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CASE REPORT AND REVIEW

Carcinoid tumor of the thymus associated with Cushing′s syndrome and dysgeusia: case report and review of the literature

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Abstract A 30-year-old man was hospitalized with edema, polyuria, and abnormalities in taste. ACTH and cortisol levels at admission were markedly elevated, even after attempted suppression with 8 mg dexamethasone. A thoracic–abdominal CT revealed an anterior mediastinal lesion and hyperplasia of both adrenal glands. After excision of the mediastinal mass, which confirmed the presence of a carcinoid thymic tumor, the patient became totally asymptomatic, with normal ACTH and cortisol levels. A carcinoid thymic tumor has a poor prognosis, especially when it is associated with Cushing's syndrome. Most patients will present recidivism or metastasis within 5 years after surgery. However, the low number of cases available for analysis makes it difficult to establish optimum therapeutic approaches.

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Introduction

In approximately 70% of Cushing's syndrome cases, excess cortisol is secondary to a pituitary tumor secreting ACTH [1]. About 20% of cases are of adrenal origin and the remaining 10–15% are caused by ectopic secretion of ACTH [1, 2].

Tumors that secrete ACTH are infrequent. First described by Brown in 1928 [3], they have been found in all organs. Small-cell lung cancer has long been considered the most common site for these tumors, although the most recent series [2, 4] found that bronchial carcinoid tumors seemed to be the primary cause, representing 30% of cases.

Other causes to consider include adrenal or extra-adrenal pheochromocytoma, medullary thyroid carcinoma, thymic carcinoids, and gastroenteropancreatic neuroendocrine tumors [5]. Finally, in 12–19% of cases the source of ACTH secretion could not be identified despite repeated studies and long-term follow-up [2, 4]. The tumors most often implicated in occult ectopic ACTH secretion are the bronchial carcinoid, thymic carcinoid, and pancreatic islet tumors [6].

Perrot et al. [3] reviewed the literature from 1972 to 2002 and found descriptions of just 25 cases of a thymic carcinoid tumor secreting ACTH. In a series of 90 cases of Cushing's syndrome from ectopic ACTH secretion studied at NIH, 5 (5.5%) were produced by a thymic carcinoid tumor [2].

A new case of a thymic carcinoid tumor secreting ACTH and producing Cushing's syndrome is presented here, with the additional element of abnormal taste

sensation, an association that, to our knowledge, has not previously been described.

Case report

A 30-year-old male patient came to our center with polydypsia, polyuria, edemas in the lower extremities and abnormal taste sensations that had evolved during the previous month. He reported upper respiratory tract catarrh 3 months prior, without other antecedents of interest, and presented with BP of 145/88 mmHg and edemas with fovea in the lower extremities. Two weeks prior, a non-pruriginous follicular papulopustular rash had erupted, predominantly in an extensive region of the arms, shoulders, and back. Analysis revealed a metabolic alkalosis (pH 7.51 and HCO_3 35.1 mmol/l) with hypokalemia (2.97 mmol/l). Renal function was normal, as was 24-h proteinuria. Given a basal cortisol of 51.8 mcg/dl (1429.16 nmol/l) (normal range 5–25 mcg/dl) and basal ACTH of 430 pg/ml (94.7 pmol/l) (normal range 5–46 pg/ml), patient received nocturnal cortisol (51.3 mcg/dl, 1415.36 nmol/l), mild suppression with 1 mg dexamethasone (cortisol 49.6 mcg/dl, 1368.5 nmol/l) and monitoring of free cortisol in urine for 24 h (10080 mcg/day, 27720 nmol/day), confirming the diagnosis of Cushing's syndrome (Table 1). Suppression with 8 mg dexamethasone produced cortisol and ACTH levels of 53.5 mcg/dl (1476.06 nmol/l) and 260 pg/ml (57.25 pmol/l), respectively. Chromogranin A was 319.7 ng/ml (normal range 19.4–98.1 ng/ml).

Due to intense polydypsia and polyuria (7 l daily), water restriction test was performed; renal response to desmopressin was adequate.

Magnetic resonance imaging (MRI) showed an unaltered pituitary gland. Thoracic computed tomography (CT) revealed the presence of a well-defined anterior mediastinal mass, 28 × 30 × 45 mm, with a necrotic cystic center, that extended in front of the ascending aorta without causing displacement or infiltration of adjacent mediastinal structures (Fig. 1a). The abdominal CT showed a bilateral hyperplasia of the adrenal glands (Fig. 1b).

Table 1 Biochemical and hormonal data before and after thymectomy

Parameter	Normal range	Before surgery	Day 1 after surgery	Day 2 after surgery	Day 5 after surgery	Day 10 after surgery	3 Months after surgery
Fasting blood glucose	70–105 mg/dl	120	92	79			94
Serum potassium	3.5–5.1 mmol/l	2.97	2.6	3.28	4.91	4.7	4.8
pH	7.31–7.41	7.51	7.46	7.42	7.36	–	–
HCO_3	22–28 mmol/l	35.1	38	30.5	29.4	–	–
Serum cortisol 8 a.m.	5–25 mcg/dl	51.8	5.5	3.5	23.1	20.7	6.5
Serum cortisol 12 p.m.	2.5–12.5 mcg/dl	51.3	–	–	–	–	–
Urinary free cortisol	10–110 mcg/24 h	10080.0	–	–	5	–	–
Serum ACTH	5–46 pg/ml	430	–	12	70	26	20
Serum cortisol after 1 mg DXM	0.01–6 mcg/dl	49.6	–	–	–	–	0.3
Serum cortisol after 8 mg DXM	0.01–6 mcg/dl	53.5	–	–	–	–	–
Serum chromogranin A	19.4–98.1 ng/ml	319.7	–	–	–	–	57.4

Conversion factors: glucose 18 mg/dl = 1 mmol/l; cortisol 1 mcg/dl = 27.59 nmol/l; ACTH 4.5 pg/ml = 1 pmol/l

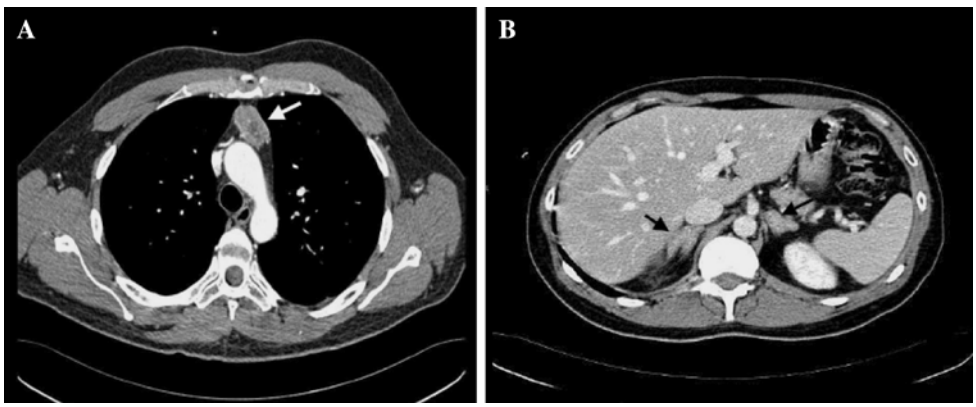

Fig. 1 Computed tomographic scan of the chest revealed a well-defined mass of 28 × 30 × 45 mm in the anterior mediastinum (**a**). Both adrenal glands were globally enlarged, with a hyperplassic appearance (**b**)

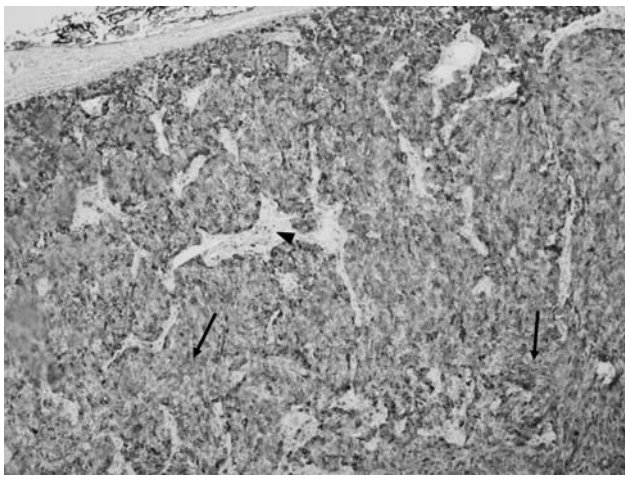

Fig. 2 The immunohistochemical analysis showed positive staining of tumor cells for ACTH, here in gray color (*arrows*). Note the negative result in the stromal component (*arrowhead*)

Surgical excision of the mediastinal mass was indicated. The anatomopathology study showed a hyperplastic thymus and a thinly encapsulated carcinoid tumor, 41 × 40 × 24 mm, in the center section. The tumor presented foci of sclerosis and necrosis, minimal evidence of mitosis, and invasion of mediastinal fat, which had thymic remnants. The immunohistochemical study of tumor cells showed the expression of low molecular weight keratins (CAM 5.2), keratin AE1–AE3, synaptophysin, chromogranin, and ACTH (Fig. 2).

No adjuvant treatments were employed. During the postoperative phase, the patient presented clear clinical improvement, with progressive disappearance of his polyuria, polydypsia, edemas, and dysgeusia. Changes in K levels were corrected gradually. At 48 h after surgery, basal ACTH was 12 pg/ml (2.20 pmol/l) and basal cortisol was 3.5 mcg/dl (96.6 nmol/l), without clinical evidence of excess glucocorticoids. A decision was made not to initiate substitutive treatment. At 5 days after surgery, basal cortisol was 23.1 mcg/dl (637.32 nmol/l). At 3 months, the patient remained asymptomatic and had a normal low-dose suppression test with dexamethasone and normal levels of basal cortisol, ACTH, and chromogranin A.

Discussion

Carcinoid tumors are classified as foregut, midgut, and hindgut tumors, depending on their origin within the primitive intestine [7]. More than 60% of carcinoid tumors reside in the gastrointestinal tract, most often in the small intestine, appendix, and colon [8]. The carcinoid thymic tumor was first described by Rosai and Higa in 1972 [9], and since then some 240 cases have been described in the literature [3]. In a series where 270 carcinoid tumors were studied, the thymus was the origin in just 2% of cases [10].

Recently, the World Health Organization reclassified carcinoid tumors of the thymus according to specific criteria, such as mitotic activity, presence of necrosis and/or atypical cells in neuroendocrine carcinoma: Stage 1, previously typical carcinoid tumor or well-differentiated neuroendocrine carcinoma; Stage 2, previously atypical carcinoid tumor or moderately differentiated neuroendocrine carcinoma; and Stage 3, previously large-cell neuroendocrine carcinoma or small-cell carcinoma [3]. Most neuroendocrine carcinomas of the thymus encountered are atypical, or Stage 2 [11]. Stage 1 is very rare, since progressive malignancy is the norm, in contrast with neuroendocrine lung tumors [12]. These tumors, then, are found on a continuous spectrum from the typical carcinoid to small-cell carcinoma [3]. The case reported here was found at Stage 2, identified by the characteristics of the pathology analysis of a tissue sample with necrotic foci and invasion of the perithymic fat and veins.

In recent years, the thymic carcinoid has been clearly related to the MEN-1 phenotype and therefore constitutes an important indicator for genetic screening [13–15]. Nonetheless, only 4% of patients with MEN-1 present a carcinoid thymic tumor [15, 16]. However, in these cases it is the primary cause of death, given local invasiveness, recurrence, and metastasis; therefore, early thoracic screening is required in all MEN-1 cases [15].

Thymic carcinoids associated with endocrinopathy tend to behave more aggressively [14] and may occur at any age. Cases have been reported from ages 4–64, although they tend to appear between ages 20–50 [3], as is the case for our patient.

Chronic hypokalemia can provoke intense polyuria, polydypsia, and nocturia, normally when potassium levels are below 3 mmol/l. This is primarily because of changes in urinary concentration capacity [17], although it has been suggested that direct thirst stimulation may occur [18]. This change, which occurs progressively over several weeks, has been associated with a decrease in the tubular response to the antidiuretic hormone [19]. In the present case, we conducted a water restriction test that showed adequate urinary concentration in response to the intravenous administration of 2 mcg of desmopressin.

Differentiating between ectopic ACTH secretion and Cushing's disease, as well as locating the causative tumor, presents a diagnostic challenge for the endocrinologist. Incidental non-secreting tumors in the pituitary gland, visible with MRI, occur in about 10% of the population aged 20–40. As a consequence, ACTH-secreting ectopic tumors may not be detected and Cushing's disease may be diagnosed in error. Carcinoid tumors of the thymus that secrete ACTH tend to have a clinical course prolonged by

the difficulty of finding the tumor source of the ACTH [20], with an average of 3 years between the onset of symptoms and diagnosis, although in some cases the process may occur slowly over the course of many years and even decades [3]. Correct diagnosis requires a combination of various imaging and analytical approaches. In our case, after obtaining diagnostic levels indicating Cushing's syndrome we undertook an etiological diagnosis. Although the ACTH levels suggested an ectopic origin, this is not always sufficient to clearly differentiate between ectopic and pituitary sources [4]. In the NIH series, a third of the patients with Cushing's syndrome due to ectopic ACTH secretion had normal ACTH levels [2]. The classical diagnostic approach is high-dose dexamethasone test, although in a third of the ectopic ACTH-syndrome cases, cortisol suppression is $\leq$50% [21]. Several strategies have been tested to improve this approach, including improved suppression of steroids for the diagnosis of Cushing's syndrome, association with a test using CRH stimulation or intravenous desmopressin [22], and higher doses of dexamethasone or intravenous instead of oral administration [5]; however, none of these techniques permitted a perfect differentiation between the two conditions [3]. In our case, the rapid clinical onset, hydroelectrolytic changes, a normal pituitary on MRI, and the ACTH levels would suggest an ectopic origin. In addition, cortisol levels were not suppressed following administration of 8 mg dexamethasone. Therefore, we decided against catheterization of the petrosal sinuses and focused on locating the tumor.

In some cases, a thoracic–abdominal CT does not detect the source of ectopic ACTH, since the thymic carcinoid tumors can be very small and can resemble remnant thymic tissue on the CT. This may result in a wrong diagnosis and an unnecessary thoracotomy [7]. Given the fact that the thymus disappears with age, the presence of soft tissue remnants in the anterior mediastinum in patients over the age of 40 who are being studied for Cushing's syndrome should raise suspicion of a carcinoid thymic tumor secreting ACTH. On the other hand, in patients in the second or third decade of life the presence of nodules 10–15 mm in diameter is common [23]. MRI is useful in cases in which the CT is dubious or negative despite heavy suspicion; it is more useful in the diagnosis of mediastinal and thymic lesions than of bronchial carcinoids [4].

Positron emission tomography (PET) is highly sensitive and specific and plays an important role in identifying cancerous states and tumor recurrence, but its usefulness in neuroendocrine tumors is more limited than in other types because they tend to be well-differentiated, with minimal cell recombination. PET with [11C]5-HTP or [11C] L-DOPA is more sensitive than FDG for visualizing carcinoids and other neuroendocrine tumors. Recent technological advances permit simultaneous data gathering from CT and PET and the fusion of the two images, which helps in locating small lesions, whether active or not [24, 25].

Determination of chromogranin A has become a key piece in the diagnosis and treatment of patients with endocrine tumors. Very high values of this marker have been associated with worse prognosis [26]. However, they tend to decrease after medical treatment begins; these changes in concentration provide useful information during follow-up. In the case of a thymic carcinoid, most of the series showed elevated serum chromogranin A. However, since this is often the case in patients with MEN-1, who frequently present other neuroendocrine tumors, this finding is not definitive.

Our patient came to the hospital with abnormal taste sensations that had been occurring for a month. Even though many diseases and medications have been associated with changes in smell and taste, there are several principal causes: nasal and sinus diseases, viral post-infections of the upper respiratory tract, and cranial trauma. Other causes, much less frequent, have been described: congenital, neurological, psychiatric, hepatic, renal, metabolic changes, and tumors. Despite extensive evaluation, the cause remains unidentified in 22% of patients [27, 28]. Our patient had an upper respiratory infection a few months prior to the consultation, but the taste abnormality did not appear at that time. The fact that it was resolved after thymectomy suggests that the cause might rather be related to the tumor or secondary to the metabolic changes resulting from Cushing's syndrome.

Surgery is the treatment of choice for neuroendocrine carcinoma of the thymus. In a review of 15 cases (14 bronchial carcinoids and 1 thymic carcinoid), 50% of cases had metastasized to the lymph nodes at the time of diagnosis; mapping or study of the ganglia was recommended. Surgery was possible in our case, although these tumors are very often inoperable and require antineoplastic therapies, which have limited effectiveness. Inhibitors of adrenal steroid synthesis (ketoconazole, aminoglutethimide, mitotane) or of ACTH (octreotide, lanreotide) have been tried [1]. In a study by Cheung and Boyages [29], octreotide was not effective in controlling Cushing's syndrome from ectopic ACTH produced by 2 carcinoid tumors. In some cases, a dopamine agonist (cabergoline) in combination with lanreotide has been effective [30]. Mifepristone, a progesterone and cortisol antagonist, may help to control symptoms derived from hypercorticism [31, 32]. Bilateral adrenalectomy is an effective palliative measure for controlling the symptoms of Cushing's syndrome in those patients whose life expectancy justifies more aggressive measures [1, 4].

Following complete removal of an ACTH-secreting tumor, suppression of cortisol levels for several weeks is a usual finding [33]. In our case, low cortisol levels at 48 h after surgery suggested this suppression, but we decided not

to begin substitutive treatment because of the absence of clinical indications compatible with mineralocorticoid deficiency. At 5 days, cortisol levels returned to normal and ACTH was 70 pg/ml (15.4 pmol/l). Although these levels suggested incomplete removal of the tumor, ACTH and cortisol levels normalized during follow-up. As described in the case report, the patient was asymptomatic at 3 months, had a cortisol level of 0.3 mcg/dl (8.27 nmol/l) after 1 mg dexamethasone, and normal ACTH and chromogranin A levels.

Despite aggressive treatment, carcinoid tumors of the thymus have poor prognosis and the majority present local recidivism or metastasis in the 5 years following surgery, with 10-year survival below 50% [3]. In a series of 74 cases studied by Wick et al. [14], the carcinoid thymic tumors associated with Cushing's syndrome had a higher 10-year mortality rate (65%) than those not associated with endocrinopathy (29%) or those associated with a multiple endocrine neoplasia (50%). The cause appears to be the greater number of complications from hypercorticism itself. In a retrospective analysis of 12 neuroendocrine carcinomas of the thymus, no stage of differentiation or histological parameter showed a significant association with prognosis. The most important prognostic factor appears to be the degree of radical surgical excision of the tumor [34]. Follow-up analysis of cortisol in serum and in 24-h urine is recommended, along with regular image testing, given the high recurrence rate [3].

In summary, neuroendocrine carcinomas of the thymus that produce Cushing's syndrome by ectopic secretion of ACTH are exceptional tumors with a high rate of malignancy and therapeutic difficulties due to the limited experience available, given the low number of cases. However, it appears that aggressive surgical intervention together with adjuvant radiation therapy can slow the rate of local recurrence and distant metastasis. In all cases, long-term follow-up is necessary.

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