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CASE REPORT

Ectopic TSH-secreting pituitary adenoma of the vomerosphenoidal junction

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Abstract

Objective: We describe an unusual case of ectopic TSH-secreting pituitary adenoma arising from the vomerosphenoidal junction.
Clinical presentation: A 52-year-old man with a long-standing history of hyperthyroidism was referred to the University Hospital in September 2001 because of increasingly disabling symptoms of nasal obstruction. For the past 18 years the patient had complained of palpitations, hypertension, weight loss, and nervousness. A presumptive diagnosis of Graves' disease was made. Treatment with methimazole was begun, but the patient was lost to follow-up. On admission, physical examination revealed signs of hyperthyroidism and a large diffuse goiter. Tests of thyroid function showed inappropriate secretion of TSH with hyperthyroidism. Both a TSH-secreting pituitary adenoma and resistance to thyroid hormone could be taken into account. There was no evidence of pituitary tumour by magnetic resonance imaging (MRI), but a large space-occupying lesion involving the nasal cavity and the nasopharynx was incidentally discovered.
Interventation and technique: Using an endoscopic endonasal approach, the tumour was removed *en bloc* together with the sphenoid floor, sphenoid rostrum, bony septum, and part of the soft palate mucosa. Histological features and immunophenotype were those of a TSH-secreting tumour.
Conclusion: Although exceedingly rare, ectopic TSH-secreting pituitary tumour should be borne in mind in cases of inappropriate secretion of TSH with hyperthyroidism and no evidence of pituitary tumour by computed tomography and/or MRI when a mass located along the migration path of the Rathke's pouch is demonstrated by radiological examination. To our knowledge, this is only the second reported case in the literature.

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Introduction

Ectopic pituitary adenomas are rare. Since the original description by Erdheim in 1909 (1), less than 50 ectopic pituitary adenomas have been reported (1–16). The majority of these tumours are located at the level of the sphenoid sinus (approximately 40%) or in the suprasellar region (approximately 33%), other locations being sporadically found in the clivus, cavernous sinus, petrous bone, sphenoid bone, mid-nasal ductus, third ventricle, and left cerebral hemisphere (2–16). Their origin remains a matter of debate. It has been proposed that these tumours can arise along the migration path of the Rathke's pouch or from aberrant anterior pituitary cells within the pituitary stalk or pars tuberalis (2, 5, 8, 15).

Herein, we report a case of ectopic thyrotrophin (TSH)-secreting pituitary adenoma (TSH-oma), which probably arose from the pharyngeal remnant of Rathke's pouch at the level of the vomerosphenoidal junction. To our knowledge, this is the second case of ectopic TSH-oma to be reported in the literature (17).

Case report

A 52-year-old man was referred to the University Hospital in Bologna in September 2001 because of increasingly disabling symptoms of nasal obstruction and a long-standing history of hyperthyroidism. We questioned the patient in more detail about his medical history. The patient had been well until 1983, when he began to complain of sweating, hypertension, palpitations, weight loss, and nervousness. At that time, thyroid function tests showed high basal levels of free thyroxine (T_4; 38.5 pmol/l; normal, 10–24) and free

tri-iodothyronine (T_3; 23 pmol/l; normal, 3–6.3), while the serum TSH levels, measured with a first generation radioimmunoassay, were normal (2 mU/l; normal, 0.5–4). A thyroid scintigraphy showed a uniform homogeneous increased uptake of radioisotope (^{99m}Tc-pertechnetate) in the area of the thyroid gland, providing also some evidence of a normal overall thyroid size. In spite of normal TSH levels, he was given a presumptive diagnosis of Graves' disease. Treatment with methimazole (30 mg daily) was begun and the patient gradually improved. Over a period of several years, the dose of methimazole was lowered step-by-step, with incomplete control of symptoms. The patient was lost to follow-up and further information about his medical history was scant. However, it is of interest that he had continued to suffer episodes of palpitations. Paroxysmal atrial fibrillation was diagnosed and drug treatment instituted.

The patient also had a 10-year history of nasal obstruction and rhinorrhea, which had become disabling some months before admission. Although he had consulted several physicians for his nasal symptoms, none had provided him with a diagnosis. He had otherwise been well. In particular, there was no history of ophthalmologic or neurological disturbances. Moreover, there was no family history of thyroid dysfunction.

On admission, physical examination revealed clinical signs of hyperthyroidism together with a diffuse enlargement of the thyroid gland. He was taking methimazole (5 mg) twice daily. No ophthalmopathy, pretibial mixedema, or acropachy was found. Thyroid function tests showed high basal TSH levels (42.9 mU/l; normal, 0.35–4.5) together with elevated free T_3 (15.5 pmol/l; normal, 3–6.3) and free T_4 (54 pmol/l; normal, 10–24) concentrations. Anti-thyroperoxidase and anti-thyroglobulin autoantibodies were negative. The remaining anterior pituitary hormones were normal. There was no dysfunction of the gonadal axis or the adrenal axis in basal biochemical testing. On the basis of these data, inappropriate secretion of TSH due to a TSH-secreting pituitary adenoma (central hyperthyroidism) was suspected. Alternatively, selective pituitary resistance to thyroid hormone could be taken into account, although serum TSH levels above 40 mU/l coupled with high free T_4 and free T_3 concentrations in a patient without previous thyroid ablation may be more frequently found in TSH-oma. Somewhat surprisingly, cerebral magnetic resonance imaging (MRI) with gadolinium contrast showed a normal pituitary gland. In addition, a large space-occupying lesion involving the nasal cavity and the nasopharynx was identified, thus explaining the symptoms of nasal obstruction that were becoming more and more disabling for the patient (Fig. 1). The lesion, probably arising from the vomerosphenoidal junction, reached the sphenoid and the soft palate. By the time the patient was admitted to hospital, he was finding it difficult to sleep because of worsening nasal obstruction, so that he was urgently evaluated for surgery. The mass was removed *en bloc* using an endoscopic endonasal approach. The resection also encompassed the bony septum, the sphenoid floor and rostrum, and part of the mucosa of the soft palate. The postoperative course was uneventful and the patient was discharged on the third postoperative day.

Histologically, the tumour consisted of nests of monomorphic polygonal epithelial cells with round to ovoid nucleus (Fig. 2). Mitoses were absent. Immunohistochemical reactions were performed with the avidin–biotin complex (ABC)/peroxidase method. The neoplastic cells were immunoreactive for cytokeratin (CAM5.2; Becton Dickinson, Franklin Lake, NY, USA; monoclonal, prediluted), synaptophysin (Neomarkers, Freemont, CA, USA; polyclonal 1:40), chromogranin (Biogenex, San Ramon, CA, USA; monoclonal 1:400) and β-TSH (Biogenex; monoclonal 1:300) (Fig. 2B). Immunoreactions for the other pituitary hormones (Biogenex kit) were negative. No α-subunit was available. The Ki67 (DAKO, Carpinteria, CA, USA; polyclonal

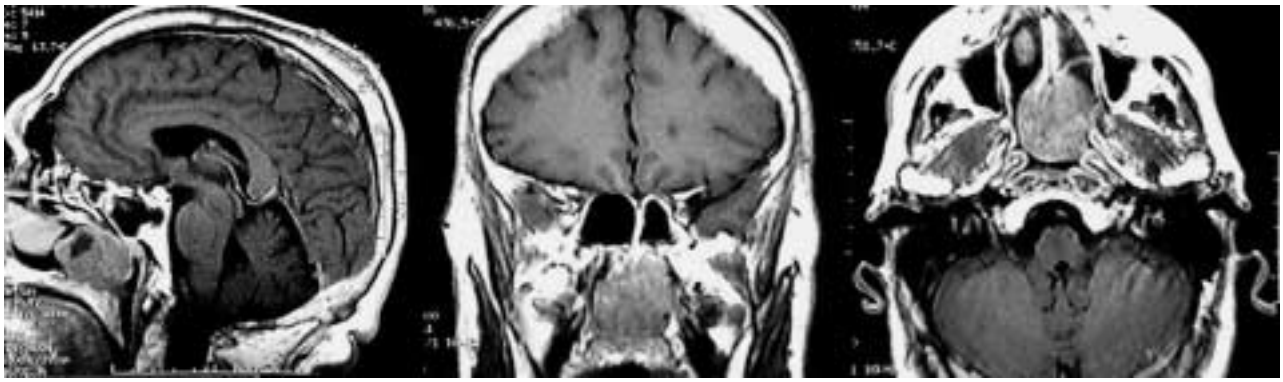

Figure 1 Preoperative MRI. The sagittal T1-weighted image shows a nasal mass occupying the rhinopharynx posteriorly. Adenohypophysis is normal (left). The coronal T1-weighted view shows the adhesion of the tumour to the sphenoidal floor (centre) and the axial view demonstrates the involvement of the bony septum (right).

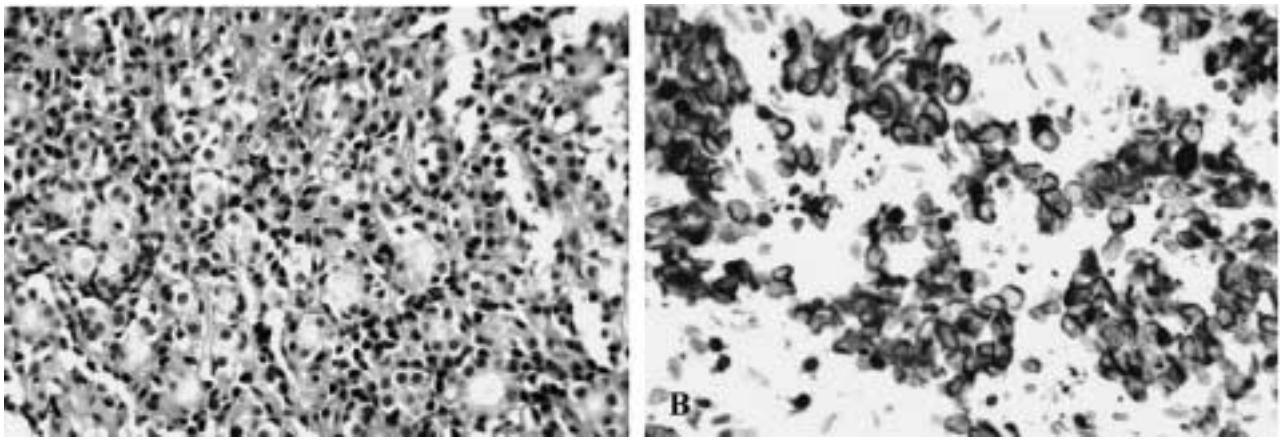

Figure 2 The tumour consists of nests of polygonal cells with round to ovoid nucleus (A) (haematoxylin and eosin; × 250). The neoplastic cells were immunoreactive for the β-TSH (B) (ABC/peroxidase; × 250).

1:50) labelling index was less than 1% and p53 (DAKO; clone DO-7) was negative.

The removal of the tumour restored TSH, free T_3, and free T_4 levels to normal (1.43 mU/l, 3.7 pmol/l, and 14.7 pmol/l respectively) with clinical remission of hyperthyroidism. Also, symptoms of nasal obstruction promptly disappeared. Methimazole administration was discontinued. When last seen in August 2002, 10 months postoperatively, the patient was in good health. He had no complaints and there was no residual tumour on MR imaging (Fig. 3). Serum TSH levels were in the normal range (2.65 mU/l), but a trend for a slight increase of free T_3 (7.9 pmol/l) and free T_4 (29 pmol/l) into the hyperthyroid range was shown, thus indicating the possibility of a recurrence or only an apparent surgical cure. Because of the long-standing history of atrial fibrillation, the T_3 suppression test, likely the most sensitive and specific test to demonstrate surgical cure of the tumour (18–20), could not be carried out. We are going to evaluate the possibility of using the slow-release preparation of somatostatin analogues for medical treatment of the disease, in order to restore euthyroidism in spite of the apparent complete removal of tumour mass.

Discussion

The patient reported here had a long-standing history of hyperthyroidism and nasal obstruction. Both the diseases had been misjudged for a long time. Our results show that he had a previously unrecognised ectopic TSH-oma of the vomerosphenoidal junction. To our knowledge, this is the second reported case in the literature after the study of Cooper & Wenig in 1996 (17).

The first case of ectopic pituitary adenoma was described in 1909 by Erdheim, who indicated that the pharyngeal hypophysis could be found on the posterior edge of the vomer (1). Ectopic pituitary adenomas are rare. They are most frequently located in extra-cranial sites, especially in the sphenoid sinus (4, 8, 10, 14, 15). Other extra-cranial sites include the nasal cavity, nasopharynx, mid-nasal duct, clivus, petrous and temporal

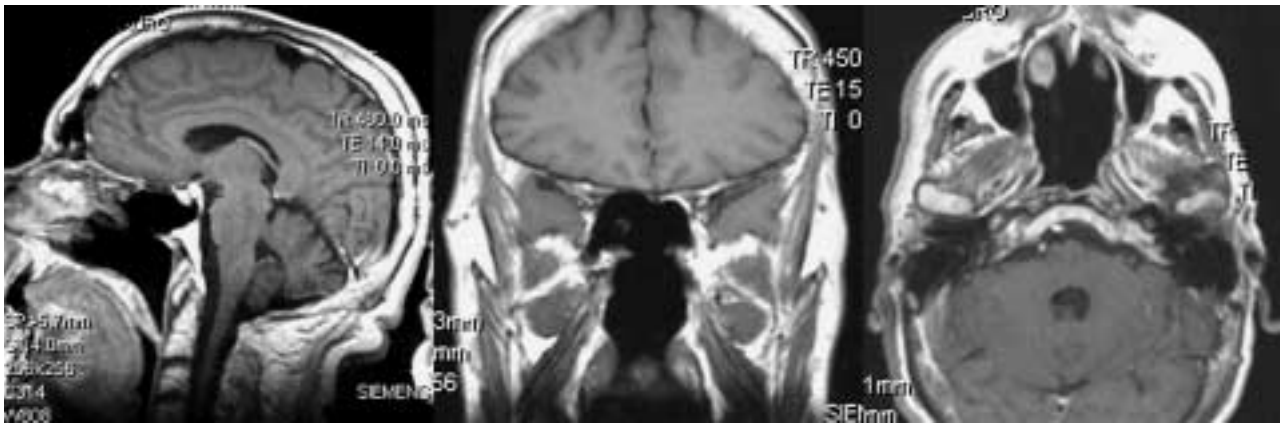

Figure 3 Postoperative NRI (sagittal, coronal, and axial views) showing the complete resection of the lesion.

bone, cavernous sinus, and third ventricle (2–16). Adenomas of the pituitary gland, especially prolactin-secreting adenomas, can spread out of the sella involving the sphenoid sinus (21) and the extrasellar component of the tumour may be sometimes the largest one, but they cannot be considered ectopic pituitary adenomas because of the concomitant pituitary involvement.

To our knowledge, about 50 ectopic pituitary adenomas have been reported so far (1–16). Signs and symptoms of presentation may be related to local mass effect and/or hormone hypersecretion (2–16). Headache may be the isolated symptom of presentation (15). Radiologically, ectopic pituitary adenomas may mimic other skull base lesions. Even histological diagnosis may be challenging; the differential diagnosis includes carcinoid, neuroendocrine carcinoma, paraganglioma, and carcinomas of the upper respiratory tract (9). Malignant transformation is exceptional (22). The majority of adenomas arising from ectopic hypophysial tissue are adrenocorticotrophin-secreting adenomas (2, 6, 8, 12). Surgical therapy is the mainstay of treatment and can be associated with postoperative radiotherapy whenever resection is incomplete.

Compared with the previous case reported by Cooper & Wenig (17), the present case shows a number of similarities, and some differences as well. Interestingly, in both cases the tumour had caused hyperthyroidism for many years and patients were misdiagnosed as having Graves' disease. As a consequence, both patients were mistakenly treated with therapies directed at the thyroid. The patient reported by Cooper & Wenig (17) had been treated with antithyroid drugs for 9 years before having radioiodine thyroid ablation. The patient reported herein had an 18-year history of hyperthyroidism and he was still receiving methimazole orally when the inappropriate secretion of TSH was suspected and neuroradiological examination of the sella turcica was performed. Interestingly, there was no evidence of sellar lesion on MRI, further confounding the diagnosis. However, MRI was useful for evaluating the extension of the extrasellar mass, the integrity of the sellar dura, and the presence of a normal pituitary gland.

TSH-secreting pituitary adenomas are uncommon, accounting for about 1–2% of all pituitary adenomas (18, 23). Diagnostic criteria include the presence of detectable TSH levels in spite of high free thyroid hormone concentrations and radiological evidence of a pituitary tumour by computed tomography and/or MRI (18, 19). Given the normal appearance of the sella turcica by MRI, the patient reported here did not completely fulfil the classical diagnostic criteria for TSH-secreting pituitary adenoma. In such instances, preoperative additional diagnostic tools (i.e. the TSH response to thyrotrophin-releasing hormone, the baseline α-subunit, the α-subunit to TSH molar ratio) might have been useful in differentiating central hyperthyroidism due to a TSH-oma from the variant of thyroid hormone resistance with predominant pituitary resistance (18–20). In fact, no significant difference in serum TSH levels and free thyroid hormone concentrations was found between patients with TSH-oma and those with thyroid hormone resistance (18, 19). Anyhow, in our patient the presence of a large mass in the sphenoid sinus was an intriguing adjunctive issue. This finding, together with disabling symptoms of nasal obstruction, which had been misjudged for many years, forwarded the diagnostic procedure and the patient was thus evaluated for surgery.

Our patient epitomises the effects of a diagnostic challenge that highlights the need to consider inappropriate secretion of TSH as part of the differential diagnosis in hyperthyroid states. Another lesson from this report is that it is important to take a thorough history and not dismiss persistent, albeit apparent minor, symptoms, such as nasal obstruction. Now and then, there may be more than first meets the eye.

Even though ectopic TSH-omas are quite unusual, they could be added to the list of the possible causes of inappropriate secretion of TSH, in order to reduce further the possibility of future pitfalls and inadequate treatment of patients.

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