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CASE REPORT

Cyclical Cushing's syndrome due to an atypical thymic carcinoid

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ABSTRACT

A 43-year-old man presented with fluctuating symptoms of weight gain, shortness of breath, pretibial oedema, associated with anxiety and memory disturbances. Laboratory investigation revealed an adrenocorticotropin (ACTH)-dependent cyclical Cushing's syndrome characterised by remarkable variations in urinary cortisol excretions ranging from 27 to 28,050 nmol/ 24 h. Magnetic resonance imaging (MRI) of the pituitary was normal and ectopic ACTH production was suspected. A tumour in the right anterior mediastinum was revealed on octreotide receptor scintigraphy, which had initially been overlooked on computed tomography (CT) scanning. A thymic carcinoid tumour was suspected, which was supported by increased levels of urinary serotonin, while platelet serotonin and urinary 5-hydroxyindoleacetic acid levels were normal. The tumour was removed surgically and histological examination revealed an atypical thymic carcinoid tumour. Postoperatively, the patient's symptoms disappeared rapidly. He underwent external radiotherapy and is still free of symptoms after almost two years of follow-up. For clinical practice, a cyclical Cushing's syndrome should be suspected in any patient with clinical signs of Cushing's syndrome but normal biochemistry. Repeated measurement of urinary cortisol excretion is then required to establish or rule out the diagnosis.

KEYWORDS

Cushing's syndrome, hypercortisolism, cyclical, thymic carcinoid

INTRODUCTION

Cushing's syndrome is a rare disorder, characterised by an inappropriately high synthesis of cortisol by the adrenal cortex. It usually results from overproduction of ACTH by a pituitary corticotroph tumour, representing the classic Cushing's disease. This accounts for 70% of patients with Cushing's syndrome. In about 20% of cases, hypercortisolism occurs without ACTH stimulation, as is found in adrenal adenoma, adrenal carcinoma or adrenal nodular hyperplasia. In the remaining cases, Cushing's syndrome is due to ectopic, i.e. nonpituitary, secretion of ACTH or (very rarely) corticotropin-releasing hormone (CRH).[1] Ectopic ACTH production is mainly associated with small-cell carcinoma of the lung but can also be found in various neuroendocrine tumours, such as bronchial, thymic, or pancreatic carcinoid, medullary carcinoma of the thyroid and pheochromocytoma.

In some cases, overproduction of cortisol occurs intermittently, resulting in high peaks of serum cortisol followed by periods with completely normal cortisol levels. This phenomenon is known as cyclical Cushing's syndrome, as first described by Bailey in 1971.[2] Clinicians should be aware of the existence of this entity, as it easily leads to confusion, misdiagnosis and consequently to treatment delay.

We present here a patient with cyclical Cushing's syndrome due to ectopic ACTH production by an atypical thymic carcinoid.

CASE REPORT

A 43-year-old man was referred for further evaluation of possible Cushing's syndrome. For eight months he had suffered from periods of weight gain associated with a swollen and red face, shortness of breath, abdominal distension, pretibial oedema and weakness in his legs. In these periods he felt anxious, confused and had memory disturbances. These symptoms could persist for days to weeks but subsided thereafter. Otherwise, his

medical history was unremarkable. Spironolactone had been used to treat his fluid retention without effect. Other medications were not given. He smoked 20 cigarettes daily and seldom used alcohol. His family history was negative with respect to endocrine diseases. On physical examination his height was 1.83 meter and his weight 90 kg with truncal obesity. Blood pressure was 140/90 mmHg. Most prominent features were a red face and bilateral oedema of the lower limbs. No typical Cushingoid stigmata, as buffalo hump, striae, acne, ecchymoses, or cutaneous hyperpigmentation, were present. Muscle strength appeared normal.

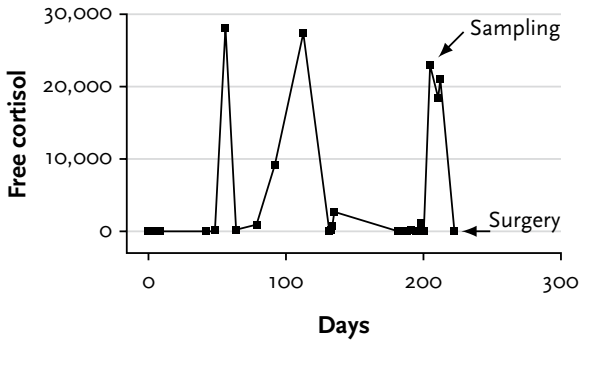
Laboratory investigation, carried out in the referring hospital, suggested ACTH-dependent Cushing's syndrome. Plasma ACTH varied between 43 and 75 pmol/l and serum cortisol between 581 and 2205 nmol/l. Urinary free cortisol excretion was sometimes extremely high (>26,000 nmol/24 h; normal range 55 to 300 nmol/24 h), interspersed by periods of normal urinary cortisol excretion. Both low- and high-dose dexamethasone suppression tests had been performed showing no suppression of serum cortisol. Extensive radiological studies had been carried out, including MRI of the pituitary as well as chest X-ray, and CT of chest and abdomen, which were all judged as normal. At the time of referral cyclical Cushing's syndrome, surreptitious use of corticosteroids (factitious Cushing's syndrome) or cortisol resistance were all considered. However, the last two diagnoses seemed unlikely as elevated ACTH levels essentially ruled out use of corticosteroids, whereas intermittent hypercortisoluria is very unusual in cortisol resistance.

In our hospital, laboratory evaluation showed mild hypokalaemic alkalosis (potassium 3.1 (normal range 3.6 to 4.8 mmol/l), bicarbonate 31 (21 to 25 mmol/l)) with normal blood cell counts and chemistry. Excretion of free cortisol in 24-hour urine was initially normal, but strongly elevated thereafter with a maximal cortisol excretion of 28,050 nmol/24 h (normal <270 nmol/24 h) (*figure 1*). Analysis of urinary steroid metabolites was performed by gaschromatography. The sum of the 24-hour urinary excretion of tetrahydrocortisol, allo-tetrahydrocortisol, tetrahydrocortisone, cortols and cortolones (reference range 11.6 to 45.9 µmol/24 h)[3] was used as an estimate of cortisol production. The excretion of these glucocorticoid metabolites was strongly increased (821.4 µmol/24 h) during a period of hypercortisoluria (cortisol excretion 28,050 nmol/24 h) and was normal (29.8 µmol/24 h) during a period of normocortisoluria. Furthermore, androgen metabolites were also elevated in parallel with increased excretion of glucocorticoid metabolites, but no abnormal glucocorticoid metabolites were detected by additional mass spectrometry. These findings essentially ruled out factitious Cushing's syndrome.

Random serum cortisol levels fluctuated from 130 to 2098 nmol/l (normal range 200 to 800 nmol/l) and plasma ACTH levels from 50 to 435 ng/l (normal range 10 to 100 ng/l). The results so far demonstrated ACTH-dependent hypercortisolism, characterised by a cyclic pattern of cortisol secretion. To elucidate the source of ACTH production (pituitary or ectopic), we repeated the dexamethasone suppression tests (DST) and performed a corticotrophin-releasing hormone (CRH) stimulation test. A low-dose DST (0.5 mg dexamethasone 6 hourly for 48 h) showed inadequate suppression of serum cortisol (290 nmol/l), in line with previous findings. Similarly, a high-dose DST (7 mg intravenously for 7 h) showed no suppression of serum cortisol levels, suggestive of ectopic ACTH secretion. The CRH test (100 µg human CRH intravenously) revealed a rise in serum cortisol of 68% (from 220 to 370 nmol/l) and a rise in ACTH of 700% (from 15 to 106 ng/l). Once Cushing's syndrome is confirmed, a ≥20% increase in cortisol and/or ≥50% increase in ACTH is regarded as consistent with Cushing's disease.[4]

Additional endocrinology evaluation showed normal thyroid function tests, normal plasma testosterone as well as a normal insulin-like growth factor-1. Plasma prolactin was modestly elevated (603, normal range <200 mU/l). Considering the normal pituitary images and the absence of a medication-related cause, its slight increase was possibly attributable to stress at the time of blood sampling. Plasma calcitonin level was normal as was the urinary excretion of catecholamine metabolites. Indium^{111} labelled pentreotide scintigraphy showed pathological uptake in the right part of the upper chest. Hence, the CT scans of chest and abdomen of the referring hospital were revised. On CT, a small tumour of 2 x 3 cm appeared to be present in the upper right anterior mediastinum, which had been overlooked initially. The anatomic localisation

Figure 1. *Excretion of urinary free cortisol (nmol/24 h) before surgical removal of the thymic carcinoid*



corresponded with the results of pentreotide scintigraphy. Taken together, a thymic carcinoid was suspected. To evaluate possible growth or metastases, an MRI of the neck, chest and abdomen was carried out, identifying the described tumour without evidence of location elsewhere.

To biochemically demonstrate carcinoid tumour, platelet serotonin and urinary excretion of both serotonin and 5-hydroxyindoleacetic acid (5-HIAA) were measured. Furthermore, serum chromogranin A was measured as a neuroendocrine tumour marker. Of these, urinary serotonin (90 µmol serotonin/mol creatinine, normal range <66 µmol serotonin/mol creatinine) and serum chromogranin A (282 µg/l, normal range <100 µg/l) were found to be elevated, indeed consistent with a carcinoid tumour.

Selective venous catheterisation for ACTH sampling was carried out to demonstrate a gradient in ACTH concentration along the veins in the tumour area.[5] ACTH levels in the femoral vein were simultaneously measured. The highest ACTH levels (422 ng/l) were found in the superior caval vein, just above the entrance of the azygos vein. Although this sampling approached the tumour region, the mediastinal to femoral vein ACTH ratio was only 1.25. On thoracotomy, a weak tumour of 4 x 3 x 3 cm, adjacent to the brachiocephalic vein, was removed. Histological examination showed an atypical thymic carcinoid tumour, angioinvasive and infiltrating into the surrounding fat tissue as far as the resection margin. Mitotic activity was high (5 per 10 high-power fields). Tumour cells were positive for immunohistological staining with ACTH, CAM 5.2, keratin, AE1/3, chromogranin, CD56 and synaptophysin. In tumour tissue, profiling of indoles (tryptophan, 5-hydroxytryptophan, serotonin and 5-HIAA) was carried out by HPLC with fluorescence detection, as described previously.[6] This revealed low concentrations of tryptophan (0.8 µmol/l) and 5-HIAA (23 nmol/l), whereas serotonin and its precursor 5-hydroxytryptophan (5-HTP) could not be detected. Furthermore, catecholamines were isolated from carcinoid tissue by paired ion extraction followed by HPLC with electrochemical detection, showing remarkably high concentrations of adrenalin (0.17 nmol/ gram tissue) and noradrenalin (1.24 nmol/ gram tissue), as compared with previous findings in foregut carcinoids.[7]

After surgery, the patient showed a spectacular clinical improvement. Particularly, his 'attacks' of confusion and anxiety as well as weight fluctuations and full moon face disappeared. As expected, he temporarily developed partial cortisol deficiency, treated with cortisone suppletion. ACTH levels declined to 15 ng/l. Plasma chromogranin A and urinary serotonin decreased to normal values. A repeated whole body indium^{111} pentreotide scintigraphy showed no abnormalities. Two and eight months after surgery, a new CT of chest and abdomen was performed to evaluate possible tumour recurrence and/or metastases. All proved normal. To prevent recurrence, external radiotherapy was given to the mediastinal region (30 times 2 Gy). Since surgery, he has now been free of symptoms for 20 months.

DISCUSSION

Cyclical Cushing's syndrome due to ectopic ACTH secretion is an intriguing but very rare clinical disorder. Its relation with a thymic carcinoid has only been described in five patients so far.[8-12] Besides its rarity, our patient had extreme fluctuations in his urinary cortisol excretion, ranging from 27 to as high as 28,050 nmol per 24 h. Such striking cortisol fluctuations have rarely been reported before.

The clinical and laboratory features of a cyclical Cushing's syndrome are often misleading so that it may take years before the correct diagnosis is made. Disease-free periods may last from days to even years.[13] Therefore, once Cushing's syndrome is highly suspected, urinary free cortisol excretion should be repeatedly measured, even when initial values are normal.

ACTH-dependent cyclical Cushing's syndrome may result either from a pituitary corticotroph adenoma or, less often, from ectopically secreted ACTH. The distinction between these entities is usually difficult to make. Clinical features of patients with ectopic ACTH production may mimic those found in patients with the classic Cushing's disease, particularly when the underlying tumour is slow growing, as with carcinoid tumours. Although ACTH plasma levels are usually higher in the ectopic ACTH syndrome, considerable overlap exists with Cushing's disease. Additional dynamic endocrine testing may be helpful but has a limited accuracy.[4] Furthermore, the need to carry out these tests during an episode of hypercortisolism often introduces logistic problems.

The search for the source of the ectopic ACTH production may be extremely difficult since as many as 50% of these patients harbour an occult underlying tumour.[1] The recommended diagnostic approach is a CT or an MRI scan of neck, chest and abdomen. MRI is preferable as it may detect bronchial carcinoid tumours overlooked on CT.[4] It should be noted that on CT scans of the anterior mediastinum, thymic remnant tissue and small thymic carcinoid tumours might have a similar appearance, potentially leading to an incorrect diagnosis and unnecessary thoracotomy.[14,15] Since thymic tissue regresses with age, this confusion will not often arise in patients aged older than 40 year.[15]

As most carcinoid tumours and other neuroendocrine tumours express somatostatin receptors, octreotide

receptor scintigraphy has been evaluated for localisation of ACTH-producing tumours. Although its sensitivity has proved to be high, it generally does not disclose tumours that are not seen on conventional imaging,[16] although exceptions have been reported.[17] Hence, octreotide receptor scintigraphy is especially indicated when an ACTH-producing tumour is suspected but CT or MRI results are negative. If the tumour remains undetected, positron emission tomography (PET) may be useful, but its exact diagnostic position has to be established.[18] For detection of carcinoid tumours, PET using the serotonin precursor ^{11}C-5-hydroxytryptophan is valuable.[18] Finally, selective venous sampling for ACTH may be a last tool for localising an occult underlying tumour.[5]

Carcinoid tumours produce biogenic amines, such as serotonin, which allows specific biochemical detection. Carcinoid tumours are classified into foregut, midgut, and hindgut tumours, according to their supposed origin from the primitive gut. Thymic carcinoids belong to the foregut tumours. For screening, urinary excretion of the serotonin metabolite 5-HIAA is widely used but has a low specificity due to interaction with ingestion of serotonin-containing foods.[19] Platelet serotonin does not show such an interaction and is the most discriminative marker as it detects smaller increases in serotonin production.[20] Foregut carcinoids have a lower serotonin metabolism than midgut carcinoids, as reflected by their low frequency of serotonin-related symptoms. These tumours usually do not secrete serotonin but its precursor 5-HTP, which is supposed to result from deficiency of the enzyme aromatic-L-aminoacid decarboxylase (AADC) required to convert 5-HTP to serotonin. Consequently, platelet serotonin may be normal in up to 55% of patients with foregut carcinoids,[21] as in our patient. Noteworthy, elevated circulating 5-HTP in foregut carcinoids can be converted to serotonin by renal AADC activity, leading to increased urinary serotonin levels. Indeed, elevated urinary serotonin levels have been found in 40% of patients with foregut carcinoids.[21] Our patient illustrates that urinary serotonin may be elevated despite normal platelet serotonin levels, underlining its value in carcinoid screening for foregut carcinoids. Unexpectedly, the tumour tissue from our patient contained neither serotonin nor its precursor 5-HTP, which is not in line with a postulated AADC deficiency. Moreover, the high concentration of tumour catecholamines rules out AADC deficiency, as this enzyme is also required for formation of catecholamines. The precise function of AADC in foregut carcinoids, therefore, remains to be established.

Thymic carcinoid tumours are very rare. As the annual incidence of carcinoids is about 1.5 per 100,000 persons a year[21] and only 2% of the carcinoids originate from the thymus,[22] the estimated incidence of thymic carcinoid tumours is three per 10,000,000 persons a year. To date, about 150 patients with a thymic carcinoid tumour have been reported.[23] Thymic carcinoid tumours tend to metastasise either lymphogenously, or haematogenously to lungs, bone, adrenals, liver, or spleen. Invasion of local thoracic structures is found in 50% of patients and extrathoracic metastases in 20 to 30%.[24] Cushing's syndrome is found in about 20% of patients with thymic carcinoid tumours.[23] Sometimes, thymic carcinoid forms part of the multiple endocrine neoplasia type I syndrome. Despite aggressive treatment, thymic carcinoid tumours have a poor prognosis with a ten-year survival rate less than 50%[23,24] with lowest survival rate (35%) in patients with associated Cushing's syndrome. In a large series of 342 cases with mediastinal or thymic carcinoid tumours, an overall survival of 38% after ten years was observed, similar to atypical and typical carcinoid tumours.[25] Surgical treatment, as radical as possible, is the treatment of choice. The role of adjuvant radiotherapy or chemotherapy has not been well assessed as the number of studied patients is low. Nevertheless, several reports suggest a response to postoperative irradiation, particularly when the thymic carcinoid tumour is invasive.[26,27] Chemotherapy has been tried in some patients without a significant effect on recurrence rate or survival.[27]

The precise mechanism of periodic hypercortisolism is largely unknown. Changes in dopaminergic tone[28] as well as influences of ghrelin[29] have been described as possible underlying mechanisms. Tumour infarction would be an alternative explanation for periodic ACTH and cortisol release. Furthermore, Cushing's syndrome may be food dependent and hence lead to periodic hypercortisolism.[30] In our patient, the cause of intermittent ACTH secretion remained unclear, although potentially relevant observations were made. Most remarkable was the high concentrations of catecholamines in the carcinoid tissue, of which the adrenalin concentration was clearly higher than previously found in other foregut carcinoid tumours.[7] It is therefore tempting to speculate that local overproduction of catecholamines may play a role in the cause of cyclic ACTH release. Interestingly, studies in rats have demonstrated that serotonin release in carcinoid tumour cells is controlled by adrenergic stimulation.[31] Assuming ACTH and serotonin are co-secreted, ACTH release might similarly be influenced by local (fluctuating) production of catecholamines, as could have been the case in our patient.

This case report illustrates several clinically relevant aspects. Firstly, cyclical Cushing's syndrome should be suspected in a patient with typical clinical findings of Cushing's syndrome but normal biochemistry. Repeated measurement of urinary cortisol excretion is then required to establish or rule out the diagnosis. Secondly, octreotide receptor scintigraphy may be helpful to detect an ectopic ACTH-producing tumour, not disclosed (or overlooked)

on CT. Finally, measurement of urinary serotonin in addition to platelet serotonin or urinary 5-HIAA might be valuable to detect foregut carcinoids.

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