Secondary Hyperthyroidism due to an Ectopic Thyrotropin-Secreting Neuroendocrine Pituitary Tumor: A Case Report

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What Is Known about This Topic?

- The differential diagnosis of secondary hyperthyroidism may lead to several challenges.
- Although very rare, ectopic thyrotropin-secreting neuroendocrine pituitary tumors (TSH-PitNETs) need to be considered in the diagnostic process.
- Biochemical tests, family history, and functional as well as non-functional imaging studies may be helpful in establishing a diagnosis.

What Does This Case Report Add?

- We present the very rare case of a patient with an ectopic TSH-PitNET.
- We give detailed advice on useful biochemical and imaging tests and compare their use to previously reported cases.
- Preoperative treatment with somatostatin analogues may be useful in achieving euthyroidism in ectopic TSH-PitNETs.
- Functional imaging with new gallium-labelled somatostatin analogues may be helpful in the diagnostic process of ectopic TSH-PitNETs.

Keywords

Thyrotropin-secreting neuroendocrine pituitary tumors · Ectopic pituitary adenoma · Secondary hyperthyroidism

Abstract

Introduction: The main differential diagnoses of secondary hyperthyroidism include thyrotropin-secreting neuroendocrine pituitary tumors (TSH-PitNETs) and resistance to thyroid hormone. As a rare cause of secondary hyperthyroidism,

ectopic thyrotropin-producing neuroendocrine pituitary tumors must also be considered. **Case Presentation:** A 48-year-old female patient with overt hyperthyroidism and elevated thyrotropin was admitted to the endocrine outpatient clinic of a secondary care hospital in March 2018. The patient had an inconspicuous pituitary MRI and F18-F-DOPA PET-CT, but showed a tumor mass located at the pharyngeal roof. Most biochemical tests and an increased tracer uptake of the pharyngeal mass in a Ga68-DOTANOC PET-CT argued for the presence of an ectopic TSH-PitNET. After treatment with octreotide over 5 days and a consecutive normalization of free thyroxine and free triiodothyronine, the tumor was endoscopically resected. Histologically, the mass consisted of small partially spindle, partially polygonal monomorphic to mildly pleomorphic cells with immunoreactivity for thyrotropin and luteinizing hormone. Postoperatively, the patient required intermittent levothyroxine therapy. **Discussion and Conclusions:** Ectopic TSH-PitNETs represent an extremely rare cause for secondary hyperthyroidism. While the diagnostic process may be complicated by negative imaging studies of the pituitary gland, family history, biochemical tests, and functional imaging using gallium-labelled somatostatin analogues may be helpful in establishing the diagnosis.

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Introduction

Thyrotropin-secreting neuroendocrine pituitary tumors (TSH-PitNETs) represent an unusual cause for hyperthyroidism and account for approximately 0.5–3% of all pituitary tumors [1]. While TSH-PitNETs are usually found within the pituitary gland, adenomas with ectopic growth are exceptionally rare findings. To this date, only a handful of cases have been reported in the literature [2–11]. Patients with TSH-PitNETs usually present with elevated concentrations of free thyroxine (fT4) and free triiodothyronine (fT3), while TSH is either inadequately elevated or within the normal range [1]. Thus and in view of the therapeutic consequences, distinction from other possible causes of hyperthyroidism with elevated or inappropriately normal TSH (secondary hyperthyroidism) is required, including in particular resistance to thyroid hormone (RTH) [1]. This differential diagnosis can be occasionally challenging, and despite careful interpretation of biochemical, functional, and imaging studies, a clear diagnosis cannot always be established [12]. In ectopic TSH-PitNETs, this process is further complicated due to mostly negative imaging studies of the pituitary

Fig. 1. Magnetic resonance imaging showing the suspicious lesion at the pharyngeal roof adjacent to the choanae.

gland. For all TSH-PitNETs, either within the pituitary or ectopic, surgical removal is the treatment option of choice [13]; further alternative treatment modalities include somatostatin analogues, dopamine agonists, and radiation therapy [1].

Due to the rarity of ectopic TSH-PitNETs, no clear guidelines and recommendations currently exist, leading to several unanswered diagnostic and therapeutic questions, since even the treatment of sellar TSH-PitNETs can be challenging. In this report, we describe the case of a 48-year-old woman with an ectopic TSH-PitNET at the pharyngeal roof. We also discuss and compare our approach to previously reported cases and give an overview of diagnostic and therapeutic steps.

Case Presentation

A 48-year-old female patient was admitted to the endocrine outpatient clinic of a secondary care hospital in March 2018. In February 2018, overt hyperthyroidism with elevated TSH had been diagnosed during routine laboratory tests. Subsequent magnetic resonance imaging (MRI) had shown no pituitary lesions, but a T1 isointense, T2 slightly hyperintense mass with few point-shaped intralésional hyperintensities and a homogenous contrast enhancement without diffusion restriction at the nasopharyngeal roof (Fig. 1). The lesion had an extent of axial 20 mm, sagittal 18 mm, and a craniocaudal extent of about 17 mm, showed regional infiltration and elevated the floor of the sphenoid sinus on the left side. After persistent uncontrolled overt hyperthyroidism had been found during the preoperative check-up for a planned biopsy of the mass, the patient was referred to the endocrine outpatient clinic.

At the time of admission to the endocrine outpatient clinic in March 2018, the patient was taking 80 mg of propylthiouracil and 2.5 mg of bisoprolol. Thyroid function tests showed elevated levels

Fig. 2. PET-CT imaging with 306.4 MBq F18-F-DOPA (left) and 130 MBq Ga68-DOTANOC (right).

of TSH (6.20 μ U/mL; normal 0.27–4.20), fT4 (45.7 pmol/L; normal 13.0–23.0), and fT3 (16.9 pmol/L; normal 3.1–6.8). Thyroid-specific antibodies, including TSH receptor antibodies, were within the normal range. Sex hormone-binding globulin (SHBG) was elevated (149.8 nmol/L; normal 19.0–117.0), while other hormonal parameters, including pituitary hormones (adrenocorticotrophic hormone [ACTH], growth hormone [GH], prolactin, luteinizing hormone [LH], follicle-stimulating hormone [FSH]), cortisol, insulin-like growth factor 1 (IGF-1), and estradiol, were within the normal range. Regarding bone turnover markers, the patient showed elevated β -crosslaps (CTX, 0.43 ng/mL; normal 0.03–0.37), osteocalcin (59 ng/mL; normal 1.0–35.0), and *procollagen type 1 N-terminal* propeptide (P1NP, 136.4 ng/mL; normal 16.0–67.0). Furthermore, the α -glycoprotein hormone subunit (α -GSU) was found to be above the normal range (2.5 U/L; normal –0.6 for premenopausal women), resulting in an α -GSU/TSH molar ratio of 4.0 (calculated as α -GSU in μ g/L divided by TSH in μ U/mL $\times 10$; upper normal range for premenopausal women with elevated TSH 0.7) [14]. Clinically, the patient reported palpitations, vertigo, hyperhidrosis, and malaise since January 2018. According to the patient, the thyroid function during pregnancy about 20 years earlier had been euthyroid. Both parents had undergone surgery for benign nodular thyroid disease, while there was no family history of autoimmune thyroid disease. Sonography revealed a slightly enlarged thyroid (total volume 19.4 mL) with normal echogenicity and vascularization and without nodules. Positron emission tomography-computed tomography (PET-CT) with 306.4 MBq F18-F-DOPA showed an inconspicuous tracer distribution with no increased tracer uptake in the pharyngeal mass (Fig. 2). During thyrotropin-releasing hormone (TRH) stimulation test, TSH increased from 6.11 to 19.66 μ U/mL.

For further evaluation, an additional PET-CT with 130 MBq of Ga68-DOTANOC was performed, showing a significantly increased tracer uptake in the suspicious lesion, corresponding to a somatostatin receptor-positive tumor (Fig. 2). In synopsis of the findings, the diagnosis of an ectopic TSH-PitNET at the pharyngeal roof was established. Thus, the planned biopsy was omitted while the patient was directly referred to surgical removal of the mass. In accordance with the findings in the recent Ga68-DOTANOC PET-CT, the patient received 100 μ g of octreotide three times daily over 5 days prior to the planned surgery, resulting in a

decrease of fT3 and fT4 into normal range. At the same time, the ongoing treatment with propylthiouracil was discontinued.

On May 15, the tumor was endoscopically resected via a transnasal approach. Histologically, it consisted of small partially spindle, partially polygonal monomorphic to mildly pleomorphic cells with immunoreactivity for chromogranin A and synaptophysin. In addition, the tumor cells revealed immunoreactivity for TSH and LH, but not for FSH, prolactin, GH, ACTH, or CD56. There was no mitotic activity and the Ki67 labeling index was less than 1%.

Postoperatively, the patient showed central hypothyroidism with decreased TSH (0.01 μ U/mL, normal 0.27–4.20), fT4 (12.1 pmol/L, normal 13.0–23.0), and fT3 (3.09 pmol/L, normal 3.1–6.8). Consequently, the patient received 100 μ g of levothyroxine daily; octreotide was not continued after surgery. Over the course of the following months, TSH showed a steady increase while the dose of levothyroxine could be slowly tapered and was eventually discontinued in September 2019 (last thyroid function test in January 2019: TSH, 0.93 μ U/mL, normal 0.27–4.20; fT4, 14.4 pmol/L, normal 13.0–23.0; fT3, 4.1 pmol/L, normal 3.1–6.8).

Discussion

We present the rare case of an ectopic TSH-PitNET with successful surgical removal following preoperative treatment with octreotide and positive imaging in a Ga68-DOTANOC PET-CT. Ectopic pituitary tumors are exceedingly rare entities: a recent literature review [15] found only 85 reported cases, of which 85% were hormonally active. While ACTH was the most frequently secreted hormone by these tumors (46%), TSH was secreted to a much smaller extent (16%) [15]. Apart from this patient, only ten other cases of ectopic TSH-PitNETs have been reported in the literature so far [2–11]. Similar to the majority of the previous cases, our patient's tumor was located within the nasopharynx. As described in some of

the existing reports on TSH-PitNETs [5, 9], pharyngeal masses may lead to symptoms of local tissue compression, e.g., nasal obstruction. This was not the case in our patient, who exclusively reported typical symptoms of hyperthyroidism.

In view of diagnostic and therapeutic consequences, RTH needs to be excluded in all patients with hyperthyroidism with elevated TSH. This is particularly important in individuals where no pituitary mass can be found in imaging studies. However, the differentiation between TSH-PitNETs and RTH can sometimes be a challenging task. In RTH, a positive family history can be found in approximately 70% of patients, owing to mutations in the thyroid hormone receptor beta gene in the majority of cases [13]. Thus, similar biochemical phenotypes in first-degree relatives are highly suggestive of RTH [13]. Measurement of α -GSU can be helpful, since its serum concentration as well as the α -GSU/TSH molar ratio is increased in most TSH-PitNETs [13]. Furthermore, increased serum concentrations of SHBG and bone turnover markers as well as an increased fT3/fT4 ratio were found to be indicative of autonomously TSH-secreting tumors. Additionally, dynamic function tests can be performed to assist in establishing the diagnosis: after TRH stimulation, patients with TSH-PitNETs usually show a blunted TSH response when compared to RTH patients or controls, in which the response to TRH is usually preserved [13]. Following administration of 80–100 μ g of liothyronine daily over 8–10 days, an inhibition of TSH secretion is exclusively seen in patients with RTH, making it one of the most sensitive and specific tests for the diagnostic workup of secondary hyperthyroidism [16]. Furthermore, as most TSH-PitNETs retain their responsiveness to somatostatin, administration of long-acting somatostatin analogues (e.g., octreotide or lanreotide) usually leads to a significant decrease in fT3 and fT4 in individuals with TSH-PitNETs, while there is no effect on thyroid hormones in RTH [16].

The susceptibility of TSH-PitNETs to somatostatin also allows the use of functional imaging studies: pituitary adenomas, and in particular TSH-PitNETs, were found to express somatostatin receptor subtype (SSTR) 2 and 5, making them ideal targets for scintigraphic studies [17]. While scintigraphy with radio-labeled octreotide may therefore detect the majority of hormone-producing pituitary-derived adenomas, somatostatin receptor PET-CT possesses superior image quality and resolution [18]. Recently, new gallium-labelled somatostatin analogues (Ga68-DOTANOC, DOTATATE, DOTATOC) were increasingly used in the evaluation of neuroendocrine tu-

mors, while the experience in pituitary adenomas is currently limited [18–20]. However, their use in detecting functional orthotopic and ectopic pituitary tissue has been reported in some cases [19–22], while their value in detecting ectopic TSH-PitNETs was also reported in one previous case [11].

In our patient, biochemical tests predominantly suggested the diagnosis of a TSH-PitNET, including elevated SHBG, bone turnover markers, and α -GSU. Still, the TSH response following TRH administration remained uncharacteristic for TSH-PitNETs. While we observed an increase in TSH of 13.55 μ U/mL ($3.2\times$ increase), available study data suggests a median increase of 1.0 μ U/mL in TSH-PitNETs and a median increase of 12.1 μ U/mL in patients with RTH [12]. However, previous reports also suggest a blunted TSH response to TRH in most but not all TSH-PitNETs [16]. Additionally, one previous case report [2] of an ectopic TSH-PitNET also reported a 3.9-fold increase in TSH after TRH administration, similar to our results. As TRH was administered in only three reported cases of ectopic TSH-PitNETs (including the current patient) [2, 6], it is currently unclear whether the increase in TSH is generally different than in sellar tumors. In our case, Ga68-DOTANOC PET-CT confirmed the expression of somatostatin receptors within the pharyngeal mass. Therefore, preoperative treatment with 100 μ g of octreotide administered three times daily over 5 days lead to normalization of the thyroid hormones. This approach to achieve euthyroidism in preparation for surgery is currently recommended by available guidelines [13] and was also successfully practiced in three cases of previous reports on ectopic TSH-PitNETs [4, 5, 7]. Unlike functional imaging with gallium-labelled somatostatin analogues, F18-F-DOPA PET-CT remained negative in our patient. Even though pituitary adenomas may appear as hypermetabolic in, for example, 18FDG PET-CT (50% of microadenomas and 100% of macroadenomas) [23, 24], somatostatin PET-CT is usually preferred and recommended [18].

Table 1 compares our patient to previously published reports of ectopic TSH-PitNETs. At the time of diagnosis, the patients' mean age was 48.3 years, while 5 of 9 patients were female. All but two TSH-PitNETs were located in the nasopharynx, and the remaining cases were located in the suprasellar space [8, 10]. While all masses were surgically resected, immunohistochemistry showed a broad variation across the reported cases. Following operative treatment, biochemical and/or radiological recurrence was not reported in any of the patients (Table 1). However, it must be noted that the criteria for the cure

Table 1. Characteristics of previously published cases of ectopic TSH-omas and the current case report

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8
Reference number	2	3	4	5	6	7	8	9
Patient age, years	66	52	50	49	41	46	46	37
Gender	female	male	female	female	male	male	male	female
Adenoma location	nasopharynx	nasopharynx	nasopharynx	nasopharynx	nasopharynx	nasopharynx	suprasellar	nasopharynx
Adenoma size	N/A	N/A	1.5×2.0 cm	2.0×2.0 cm	1.9×1.7 cm	1.4 cm	1.5×1.2×1.0 cm	N/A
TRH stimulation test	3.9× increase	N/A	N/A	N/A	Increase <2 µU/mL	N/A	N/A	N/A
α-GSU/TSH ratio	increased	N/A	N/A	N/A	N/A	N/A	N/A	N/A
SHBG	normal	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Bone turnover markers	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Functional imaging	N/A	N/A	N/A	99-mTc octreotide scan (positive)	technetium emission computed tomography (positive)	positron emission tomography (positive)	N/A	N/A
Preoperative application of somatostatin analogues	–	–	–	+	+	–	+	–
Immunohistochemistry								
TSH	+	+	+	+	+	+	+	+
FSH	+	–	+	–	–	N/A	N/A	N/A
LH	+	–	+	–	–	N/A	N/A	N/A
ACTH	+	–	–	–	–	N/A	N/A	N/A
GH	+	–	+	+	+	N/A	N/A	N/A
Prolactin	+	–	–	(+)	–	N/A	N/A	N/A
Histologic structure	cell nests, round nuclei, dispersed chromatin, granular eosinophilic cytoplasm	nests of monomorphic polygonal epithelial cells with round to ovoid nuclei	N/A	monomorphic cells, distinct cell border, abundant granulated cytoplasm, round or oval nuclei	polymorphous cells with secretory granules	monomorphic polygonal epithelial cells, round to ovoid nuclei, dispersed chromatin, granular eosinophilic cytoplasm	N/A	N/A
Follow-up	2 months; no reoccurrence	10 months; possible reoccurrence	4 months; no reoccurrence	3 months; no reoccurrence	48 months; no reoccurrence	3 years; no reoccurrence	6 months; no reoccurrence	3 years; no reoccurrence
	Case 9	Case 10	Case 11					
Reference number	10	11	Current case					
Patient age	41	48	48					
Gender	male	female	female					
Adenoma location	suprasellar	nasopharynx	nasopharynx					
Adenoma size	N/A	0.9×1.0 cm	2.0×1.6 cm					
TRH stimulation test	N/A	N/A	3.2× increase					
α-GSU/TSH ratio	N/A	increased	increased					
SHBG	N/A	N/A	increased					
Bone turnover markers	N/A	N/A	increased					
Functional imaging	18F-FDG PET (negative)	DOTATATE PET-CT (positive)	F-DOPA (negative) and DOTANOC PET-CT (positive)					
Preoperative application of somatostatin analogues	–	–	+					
Immunohistochemistry								
TSH	+	+	+					
FSH	–	N/A	–					
LH	–	N/A	+					
ACTH	–	–	–					
GH	–	N/A	–					
Prolactin	–	+	–					
Histologic structure	diffusely growing adenoma cells, acidophilic or chromophobic cytoplasm	N/A	small partially spindle, partially polygonal monomorphic to mildly pleomorphic cells					
Follow-up	7 years; no reoccurrence	5 months; no reoccurrence	1 year; no reoccurrence					

α-GSU, α-glycoprotein hormone subunit; ACTH, adrenocorticotrophic hormone; FSH, follicle-stimulating hormone; GH, growth hormone; LH, luteinizing hormone; SHBG, sex hormone-binding globulin; TRH, thyrotropin-releasing hormone; TSH, thyrotropin.

of TSH-PitNETs (either orthotopic or ectopic) are currently not clearly established. In general, clinical and biochemical examinations are recommended during the first postoperative year, followed by yearly controls in the subsequent years. At least after surgical resection of TSH-PitNETs within the pituitary, imaging studies are recommended every 2 or 3 years or after biochemical resurgence [13].

Conclusions

In conclusion, ectopic TSH-PitNETs represent an extremely rare cause for hyperthyroidism with inadequately high or normal TSH. Challenges in the diagnostic process may arise due to negative imaging studies of the pituitary gland, making the distinction from RTH paramount. Family history and biochemical tests, including the measurement of α -GSU, the α -GSU/TSH molar ratio, bone turnover markers, and SHBG may prove helpful. Furthermore, functional tests, i.e., monitoring of TSH response to TRH and liothyronine administration, may also help to distinguish between TSH-PitNETs and RTH. Regarding functional imaging, somatostatin receptor PET-CT, especially with new gallium-labelled somatosta-

tin analogues, is able to detect suspicious extrasellar lesions in cases with missing pituitary masses but with biochemical findings suggestive of a TSH-PitNET.

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Statement of Ethics

Written informed consent to publish this case report was obtained from the patient.

Disclosure Statement

The authors have no conflicts of interest to declare.

Author Contributions

All persons listed as authors made significant contributions to the design, analysis, and interpretation of the included data, as well as assisted with critical revisions of the writing, and approved the final version for submission for publication.

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