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CASE REPORT

Recurrent Cushing's Disease Caused by a TPIT-Lineage Densely Granulated Corticotroph Pituitary Neuroendocrine Tumor: A Case Report.

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Abstract

INTRODUCTION: Recurrent Cushing's disease (recurrent CD) is an uncommon and intricate clinical form of Cushing's syndrome. However, the connection between the pathological types of ACTH-secreting PitNETs and the clinical signs of recurrent CD remains uncertain.

CASE DESCRIPTION: A 64-year-old woman, previously diagnosed with renal carcinoma, was admitted to our hospital due to recent weight gain. Previous endocrine tests indicated fluctuating hypercortisolemia and a recurrent pituitary tumor over the past six years. She underwent two transsphenoidal hypophysectomies, and histopathological analysis of the tumor revealed it as a densely granulated corticotroph tumor (DGCT), a subtype of TPIT-lineage PitNET, accompanied by tumor apoplexy.

CONCLUSION: This case highlights the connection between recurrent CD and the pathological subtypes of TPIT-lineage DGCT-PitNETs.

Abbreviations:

CD	- Cushing's disease
DGCT	- densely granulated corticotroph tumor
SGCT	- sparsely granulated corticotroph tumor
PitNET	- pituitary neuroendocrine tumor
ACTH	- adrenocorticotropic hormone
UFC	- urine free cortisol
LDDST	- low-dose dexamethasone suppression test
HDDST	- high-dose dexamethasone suppression test
BIPSS	- bilateral inferior petrosal sinus sampling

INTRODUCTION

Cushing's disease occurs when a pituitary neuroendocrine tumor (PitNET) secretes adrenocorticotropic hormone (ACTH), resulting in an ACTH-secreting PitNET. Recurrent Cushing's disease (recurrent CD) is an infrequent clinical manifestation of Cushing's syndrome characterized by fluctuating patterns in the patient's Cushingoid symptoms or biochemical hypercortisolism states. It is believed that the clinical phenotypes are rooted in the underlying pathology. In this report, we present a case of recurrent CD in a female patient.

CASE PRESENTATION

In February 2023, a 64-year-old woman presented at our hospital, reporting an 8 kg weight gain in the last two months. The patient had a history of hyperthyroidism caused by multinodular toxic goiter and, twelve years prior, had undergone levothyroxine therapy following radioactive iodine treatment.

In 2017, the patient's physical parameters were recorded as height 145 cm, weight 43 kg, and a BMI of 20.45 kg/m^2. She had undergone a radical nephrectomy for a right kidney mass diagnosed as clear cell carcinoma. Despite the successful mass removal, she developed occasional headaches and was otherwise in good health. An MRI revealed a pituitary mass in the left aspect of the sella turcica, surrounding the left internal carotid artery, measuring approximately 20 × 17 mm with medium contrast enhancement. Following the MRI, laboratory findings indicated hypercortisolism with elevated 8 am serum cortisol, 8 am serum ACTH, and 24-hour urine free cortisol (UFC) levels on the basis of mild renal insufficiency (eGFR≈81.4 mL/min/1.73 m^2). The other pituitary hormones were as follows: prolactin 0.19 ng/mL (RR: 2.74-19.64), estradiol: < 20.00 pg/mL (RR: 0-25), LH 5.23 mIU/mL (RR: 10.87-58.64), FSH 23.55 mIU/mL (RR: 16.74-113.5), FT4 9.38 pmol/L (RR: 7.98-16.02), TSH 0.043 μIU/mL (RR: 0.560-5.910), fasting growth hormone < 0.141 ng/mL (RR: 0.010-3.607). Opting for close follow-up rather than surgery, one year later, hormone evaluations showed normalized levels.

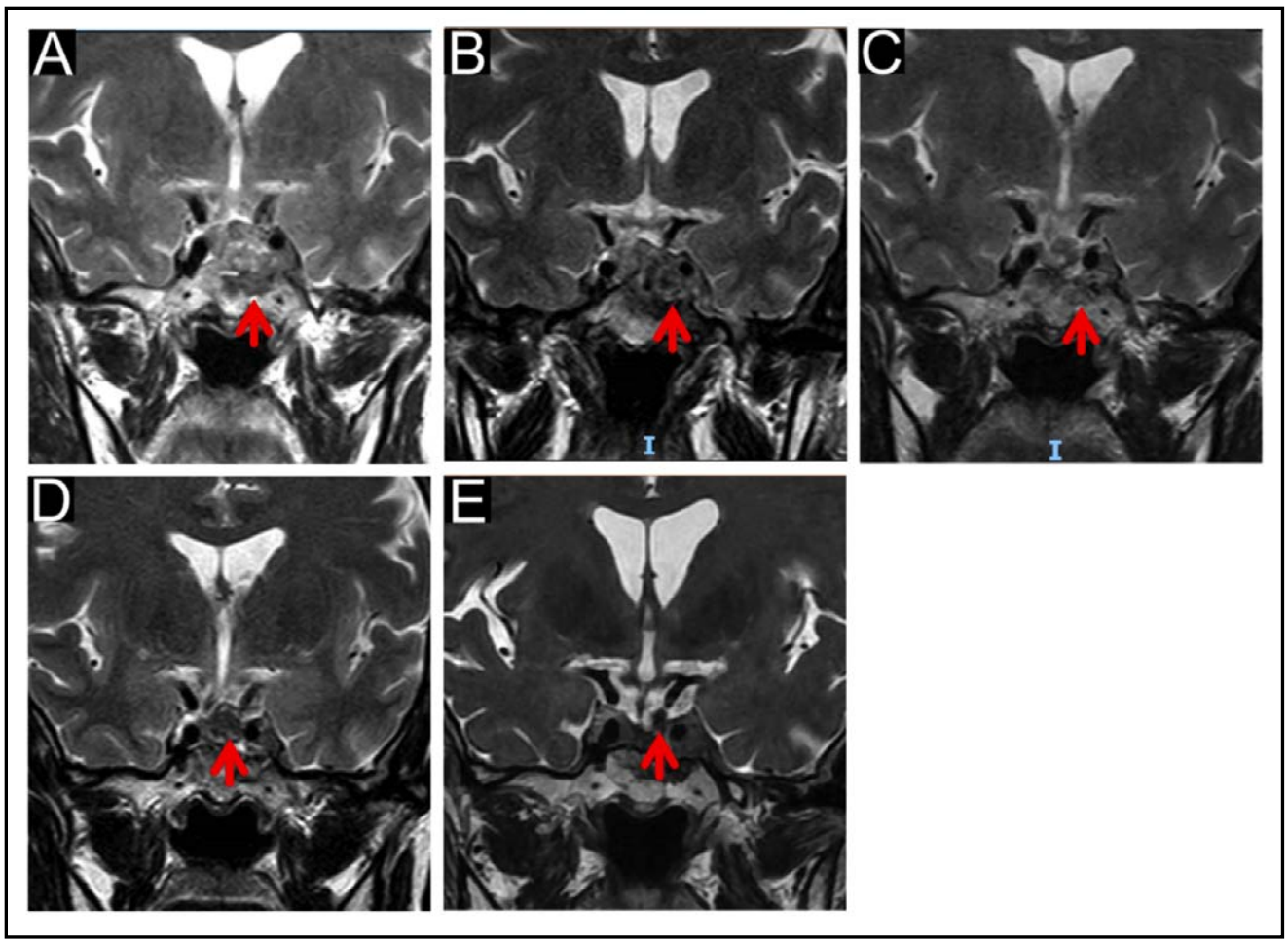

Fig. 1. MRIs of the Pituitary Tumor (Coronal View)
(A) Image in September 2017, with a tumor size of 20 × 17 mm. (B) Image in March 2019, with a tumor size of 26 × 18 mm. (C) Image in November 2021, with a tumor size of 19 × 12 mm. (D) Image in November 2022, with a tumor size of 11 × 12 mm. (E) Image in February 2023, with a tumor size of 5 × 4 mm.

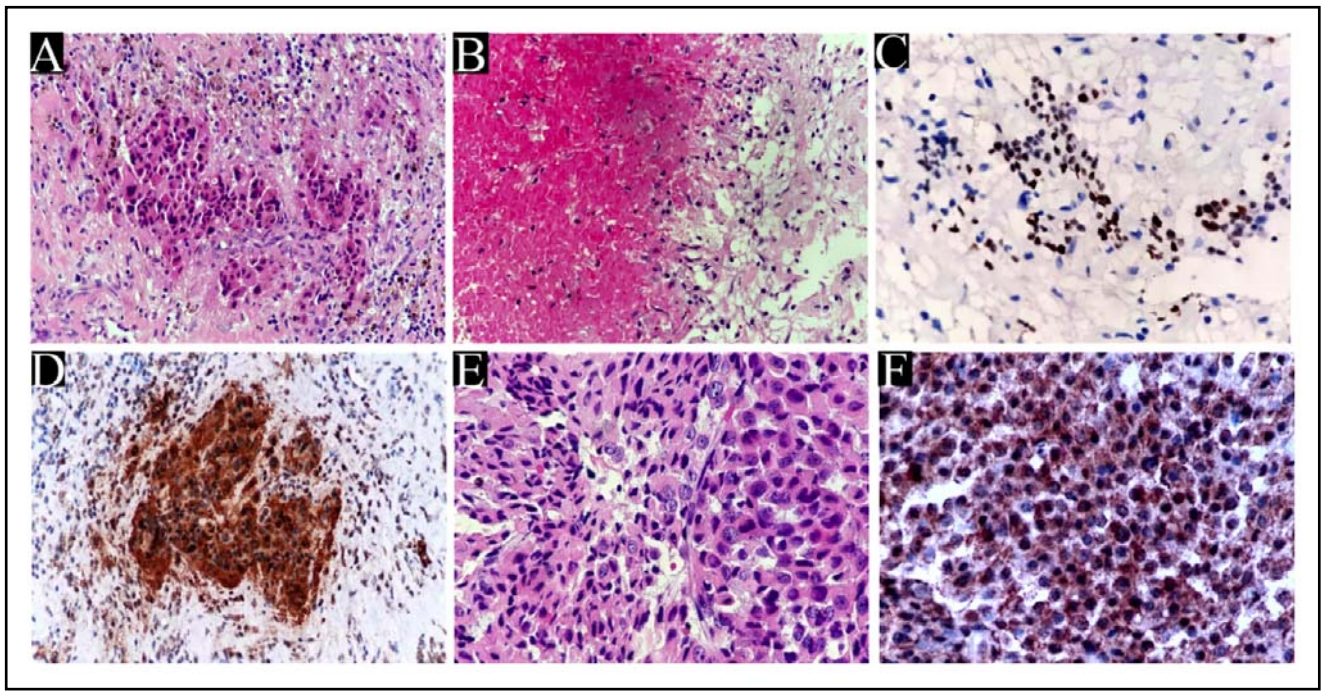

Fig. 2. Pathological Findings of Tumors

(A-D) Pathological findings in 2019. (E-F) Pathological findings in 2023. (A) The primary tumor consisted of a monomorphic cell population with eosinophilic cell cytoplasm. Nuclei tended to be bland with regularly distributed chromatin. (B) Abundant tumor coagulated necrosis and reactive macrophages were found in the tumor, indicating tumor apoplexy. (C) Tumor cells showed immunoreactivity for TPIT. (D) Tumor cells were diffusely strongly positive for ACTH. (E) Recurrent tumor was observed to have relatively monomorphic, polygonal cells with some degree of nuclear pleomorphism. (F) Tumor cells displayed strong ACTH staining dispersed diffusely throughout the entire tumor and were TPIT positive (not shown). (HE and immunohistochemical staining, with original magnification 400×)

However, in 2019, she experienced sporadic headaches accompanied by nausea and vomiting. Laboratory studies indicated elevated serum cortisol, ACTH levels, and 24-hour UFC. A follow-up MRI revealed tumor growth to 26 × 18 mm, leading to transsphenoidal hypophysectomy. Postoperative pathology identified a densely granulated corticotroph tumor with apoplexy. The immunohistochemistry revealed ACTH (+), FSH (-), TSH (-), hGH (-), LH (-), and prolactin (-) (Fig. 2A, 2B, 2C, 2D). Three days post-surgery, cortisol and ACTH levels markedly decreased. Low-dose cortisol replacement was administered for seven days, resulting in gradual hormone level normalization.

In 2021, a follow-up MRI indicated tumor recurrence, with the patient opting for symptomatic treatment over additional surgery. In 2022, the tumor size reduced to 11 × 12 mm. However, in February 2023, the patient presented with abnormal weight gain, a height of 145 cm, weight of 49.4 kg, centripetal obesity, moon face, and abdominal purple striae. Lab results revealed elevated serum cortisol, ACTH, and 24-hour UFC levels. No suppression was observed in low-dose and high-dose dexamethasone suppression tests (LDDST and HDDST). An MRI showed a reduced tumor size of 5 × 4 mm compared to previous imaging (Fig. 1). [^{68}Ga]-DOTANOC PET-CT/MR and bilateral inferior petrosal sinus sampling (BIPSS) ruled out ectopic ACTH syndrome.

The patient underwent a repeat pituitary surgery, revealing the pathology as a subtype of pituitary neuroendocrine tumors (PitNETs) identified as a densely granulated corticotroph tumor (DGCT). Immunohistochemical analysis demonstrated the tumor to be ACTH (+), TPIT (+), and negative for various other hormone markers (Fig. 2E, 2F). The Ki-67 labeling index was 3%, indicating an increased rate of cellular proliferation.

Following surgery, the patient's serum cortisol and ACTH levels began to normalize, obviating the need for cortisol replacement. Specifically, one day post-surgery, her 8 am serum cortisol level was 821.9 nmol/L, and her 8 am serum ACTH level was 15.16 pmol/L. Three weeks later, these levels further normalized to 8 am serum cortisol of 576.1 nmol/L and 8 am serum ACTH of 1.56 pmol/L. Two months post-surgery, her 8 am serum cortisol was 287.3 nmol/L, and her 8 am serum ACTH was 1.62 pmol/L (Table 1).

DISCUSSION

This case represents a rare clinical manifestation of recurrent Cushing's disease (recurrent CD) characterized by fluctuating hypercortisolemia in endocrine tests, displaying three peaks and three troughs in the past six years including two perioperative periods. The postoperative pathology revealed a subtype of densely

Tab. 1. Clinical Phenotype of Recurrent CD Characterized by Three Peaks and Three Troughs Including Two Perioperative Periods

	Reference range	09/2017	08/2018	03/2019	04/2019	11/2021	11/2022	03/2023	04/2023
8 am cortisol (nmol/L)	185.2-624.7	905.4	213.1	> 1727.0	31.1	273.6	407.6	> 1705.0	287.3
8 am ACTH (pmol/L)	1.60-13.90	29.4	5.83	164.7	2.29	19.84	18.65	35.89	1.62
24-hour UFC (nmol/L)	160.3-1113.9	7410.6	273.1	22120.3	NA	445.2	626.7	NA	NA
post-surgery					×				×

ACTH: adrenocorticotropic hormone, UFC: urine free cortisol, NA: not available.

granulated corticotroph tumor within pituitary neuroendocrine tumors (TPIT-lineage DGCT-PitNETs).

Recurrent CD is a complex clinical phenotype of CD where patient's clinical Cushingoid symptoms or hypercortisolism states manifest in a fluctuating pattern. In this case, during the close follow-up, an unexpected desynchronization between the size of the pituitary tumor and the levels of biochemical serum cortisol was observed. The diverse clinical phenotypes of complex Cushing's disease are closely tied to the underlying pathological subtype of the tumor. In a recent cohort study involving 277 Cushing's disease patients by Rak *et al.* DGCTs were predominantly microadenomas, while SGCTs (sparsely granulated corticotroph tumors) were larger, more invasive, and reached higher Knosp's scale grades and tumor volumes (Rak *et al.* 2021). Crooke cell tumors, identified as macroadenomas, often exhibit a higher frequency of aggressive behavior in terms of cavernous sinus invasion (Oldfield *et al.* 2015; Burman *et al.* 2023). However, few articles have explored the link between recurrent CD and the pathologic subtypes of TPIT-lineage PitNETs. In this patient, the recurrent hypercortisolism observed clinically was associated with the pathology subtype of TPIT-lineage DGCT-PitNETs.

For this patient, pituitary tumor infarction based on the pathology subtype of TPIT-lineage DGCT-PitNETs provides the most plausible explanation for the fluctuating pattern of biochemical hypercortisolism states. In a recent case reported by Liu *et al.* a corticotroph pituitary macroadenoma with apoplexy resulted in a remission of hypercortisolism and led to clinically observed recurrent CD (Liu *et al.* 2022). This aligns with the case presented by Pignatta, where an infarcted microadenoma near the pituitary stalk caused spontaneous remission of CD (Pignatta *et al.* 2004). In another instance reported by Alarifi *et al.* a patient experienced recurrent alternating periods of hypercortisolism and adrenal insufficiency due to pituitary macroadenoma infarcts (Alarifi *et al.* 2005). It is theorized that rapid tumor growth may outpace its blood supply or exert pressure on blood arteries, reducing blood supply and ultimately decreasing cortisol secretion.

In contrast to Cushing's syndrome caused by ectopic ACTH sources, cases induced by pituitary involvement often require transsphenoidal surgery (Fleseriu *et al.* 2021). Such interventions inevitably bring about changes in both clinical and biochemical profiles. Various factors have been identified as potential predictors for the recurrence of pituitary-induced CD, including a younger age at diagnosis, comorbidity with osteoporosis, preoperative serum ACTH levels exceeding 55 pg/mL, tumor diameter surpassing 9.5 mm, postoperative residual, absence of postoperative hypocorticoidism, higher Ki-67 index, and early recovery of the adrenal axis during the postoperative period (Zachariah *et al.* 2023). In this case, the pathology revealed TPIT-lineage DGCT-PitNETs with a Ki-67 labeling index of 3%, potentially contributing to the clinical manifestation of recurrent CD. Considering the absence of postoperative hypocorticoidism and the relatively large tumor size, caution should still be exercised regarding the possibility of tumor regrowth in the future. Further studies and analysis on the pathologic-clinic connection of recurrent CD are warranted.

CONCLUSION

This case demonstrates the relevance between recurrent CD and the pathological subtypes of TPIT-lineage DGCT-PitNETs. Therefore, heightened vigilance and ongoing monitoring are recommended for patients with this specific subtype of pituitary tumor.

ETHICS STATEMENT

Informed consent was obtained from the patient before sharing all the aforementioned information and images.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest associated with this manuscript.

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REFERENCES

1 Alarifi A, Alzahrani AS, Salam SA, Ahmed M, Kanaan I (2005). Repeated Remissions of Cushing's Disease Due to Recurrent Infarctions of an ACTH-Producing Pituitary Macroadenoma. Pituitary. **8**(2): 81–7.

2 Burman P, Casar-Borota O, Perez-Rivas LG, Dekkers OM (2023). Aggressive pituitary tumors and pituitary carcinomas: from pathology to treatment. J Clin Endocrinol Metab: dgad098.

3 Fleseriu M, Auchus R, Bancos I, Ben-Shlomo A, Bertherat J, Biermasz NR, (2021). Consensus on diagnosis and management of Cushing's disease: a guideline update. Lancet Diabetes Endocrinol. **9**(12): 847–75.

4 Liu T, Rossiter JP, Houlden RL, Awad S (2022). Sparsely Granulated Corticotroph Pituitary Macroadenoma Presenting With Pituitary Apoplexy Resulting in Remission of Hypercortisolism. AACE Clin Case Rep. **8**(4): 166–70.

5 Oldfield EH, Vance ML, Louis RG, Pledger CL, Jane JA, Lopes M-BS (2015). Crooke's Changes In Cushing's Syndrome Depends on Degree of Hypercortisolism and Individual Susceptibility. J Clin Endocrinol Metab. **100**(8): 3165–71.

6 Pignatta AB, Díaz AG, Gómez RM, Bruno OD (2004). Spontaneous remission of Cushing's disease after disappearance of a microadenoma attached to the pituitary stalk. Pituitary. **7**(1): 45–9.

7 Rak B, Maksymowicz M, Pękul M, Zieliński G (2021). Clinical, Biological, Radiological Pathological and Immediate Post-Operative Remission of Sparsely and Densely Granulated Corticotroph Pituitary Tumors: A Retrospective Study of a Cohort of 277 Patients With Cushing's Disease. Front Endocrinol. **12**: 672178.

8 Zachariah MA, Cua S, Muhlestein WE, Otto BA, Carrau RL, Kirschner LS, (2023). Intraoperative Predictor of Remission in Cushing Disease. Oper Neurosurg Hagerstown Md. **24**(4): 460–7.