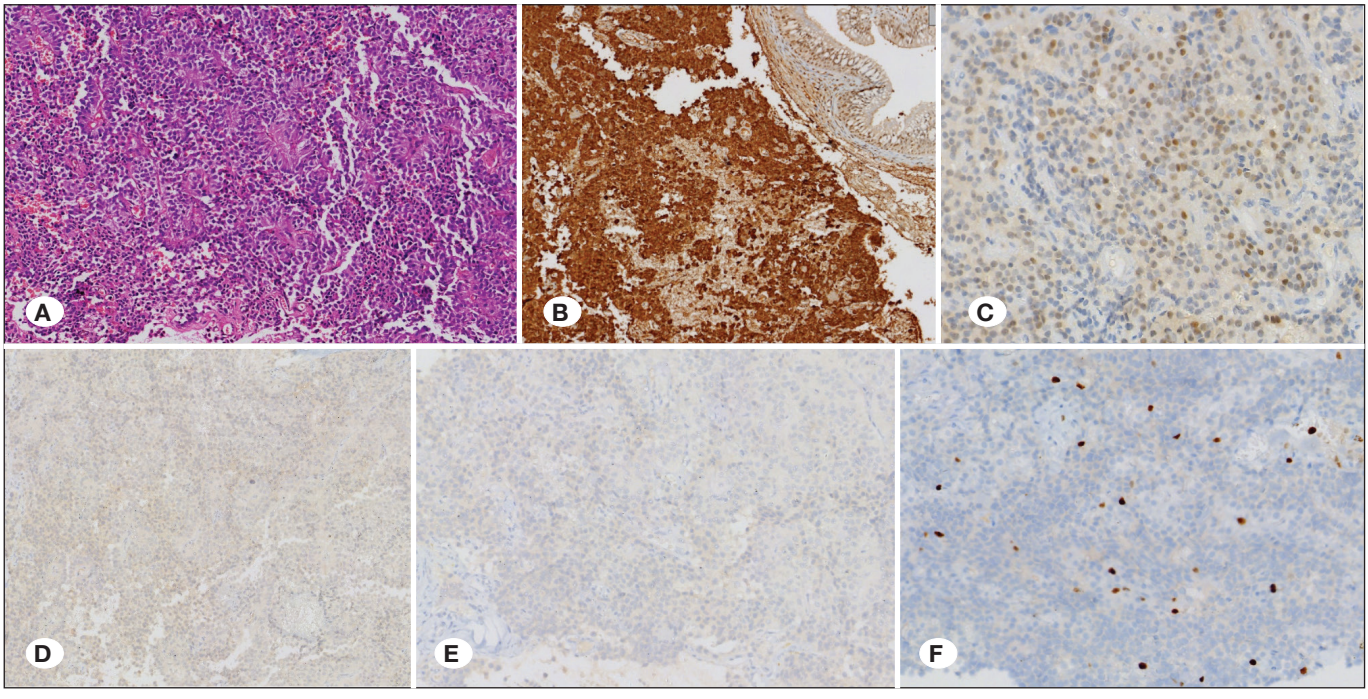


**Figure 2: A)** Photomicrograph of the corticotroph pituitary neuroendocrine tumour excised in 2021, highlighting its papillary architecture with immunopositivity for **(B)** ACTH and **(C)** Tpit and immunonegativity for **(D)** Pit-1 **(E)** SF-1 and **(F)** a Ki 67/MIB-1 labelling index of ~5% (x200).

display a significantly greater prevalence of diabetes mellitus, female preponderance and higher serum cortisol and ACTH levels (3). This highlights the existence of a spectrum of "silence" in corticotroph PitNETs, that may be "totally silent" with normal cortisol levels, "clinically silent" with mildly elevated ACTH and serum cortisol without any clinical features of Cushing's syndrome, and finally, "whispering adenomas" when clinical features of hypercortisolism are subtle and may be easily overlooked (2,4,8). This may result from varying levels of expression of PC1/3 among clinically silent corticotroph PitNETs. Additionally, the overt phenotypic transformation from clinically silent to Cushing's disease is associated with PC1/3 upregulation (11). However, the process triggering increased expression of PC1/3 in tumours that previously lacked the capacity has not been elucidated and requires further investigation.

### Utility of Transcription Factor Analysis Among Pituitary Adenomas

This report highlights the use of transcription factors in categorizing PitNETs as per the WHO 2021 classification (10). This information is significant in light of data from our centre (3) as well as several others (2,5,6,9) that demonstrate that this subset of PitNETs follow an aggressive clinical course, and the need for reoperation for recurrence may be obviated by the use of early adjuvant radiation following excision. The 5th edition of the WHO Classification of Endocrine and Neuroendocrine Tumors removed silent corticotroph adenoma as a subtype, stating that this was a clinical and not a morphological subtype. However, given its aggressive nature, it will perhaps be prudent to reinstate this as a variant of corticotroph PitNET.

## CONCLUSION

Corticotroph PitNETs are a rare but aggressive subtype of PitNET/adenoma. Although their initial presentation may be that of a non-functional pituitary adenoma, they may transform into functional corticotroph adenomas even after complete excision. This report of a functional transformation more than 10 years after radical excision, highlights the importance of long-term follow-up of patients with clinically silent corticotroph PitNETs and vigilance for features of hypercortisolism. Transcription factors aid in the diagnosis of corticotroph PitNETs when hormonal profiles are negative or ambiguous. Surgery followed by early adjuvant radiation may be an advisable strategy to treat recurrent clinically silent corticotroph PitNETs.

**Declarations**

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**Availability of data and materials:** The datasets generated and/or analyzed during the current study are available from the corresponding author by reasonable request.

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**AUTHORSHIP CONTRIBUTION**

Study conception and design: AGC, APA
Data collection: AGH, APA, HSA
Draft manuscript preparation: AGH, APA
Critical revision of the article: HSA, AGC, GC
All authors (AGH, APA, HSA, GC, AGC) reviewed the results and approved the final version of the manuscript.

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