CASE REPORT

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Diagnostic and therapeutic challenges in ectopic Cushing's syndrome without detectable tumour focus – a case report

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Abstract

Ectopic adrenocorticotropin (ACTH) secretion is a rare cause of Cushing's syndrome, often posing a diagnostic challenge, particularly when the source of excessive ACTH secretion cannot be localized. The case is presented of a 70-year-old woman with Cushing's syndrome caused by ectopic ACTH secretion from an elusive location. Despite extensive imaging (CT, MRI, PET/CT with 68Ga-DOTATATE), no tumour site could be identified. Metyrapone led to normalization of cortisol and ACTH levels and a two-year remission. After a recurrence of hypercortisolaemia, osilodrostat therapy was initiated, achieving renewed hormonal and clinical stabilization. This case highlights the importance of pharmacotherapy with steroidogenesis inhibitors as an effective alternative to surgery in patients with an unlocalized source of ectopic ACTH secretion, and the need for long-term endocrine follow-up.

Key words

metyrapone, Cushing's syndrome, Pituitary adenocorticotropic hormone, ectopic secretion, osilodrostat

INTRODUCTION

Pituitary adenocorticotropic hormone (ACTH) and corticotropin-releasing hormone (CRH), secreted by the hypothalamus, play a key role in regulating cortisol production in the adrenal cortex in the hypothalamic-pituitary-adrenal axis. Excessive ACTH production leads to increased stimulation of the adrenal cortex, resulting in increased cortisol levels in the blood. This condition can lead to the development of Cushing's syndrome, a set of clinical symptoms caused by hypercortisolaemia [1]. The most common cause of elevated cortisol levels in the blood is its exogenous supply, especially in the form of a drug, although a much rarer cause is excessive endogenous production of this hormone [2]. In turn, excessive secretion of ACTH or CRH may result from the presence of a neuroendocrine tumour that contributes to the ectopic secretion of these hormones [3].

Studies have shown that the annual incidence of Cushing's syndrome worldwide ranges from 1.8 – 3.2 cases per million people in the population [4]. Women are three times more likely to become ill than men [1]. It is estimated that approximately 10–20% of cases of Cushing's syndrome are due to ectopic ACTH secretion, while approximately 70% are due to Cushing's disease. In 20% of patients with ectopic ACTH secretion, the primary source of the hormone hypersecretion cannot be located. Finding the site of ectopic ACTH is crucial, as removal of the abnormal masses leads to disease remission in 80% of patients [5]. In patients with ectopic ACTH secretion, the most favourable prognosis is achieved when the primary source of secretion is unequivocally identified and subjected to radical surgical resection. However, there is a need for systematic, targeted pharmacotherapy to control the symptoms of patients with an undetected source of secretion to protect them from double adrenalectomy [2].

Symptomatology of Cushing's syndrome. Symptoms of Cushing's syndrome include central obesity, dyslipidemia, type 2 diabetes, hypertension, menstrual irregularities, osteoporosis, and hirsutism. Cognitive abnormalities and psychiatric disorders have also been observed [6]. Arterial hypertension occurs in 75% of patients at the time of diagnosis of Cushing's syndrome, and in cases of ectopic hormone secretion, hypertension is observed in 88% of patients [7]. Among electrolyte disturbances, hypokalaemia is more common in patients with ectopic ACTH secretion than in those with idiopathic Cushing's syndrome. Chronically high cortisol levels can lead to secondary cardiac damage caused by structural and functional changes in the myocardium [8]. Physiologically, 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) inactivates cortisol to cortisone. When cortisol levels are high, this enzyme does not inactivate sufficient cortisol to bind to mineralocorticoid receptors, causing them to become activated. Excessive sodium and water retention and potassium excretion occur, causing hypernatraemia, hypokalaemia, and hypertension [7]. The most common symptoms of Cushing's syndrome are presented in Figure 1.

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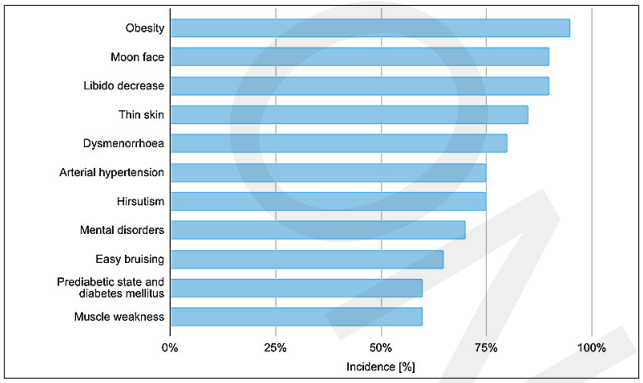

Figure 1. Prevalence of symptoms in Cushing's syndrome [9]

Diagnosis of Cushing's syndrome. Laboratory diagnosis of Cushing's syndrome involves the multi-stage use of a number of complementary tests, and it is worth emphasizing that no single test has sufficient sensitivity or specificity. The basic treatment algorithm includes, among others: confirming hypercortisolism, differentiating ACTH-dependent from ACTH-independent forms, and determining the final etiology [1]. In clinical practice, the most useful screening tests include:

- dexamethasone 1 mg inhibition test with a sensitivity exceeding 95%;
- determination of free cortisol in 24-hour urine collection;
- determination of evening salivary cortisol concentration, which is characterized by high sensitivity (95–98%) and is not influenced by changes in binding protein concentrations [10].

The key factors in differentiating ACTH-dependent forms of Cushing's syndrome are:

- high-dose dexamethasone suppression test (8 mg/day/2 days, DEX8) / low-dose suppression test (2 mg/day/2 days, DEX2) – Liddle's test, where the lack of a significant (>50%) decrease in cortisol suggests ectopic ACTH secretion syndrome (EAS);
- CRH stimulation test, used to differentiate the source of excessive ACTH secretion;
- blood sampling from the inferior petrosal sinuses (BIPS) to assess ACTH concentration is considered the most sensitive differential test, but is highly invasive.

It should be emphasized that the interpretation of the results must take into account the possibility of the occurrence of cyclic Cushing's syndrome and pseudo-hypercortisolism states [9].

In order to identify the location of ectopic ACTH secretion, computed tomography of the chest, abdomen and pelvis, followed by magnetic resonance imaging, can be used in the diagnosis, as the most common locations of ectopia are the bronchi, lungs, thymus, adrenal glands and pancreas [11].

Alternative methods for detecting the source of ectopic ACTH secretion include Ga-68 DOTATATE PET/CT or PET/MRI, which, due to its high affinity for the somatostatin receptor (SSTR) type 2, is the recommended method for detecting both occult primary tumours and metastases in EAS. Detectability depends on tumour location, as different sites have different specificities, and cells with low SSTR expression and high metabolic activity may appear as false negatives in scintigraphy [12]. Sumushkin et al. reported the case of an elusive ACTH-secreting tumour that was localized using somatostatin receptor-targeted positron emission tomography (PET)/CT and fluorine-18 fluorodeoxyglucose PET/CT [13]. An alternative to this method may be the use of 11 C Methionine PET co-registered with high-resolution MRI, which enabled localization of ectopic ACTH-secreting membranous adenomas that caused Cushing's syndrome in another case reported by Lurquin et al. [14].

Treatment of Cushing's syndrome. The first-line and preferred treatment for ectopic ACTH secretion is surgical removal of the source of secretion [2]. If surgical removal of the source of excessive ACTH secretion is not possible, second-line therapy is initiated, including pharmacotherapy, which mainly involves the use of steroidogenesis inhibitors [12].

The mechanism explaining the effect of steroidogenesis inhibitors on limiting ectopic ACTH production or direct tumour regression is not fully understood. In addition to the direct effect of the drugs on tumour regulation, high cortisol levels themselves may play a role [15]. The most commonly used drug in this group is ketoconazole, but its enantiomer – levoketoconazole – is also used, as is metyrapone, a potent 11β-hydroxylase inhibitor and partial 18-hydroxylase inhibitor. In several cases, similar treatment results with metyrapone have been reported with osilodrostat, a rapid-acting 11β-hydroxylase inhibitor [12]. Importantly, there are reports of regression of an ectopic lung tumour that produced ACTH only after six months of metyrapone therapy [16].

In the example of a man with Cushing's disease caused by ectopic ACTH secretion, the effectiveness of long-term use of metyrapone was proven, enabling the normalization of ACTH and cortisol secretion and the absence of tumour growth within three years of therapy [15]. The patient, in whom metyrapone therapy proved insufficient, was treated with osilodrostat, which resulted in a reduction of the adrenal glands, which, together with the improvement in the clinical condition, influenced the decision to reduce the osilodrostat dose [17]. The effectiveness of osilodrostat in cases of ectopic ACTH secretion and paraneoplastic Cushing's syndrome was also demonstrated in a multicentre study conducted in France. However, the main side-effect of the therapy was considered to be adrenal insufficiency [18].

Moreover, experimental therapeutic agents, such as roscovitine and ATR-100, as well as glucocorticoid receptor–targeted agents, including mifepristone and relacorilant, warrant particular attention. These studies suggest potential benefits from combination therapy with the aforementioned drugs [10]. Abiraterone acetate, an irreversible and selective inhibitor, has been used in the temporary treatment of malignant ectopic Cushing's syndrome (EAS). 17α-hydroxylase/17,20-lyase inhibitor, which blocks adrenal steroidogenesis, including cortisol synthesis. It allows for a rapid quantitative reduction in serum cortisol levels and sufficient improvement in the patient's clinical condition for invasive procedures, after which abiraterone treatment was discontinued [19]. If the symptoms of hypercorticosteroids are not adequately controlled by pharmacological treatment, bilateral adrenalectomy is possible, which involves lifelong replacement therapy with hydrocortisone and fludrocortisone preparations [9].

CASE REPORT

In July 2020, a 70-year-old patient was referred with suspected ectopic ACTH secretion and diagnosed with Cushing's syndrome, electrolyte disturbances, obesity (BMI 34), hypertension, type 2 diabetes, and megaloblastic anaemia. The patient remains under endocrinological care at the Outpatient Clinic and the Department of Endocrinology and Neuroendocrine Tumours of the University Clinical Centre of the Silesian Medical University in Katowice, southwest Poland.

Upon admission, the patient reported weakness, palpitations, numbness in the extremities, and headaches. Physical examination revealed abdominal obesity (hip circumference: 111 cm, abdominal circumference: 106 cm), lower limb oedema, and high blood pressure. Laboratory tests revealed hypercortisolemia (morning cortisol: 72.7 µg/dl [4.82–19.5 µg/dl], evening cortisol: 82.5 µg/dl [2.47–11.9 µg/dl] – lack of circadian rhythm), high ACTH levels -220 pg/ml [7.2–63.3 pg/ml], DHEA-S (285.7 µg/dl [9.4–246.0 µg/dl]), and secondary hypothyroidism. Mineralocorticoid and catecholamine levels remained within normal limits. During the hospital stay, significant fluctuations in blood glucose were observed (lowest level: 112 mg%, highest: 496 mg%), hypomagnesemia, hypoalbuminemia, and hypokalemia. A CRH stimulation test was performed, confirming ectopic ACTH secretion. Imaging studies included computed tomography of the chest and abdomen, and magnetic resonance imaging of the pituitary gland. Imaging studies revealed no pathological changes. Treatment was initiated with metyrapone 250 mg three times daily for two months, L-thyroxine 50 µg daily, insulin therapy, and electrolyte supplementation. After this period, a follow-up blood test was performed, which showed normal ACTH levels (average 60 pg/ml) and morning cortisol levels. Due to improvement in blood parameters, treatment with metyrapone (250 mg) was modified to one pill a day.

In August 2020, a ^{68}Ga-DOTA-TATE PET/CT scan was performed, demonstrating intense radiotracer uptake in the dorsal aspect of the pancreatic head and the uncinate process, as well as markedly increased uptake in both adrenal glands. Additionally, focal radiotracer accumulation was observed near the peripheral region of the left thyroid lobe. Endoscopic ultrasound (EUS) showed a pancreas with homogeneous echotexture and no detectable focal lesions.

The patient's next health checkup took place in November 2020, which revealed normal blood counts, normal ACTH and cortisol levels. A physical examination revealed obesity and lower limb oedema. Therefore, metyrapone was recommended to be reduced to 250 mg one pill every other day. Metyrapone treatment was discontinued in 2021 due to persistently normal cortisol and ACTH levels. A follow-up abdominal computed tomography scan revealed normal adrenal gland shape and size. Cortisol and ACTH levels remained within the normal range until January 2023, when an increase in morning cortisol (52.5 µg/dl) and ACTH (295.9 pg/ml) was detected. The patient was re-hospitalized in the Department of Endocrinology and Neuroendocrine Tumours, reporting weakness, decreased exercise tolerance, and muscle tremors for several weeks. A CT scan of the chest and abdomen performed in March 2023 revealed focal lesions in the spleen. No other abnormalities were seen in the abdominal or thoracic cavities.

In January 2024, a dynamic MRI of the pituitary gland with contrast was performed, which revealed no changes suggestive of a pituitary adenoma. A thyroid ultrasound also did not reveal focal lesions. A follow-up abdominal CT scan performed in January 2024 revealed stable hypodense lesions in the spleen, compared to the image from March 2023. The visualized adrenal glands were normal in shape with signs of thickening. A further CT scan of the chest was performed in June 2024, which revealed minor fibrotelectatic changes in the lungs. A CT scan of the chest, abdomen, and pelvis on 14 August 2025, revealed a significant reduction in the degree of thickening of both adrenal glands, and the lungs were free of suspicious nodules. Due to the 6-year history of ectopic ACTH secretion and persistent symptoms of Cushing's syndrome, as well as abnormal hormonal results, the patient was qualified for osilodrostat therapy at a dose of 1 mg per day under the programme Emergency Access to Drug Technologies (RDTL). Figure 2 shows cortisol concentration over time, while Figure 3 shows ACTH concentration in the patient's blood from July 2020 – January 2025.

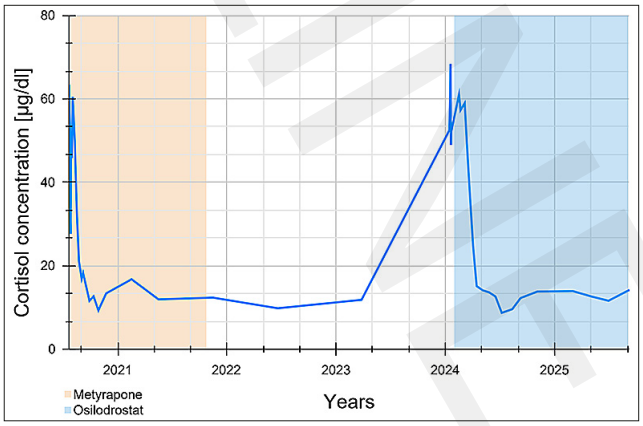

Figure 2. Change in the patient's blood cortisol concentration over the years

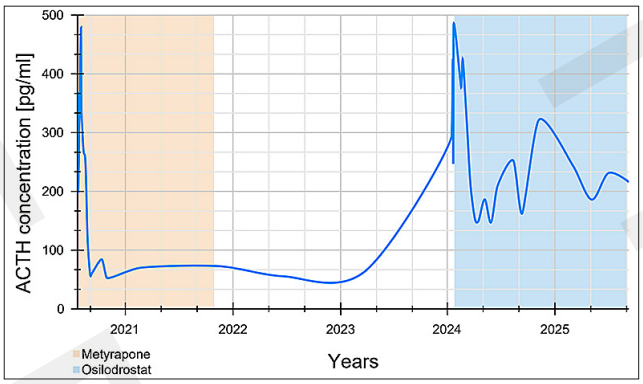

Figure 3. Change in ACTH concentration in the patient's blood over the years

DISCUSSION

The case study in this article concerns a patient with Cushing's syndrome, a diagnostic challenge caused by ectopic ACTH secretion. The source of the syndrome could not be identified despite advanced imaging. According to the literature, up to 10–20% of cases of Cushing's syndrome are due to ectopic ACTH secretion [5], and locating the focus of neuroendocrine tumours secreting this hormone takes several or even a dozen years [13, 20].

The patient underwent comprehensive biochemical diagnostics, confirming hypercortisolism, electrolyte imbalance, and hyperglycaemia. A CRH stimulation test confirmed ectopic ACTH secretion, which ruled out Cushing's disease. Imaging studies revealed suspicious lesions in the pancreas, spleen, and lung. The lesion in the head of the pancreas was not visualized on EUS, and the lesions in the spleen and lung did not show morphological progression over time, suggesting a coincidental finding or no association with the ectopic lesions. These changes require further monitoring, but the lack of progression of the detected lesions indicated their limited clinical significance.

Literature data have shown that the effectiveness of 68Ga-DOTATATE PET/CT scintigraphy in localizing NETs is 65% and is closely dependent on the expression of somatostatin receptors, particularly the SSTR2 type. Sumushkin et al. cited studies confirming the effectiveness of FDG-PET in localizing the source of ectopic lesions, with a sensitivity of approximately 52%. At the same time, other studies they cited by Sumushkin demonstrated 100% effectiveness of FDG-PET in identifying lesions located in the pancreas. Therefore, Sumushkin et al. they decided to perform FDG-PET in their patient with ectopic ACTH secretion, which revealed the source of ectopic lesions 16 years after the diagnosis of Cushing's syndrome [13]. The above data highlight the effectiveness of FDG-PET in localizing the source of ectopic ACTH secretion, which, in the opinion of the authors of this paper, should be considered in further diagnostics.

Bilateral inferior petrosal sinus sampling (BIPSS) plays an important role in the differential diagnosis between Cushing's disease and ectopic ACTH syndrome, especially in cases of equivocal biochemical and imaging test results. This test allows for the assessment of ACTH concentration in the central circulation and comparison of ACTH concentrations in the periphery, both in basal conditions and after CRH stimulation, enabling reliable differentiation of the source of excessive hormone secretion [21]. In the presented case, the diagnosis of ectopic ACTH secretion was made based on the clinical picture, biochemical test results, and the CRH stimulation test, which allowed for the exclusion of Cushing's disease. However, in diagnostically questionable situations, particularly with equivocal dynamic test results or the presence of pituitary lesions of uncertain clinical significance, BIPSS remains a crucial test, enabling appropriate therapeutic decisions [22].

In the presented case, to alleviate the effects of Cushing's syndrome, the patient was initially treated with metyrapone. This treatment resulted in a very good response, with normalization of cortisol and ACTH levels maintained for two years after discontinuation of the medication. The achieved remission confirmed the effectiveness of metyrapone treatment in Cushing's syndrome, which is consistent with the observations of other authors. [12, 15, 16]. During the patient's next follow-up visit in 2023, hypercortisolemia was diagnosed, which was treated with osilodrostat, resulting in disease remission. Given the recurrence of hypercortisolemia, lack of localization of the ectopic lesion, and regression following metyrapone and osilodrostat administration, a microscopic neuroendocrine tumour – invisible on imaging studies – may be suspected. If cortisol and ACTH levels continue to fail to normalize after osilodrostat discontinuation, treatment with the highest efficacy should be implemented, consistent with current recommendations and the literature data included in this case study.

CONCLUSIONS

1) The presence of ectopic ACTH secretion requires regular monitoring of cortisol and ACTH levels in the blood, and assessment of the progression of changes in imaging studies.
2) Despite the advancement of imaging techniques, there are cases of patients with unidentified foci of ectopic ACTH secretion.
3) Pharmacological treatment with metyrapone and osilodrostat (steroidogenesis inhibitors) can provide long-term stabilization of hormone levels and improvement in the clinical condition of the patient.
4) The above case demonstrates the need for interdisciplinary and individualized treatment of Cushing's syndrome.

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