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Plurihormonal Pituitary Tumor of Pit-1 and SF-1 Lineages, with Synchronous Collision Corticotroph Tumor: a Possible Stem Cell Phenomenon

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Abstract

Thyrotropin (TSH)-secreting pituitary tumors are the rarest functioning pituitary tumors. Nonetheless, they are not infrequently plurihormonal, as they may express/secrete hormones made by other pituitary cells derived from the Pit-1 lineage such as growth hormone (GH), prolactin (PRL), and α-subunit (αSU). However, adrenocorticotropin (ACTH) or gonadotropin secretion by such a tumor is exceptional. Although double pituitary tumors are rare, they often combine ACTH and GH secretion. A 41-year-old presented almost 2 years after delivering her 10th child; she had thyrotoxicosis (goiter and palpitations) masquerading as autoimmune postpartum thyroiditis. She was still breastfeeding and amenorrheic. She proved to have TSH, GH, PRL, and ACTH hypersecretion. Imaging revealed an invasive pituitary macrotumor. She had stigmata neither of Cushing's disease nor of acromegaly. Prior to surgery, hormonal control was achieved for close to 1 year by combined octreotide and cabergoline treatment with significant shrinking of the tumor. Following surgery, pathology revealed a collision tumor; the dominant lesion was positive for GH, βTSH, βFSH, and αSU and expressed both Pit-1 and SF-1.The smaller lesion was a corticotroph tumor. We report an unusual plurihormonal tumor co-expressing Pit-1 and SF-1 along with hormones made by cells of both lineages. Its simultaneous occurrence adjacent to a corticotroph tumor raises questions regarding the pathogenesis of these tumors. We propose the possibility of a stem cell tumor with multiple lineage differentiation. We hypothesize that pregnancy might have played a permissive role in tumorigenesis.

Keywords Pituitary tumor · SF-1 · Pit-1 · Stem cell · Collision · Double tumor · Plurihormonal

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Background

Pituitary tumors presenting with thyrotropin (TSH) excess are the rarest type of adenohypophysial neoplasms, comprising 1.2 to 3% in large surgical series [1–6]. TSH excess can be caused by thyrotroph tumors or by other TSH-producing tumors, and the variations among published series may reflect definition bias [1–6]. There is agreement that these tumors are usually macrotumors, which tend to be invasive and produce mass effects.

True thyrotroph tumors are monohormonal neoplasms. Plurihormonal tumors producing TSH are usually of the cell lineage specified by the transcription factor Pit-1 that regulates production of growth hormone (GH), prolactin (PRL), βTSH, and α-subunit (αSU); they may be either poorly differentiated Pit-1 lineage tumors [6] or mature plurihormonal tumors resembling mammosomatotrophs [7]. In contrast, unusual plurihormonal tumors do not reflect lineage specificity. The distinction is dependent on

systematic immunohistochemical analysis of the tumor, which tends to be inconsistent [8, 9].

We report an extremely unusual case of a 41-year-old woman with a clinically and biochemically active pituitary macrotumor secreting TSH, GH, PRL, and adrenocorticotropin (ACTH), who presented with thyrotoxicosis presumed to represent postpartum thyroiditis.

Case Report

A 41-year-old Caucasian lady of Ashkenazi descent was referred in April 2016 for what appeared to be an unusual case of postpartum thyroiditis. As a grand multipara, she had delivered her 10th child in May 2014, following an uncomplicated pregnancy, including a normal glucose tolerance test. Her previous deliveries had been at 2-year intervals. Seven months after giving birth, on routine blood tests, she was noted to have a serum TSH of 8.2 mIU/L (laboratory reference 0.5–4.8), with a normal free thyroxine (fT4) of 12.3 pmol/L (10.3–19.7). A repeat thyroid function test done 2 months later yielded a similar result (TSH 6.8 mIU/L and fT4 12.8 pmol/L); however, at this time, she had an elevated titer of thyroid peroxidase antibodies of 208 IU/mL, supporting a diagnosis of autoimmune postpartum thyroiditis. At this stage, her primary care physician initiated thyroxine supplementation at a weekly dose of 500 μg. Three months later, the TSH concentration was still slightly elevated at 5.7 mIU/L, while the fT4 had increased to 15.6 pmol/L. The thyroxine weekly dose was increased to 600 μg, following which TSH was still above normal at 6.75 mIU/L, and fT4 demonstrated a further rise to 19.3 pmol/L. This result led her treating physician to further increase the dose to 700 μg. She was finally referred when the TSH remained elevated at 6.3 mIU/L while fT4 had reached 26.7 pmol/L. At her first visit at the consulting institution, she reported being still amenorrheic, a fact she ascribed to prolonged breastfeeding; a pregnancy test was negative. She denied any previous medical history with the exception of the surgical correction of a carpal tunnel syndrome a month prior to her referral. She also noted she had recently experienced palpitations but denied headaches, visual disturbances, weight gain, or acral enlargement. There was no relevant family history. On physical examination, she had no stigmata of any endocrinopathy. At 174 cm, she weighed 77 kg (BMI 25.4 kg/m^2). She had a regular heart rate of 110 per minute, a blood pressure of 110/70 mmHg. The only relevant finding was a diffusely enlarged, soft, and smooth thyroid gland. She was requested to discontinue the thyroxine treatment, following which a repeat TSH was 5.6 mIU/L, but the fT4 had further risen to 30.2 pmol/L, and an elevated fT3 was documented for the first time at 11.5 pmol/L (normal range 3.5–6.5). As she had had several documented normal thyroid function results prior to her last pregnancy, thyroid hormone resistance was deemed unlikely, and a TSH-secreting tumor was suspected. A full pituitary function profile was obtained (Table 1), which suggested secretion of prolactin, TSH, and GH by a plurihormonal tumor. Indeed, magnetic resonance imaging (MRI) demonstrated the presence of an invasive left-sided intrasellar and suprasellar 23.8 × 20.8-mm macrotumor, invading the cavernous sinus and extending to the base of the skull (Fig. 1a). The optic chiasm was spared, consistent with normal visual fields.

Other baseline laboratory tests were notable for a high normal fasting blood glucose (99–101 mg/dL), along with a slightly elevated hemoglobin (Hb)A1c of 5.8%. She also had an abnormal alkaline phosphatase concentration on account of an elevated bone isoenzyme of 132 U/L (normal up to 69), and a slight hyperphosphatemia of 1.68 mmol/L, all consistent with GH hypersecretion.

As there was no danger to her vision, medical treatment was offered first to control hypersecretion, while possibly shrinking the tumor prior to surgery. She was started on cabergoline at a dose of 0.5 mg twice weekly and long-acting octreotide depot 20 mg monthly. Menses resumed within 1 month, she soon became asymptomatic, and she was advised to start using barrier contraception. The hormonal response to therapy, indicating full control of hypersecretion, is shown in Table 1. Additionally, within 5 months of treatment, considerable shrinkage of the tumor was noted on MRI (Fig. 1b). It was thus decided to continue medical treatment in the hope that further tumor volume reduction would be achieved, possibly facilitating subsequent surgery. Despite the octreotide treatment, an increase in the fasting blood glucose to 6.4 mmol/L along with a rise in HbA1c to 6.1%, and triglycerides to 2.19 mmol/L together with some weight gain, prompted formal testing to exclude Cushing's disease. Although repeated 24 h urine collections for cortisol were always in the normal range, morning serum cortisol concentrations were consistently elevated (620–820 nmol/L), suppression with 1 mg dexamethasone was inadequate (80 nmol/L, normal< 50 nmol/L), and midnight salivary cortisol values were repeatedly elevated, confirming hypercortisolism. ACTH levels were not suppressed, suggesting that the hypercortisolism was also due to the pituitary process. Seven months after medical therapy was started, some escape from control over GH secretion was noted, and the patient was referred for transsphenoidal surgery. All medications were withheld. Table 1 shows the patient's pre- and postoperative hormonal values. As the cavernous sinus was invaded, no cure was expected, but a further significant anatomical improvement was achieved. Octreotide was eventually resumed 4 months after surgery, when IGF1 levels and thyroid hormones started rising. Full hormonal control was again achieved. Prolactin levels also started rising within the normal range 3 months after surgery to become frankly abnormal after 1 year. Despite the fact the patient still experienced

Table 1 Hormonal and biochemical evaluations at presentation, under medical treatment only and after surgery

	Baseline	4 months on medications[a]	9 months on medications	2 months postop off medications	4 months postop off medications[b]	15 months postop on octreotide[c]
FT4 (pmol/L) (10.3–19.7)	30.2	10.6	13.9	14.5	18	13
FT3 (pmol/L) (3.5–6.5)	11.5	3.6	4.8	4.5	6.7	4.5
TSH (mIU/L) (0.5–4.8)	5.7	4.7	5.2	5.2	7.18	5.1
Prolactin (mIU/L) (59–619)	4031	25	< 16	46	304	962
GH (μg/L) (0–8.0)	14.4	2.8	8.5	3.38	3.8	3.5
IGF1 (nmo/L) (5.63–27.38)	122.35	30	38.65	15.98	29.48	23.32
Cortisol 08:00 (nmol/L) (118–618)	623	814	862	426	674	566
Salivary cortisol (nmol/L) (0.0–3.31)			9.38	1.66	1.1	0.83
Glucose (mmol/L) (3.9–5.6)	5.5	6.4	6.4	5.6	6.2	5.8
HbA1c (%) (4.5–5.6)	5.8	5.8	6.1	5.8	5.8	5.7

[a] Medications consisted of octreotide depot 20 mg monthly and cabergoline 0.5 mg twice weekly

[b] Following this set of results, octreotide treatment was resumed

[c] Following these results, cabergoline treatment was resumed

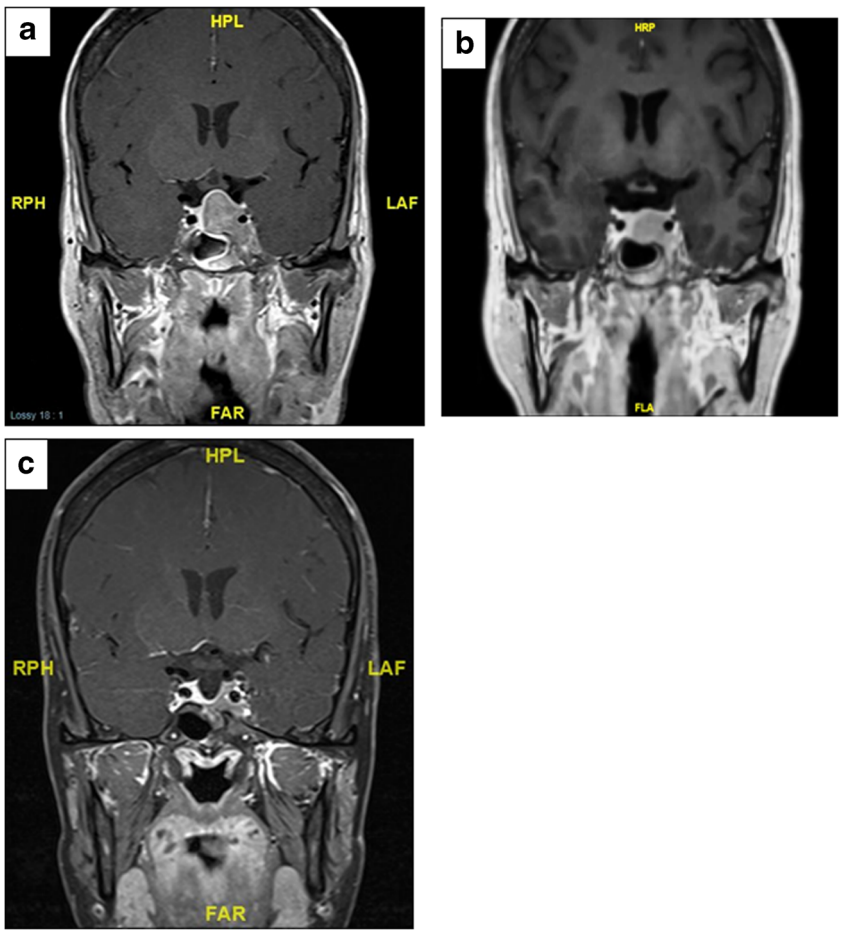

Fig. 1 T1-weighted contrast-enhanced imaging of the pituitary tumor. **a** At the time of presentation. **b** Six months into combined octreotide and cabergoline treatment before surgery, a significant shrinkage of the tumor can be seen. **c** Fifteen months after surgery under octreotide treatment, before resumption of cabergoline. The pictures clearly show the stalk free of any impingement as early as 6 months into the treatment

regular menses, cabergoline treatment was also resumed. As for hypercortisolism, there have been some fluctuating midnight salivary cortisol results; however, ACTH and morning cortisol values have been in the normal range. The patient continues to be free of any signs of Cushing's syndrome or acromegaly, and the thyroid gland is back to normal size. On the last MRI study, there was evidence of additional shrinkage of the postsurgical tumor remnant; the stalk was deviated but was free of any mass effect (Fig. 1c).

Histopathology Studies

The surgically resected tissue was collected in 10% buffered formalin and embedded in paraffin; no tissue was fixed for electron microscopy. Paraffin sections were stained with hematoxylin–eosin (H&E), the Gordon–Sweet silver stain for reticulin, and a panel of immunostains to detect the transcription factors Pit-1; steroidogenic factor-1 (SF-1); estrogen receptor alpha (ER); GATA-3 [10]; and thyroid transcription factor-1 (TTF-1); the hormones ACTH, GH, PRL, αSU, βTSH, βFSH, and βLH; and keratins (CAM 5.2 for keratins 8 and 18 and the AE1/AE3 antibody cocktail that identifies pancytokeratins). In addition, stains were also performed for p27, menin, and SDHB. The Ki67 proliferation index was obtained on sections stained with the MIB-1 antibody using the Leica Biosystems automated nuclear image analysis algorithm.

On hematoxylin and eosin (H&E) staining, the tumor appeared to consist of two discrete lesions with disrupted reticulin (Fig. 2a). The larger lesion was very strongly positive for GH but was unusual. It had focal spindle cell morphology and nuclear pleomorphism with prominent nucleoli. The tumor cell cytoplasm was vacuolated. It also stained for alpha-subunit, βTSH and βFSH. Pit-1 staining was diffusely positive but weaker than usual for a Pit-1 lineage tumor; SF-1 was also weakly and focally positive and scattered cells were positive for GATA-3. This tumor was negative for ER and PRL as well as βLH. The keratin pattern was nonspecific—perinuclear with no fibrous bodies. This tumor was therefore classified as a very unusual poorly differentiated plurihormonal tumor that showed features of Pit-1 lineage, similar to poorly differentiated tumors of Pit-1 lineage (6), but in addition with SF-1 lineage and βFSH expression. This pattern of

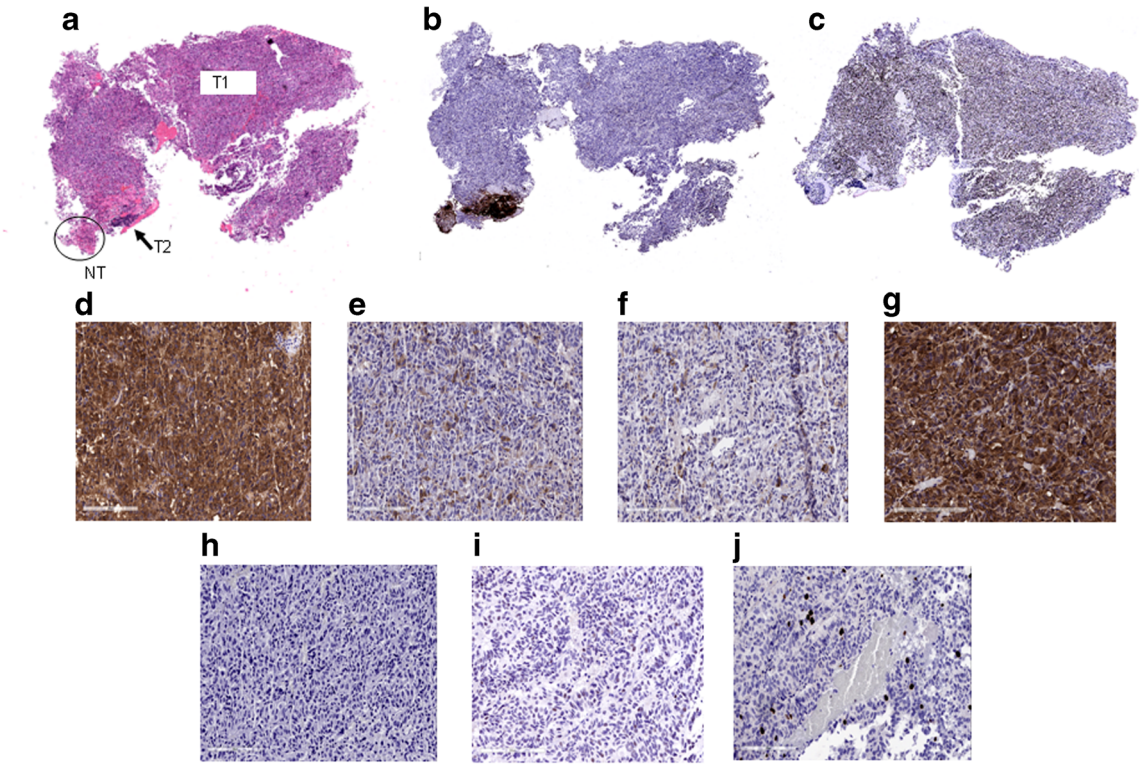

Fig. 2 Histology and immunohistochemistry of the double tumor. **a** A × 10 magnification H&E stain showing the two components of the lesion, the dominant tumor labeled T1, and the smaller tumor labeled T2; circled at the edge of the specimen is an area of normal tissue labeled NT with preserved reticulin pattern (not shown). **b** Intense ACTH staining in the smaller lesion, clearly demarcated from T1, with some staining in the normal tissue. **c** Positive Pit-1 staining in T1 but negative in T2. All following slides are from areas of T1 and are shown higher magnification; the bar at the bottom of each slide measures 200 μM. **d** Intense GH staining. **e** Patchy βTSH staining. **f** Weak but clear βFSH reactivity. **g** αSU staining. **h** Negative staining for PRL. **i** Focal and scattered positive staining for SF-1. **j** Ki67 staining estimated at 3.65 in T1

immunoreactivity indicates a possible stem cell tumor with dual lineage differentiation. The Ki67 of this tumor was 3.65 in an automated count of 959 cells using the Leica Biosystems automated nuclear algorithm.

The smaller lesion in this biopsy was a corticotroph tumor that was at one edge of the tissue and was very crushed. Despite the lack of good morphology, it was clearly positive for ACTH; although it was negative with Cam 5.2, an unusual feature for corticotrophs, it stained with pankeratins. It was negative for GATA-3, excluding the possibility of paraganglioma with ectopic ACTH, and it was negative for TTF-1, therefore not likely to be a metastasis of a lung, thyroid, or thymic neuroendocrine tumor. Staining for p27 was completely negative in this lesion, consistent with a functioning corticotroph tumor. The Ki67 of this lesion was hard to determine because of crush artifact but appeared to be low, making a metastasis less likely.

There was a small piece of nontumorous tissue adjacent to the corticotroph tumor that had freezing and crush artifact; it could not be used to evaluate Crooke's hyaline change.

Given the presence of multiple and unusual tumors, testing for genetic predisposition was performed. Stains for menin and SDHB showed intact reactivity, suggesting that these are not implicated [11]. The retained p27 reactivity in the dominant tumor makes this variant of MEN4 unlikely.

For clarity, comprehensive immunohistochemical characteristics of both components are shown in Table 2. The process was summarized as being a double neoplasm with a dominant, poorly differentiated, plurihormonal tumor with both Pit-1 and SF-1 lineage features, producing GH, βTSH, and βFSH. The smaller collision tumor was a corticotroph tumor NOS.

Table 2 Summary of immunohistochemical studies

	Dominant tumor	Small tumor
βTSH	+	–
GH	+++	–
PRL	–	–
βFSH	+	–
αSU	+	–
ACTH	–	++
Pit-1	+	–
SF-1	+	–
ER	–	–
PanCK	+	+
Cam 5.2	+	–
P27	+	–
TTF-1	–	–
GATA-3	+	–
Ki67	3.5	< 1

Discussion

Our patient, who presented as a case of "atypical autoimmune postpartum thyroiditis," turned out to have a double or "collision" pituitary tumor, consisting of a dominant poorly differentiated plurihormonal macrotumor of dual Pit-1 and SF-1 lineage, together with a corticotroph microtumor. Although she was not severely symptomatic, the dominant clinical picture was that of thyrotoxicosis with goiter and amenorrhea due to hyperprolactinemia in the typical macroprolactinoma range [12]. She had biochemical evidence of very significant GH hypersecretion, and mild, but unequivocal, hypercortisolism. However, none of these were clinically apparent.

Until the pathology was reported, we had anticipated this was possibly an additional case of bimorphous plurihormonal tumor positive for GH/TSH/PRL and ACTH.

There have been over 20 published cases of pituitary tumors expressing both GH and ACTH, with just a few exhibiting the expression of an additional hormone; in almost all cases, these tumors were collision tumors comprised of separate populations of cells [13]. We are aware of one just case in which a TSH-secreting tumor displayed immunoreactivity for PRL, GH, and ACTH, all of which were biochemically silent [14]. The discovery that this was a case of a double tumor came as a surprise as there was no prior indication upon imaging.

More frequently identified nowadays, multiple pituitary tumors are rare. In an unbiased series of 470 autopsies, they were present in 0.9% [15]. A compilation of seven large surgical studies suggests they amount to only 0.7% of all operations performed for pituitary tumors [6, 15–17]. A recent systematic review, which required preoperative MRI imaging pointing to the existence of multiple pituitary tumors, retrieved only 17 published reports out of a large number of potentially relevant studies [18], attesting to the fact that even with current imaging techniques, a preoperative diagnosis of a double tumor is not the rule. It was suggested that preoperative diagnosis of a double tumor accounts for no more than 25% of all proven cases, with contiguous tumors presenting a particular challenge to such an imaging-based diagnosis. In our case, even on repeated gadolinium-enhanced T1 weighted MRI imaging, there was no suggestion of the presence of the small, contiguous but well-demarcated corticotroph tumor.

While the pathogenesis of multiple tumors remains poorly understood, the hormonal activity of these tumors is for the most part characteristic of the present case. Indeed, in a review of the immunohistochemical pattern of double tumors [16], ACTH was identified in over 50% of the cases in one of the lesions, making Cushing's disease the most common clinical presentation (38%), followed by acromegaly (35%). Either clinical presentation or both are documented in approximately 70–80% of subjects with double tumors [15–18]. In the present case, although there was clear biochemical and

immunohistochemical expression of both ACTH and GH, the patient displayed no evidence of either acromegaly or Cushing's disease.

The clinical presentation was that of a TSH- and prolactin-secreting tumor, which together with major hyperprolactinemia, suggested a Pit-1 derived plurihormonal tumor. Because of the total lack of prolactin immunoreactivity in the tumor, it was first felt that the hyperprolactinemia represented an extreme case of stalk effect. However, the levels of prolactin at presentation together with the recurrence of hyperprolactinemia after surgery when the patient was off cabergoline and the stalk was completely free of any compression suggest that the residual tumor, like the original one, is indeed the source of prolactin oversecretion. Although it is unusual to see complete depletion of prolactin within a prolactin-producing tumor following prolonged dopamine agonist treatment, this has been previously reported [19]. We believe that prolonged treatment could explain the lack of prolactin reactivity in this case.

The unexpected feature of the dominant tumor, which we had previously encountered only once [17], was that it appeared to express both Pit-1, which regulates GH, βTSH, αSU, and PRL expression, and to a much lesser extent SF-1, possibly explaining the presence of βFSH-positive cells. As these transcription factors determine the terminal differentiation of separate anterior pituitary cell lineages, this previously unreported co-expression in the same tumor suggests the possibility that this could represent a poorly differentiated stem cell tumor. While evidence for pituitary stem cells (PSC) in adult pituitary tissue has been provided (reviewed in [20]), their role in tumorigenesis is still debated. Suggested more than 20 years ago [21], the evidence for the presence of such cells in human pituitary tumors required the advent of more sophisticated techniques, but it is now mounting [20]. Their precise role in the pathogenesis of pituitary tumors, and particularly in that of unusual plurihormonal tumors, is still unclear. Nonetheless, putative PSCs that express pituitary progenitor cell markers such as Sox-2 have been extracted from pituitary somatotroph and nonfunctioning tumors. Moreover, these cells divided in culture and could be induced to lose some stem cell markers and develop both Pit-1 and GH expression [22]. Thus, the theory that our patient's multi-lineage tumor emerged from dual pathway differentiation of PSC is a distinct possibility. It is also possible that the entrapped corticotroph tumor may reflect maturation of a common PSC. Future studies focusing on plurihormonal tumors might provide a more definite answer.

Finally, given the patient's impressive reproductive history, we assume the growth of the tumor itself was rapid, suggesting a role for pregnancy despite the absence of ER expression in the tumor. The numerous gestations this patient experienced could have played a permissive role in the course of events.

In summary, we have described an unusual case of a patient who presented with thyrotoxicosis, masquerading as autoimmune postpartum thyroiditis, due to a double pituitary tumor: a dominant TSH-secreting invasive unusual plurihormonal tumor of Pit-1 and SF-1 lineages that co-secreted GH, and PRL as well as expressing FSH, and a much smaller but contiguous ACTH-secreting corticotroph tumor. While she also had amenorrhea due to the hyperprolactinemia, there was biochemical evidence of GH and ACTH secretion that remained completely asymptomatic. Although surgery was required, albeit not curative due to cavernous sinus invasion, the plurihormonal tumor continues to be exquisitely responsive to octreotide and cabergoline. The multilineage features of this dominant tumor suggest that it might derive from an adenohypophysial stem cell that may also be the source of the adjacent corticotroph tumor. Future studies on the cell of origin and mechanisms of adenohypophysial tumorigenesis and possible links with pregnancy are needed.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Informed Consent The patient gave her consent to have the case reported; there are no details in the manuscript that could allow identification.

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