Case Report

Characteristics and treatment of a silent somatotroph tumor that had transformed to a functional type: a case report and literature review

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Background: "Functionalization" of silent pituitary neuroendocrine tumors (PitNETs) is a pretty rare clinical phenomenon that reportedly occurs most often with silent corticotroph tumors (SCTs). We report the case of silent somatotroph tumor (SST) that had transformed to functional type. We also review similar cases of SST with functionalization.

Case Description: A 43-year-old man without suggestive symptoms of a pituitary tumor was referred with a lesion in the sellar region detected incidentally. Serum insulin-like growth factor 1 (IGF-1) (348 ng/mL) was high, whereas growth hormone (GH) was within the normal range. A glucose GH inhibition test showed inhibition of GH to 0.4 ng/mL. Subtotal tumorectomy was performed via a transnasal-sphenoidal approach. Histopathological examination of the operative specimen showed weak expression of GH and diffuse staining of pituitary-specific transcription factor-1 (Pit-1). The final pathological diagnosis was SST. Five years after the first surgery without follow-up, the patient presented again because of headache, impaired vision, bone pain, and high blood glucose concentrations for 2 months. Physical examination showed early acromegalic features. Of interest, greatly increased concentrations of GH (7.2 ng/mL) and IGF-1 (533 ng/mL) were found. Magnetic resonance imaging showed the recurrence of tumor. A diagnosis of acromegaly was considered. The patient underwent a second transsphenoidal pituitary tumor resection, after which his serum GH and IGF-1 concentrations decreased. Unlike the original surgical specimen, immunohistochemical examination of the tissue resected during the second surgery showed strong GH positivity, with similarly strong Pit-1 positivity. The patient was followed up for 6 months without octreotide treatment. At the last follow-up, he was found to have high serum concentrations of GH and IGF-1, which demonstrated another progression of the remnant PitNET. After two courses of octreotide acetate microspheres (20 mg/month), the acromegaly was under control.

Conclusions: In addition to SCTs, other silent PitNETs could also functionalize. Medical teams of PitNETs should recognize this rare phenomenon and conduct long-term follow-up. After functionalization, these tumors have a high recurrence rate, requiring multiple therapies and long-term follow-up. Further research is essential to determine the mechanism of regulation of secretion of GH by such tumors.

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Keywords: Acromegaly; pituitary adenoma; pituitary neuroendocrine tumor (PitNET); silent somatotroph adenoma; case report

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Introduction

Pituitary neuroendocrine tumors (PitNETs), formerly known as pituitary adenomas, originate from anterior pituitary gland cells (1). They are the second most common intracranial tumors, accounting for 15–20% of them (2). Some PitNETs overproduce specific hormones, leading to the corresponding clinical syndromes. The 15–30% of PitNETs that do not secrete hormones are known as non-functioning pituitary tumors (NFPTs). The 5th edition of the Word Health Organization (WHO) Classification of Endocrine and Neuroendocrine Tumors [2022] proposes that PitNETs should be classified on the basis of hormones, transcription factors, and other biomarkers, as determined by immunohistochemical (IHC) findings (1). Most NFPTs are asymptomatic and are associated with normal serum concentrations of pituitary hormones; however, most of them express hormones and specific transcription factors on IHC testing. This subset is called silent pituitary tumors (SPTs). Accounting for approximately 99.4% of NFPTs (the other 0.6% is called null cell tumor), SPTs derive from specific pituitary cell lineages based on transcription factors, as do functional PitNETs (3). By definition, silent somatotroph tumors (SSTs) derive from a pituitary-specific transcription factor-1 (Pit-1) lineage and show positive immunostaining for growth hormone (GH), but lack clinical or serological evidence of acromegaly (4). Modification of hormone secretion by PitNETs after recurrence is rare. Most documented cases are of silent corticotroph tumors (SCTs) transforming to causing Cushing disease (4-6).

Here, we report a patient with a PitNET that changed from an SST to a functional somatotroph tumor over a 5-year period. Our patient's tumor was invasive and regrew repeatedly. We have also reviewed similar reported cases (7,8) (*Table 1*). We present this case in accordance with the CARE reporting checklist (available at https://gs.amegroups.com/article/view/10.21037/gs-24-79/rc).

Highlight box

Key findings

- Functionalization of silent pituitary neuroendocrine tumors (PitNETs) can also happen in silent somatotroph tumor (SST).
- The somatotroph tumors after functionalization tend to recurrent and need multiple therapies.

What is known and what is new?

- The PitNETs tend to express stable secretory model in the course. The phenotype transformation is a rare biological behavior, of which the most common form is functionalization of silent corticotroph tumors.
- SST may transform to acromegaly when the tumor recurs. This interval may be years. Therefore, a long-term follow-up is necessary for these silent PitNETs. The tumor after functionalization may be hard to control.

What is the implication, and what should change now?

- Medical teams of PitNETs are supposed to recognize the phenotype transformation of SSTs. These cases may help us figure out the mechanism of growth hormone regulation in somatotroph tumor.

Case presentation

A 43-year-old man was referred to the neurosurgery department of Peking Union Medical College Hospital with a lesion in the sellar region that had been detected incidentally during treatment for type 2 diabetes and primary hypothyroidism (treated with 75 μg/day during the perioperative period and for long term). The patient had no suggestive symptoms nor other evidence of a pituitary tumor such as headache, visual loss, or pituitary-related hormonal syndromes. Measurements of serum pituitary-related hormones showed high concentrations of thyroid stimulating hormone (60.97 μIU/mL; normal range, 0.380–4.340 μIU/mL), prolactin (PRL) (19.72 ng/mL; normal range, 2.6–13.1 ng/mL), and insulin-like growth factor 1 (IGF-1) (348 ng/mL; normal range, 101–267 ng/mL) and low concentrations of free thyroxine (fT4) (0.648 ng/dL; normal range, 0.81–1.89 ng/dL) and testosterone (1.74 ng/mL; normal range, 1.75–7.81 ng/mL), whereas GH and cortisol were within the normal range. A glucose GH inhibition test showed inhibition of GH to 0.4 ng/mL, ruling out the

Table 1 Reported cases of SSTs that changed to functional GH tumors

Case	Author, year	Sex/age of first visit (years)	Time up recurrence (years)	Timing before/after the transformation	GH level (ng/mL)	IGF-1 level (ng/mL)	Staining of GH	Staining of Pit-1	Ki-67 index before and after functionalization	Treatment
1	Daems, 2009 (7)	M/41	7	Before	0.7	Not tested	Strong positivity for GH in most cells	Not tested	Not mentioned	Transsphenoidal surgery
				After	4.0↑	609↑	Refusing the second surgery	Not tested	Not mentioned	Refusing the second surgery; octreotide and cabergoline did not work but the pegvisomant was effective
2	Batisse, 2013 (8)	M/47	9	Before	Not mentioned	180	5% of the cells were positive for GH	Not tested	Negative	Transsphenoidal surgery and radiotherapy
				After	2.2↑	486↑	40% of cells were positive for GH	Not tested	6%	A second transsphenoidal surgery, octreotide, TMZ and combine chemotherapy by cisplatin and adriamycin was not effective
Our case	–	M/43	5	Before	1.4	348↑	Weakly positive for GH	Positive for Pit-1 in most cells	5%	Transsphenoidal surgery
				After	8.2↑	533↑	Densely and strongly positive for GH	Positive for Pit-1 in most cells	3%	A second transsphenoidal surgery and octreotide

One case reported by Bengtsson *et al.* (9) and one by Langlois *et al.* (10) were excluded because of insufficient data. ↑: above the normal range. SSTs, silent somatotroph tumors; GH, growth hormone; M, male; IGF-1, insulin-like growth factor 1; Pit-1, pituitary-specific transcription factor-1; TMZ, temozolomide.

diagnosis of acromegaly. Magnetic resonance imaging (MRI) (*Figure 1*) showed an approximately 11 mm × 11 mm × 12 mm mass in the right sellar region and invading the right cavernous sinus (*Figure 1A*) and the pituitary stalk is normal. Tumors located in the front and the right of the pituitary stalk, normal pituitary gland tissue left. The provisional diagnosis was non-functioning pituitary macroadenoma. Considering the tumor size (>1 cm), invasion and risky location, subtotal tumorectomy was therefore performed via a transnasal-sphenoidal approach (*Figure 1B*) and the remnant is about 6 mm × 5 mm × 6 mm. Histopathological examination (*Figure 2*) of the operative specimen showed solid pituitary adenoma nest weak in haematoxylin and eosin (H&E) staining (*Figure 2A*). IHC staining showed positivity of GH (60%) and diffuse expression of Pit-1 (*Figure 2B*,*2C*) and was negative for expression of

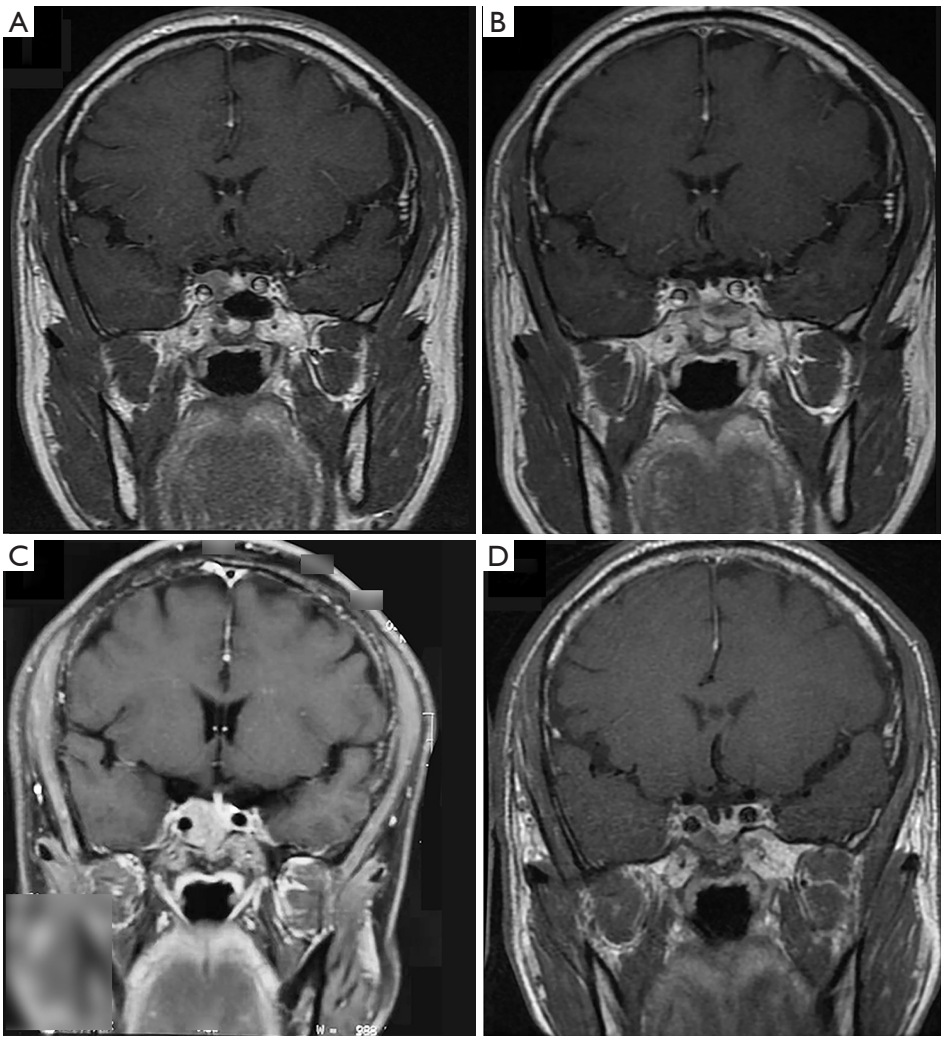

Figure 1 Images in different stages. (A) Preoperative MRI image in April 2017: there is an 11 mm × 11 mm × 12 mm macroadenoma surrounding the internal carotid artery. (B) MRI image 3 months postoperatively showing some remnant tumor tissue (6 mm × 5 mm × 6 mm) in irregular shape surrounding the internal carotid artery. (C) Preoperative MRI image in 2022 showing tumor regrowth (17 mm × 17 mm × 19 mm). (D) MRI image 3 months after the second surgery showing some remnant tumor tissue (8 mm × 10 mm × 8 mm) still existing. MRI, magnetic resonance imaging.

other pituitary hormones and transcription factors. The globular fibrous bodies strongly positive for CAM5.2 were visible in the cytoplasm of most cells to (*Figure 2D*). The final pathological diagnosis was sparsely granulated somatotroph adenoma. The patient recovered successfully and his postoperative serum GH concentration was normal (*Figure 3*). And the PRL decreased to 13.67 ng/mL. The patient did not receive regular postoperative follow-up because of the distance and lack of symptoms.

Five years after the first surgery, the patient presented again because of headache, impaired vision, bone pain, heavy snoring and high blood glucose concentrations for 2 months. Physical examination showed early acromegalic features: thick toes, frontal bossing and wide nose. We reexamined the sellar region with MRI and reassessed blood concentrations of pituitary hormones. Of interest, we found greatly increased concentrations of GH (7.2 ng/mL; normal range, 0.1–2.0 ng/mL) and IGF-1 (533 ng/mL). Concentrations of other pituitary hormones were normal. An MRI showed a recurrent sellar region lesion that was larger than the previous one (*Figure 1C*). A diagnosis of acromegaly was considered. The patient underwent a second

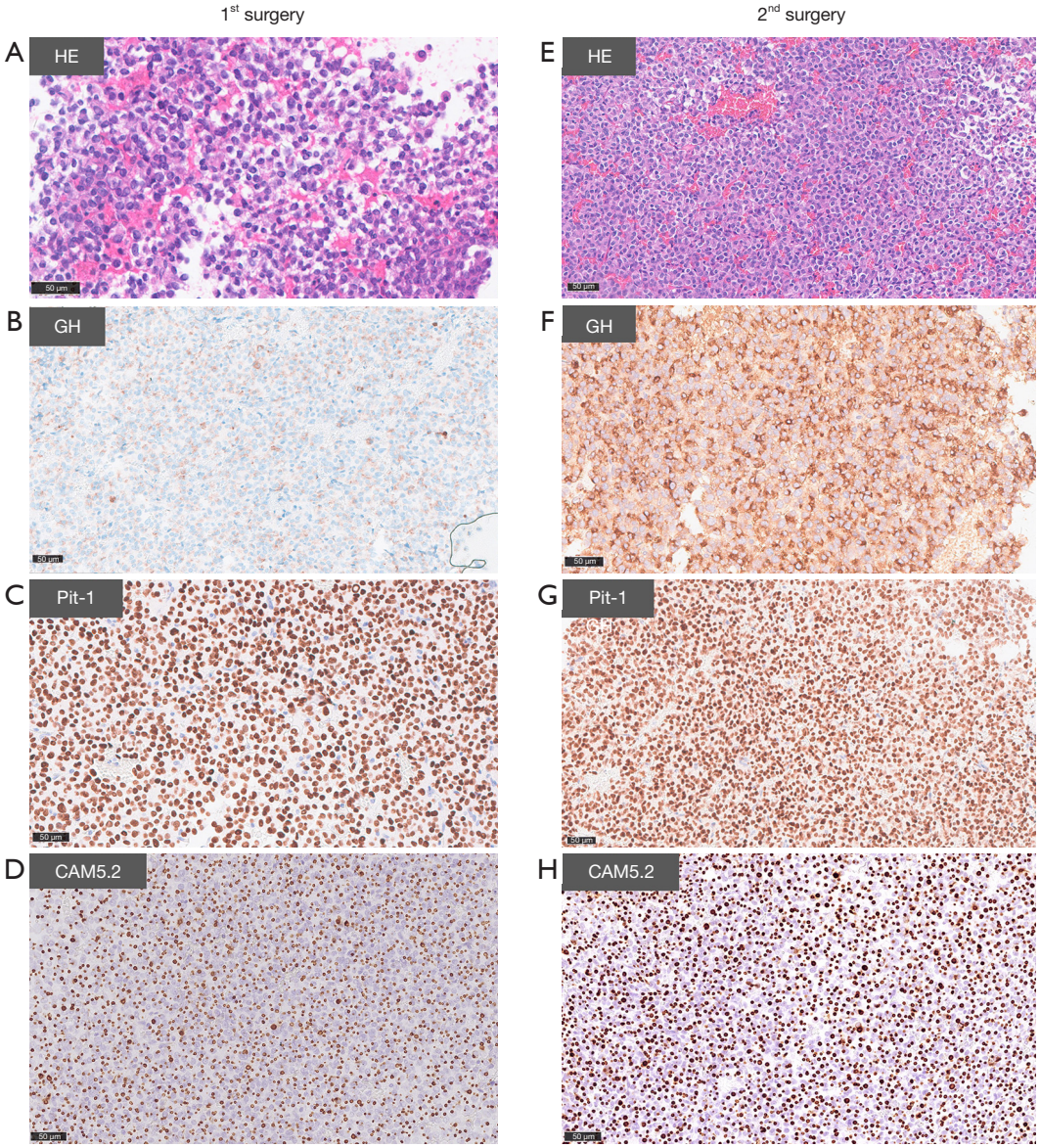

Figure 2 Immunostaining of tumors in two stages. (A) H&E staining shows a solid pituitary adenoma nest (160×); (B) weakly positive staining for GH (IHC staining, 120×); (C) diffuse staining for Pit-1 in most tumor cells (IHC staining, 120×); (D) globular fibrous bodies strongly positive for CAM5.2 were visible in the cytoplasm of most cells (IHC staining, 120×). (E) H&E staining shows a solid pituitary adenoma nest in the 2nd stage (100×); (F) strong, dense positivity for GH (IHC staining, 100×); (G) diffuse staining for Pit-1 in most tumor cells (IHC staining, 90×); (H) the image shows sparsely positive for CAM5.2 were visible in the cytoplasm (IHC staining, 120×). H&E, haematoxylin and eosin; GH, growth hormone; IHC, immunohistochemical; Pit-1, pituitary-specific transcription factor-1.

transsphenoidal pituitary tumor resection (*Figure 1D*), after which his serum GH and IGF-1 concentrations decreased (*Figure 3*). Unlike the results of pathological staining on the original surgical specimen, IHC examination of the tissue resected during the second surgery showed strong, dense GH positivity (*Figure 2F*), with similarly strong Pit-1 positivity (*Figure 2G*). The H&E staining (*Figure 2E*) and keratin CAM5.2 staining pattern (*Figure 2H*) was also similar, the staining of SSTR2 and MGMT was both positive. Postoperative serum GH (2.9 ng/mL) and IGF-1 (365 ng/mL) concentrations were markedly lower than the preoperative values (*Figure 3*). The patient was followed

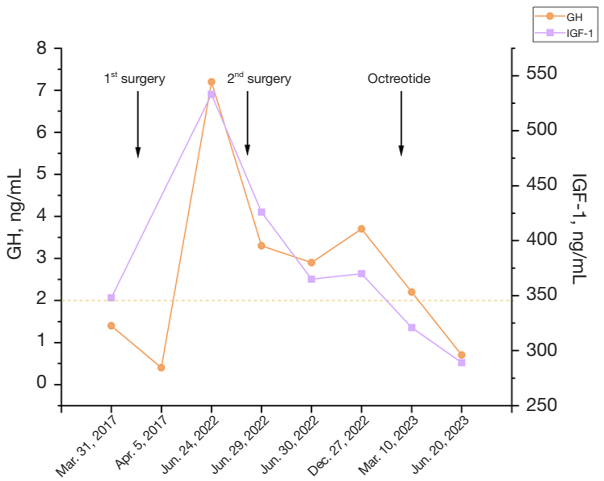

Figure 3 Variations in serum GH and IGF-1 concentrations before and after both surgeries. The IGF-1 after the 1st surgery is not tested occasionally. GH, growth hormone; IGF-1, insulin-like growth factor 1.

up for 6 months without octreotide treatment. At the follow-up in Dec. 2022, he was found to have high serum concentrations of GH (3.7 ng/mL) and IGF-1 (370 ng/mL), which elevated compared with the postoperative values. In response to the findings on serum hormone tests, the patient was prescribed octreotide acetate microspheres (20 mg/month). After half a year of this treatment, the concentrations of GH (0.7 ng/mL) and IGF-1 (289 ng/mL) had decreased markedly and his blood glucose and bone pain were also under control. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Declaration of Helsinki (as revised in 2013). Written informed consent was obtained from the patient for the publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Discussion

We herein reported a relatively rare case of PitNET with a phenotype switch from an SST to its functional (secretory) counterpart. SSTs are a rare subtype of PitNETs, comprising 2–4% of operated PitNETs (4) and 4.2–7% of GH-secreting pituitary tumors (11). By definition, SSTs are characterized by GH (+) and Pit-1 (+) on IHC staining without clinical or biochemical evidence of acromegaly (4). The same tumor presenting initially as silent and later as a functional somatotroph tumor may provide a precious opportunity for exploring these two subtypes. On the first presentation, we did not consider the diagnose of acromegaly for the baseline GH concentration (1.4 ng/mL) and a glucose inhibition test (inhibited to 0.4 ng/mL), despite the IGF-1 concentration being slightly elevated.

Actually, an excess of IGF-1 together with a normal GH concentration has previously been reported in some patients with "clinically" SSTs (11,12). It is noted that the secretion of GH is fluctuant and affected by some factors, and the IGF-1 is more stable compared with serum GH (12). The IGF-1 is recommended as a first-line biochemical test and the GH_{nadir} during oral glucose tolerance test (OGTT) is advised as a confirmatory test. According to some guideline of EndocSrine Society, a cutoff of GH <1 μg/L after the glucose load is sufficient for excluding the diagnosis. Therefore, we excluded this diagnose in 2017. However, it is noteworthy that some articles tend to adopt GH_{nadir} <0.4 μg/L as the excluding criteria (13) and in this condition, we should consider the possibility of acromegaly without symptoms. It was a pity that the value of IGF-1 was not tested after the first surgery, which could have offered some evidence for the diagnose.

We also searched the PubMed online database through to January 2024 using the following keywords: [silent somatotroph adenoma] OR [silent somatotroph tumor] OR [silent growth hormone adenoma] OR [pituitary adenoma with changing phenotype]. The criteria for inclusion were as follows: (I) no clinical evidence of acromegaly and serum IGF-1 within the normal range at the first visit; (II) had undergone at least one surgery for a pituitary tumor and pathological examination had supported a diagnosis of pituitary somatotroph tumor, that is, GH (+) ± Pit-1 (+); and (III) clinical or serological evidence of acromegaly during postoperative follow-up. The criteria for exclusion were as follows: (I) a diagnosis of SST could not be made on the basis of findings on IHC staining; (II) no functionalization of tumor during follow-up; (III) report not in English; and (IV) insufficiently detailed data provided. Finally, four articles that described functional SSTs were identified, two of which included detailed case reports. The relevant clinical data of these two cases and the present case are presented in *Table 1*.

About 90% of patients with SSTs are female (4). However, the three reported cases of functional SST were all male. These three patients were all in their 40s,

consistent with the typical age range of 20–40 years of patients with SSTs (4). It noted that SST is a clinical diagnosis. Mono-hormonal SSTs show various pathological features like acromegaly-related tumors and can be also classified as sparsely granulated somatotroph tumor (the most common type), densely granulated somatotroph tumor even immature PIT1 lineage tumor (4,14,15). SSTs show a smaller percentage of GH-positive cells on IHC staining than do tumors associated with acromegaly (16). In the present case, the weak staining in the initial tumor and diffuse staining after development of acromegaly supported our conclusions. The Ki-67 index of the tumor changed differently in each of the reported cases. In the second case it changed from negative to 6%, consistent with the high recurrence rate and invasion after functionalization. Our patient showed a decrease in Ki-67 index after recurrence; however, his tumor was still invasive during follow-up.

It is known that the PitNETs are monoclonal tumors, that is, they arise from a specific cell (17), and their pathological types often remain constant over time. Recurrent tumors are therefore expected to have the same phenotype as the primary tumor (5). Thus, modification of the secretory phenotype after recurrence is a little-known and unexpected phenomenon, occurring in 7.7% of recurrent PitNETs (18). The classical and well-known change in phenotype is an SCT undergoing functionalization and causing Cushing disease (3,5). Other types of transformation of phenotype have also been reported, including functionalization of other types of PitNET (7), silencing of functional PitNETs (19), and even substitution of one type of hormone for another (5,20). Because only two cases of functionalization of SST have previously been reported, the patient characteristics, clinical manifestations, and IHC features cannot be analyzed, let alone the underlining mechanisms of this phenomenon. Similar to SCTs (6,21), the case reported by Batisse *et al.* and our patient suggest that functionalization is associated with refractory PitNETs (the tumor reported by Batisse *et al.* was aggressive and resistant to multiple treatments) (8). In addition to surgery, multiple therapies such as radiotherapy, somatostatin analogs, and temozolomide, should be considered. IHC staining for GH demonstrates that the phenotype modification is attributable to increased hormone production rather than secretion or some other reason. IHC staining for GH also confirmed that modification of phenotype is attributable to increased hormone production rather than upregulation of secretion or any other reasons. There was no significant difference in Pit-1 staining between the two tumors, both showing 100% positive nuclei, which is first report of Pit-1 staining in the functional SST.

Despite extensive research and numerous hypotheses, why some somatotroph tumors are silent is still unknown. Regulation of secretion of GH involves multiple factors, including hypothalamic hormones (such as GH-releasing hormone and somatostatin), gene transcription, RNA processing, pre-mRNA processing, translation, and protein transport and secretion (22). As yet, the mechanism of GH synthesis remains not entirely clear. GH-releasing hormone stimulates the synthesis and release of GH; however, there is no significant difference in GH-releasing hormone mRNA expression between SSTs and functional tumors. Pit-1, a key transcription factor for GH, is the limiting factor for GH synthesis in many cells, and has been studied extensively (23). However, reverse transcription polymerase chain reaction has shown that Pit-1 mRNA expression in SSTs is similar to that in tumors associated with acromegaly and that 100% of nuclei in most SSTs stain positive for Pit-1 (16,24). These findings suggest that the mechanism of SSTs is not related to the transcription and translation of Pit-1. The outcome of Pit-1 staining in our case also supported the point. On testing, GH hormone mRNA is weak in almost all tumor cells. This does not fully explain why these tumors are silent, because cells that are negative for GH express GH mRNA (25,26), which may mean that mRNA transport or translation is also affected. *In vitro* culture of SST cells is also informative (26). Cultured SST cells reportedly secrete 10 times as much GH after a few days as they did initially. In another word, they functionalize *in vitro*, which suggest that some factors inhibit transcription of GH mRNA *in vivo*.

Transformation of the phenotype of a PitNET, which is called functionalization in this case, is a rarely reported phenomenon. The mechanism of transformation of these tumors is unclear. Such transformation usually occurs in SCTs. Some studies have shown that silencing and secretory transformation is related to an excess of proopiomelanocortin (the precursor of ACTH) and changes in the quantity of prohormone convertase 1/3, an enzyme that can cleave proopiomelanocortin (27,28). Functionalization of SSTs is rarer than functionalization of SCTs and requires further study to better understand the mechanism of regulation secretion of GH by tumors. Lania *et al.* reported a PRL adenoma which co-secreted PRL and GH when recurred (20). They also found a mutation of *GNAS* gene (present in up to 40% GH tumors) in the tissue after the transformation, which is absent in the previous

surgical specimen. It is can be speculated that the mutation of some oncogenes may be the underlying mechanism of this transformation (it is a pity that the tumor from the first operation was not preserved for a long time). Future research should shed light on the genetic differences between the two stages.

Conclusions

To the best of our knowledge, this is the third detailed case report of functionalization of an SST. Medical teams of PitNETs should recognize this rare phenomenon and conduct long-term follow-up. After functionalization, these tumors have a high recurrence rate, requiring multiple therapies and long-term follow-up. Further research is essential to figure out the mechanism of regulation of secretion of GH by such tumors.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://gs.amegroups.com/article/view/10.21037/gs-24-79/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://gs.amegroups.com/article/view/10.21037/gs-24-79/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Declaration of Helsinki (as revised in 2013). Written informed consent was obtained from the patient for the publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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