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Challenges in the Management of Cushing's Syndrome Associated with Double ACTH-Secreting Pituitary Adenomas: A Case Report

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Abstract

Cushing's disease (CD) is a rare endocrine disorder primarily caused by a corticotroph pituitary microadenoma. The occurrence of double pituitary adenomas (DPA), particularly with two ACTH-secreting microadenomas, is exceptionally uncommon. Untreated or poorly managed CD can lead to severe complications, such as bilateral avascular necrosis of the femoral heads.

Case Report

A 33-year-old male diagnosed with CD presented with overt Cushing's syndrome, bilateral avascular necrosis of the femoral heads, and grade 1 hypertension. Hormonal evaluations confirmed ACTH-dependent hypercortisolism, supported by a positive high-dose dexamethasone suppression test. Preoperative MRI identified a 5 mm right-lateralized pituitary microadenoma. Following transsphenoidal surgery (TSS), the adenoma was confirmed as ACTH-secreting; however, hypercortisolism persisted. Eleven months later, MRI revealed a previously undetected 5 mm left-sided sellar microadenoma, which was also confirmed as ACTH-secreting after a repeat TSS. Despite the second surgery, hormonal assessments indicated ongoing CD, with no detectable recurrence on MRI. Evaluation for multiple endocrine neoplasia was negative. Due to persistent hypercortisolism and a suspicious adrenal mass on CT, the patient underwent bilateral adrenalectomy, resulting in remission and an improvement in quality of life, although subsequent adrenal insufficiency occurred.

Conclusion

Managing CD with DPA poses significant challenges, including low detection rates on imaging, diagnostic complexities, and difficulties achieving complete adenoma resection. In complex cases, bilateral adrenalectomy may be necessary as a last resort to control hypercortisolism, particularly in younger patients with DPA.

Abbreviation:

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CD: Cushing's disease, **DPA**: double pituitary adenomas, **TSS**: transsphenoidal surgery, **BAN**: bilateral avascular necrosis

Keywords

ACTH, bilateral avascular necrosis, Cushing's disease, Double adenomas, Pituitary.

Introduction:

Cushing's disease (CD) is an uncommon endocrine disorder characterized by an overproduction of adrenocorticotropic hormone (ACTH), which can result in considerable morbidity and, if untreated, a high mortality rate. In approximately 90% of cases, is caused by a corticotroph pituitary microadenoma, typically a small tumor less than 6 mm in diameter located in the pituitary gland (1,2).

While single pituitary adenomas are common in CD, the occurrence of double pituitary adenomas (DPA) is relatively uncommon. DPA is defined by the simultaneous presence of two distinct adenomas within the pituitary gland, each with unique morphological and immunohistochemical characteristics. This condition is distinct from plurihormonal adenomas, where a single tumor secretes two or more pituitary hormones and consists of a histologically uniform cell population (3).

Epidemiological studies indicate that multiple and double pituitary adenomas are present in approximately 0.9% of random autopsy samples of the pituitary gland, while surgical case series report a slightly higher prevalence, ranging from 0.2% to 2.6% of all resected pituitary adenomas (4). Nonetheless, there is a scarcity of information concerning the oncogenesis of multiple adenomas in the pituitary gland (4).

The occurrence of multiple pituitary adenomas, particularly with two ACTH-secreting microadenomas, is exceedingly rare. The first reported case of double ACTH-secreting adenomas was described by Massimiliano Andrioli et al. in 2010 (5).To date, only a few such cases have been documented in the literature. A recent systematic review identified 3 cases of double ACTH-secreting adenomas among 59 cases of functional DPA, highlighting the rarity of this condition (6).

According to current guidelines, the first-line treatment for CD is the surgical resection of the pituitary tumor, typically performed via transsphenoidal surgery (TSS). The primary goal of this treatment is the complete excision of the adenoma while preserving normal pituitary function. However, missing a second lesion during surgery can lead to incomplete biochemical remission, posing a significant challenge in the management of DPA (7,8).

In this study, we report a unique case of DPA, revealed by osteonecrosis of bilateral femoral heads with a focus on the diagnostic challenges and treatment outcomes associated with this rare condition.

Case report:

A 33-year-old man presented with a limp and progressive bilateral hip pain. He was admitted to the rheumatology department for evaluation and management of aseptic necrosis of both femoral heads. On physical examination, the patient exhibited typical signs of Cushing's

syndrome, including central obesity, moon face, buffalo hump, abdominal and thigh striae, easy bruising on the limbs, and hypertension.

Biochemical analysis showed markedly elevated 24-hour urinary free cortisol levels, along with non-suppressed cortisol levels following a low-dose dexamethasone suppression test (Table 1). Elevated ACTH concentrations and a positive response to the high-dose dexamethasone suppression test confirmed the presence of ACTH-dependent hypercortisolism.

Preoperative pituitary MRI identified a 5 mm right-lateralized pituitary microadenoma (figure1). The patient subsequently underwent TSS(TSS) for resection of the identified lesion. Immunohistochemical staining confirmed ACTH-positive cells in the excised pituitary adenoma.

Despite surgery, hypercortisolism persisted 11 months postoperatively, with an ACTH level of 65 pg/mL. Follow-up pituitary MRI revealed the emergence of a new 5 mm left-sided sellar microadenoma (figure 2) that had not been detected on initial imaging. A repeat TSS confirmed the presence of a second ACTH-secreting adenoma.

Three months postoperative, hormonal evaluation showed persistent CD (Table 1), despite no detectable recurrence on follow-up pituitary MRI.

Evaluation for multiple endocrine neoplasia was negative. Given the ongoing uncontrolled hypercortisolism, a CT scan of the adrenal glands was performed to evaluate for a potential cortisol-secreting tumor. The imaging revealed a suspicious 2 cm adrenal mass, leading to a decision for bilateral adrenalectomy, which resulted in remission with subsequent adrenal insufficiency.

Postoperative hormone levels showed a morning cortisol level of 7 ng/mL and an ACTH level of 565 pg/mL. The patient was started on replacement therapy with 20 mg/day of hydrocortisone and 50 µg/day of fludrocortisone to manage adrenal insufficiency.

The patient also underwent bilateral total hip replacement due to extensive avascular necrosis of the femoral heads. Postoperatively, his blood pressure stabilized, which permitted the discontinuation of antihypertensive medications. The patient reported satisfaction with the overall management and clinical outcomes, and he reported an improvement in his quality of life, and he was able to integrate back into his professional life.

Discussion:

The patient was presented with Cushing's syndrome and an exceptionally rare complication: bilateral avascular necrosis (AVN) of the femoral heads. While AVN is a well-documented complication of exogenous steroid therapy, its occurrence due to endogenous hypercortisolism is notably rare, with fewer than 20 cases reported to date where AVN was directly attributed to endogenous cortisol excess (9).

In this case, the patient's hypercortisolism was confirmed to be of pituitary origin, characterized by elevated ACTH levels, the identification of a pituitary adenoma on MRI, and suppressed cortisol levels following a high-dose dexamethasone suppression test. Despite the successful resection of the adenoma, as confirmed by histopathological analysis, the

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patient continued to exhibit persistent hypercortisolism. This persistence was ultimately traced to a previously undetected second pituitary adenoma, which was not visualized on preoperative MRI and was not identified or resected during the initial TSS.

MRI is the primary imaging technique for detecting pituitary tumors; however, it is not uncommon for ACTH-secreting pituitary microadenomas to be overlooked, with non-detection rates ranging from 30% to 50% in some cases (10).

For instance, Ratliff et al. reported that, in five out of twelve cases involving multiple adenomas, MRI images were interpreted as normal (11).

Similarly, a recent systematic review of 63 patients with 129 synchronous pituitary adenomas, including 60 double and three triple adenomas, found that more than 50% of patients with CD had no evidence of an adenoma on MRI (3).Typically, imaging may reveal either a single tumor or nonspecific abnormalities such as an asymmetric or inhomogeneous pituitary gland, or global gland enlargement (5).

In our case, preoperative MRI only detected one adenoma, whereas histopathological analysis later showed the presence of two distinct adenomas found in different sites within the pituitary gland. This aligns with findings from Massimiliano Andrioli, who reported an asymmetric pituitary gland featuring an inhomogeneous area on the right side and a contrast-enhanced microadenoma on the left side, with pathology confirming two distinct adenomas (5).

Detecting DPA through preoperative imaging remains challenging, because at least one of the tumors is small in size, with some lesions measuring under 3 mm (12).

To improve detection rates, high-resolution MRI techniques are crucial. Thin-slice and dynamic MRI provide enhanced resolution and can aid in the detection of multiple lesions. Furthermore, 3.0-T MRI offers superior detection capabilities compared to 1.5-T MRI, particularly for microadenomas (13).

The utilization of spoiled gradient recalled acquisition sequences has shown improved detection rates for ACTH-producing adenomas. Recently, advanced imaging techniques such as MET-PET combined with 3.0-T MRI have demonstrated higher sensitivity in detecting ACTH-secreting microadenomas compared to traditional and dynamic MRI methods (14).

The management of CD (CD) complicated by DPA presents unique challenges, particularly in achieving complete biochemical remission. Several cases of persistent hypercortisolism have been reported post-surgery due to failure in identifying and resecting all causative tumors (15).

Inconsistencies between the dominant side suggested by bilateral inferior petrosal sinus sampling and MRI findings, as well as ambiguous or undetermined pituitary abnormalities on imaging, should be recognized as potential high-risk indicators for DPA. For patients exhibiting these risk factors, meticulous intraoperative exploration is crucial to avoid overlooking additional lesions (16).

Thorough surface exploration of the pituitary gland can significantly reduce the chances of missing small secondary tumors. The use of intraoperative imaging techniques, including

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intraoperative ultrasound, has proven effective in detecting MRI-negative pituitary adenomas, enhancing tumor identification and ensuring complete resection (17).

For patients with refractory CD, bilateral adrenalectomy (BAE) serves as an effective and potentially life-saving therapeutic option for controlling hypercortisolism, particularly when complete surgical resection of all adenomas is not feasible or when the disease persists after multiple surgeries, as seen in our case (18).

In a German study, the frequency of BAE was reported at 18% among 124 patients with CD, while an Italian multicenter study found a frequency of 10% among 288 cases (8,19). Although BAEprovides immediate control of hypercortisolism, it requires careful postoperative management and lifelong follow-up due to the risk of severe complications, including Nelson's syndrome. This risk is particularly significant in patients with residual pituitary tumors or elevated ACTH levels after surgery, highlighting the importance of vigilant long-term monitoring (19, 20).

Conclusion:

The rarity of DPA combined with limitations in current imaging modalities often leads to missed diagnoses and persistent hypercortisolism despite initial surgical interventions.

Bilateral adrenalectomy, while an effective and potentially life-saving treatment for refractory CD, should be considered as a last resort when complete surgical resection of adenomas is unfeasible or when the disease persists despite multiple surgeries.

It is crucial to ensure careful postoperative management and long-term follow-up to address potential severe complications, such as Nelson's syndrome, and to optimize patient outcomes.

Declaration of patient consent

The authors certify that they have obtained all necessary patient consent forms. In these forms, the patient(s) have granted permission for their images and other clinical information to be published in the journal. The patients are aware that their names and initials will not be published, and due efforts will be made to protect their identity; however, complete anonymity cannot be assured.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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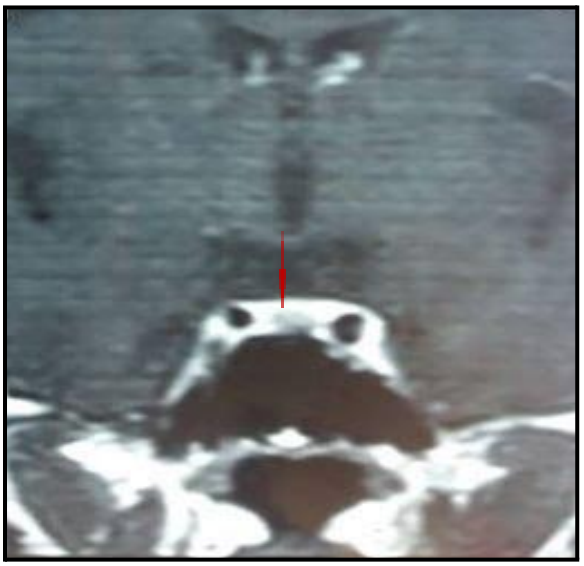
Annex :

Figure 1: Pre-operative pituitary MRI of patient



Dynamic coronal section: the anterior pituitary gland is normal in size. It is the site of a 5 mm round lesion lateralized to the right, which remains in hyposignal after dynamic injection of Gadolinium (↓)

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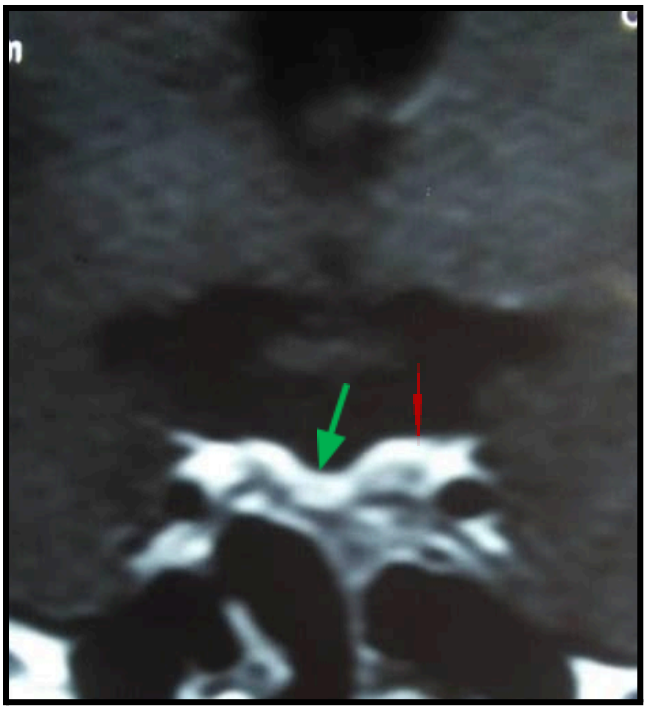

Figure 2: Post-operative pituitary MRI of patient

Coronal section in dynamic sequence: *rounded lesion of 5 mm in the left latero-sellar region which remains in hyposignal after dynamic injection of Gadolinium ( ).

*post-operative collapse of the right lobe of the anterior pituitary gland ( ).

Table 1 : Changes in hormone levels

TSS:

Hypercortisolism Evaluation	**Preoperative**	**Post-TSS 1**	**Post-TSS 2**	**Normal range**
ACTH **((pg/ml)**	67	65	64,4	10-60
24-h urine cortisol ug/24h	650	170	200	25-120
8-h Cortisol ng/ml	290	210	210	50-230
8-h Cortisol after **(**ng/ml) Low –dose dexamethasone suppression test	225	90	145	<18
8-h Cortisol after High dose dexamethasone suppression test	80	50	35	decrease by at least 50% indicati of Cushing's disease

transsphenoidal surgery