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Empty Sella and Cushing's Disease: Lessons Learned from a Diagnostically Challenging Case

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Abstract

INTRODUCTION: Pituitary adenomas are the primary cause of Cushing's disease (CD), yet they can produce negative MRI findings when coexisting with empty sella syndrome, complicating diagnosis. This case illustrates how advanced imaging and endocrine testing overcome this diagnostic challenge.
CASE DESCRIPTION: A 54-year-old woman was admitted to our hospital due to facial plethora, hyperglycemia and forearm pustules. The endocrine function test suggested CD at first. However, the initial enhanced MRI revealed an empty sella. Based on the positive results of bilateral inferior petrosal sinus sampling, we performed high-resolution dynamic enhanced MRI of pituitary gland. Finally, we discovered pituitary nodules on the background of empty sella. The patient accepted surgical treatment and the postoperative outcomes were favorable.
CONCLUSION: Empty sella does not exclude the diagnosis of CD. Standardized endocrine function tests and advanced imaging technology play decisive roles in the qualitative and etiological diagnosis of CD, and we also emphasize the importance of clinical thinking.

Abbreviations:

1mg-DST	- Overnight 1mg dexamethasone suppression test
24h-UFC	- 24 hours urinary free cortisol
ACTH	- Adrenocorticotropic hormone
ALD	- Aldosterone
BIPSS	- Bilateral inferior petrosal sinus sampling
CD	- Cushing's disease
CS	- Cushing syndrome
CT	- Computed tomography
HDDST	- High-dose dexamethasone suppression test
LDDST	- Low-dose dexamethasone suppression test
MRI	- Magnetic resonance imaging
PTC	- Plasma total cortisol

CASE REPORT

INTRODUCTION

Cushing's disease (CD) is caused by a pituitary adenoma that secretes excessive adrenocorticotropic hormone (ACTH), leading to hypercortisolemia. Empty sella, first described by Busch in 1951, is identified in 5.5%-28% of the general population (Busch, 1951; Bergland *et al.* 1968; Foresti *et al.* 1991; Molitch 1995). Although often associated with hypopituitarism, empty sella may occasionally co-occur with functional pituitary adenomas leading to hormonal excess or suppression (Mehta *et al.* 2014; Auer *et al.* 2018). Empty sella alters the morphology of the pituitary gland, complicating the precise localization of pituitary adenomas. Himes *et al.* reported that MRI-negative findings were present in 18 (37%) of 49 cases with empty sella, compared with 22 (15%) of 148 cases without empty sella, concluding that empty sella is associated with an approximately 2.5-fold increased rate of MRI-negative CD (Himes *et al.* 2020).

The coexistence of a pituitary adenoma and an empty sella, while not rare, poses a significant diagnostic dilemma that can lead to misdiagnosis and treatment delays. Here, we report a case of CD with concurrent empty sella, exhibiting both hypercortisolism and hypopituitarism. We highlight the diagnostic challenges in etiological localization for CS under such complex anatomical conditions. Ethics approval was waived for this case report, and written informed consent was obtained from the patient for the publication of this case report and associated images.

CASE PRESENTATION

A 54-year-old woman was admitted to our hospital due to "facial plethora for 10 years, hyperglycemia for over 3 years, and forearm pustules for 3 months". A timeline depicting the historical progression of the patient's illness is presented in Figure 1. Her medical history included: (1) hypertension for over 9 years, treated with amlodipine benazepril, with blood pressure maintained at 140-150/80-90 mmHg; (2) T11 vertebral fracture for over 2 years following a fall, treated with percutaneous vertebroplasty; (3) hypothyroidism for 6 months, managed with levothyroxine 50 μg daily, with normalization of thyroid function. She denied any significant family history of CS, diabetes, or hypertension, as well as personal history of exogenous glucocorticoid use.

Upon admission, the patient's vital signs and anthropometric measurements included a blood pressure of 147/82 mmHg, height of 154 cm, weight of 47 kg, body mass index of 19.8 kg/m², waist circumference of 89 cm, hip circumference of 86 cm, and a waist-to-hip ratio of 1.03. Physical examination revealed full moon face, plethora, and fat pads behind the neck. Scattered deep purple pustules, ranging in diameter from 0.5-1 cm, were seen at the dorsum of right hand and forearm of the patient, some of which were fused into pustules. The lesions were dry and non-exudative. Her skin of the lower limbs was thin with visible capillaries.

Laboratory and imaging examinations

Based on the patient's clinical signs and symptoms, and after excluding conditions such as chronic alcoholism, psychiatric disorders, and exogenous glucocorticoid use, Cushing's syndrome was suspected. Laboratory investigations revealed elevated 8:00 AM plasma total cortisol (PTC) at 469 nmol/L (reference range: 133–537) and markedly increased midnight PTC of 579 nmol/L (reference: <50). The 24-hour urinary free cortisol (24h-UFC) was elevated at 322.3 μg (reference: 20.3–127.6). Following an overnight 1 mg dexamethasone suppression test (1mg-DST), morning PTC remained unsuppressed at 299 nmol/L. Both PTC and 24h-UFC

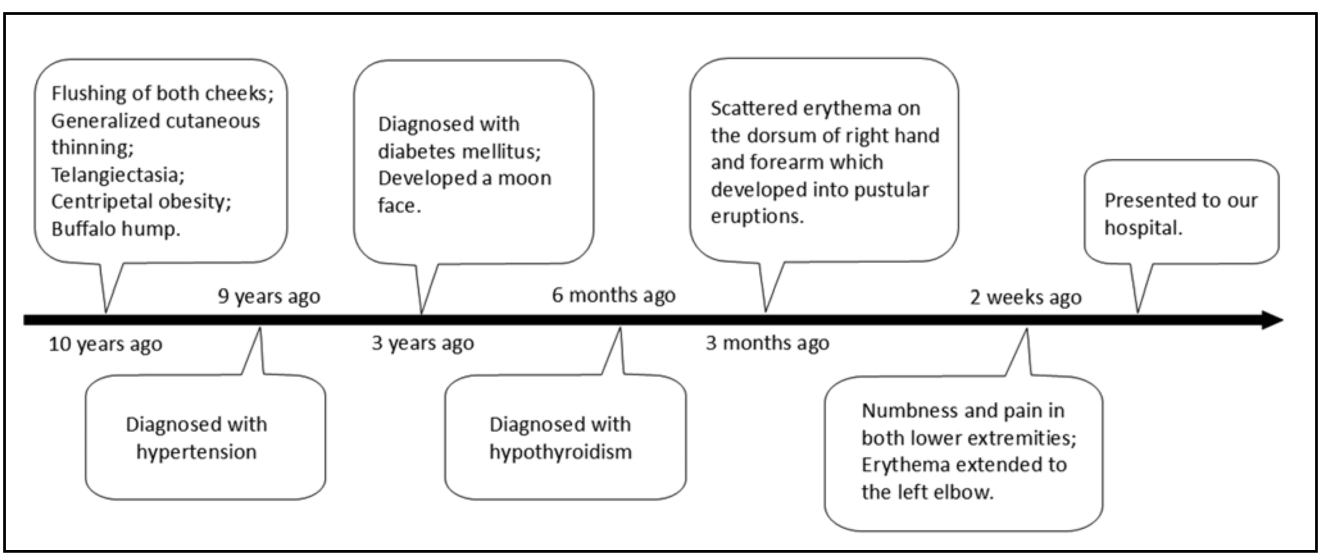

Fig. 1. Timeline of the patient's history of illness. It outlines the patient's clinical course, with a timeline of symptomatic progression and key diagnostic milestones for comorbidities.

Tab. 1. Laboratory Results

Laboratory Test	**Result**	**Reference Value**
PTC (8 AM)	469 nmol/L	133-537
PTC (midnight)	579 nmol/L	<50
PTC (after 1mg-DST)	299 nmol/L	
PTC (before LDDST)	564 nmol/L	
PTC (after LDDST)	269 nmol/L	
PTC (before HDDST)	601 nmol/L	
PTC (after HDDST)	16.3 nmol/L	
24h-UFC	322.30 ug	20.3-127.6
24h-UFC (before LDDST)	390.38 ug	
24h-UFC (after LDDST)	347.67 ug	
24h-UFC (before HDDST)	284.60 ug	
24h-UFC (after HDDST)	21.00 ug	
ACTH	90.38 ng/L	5-78
K^+	3.35 mmol/L	3.5-5.5
HbA1c	7.0%	4.5-6.1
Thyroid function		
TSH	0.103 mU/L	0.27-4.2
FT3	1.88 pmol/L	3.6-7.5
FT4	11.7 pmol/L	12.0-22.0
rT3	1.12 nmol/L	0.78-1.38
Gonadal function		
LH	1.5 IU/L	postmenopause: 7.7-58.8
FSH	5.1 IU/L	postmenopause: 25.8-134.8
E	35.4 pg/ml	postmenopause: <138
PRL	11.2 ng/ml	6.0-29.9
GH	0.78 ng/ml	0.126-9.88
PTH	6.68 pmol/L	1.6-6.9
25-OHD	38.9 nmol/L	47.7-144
β-CTX	0.216 ng/ml	0.556-1.008
PRA (recumbent)	2.95 ng/ml.h	0.05-0.79
ALD (recumbent)	14.86 ng/dl	4.5-17.5
ARR (recumbent)	5.04	
PRA (upright)	>12 ng/ml.h	0.93-6.56
ALD (upright)	12.86 ng/dl	4.5-17.5
BNP	6909 ng/L	<334

ACTH, adrenocorticotropic hormone; ALD, aldosterone; ARR, aldosterone to renin ratio; BNP, brain natriuretic peptide; E, estrogen; FSH, follicle stimulating hormone; FT3, free triiodothyronine; FT4, free thyroxin; GH, growth hormone;HbA1c, hemoglobin A1c; HDDST, high-dose dexamethasone suppression test; K+, serum potassium; LDDST, low-dose dexamethasone suppression test; LH, luteinizing hormone; PRA, renin activity; PRL, prolactin; PTC, plasma total cortisol; PTH, parathyroid hormone; rT3, reverse triiodothyronine; TSH, thyroid stimulating hormone; 1mg-DST, overnight 1mg dexamethasone suppression test; 24h-UFC, 24 hours urinary free cortisol; 25-OHD, 25-hydroxyvitamin D; β-CTX, β-carboxy-terminal cross-linked telopeptide of type 1 collagen

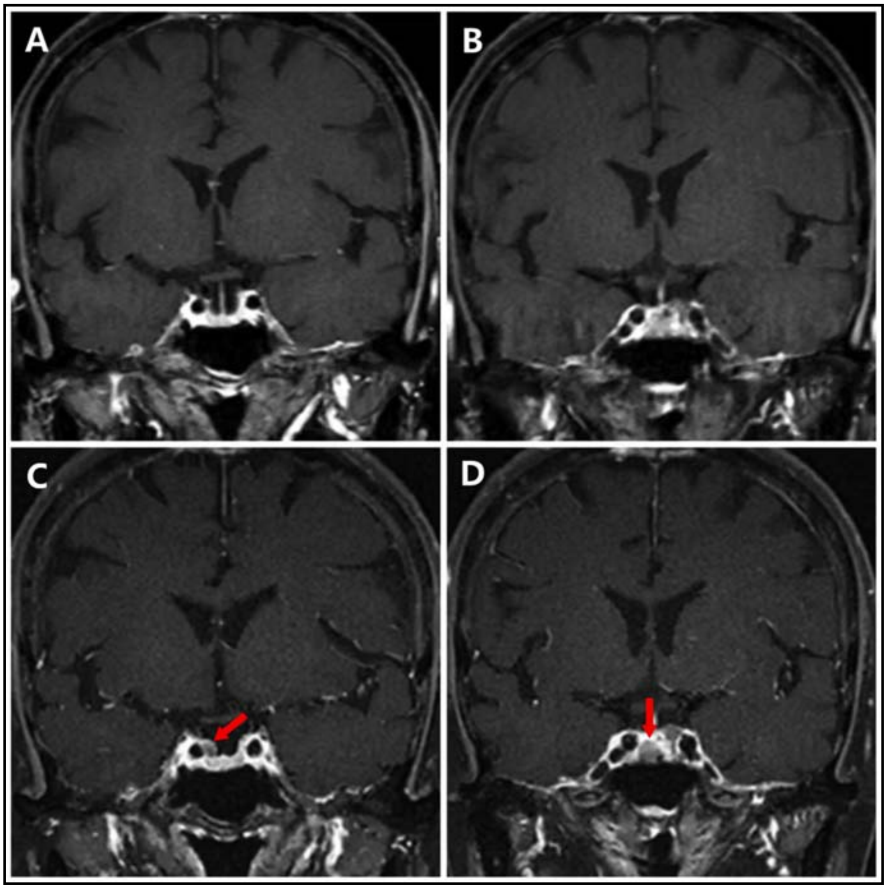

Fig. 2. Coronal enhanced MRI.
(A-B) Initial 1.5T scan: enlarged sella with thinned pituitary; no adenoma visible (empty sella).
(C-D) High-resolution 1.5T dynamic scan: two 0.5 cm low-enhancement nodules (red arrows) in right and posterior pituitary at 6 min post-contrast.

failed to suppress with the low-dose dexamethasone suppression test (LDDST). Based on an elevated ACTH level of 90.38 ng/L (reference: 5–78), ACTH-dependent Cushing syndrome was suspected. Hormonal evaluation also indicated hypofunction of the pituitary-thyroid and pituitary-gonadal axes; additional profiles are summarized in Table 1.

The high-dose dexamethasone suppression test (HDDST) was performed to differentiate between pituitary and ectopic sources of ACTH-dependent Cushing syndrome. Results showed greater than 50% suppression in both 24h-UFC and morning PTC, suggesting a pituitary origin of the lesion. Enhanced MRI was performed on a 1.5T scanner (uMR 588, United Imaging) following intravenous bolus administration of gadolinium-based contrast at 0.1 mmol/kg. Contrast was injected via an antecubital vein at 2–3 mL/s. Dynamic coronal T1-weighted fast spin-echo imaging commenced simultaneously with contrast injection, lasting 80 seconds with a temporal resolution of 3.2 seconds per phase. Key acquisition parameters were: repetition time = 452.00 ms, echo time = 11.08 ms, matrix = 224 × 134, slice thickness = 2.0 mm. The study revealed no clear evidence of abnormal enhancement but showed an empty sella (Figure 2A–B). Bilateral inferior petrosal sinus sampling (BIPSS) was subsequently performed. With arginine vasopressin stimulation, the procedure demonstrated central-to-peripheral ACTH ratios of ≥2.0 at baseline and ≥3.0 post-stimulation, confirming a central (pituitary) source and excluding ectopic ACTH secretion. Detailed BIPSS results are summarized in Table 2.

Initial endocrine testing confirmed ACTH-dependent Cushing syndrome; however, standard MRI showed only empty sella without adenoma. BIPSS confirmed central ACTH excess, prompting dynamic high-resolution MRI for adenoma localization. The follow-up MRI was conducted on the same scanner using an identical contrast injection protocol as in the initial examination. Dynamic coronal T1-weighted fast spin-echo sequencing was initiated simultaneously with contrast administration, with an extended acquisition time of 382 seconds and a temporal resolution of 10.9 seconds per phase. Key imaging parameters were as follows: repetition time = 405.00 ms, echo time = 12.38 ms, matrix = 256 × 192, slice thickness = 2.0 mm. The results revealed two 0.5 cm low-enhancement nodules within the right and posterior pituitary gland against the background of an empty sella (Figure 2 C-D).

<u>*Diagnosis*</u>

The final diagnosis was as follows: 1. ACTH-dependent Cushing's syndrome: Cushing's disease, 2. Right anterolateral and posterior pituitary nodules (each approximately 0.5 cm in diameter), 3. Hypofunction

Tab. 2. The results of BIPSS

	Peripherally		Left petrosal sinus		Right petrosal sinus	
	PRL	ACTH	PRL	ACTH	PRL	ACTH
-15min	14.6 ng/ml	73.04 ng/L				
0min	15.1 ng/ml	67.36 ng/L	28.1 ng/ml	272.93 ng/L	27.1 ng/ml	296.17 ng/L
3min	14.8 ng/ml	74.3 ng/L	30.0 ng/ml	470.9 ng/L	32.2 ng/ml	420.3 ng/L
5min	14.9 ng/ml	97.8 ng/L	29.3 ng/ml	531.6 ng/L	28.0 ng/ml	672.4 ng/L
15min	14.1 ng/ml	111.4 ng/L	32.5 ng/ml	505.2 ng/L	33.4 ng/ml	538.8 ng/L

ACTH, adrenocorticotropic hormone; BIPSS, bilateral inferior petrosal sinus sampling; PRL, prolactin
Test procedures and interpretation: BIPSS was performed following standard guidelines. Catheters were placed bilaterally via the femoral veins into the inferior petrosal sinuses. Baseline blood samples were drawn from the femoral vein and both sinuses. After intravenous injection of 10 μg arginine vasopressin, sampling was repeated at 3, 5, and 10 minutes at the same sites for ACTH and PRL measurement. All samples were centrifuged under refrigeration within 30 minutes, with plasma separated for prompt assay.
A central-to-peripheral ACTH ratio ≥ 2 at baseline and/or ≥ 3 after stimulation indicated CD. Alternatively, a corrected IPS/P ratio > 0.8 was diagnostic, calculated as the maximum value of (ACTH IPS/P ÷ PRL IPS/P) across all time points.

of pituitary-thyroid axis and pituitary-gonadal axis, 4. Partial empty sella, 5. Pulmonary cryptococcal infection, 6. Mycobacterium infection of bilateral upper limb skin, 7. Diabetes, 8. Severe osteoporosis with pathological fractures (T7, T9, T11, bilateral multiple ribs).

Treatment

The patient was treated with amlodipine benazepril and metoprolol for hypertension, along with metformin, insulin aspart, and insulin glargine for diabetes mellitus, resulting in well-controlled blood pressure and blood glucose. Fluconazole was administered for cryptococcal infection. Osteoporosis was managed with zoledronic acid, alfacalcidol, and calcium supplementation, and levothyroxine was provided for secondary hypothyroidism. The patient successfully underwent transnasal neuroendoscopic resection of pituitary nodules with the help of multidisciplinary consultation. The results of pathology and immunohistochemistry suggest hyperplasia of adenohypophysis with the immunophenotype of positive ACTH. The dyeing of the netted fibers shows a continuous distribution. Postoperatively, transient diabetes insipidus occurred but resolved within six days.

Outcome and follow-up

At a six-month follow-up, her mental state, diet, and activity tolerance were improved significantly. Laboratory results confirmed a low morning PTC and ACTH, while potassium levels were normal. Her thyroid hormone levels also returned to normal (Table 3). Blood pressure and blood glucose were well controlled. Her anti-osteoporosis treatment continues, and we continue to monitor her bone mineral density and bone turnover markers.

DISCUSSION

This report highlights the challenge of confirming CD in the context of an empty sella. Although biochemical profiles were consistent with CD, the initial MRI revealed an empty sella. The diagnosis was ultimately guided by BIPSS, which confirmed a pituitary source and warranted a repeat MRI. This subsequent scan successfully detected pituitary nodules, with postoperative pathology confirming ACTH cell hyperplasia.

For the etiological diagnosis of patients with suspected CD, a pituitary/sella enhanced MRI is recommended as the first diagnostic approach (Fleseriu

Tab. 3. Laboratory results at six-month post-operative follow-up demonstrating biochemical remission and recovery of secondary hypothyroidism

Laboratory Test	Result	Reference Value
PTC (8 AM)	53.3 nmol/L	133-537
ACTH	5.01 ng/L	5-78
TSH	2.08 mU/L	0.27-4.2
FT4	16.10 pmol/L)	12.0-22.0
PRL	8.4 ng/ml	6.0-29.9
Na^+	140.8 mmol/L	137-147
K^+	4.21 mmol/L	3.5-5.5

ACTH, adrenocorticotropic hormone; FT4, free thyroxin; K+, serum potassium; Na+, serum sodium; PRL, prolactin; PTC, plasma total cortisol; TSH, thyroid stimulating hormone *et al.* 2021), however over 20% of the imaging results are negative, resulting in the concept of MRI-negative CD. Himes *et al.* reported 197 cases of CD; 40 (20%) presented as MRI-negative (Himes *et al.* 2020). The primary reasons for these negative findings include: ACTH cell proliferation or an adenoma that does not reach the size needed to be properly resolved by MRI, abnormal peak time of the pituitary blood supply, developmental pituitary morphological abnormalities mainly manifested as small volume (such as empty sella) and inappropriate use of gray-scale debugging.

Standard 1.5T MRI can only detect approximately 50% of ACTH-secreting microadenomas. Using weighted turbo spin echo sequences and ultra-high field, such as 3.0T and 7.0T, MRI may help to improve the positive detection rate of microadenomas (Patel *et al.* 2020). Comparative analysis of the two MRI examinations in this case revealed that the prolonged dynamic MRI acquisition proved to be decisive. Our findings indicate that a prolonged scanning time is critical for visualizing microadenomas with atypical enhancement kinetics, which would otherwise remain occult on a standard, shorter dynamic protocol. In recent years, positron emission tomography has been proposed as an alternative method for localizing pituitary tumors, particularly with the development of novel radiotracers, such as ^{68}Ga-DOTATATE and ^{68}Ga-Pentixafor. However, its clinical utility requires further validation.

For the localization diagnosis of pituitary tumors, early studies suggested that BIPSS could be used to differentiate tumor laterality. Specifically, a ratio of ACTH concentration in the dominant inferior petrosal sinus to that in the contralateral side >1.4 was considered helpful for lateral localization of adenomas. However, large-scale studies have confirmed that this method has limited accuracy (Oldfield *et al.* 1985; Wind *et al.* 2013; Bonelli *et al.* 2000; Chinese Medical Association Rare Diseases Branch, Hypothalamic and Pituitary Disease Group of China Alliance of Rare Diseases (CARD) & Innovation Center of Pituitary Diseases, Peking Union Medical College Hospital, 2023). The failure of lateralization for pituitary tumors in our BIPSS results may be attributed to the following reasons: different individuals may exhibit anatomical variations and distinct patterns of peripituitary venous drainage; inaccurate catheterization positioning may cause blood mixing, thereby underestimating the differences between the two sides; and excessively small tumor volume may fail to significantly alter the bilateral ACTH gradient. BIPSS may serve as an auxiliary tool for patients with negative MRI findings.

Tab. 4. Clinical profiles and treatment outcomes in CD with empty sella

Investigator	Sex	Age	Clinical Presentation	Diagnostic Method	Treatment	Outcome/ Complications
Yamamoto N, *et al.* (Yamamoto *et al.* 1985)	F	44	NA	BIPSS	Transsphenoidal surgery	NA
Spagnolli W, *et al.* (Spagnolli *et al.* 1996)	F	48	Uncontrolled insulin-dependent diabetes mellitus, severe hypertension, hypercortisolism	MRI	Ketoconazole (600 mg daily)	Normal cortisol and Improved symptoms/ No side effects.
Habib T, *et al.* (Habib *et al.* 2023)	M	47	Muscle weakness, gait instability, weight loss, easy bruising, acanthosis nigricans, hyperpigmentation	Pituitary MRI brain protocol for adenoma	Transsphenoidal adenomectomy	NA/ CSF leakage
Manavela MP, *et al.* (Manavela *et al.* 2001)	Ten female, one male	36-73	NA	MRI	Transsphenoidal surgery (6 patients); Radiotherapy for (1 patient); Ketoconazole (400-600 mg daily) (6 patients)	5 surgical patients relieved, unknown for others/ Postoperative CSF leakage, DI, hypopituitarism.
Herrmann BL, *et al.* (Herrmann *et al.* 2001)	F	70	Truncal obesity, moon face, myopathy, bilateral ankle edema, hirsutism	BIPSS	Etomidate; Transsphenoidal surgery	NA/ Postoperative hypopituitarism

CD, Cushing's disease; CSF, cerebrospinal fluid; F, female; BIPSS, bilateral inferior petrosal sinus sampling; M, male; MRI, magnetic resonance imaging; NA, not available; DI, diabetes insipidus.

Previous studies have documented some cases of CD associated with empty sella, exhibiting no distinct patterns in age or gender at clinical presentation (Table 4). Symptoms among these patients are diverse, including weight loss, fatigue, easy bruising, acanthosis nigricans, and more (Yamamoto *et al.* 1985; Spagnolli *et al.* 1996; Manavela *et al.* 2001; Herrmann *et al.* 2001; Habib *et al.* 2023). Pituitary surgery is the primary treatment. Approximately 80% of patients with CD and empty sella achieve immediate postoperative biochemical remission; however, they face a higher risk of recurrence in the long term compared to those without empty sella. The presence of complete empty sella significantly increases the chances of surgical failure or recurrence (Mehta *et al.* 2014). Postoperative complications are more common in these patients, such as cerebrospinal fluid (CSF) leakage, diabetes insipidus (DI), and Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH). Despite these risks, surgery is still considered a reasonable and beneficial treatment option (Jagannathan *et al.* 2007; Yang *et al.* 2022). Alternative treatments include repeat surgery, radiotherapy, bilateral adrenalectomy, and medications such as ketoconazole. For patients without MRI-detectable tumors, with persistent hypercortisolism post-surgery, or refusing surgery, these could be viable treatment alternatives. Cushing's syndrome may have multiple comorbidities at the same time. It is necessary to combine multidisciplinary consultation for the diagnosis and treatment to determine the best individual therapeutic strategy. Cushing's syndrome requires lifelong follow-up, which plays a vital role in the prognosis.

CONCLUSION

CD complicated by empty sella requires a systematic diagnostic approach: (1) standardized endocrine tests to confirm ACTH dependence; (2) BIPSS to exclude ectopic ACTH source; (3) high-resolution dynamic MRI for adenoma localization. Lifelong follow-up is essential to detect recurrence.

ETHICAL APPROVAL AND CONSENT TO PARTICIPATE

This single-case report was performed in compliance with institutional guidelines; formal IRB approval was waived for de-identified case reports.

CONSENT FOR PUBLICATION

Written informed consent was obtained from the patient for publication of this de-identified case and accompanying clinical images.

AVAILABILITY OF DATA

The data used in this study are available from the corresponding author upon reasonable request. The data are not publicly available due to ethical restrictions.

DISCLOSURE

All authors have no financial interests in this manuscript and no affiliations (relationships) to disclose.

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AUTHOR CONTRIBUTIONS

Conceptualization and methodology, all authors; Writing-original draft preparation, Tang JH, Li Y and Wu NW; Writing-review and editing, all authors; Visualization, Tang JH; Supervision, Ran XW and Tong NW; Resources, Zhou PZ; Funding acquisition, Lü QG. All authors have read and agreed to the published version of the manuscript.

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