Growth hormone-producing pituitary adenomas in childhood and young adulthood: Clinical features and outcomes

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ABSTRACT

Purpose

Growth hormone (GH)-producing pituitary adenomas (PAs) in childhood or young adulthood are rare, and the details surrounding these tumors remain enigmatic. We present the clinical, pathological and genetic features of this disease.

Methods

We identified 25 patients aged 20 years or younger with GH-producing PAs who underwent surgery between 2003 and 2016 at Toranomon Hospital in Tokyo. We retrospectively reviewed the clinical data, treatment outcomes and pathological features of these patients to shed light on childhood acromegaly.

Results

The cohort comprised 14 male and 11 female patients whose average age at the time of surgery was 17.3 years. Germline *AIP* mutations were present in 5 of 13 patients examined, and Carney complex was identified in 2 of 25 patients. The mean maximum tumor diameter was 26.7 mm, and total resection assessed during surgery was achieved in 17 patients. Based on their respective pathological findings, patients were divided into the following 4 groups: sparsely granulated adenomas (5), densely granulated (DG) adenomas (6), plurihormonal adenomas (9), and silent subtype 3 (SS3) adenomas (5). During the mean follow-up period of 50.3 months, complete endocrinological remission was achieved in 14 of 25 patients (56%) by surgery alone and in 19 patients (76%) after postoperative adjuvant therapy.

Conclusions

GH-producing PAs in young patients are intriguing and difficult to treat due to their distinct tumor characteristics, including a lower incidence of the DG subtype and a higher incidence of SS3 adenomas and genetic abnormalities. Therefore, multi-modal therapies are essential to achieve optimal clinical outcomes.

Key words: growth hormone-producing pituitary adenoma; young; gigantism; clinical feature; pathology; acromegaly

INTRODUCTION

Excess secretion of growth hormone (GH) causes acromegaly, which is associated with increased morbidity and mortality. Several heterogeneous disorders, such as pituitary adenoma (PA), pituitary hyperplasia, excess ectopic GH release from the bronchial carcinoid, and ectopic GH secretion from lymphomas, have been reported to cause excessive GH secretion [1-3]; furthermore, primary GH hypersecretion from PAs is the most common cause of acromegaly. Moreover, excessive GH secretion during childhood before complete epiphyseal closure can lead to gigantism. Because GH-producing PAs during childhood or young adulthood are rare, the mechanisms are poorly understood. In this study, we reviewed young patients with GH-producing PAs who underwent tumor resection at Toranomon Hospital (Tokyo, Japan). GH-producing PAs in young patients have been described as aggressive [4-6]; however, the aggravating factors of this clinical entity remain unclear. Therefore, we studied the clinical, pathological, and genetic features of younger patients with GH-producing PAs to identify factors that exacerbate this clinical condition.

METHODS

Patients

We retrospectively reviewed the data of 25 patients with GH-producing PA who were 20 years old or younger at the time of operation. All patients underwent surgery at Toranomon Hospital between 2003 and 2016, and a diagnosis of GH-producing PA was confirmed by pathological examination. All patients were native Japanese. The mean follow-up period was 50.3 months (range 1-166). Tumor samples were evaluated upon approval from the institutional review boards at Toranomon Hospital and Tokushima University.

Imaging studies

All patients underwent preoperative contrast-enhanced magnetic resonance imaging (MRI). The Knosp classification was assessed using coronal images to determine lateral tumor extension, and the maximum tumor diameter was also measured in all patients. The

degree of tumor resection was assessed during surgery and was confirmed by postoperative MRI, which was generally performed a few days after surgery. Repeated MRI was performed several months later when it was difficult to evaluate the tumor excision rate via postoperative MRI. Patients with residual tumors underwent postoperative MRI once or twice per year to assess tumor regrowth.

Endocrinological evaluations

Endocrinological examinations were performed in all patients by assessing the serum levels of GH and insulin-like growth factor-1 (IGF-1) preoperatively, at postoperative week 1 and twice per year thereafter. GH levels were measured with a fluorescent enzyme immunoassay (ST AIA-PACK HGH, Tosoh Co., Tokyo, Japan). Serum IGF-1 levels were measured using an immunoradiometric method (IGF1 IRMA Daiichi, TFB Co., Tokyo, Japan). Responses to medical therapy were assessed preoperatively using the octreotide and bromocriptine tests, whereas postoperative biochemical remission was defined as a nadir serum GH level of <0.4 ng/ml after an oral 75 g glucose load and subsequent normal IGF-1 levels adjusted for sex and age. For patients receiving postoperative medication or radiotherapy (RT), biochemical control at the last follow-up was defined as subsequent normal sex- and age-adjusted IGF-1 levels.

Treatments

Preoperative medication (typically one to three doses of a long-acting somatostatin analog (SSA)) was routinely administered to all the patients except those with microadenomas. All 25 patients underwent surgical treatment. Most PAs were resected via conventional transsphenoidal surgery (TSS), which was performed via an operating microscope between 2003 and 2012 and via a neuroendoscope between 2013 and 2016. Extended TSS (eTSS) and simultaneous combined TSS and transcranial surgery (TCS) were also performed. The details of the surgical strategies used are described in our previous study [7].

Repeated surgery was performed in patients with residual tumors located in a

surgically resectable site. Patients without postoperative endocrinological remission began medical therapy. Stereotactic radiotherapy (SRT) was generally implemented when endocrinological remission was not achieved using postoperative medication alone and when the residual tumor was located in a surgically unresectable location.

Pathological examinations

Adenoma tissues were evaluated via routine pathological and immunohistochemical examinations. Sections were incubated with antibodies targeting the following proteins for immunohistochemical evaluation: GH (Dako, Carpinteria, CA, USA; A0570), prolactin (PRL) (Dako, Carpinteria, CA, USA; A0569), beta subunit of thyroid-stimulating hormone (TSH) (Kyowa Medex Co., Ltd, Tokyo, Japan; AM0335M), adrenocorticotropic hormone (ACTH) (Dako, Carpinteria, CA, USA; A0571), follicle-stimulating hormone (FSH) (BioGenex, San Ramon, CA, USA; MU026-UC), luteinizing hormone (LH) (Nichirei Biosciences Inc., Tokyo, Japan; 412481), cytokeratin (CK) (CAM 5.2) (BD Biosciences, San Jose, CA, USA; 345779), Pit-1 (Santa Cruz Biotechnology, TX, USA; sc-393943), Ki67 (Dako, Carpinteria, CA, USA; M7240) and type 1-alpha regulatory subunit of protein kinase A (PRKAR1A) (BD Biosciences, San Jose, CA, USA; 61010).

Electron microscopy was used for a final diagnosis when we could not reach a final morphological diagnosis by a conventional histological examination alone.

Genetic analysis

Genetic analysis for *AIP* mutations was performed in 13 of 25 patients. The details regarding the genetic analysis of *AIP* and *PRKAR1A* mutations have been described in our previous studies [8, 9]. Briefly, genomic DNA isolated from leukocytes and PA tissue was subjected to 30 cycles of polymerase chain reaction (PCR), the products of which were directly sequenced.

Statistical analysis

Statistical analyses were performed using the Chi square test and the Mann-Whitney

U test. Differences of $p<0.05$ were considered statistically significant.

RESULTS

Twenty-five patients with GH-producing PA who were 20 years old or younger accounted for 2.1% of the 1205 acromegalic patients who underwent surgical treatment for PA at Toranomon Hospital during the same period. These 25 patients comprised 14 males and 11 females with a mean age of 17.3 years (range 7-20 years). Only 3 patients (12%) were younger than 15 years old. Four patients had recurrent disease and had undergone initial tumor resection at other hospitals. Regarding clinical manifestations, gigantism (height taller than +2S.D. of the mean sex- and age-adjusted height) was detected in 13 patients (52%), and acromegalic features were confirmed in 22 patients (88%). The preoperative endocrinological tests showed that octreotide successfully suppressed the GH levels (>50%) in 14 patients and that bromocriptine suppressed the GH levels in 14 of 18 patients examined.

Tumor characteristics

The tumors consisted of 4 microadenomas (<10 mm maximum tumor diameter), 18 macroadenomas (10-40 mm), and 3 giant adenomas (>40 mm); the overall mean maximum tumor diameter was 26.7 mm (range 7.5-82 mm). Eight adenomas (32%) were either grade 3 or 4 on the Knosp classification scale. The tumor characteristics of all the patients are shown in Table 1.

Treatments

Data regarding preoperative medical therapy were available for 23 patients. Fifteen patients underwent preoperative medication, whereas the remaining 8 patients did not. Among the preoperative medication cohort, 11 patients were administered octreotide, one patient lanreotide, one patient cabergoline, one patient lanreotide and cabergoline, and one patient an unknown SSA.

All patients underwent surgical treatment(s) as follows: conventional TSS (20), extended TSS (2), or simultaneous combined TSS and TCS (3). Gross total tumor resection

(GTR) was achieved in 17 of 25 cases (68%); among the 8 patients without GTR, 3 underwent secondary TSS, one of whom achieved GTR. Fourteen patients (56%) achieved endocrinological remission after surgery alone, and none of these patients have shown endocrinological relapse during the mean follow-up period of 29.5 months (range from 1 to 166 months).

After surgery, 9 patients with residual tumors or without endocrinological complete remission received postoperative adjuvant therapy, 7 received medical therapy, and 6 received SRT. At the time of last follow-up, endocrinological control was achieved in 19 patients (76%). These treatment outcomes are summarized in Table 1.

Pathology

Based on their pathological findings, 5 adenomas were classified as sparsely granulated (SG) subtype, 6 adenomas as densely granulated (DG) subtype, 9 adenomas as plurihormonal (PH) subtype (including 6 mammosomatotroph adenomas, 2 acidophil stem cell adenomas, and 1 mixed GH-PRL adenoma), and 5 adenomas as silent subtype 3 (SS3) adenoma. Patients with DG adenomas presented the highest preoperative serum GH and IGF-1 levels. The endocrinological remission rate of patients with SG adenomas was lower than that of patients with DG adenomas, although those with SG adenomas showed lower Knosp grades and a higher rate of GTR. In contrast, SS3 adenomas showed the largest mean maximum tumor diameter (43.2 mm, range 23.5-82 mm) and the highest cavernous sinus (CS) invasion rate (60%); thus, none of the 5 patients with SS3 adenomas achieved GTR. The mean Ki67 labeling index of the SS3 adenomas (3.36%, range 0.2-12%) was the highest among these pathological groups. PH adenomas showed the smallest mean tumor size (14.5 mm, range 7.5-23.8 mm) with a low frequency of CS invasion (11.1%), and GTR was achieved in all patients with PH adenomas. The tumor characteristics and clinical outcomes of each pathological group are summarized in Table 2.

Genetic anomalies

In this patient cohort, there were 5 patients with a germline *AIP* mutation and 2

patients with a germline mutation in *PRKAR1A*, which is the gene responsible for Carney complex. Both gigantism and acromegalic features were observed in these 7 patients, and the mean maximum tumor diameter of patients with an *AIP* mutation was 28.9 mm (range 23.8-36.4). Three of the 5 patients achieved GTR. Two patients achieved endocrinological remission by surgery alone, and 3 patients achieved endocrinological control at the last follow-up. Moreover, isolated familial somatotropinoma was found in one patient with an *AIP* mutation.

In contrast to the characteristics of patients with an *AIP* mutation, the mean maximum tumor diameter of patients with Carney complex was 14.7 mm (9.9 and 19.5 mm), but endocrinological remission was obtained neither by surgery alone nor by surgery with postoperative adjuvant therapy despite these 2 patients achieving GTR.

DISCUSSION

GH-producing PAs in young patients is a rare clinical condition; only 2.1% of the 1205 patients with GH-producing PAs admitted to Toranomon Hospital were considered young patients. Therefore, the details of this intriguing clinical condition within this subpopulation remain unclear. In this article, we reviewed the characteristics of a considerable number of young patients with GH-producing PAs who underwent surgery. The overall surgical remission rate of young patients (56%) was significantly lower than that of our previous series, including acromegalic patients of all ages (84.7%, p=0.002) [7]. Although the clinical aggressiveness of GH-producing PAs in young patients has been reported [4-6], we assessed the factors that contributed to this poor therapeutic outcome in our cohort of young patients.

Tumor factors

Previous surgical series of patients with GH-producing PAs have shown that the mean maximum tumor diameter ranges from 17.4 to 19.4 mm; however, our cohort presented with larger mean tumor diameters (26.7 mm) than the tumors in those series [10-12]. The tumor sizes of the 25 adenomas in this study were significantly larger than those in our previous

study, which included 150 GH-producing PAs (17.8 mm, p=0.001) [7]. Moreover, 8 of the 25 patients (32%) in our cohort had PAs with Knosp grades 3 and 4; this ratio is higher than those described in previous reports (17.3-27.4%) [7, 11, 12]. A high rate of CS invasion of GH-producing PAs in young patients has also been reported in the literature [6]. Several studies have shown that surgical remission is less likely to be achieved in patients with larger tumors or with CS invasion [7, 13, 14]. Thus, the tumor characteristics, such as larger tumor size and a higher frequency of CS invasion, observed in these 25 young patients with GH-producing PAs could be exacerbating factors of this clinical condition.

Pathological factors

Surgical outcomes are usually better in patients with DG adenomas than in those with SG adenomas [15, 16]. DG adenomas accounted for 24% of the cases in this study, which appeared to be markedly lower than the rate reported in previous studies by our group and others [17-19]. This rate may be another contributing factor for the poor surgical outcomes observed in the present study. Interestingly, in this study, patients with DG adenomas presented a higher Knosp grade and a lower GTR rate than those with SG adenomas. However, the overall endocrinological control rate of DG adenomas was higher than that of SG adenomas. It is plausible that the increased responsiveness of DG adenomas to SSA treatment, which has been reported in other studies [15, 20-23], could improve the overall remission rate of DG adenomas in this series. On the other hand, SS3 adenomas, which were originally proposed as a variant of silent corticotroph adenomas [24], are now considered a distinct and aggressive histologic variant of PA that are positive for the pituitary-specific transcription factor Pit-1 [25-31]. SS3 adenomas have been termed “silent”, whereas some SS3 adenomas were reported to be associated with conditions indicative of hormonal excess, including acromegaly [27, 29]. In this study, SS3 adenomas showed radiologically and pathologically aggressive features, including the largest mean tumor diameter, the highest CS invasion rate and the highest mean Ki67 labeling index. In addition, 5 of 25 patients (20%) were diagnosed with this type, which indicates a higher incidence of SS3 adenomas among a younger population than that stated in previous reports [28]. According to the literature, SS3

adenomas are estimated to encompass approximately 1.5% of all PAs. The higher incidence of SS3 adenomas might be another aggravating factor of poor surgical outcomes in the present study. However, 4 of 5 patients with SS3 adenoma eventually achieved endocrinological control at the last follow-up. Some SS3 adenomas have also been reported to potentially respond well to SSAs and RT [31]. However, close follow-up is needed in patients with SS3 adenomas because higher recurrence rates of SS3 adenomas have also been reported [27-29].

PH adenomas presented the smallest tumor size and the lowest Knosp grade in this series. All these patients achieved GTR, and the endocrinological remission rate was favorable. In some articles, mammosomatotroph adenoma showed an equally good prognosis as DG adenomas, whereas acidophil stem cell adenoma and mixed GH/PRL cell adenomas exhibited more aggressive behavior [32, 33]. In this series, 6 of 9 patients with PH adenomas presented with the mammosomatotroph adenoma subtype.

Genetic factors

In this series of patients, 7 had GH-producing adenomas due to genetic abnormalities (5 with an *AIP* mutation and 2 with *PRKAR1A* mutations). The physical manifestations of gigantism were observed in these 7 patients, suggesting that disease onset in these patients was earlier than in patients without genetic anomalies. In fact, the mean age at operation in patients with genetic abnormalities was 15.4 years (range 7-19 years), which is younger than that of patients without genetic abnormalities (18 years (range 14-20 years)), although this difference is not statistically significant (p=0.07). Moreover, among these 7 patients with genetic abnormalities, only 3 (42.9%) achieved endocrinological remission at the last follow-up. The overall endocrinological control rate in patients with genetic abnormalities was statistically lower than that of patients without genetic abnormalities (88.9%, p=0.03). This outcome suggests the intractability of GH-producing PAs in patients with genetic abnormalities.

Among the 5 patients with an *AIP* mutation, all presented with large macroadenomas (28.9 mm of mean maximum tumor diameter), and 1 patient showed CS invasion.

Endocrinological control was achieved in 3 of the 5 patients at the time of last follow-up. Daly *et al*. reported that somatotropinomas with an *AIP* mutation tend to be larger in size and have a worse disease control rate over a long-term period [34]. *AIP* mutations have been reported to be an unfavorable factor for the SSA treatment response in patients with acromegaly [34]. Consistent with other reports, poor outcomes in patients with an *AIP* mutation were also noted in our series. Vierimaa et al. reported that 40% of patients with GH-producing PAs diagnosed when they were younger than 35 years of age had AIP mutations [35]. The proportion of AIP mutation in our study (5/13, 38.5%) seemed to be equivalent to the ratio. However, the number of samples was too small to reach a definitive conclusion (genetic analyses of AIP mutations were performed in only 13 patients in this series). Moreover, our cohort included only 1 patient with familial isolated pituitary adenoma (isolated familial somatotropinoma) with an *AIP* mutation.

Neither of the 2 patients with Carney complex achieved endocrinological control by the last follow-up, although they both presented with small maximum tumor diameters (9.9 and 19.5 mm) and lower Knosp grades (grade 0 and 2, respectively). PAs due to Carney complex are reported to have multiple tiny tumor nodules in addition to an isolated primary tumor mass [36, 37]. Watson *et al*. described a patient with Carney complex in which the microadenoma was not detected on preoperative MRI [38]. Similarly, small scattered islands of adenoma cells were detected within the adjacent normal pituitary in patients in the present study (Figure 1). This finding could be a major contributor to the failure to achieve surgical remission in patients with Carney complex.

Multi-modal therapy

Among the patients within our cohort, the surgical remission rate was 56%, whereas the endocrinological control rate at the last follow-up increased to 76%. Several studies have demonstrated that GH-producing PAs in young patients cannot be adequately controlled by surgery alone and that a combination of medical therapy and/or RT is necessary [4, 5]. In our series, most patients exhibited sufficient GH suppression in the preoperative octreotide and bromocriptine tests. Five of 11 patients who failed to achieve surgical remission eventually

attained endocrinological control with postoperative adjuvant therapy. Thus, multi-modal therapies, such as surgical resection combined with medical treatment and/or RT, are essential to achieve an optimal clinical outcome for young individuals with difficult-to-treat GH-producing adenomas.

CONCLUSIONS

GH-producing PAs in childhood or young adulthood are rare but intriguing and difficult to treat due to their distinct tumor characteristics (including large tumor size with frequent CS invasion), a lower incidence of the DG subtype, a higher incidence of SS3 adenoma, and genetic abnormalities (in some patients). The overall surgical remission rate tends to be lower in these patients than in adults; thus, multi-modal therapies must be considered to achieve optimal clinical outcomes.

COMPLIANCE WITH ETHICAL STANDARDS

Disclosure of potential conflicts of interest: The authors declare that they have no conflicts of interest.

Ethical approval: All the procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional or national research committee and with either the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. For this type of study, formal consent was not required.

Informed consent: Informed consent was obtained from all individual participants who were included in the study.

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FIGURE CAPTION

Fig. 1 Pathology of a normal pituitary gland in a patient with Carney complex (patient 18 in Table 1). **a** A small island of tumor cells (black circle) was detected in the normal pituitary anterior lobe using Hematoxylin-eosin staining. **b** The tumor mass was detected as the immunonegative area (red circle) using anti-PRKAR1A staining, which indicates that the tumor etiology is Carney complex

Table 1. Clinical presentation, pathological classification and treatment outcome of all patients

No. of patient	Age/ Gender	Acromegaly/ Gigantism	Preoperative serum level of GH/ IGF-1 (ng/mL)	Oct/ Brom test	Prim or Rec	Size (mm)/ Knosp grade	Genetic abnormality	Preoperative medication	Operation/ Degree of resection	Pathology/ Ki67 (%)	Postoperative adjuvant therapy	Endocrinological remission by surgery alone	Overall endocrinological control
1	19/ F	+/ -	43/ 1000	UA	Prim	8/ 1	No	None	TSS/ GTR	PH/ 3.2	None	Yes	Yes
2	19/ M	+/ +	101.15/ 1527.8	+/UA	Prim	20/ 1	No	Oct	TSS/ GTR	DG/ 0.4	None	Yes	Yes
3	16/ M	+/ +	97.4/ 981	-/+	Prim	40/ 4	No	None	TSS/ STR	DG/ 1.4	SRT, Cab	No	Yes
4	19/ F	+/ -	477/ 1040	+/-	Prim	40/ 4	No	Oct	TSS/ STR	DG/ 0.2	TSS, SRT, Oct, Cab	No	Yes
5	20/ F	-/ -	15.63/ 554	UA	Prim	24/ 0	No	UA	TSS/ GTR	SG/ 1.5	None	Yes	Yes
6	18/ M	+/ +	23.3/ 660	UA	Prim	27/ 0	*AIP* mutation	None	TSS/ GTR	DG/ 0.1	Oct, Cab	No	No
7	20/ M	-/ -	7.7/ 778	+/+	Prim	46.3/ 4	No	Oct	TSS/ STR	SS3/ 0.3	SRT	No	Yes
8	20/ M	+/ -	17.9/ 617	+/+	Prim	13.5/ 1	No	Oct	TSS/ GTR	PH/ 3.6	None	Yes	Yes
9	18/ F	-/ -	6.1/ 537	-/-	Rec	23.5/ 1	No	UA	eTSS/ STR	SS3/ 12	TSS, SRT	No	No
10	18/ F	+/ +	24.7/ 1200	-/+	Rec	18.9/ 0	No	Cab	TSS/ GTR	PH/ 3.5	None	Yes	Yes
11	7/ M	+/ +	42/ 1080	UA	Prim	27.9/ 0	*AIP* mutation	Oct	eTSS/ STR	SS3/ 2.5	TSS	Yes	Yes
12	18/ F	+/ +	86.9/ 972	+/-	Rec	36.4/ 4	*AIP* mutation	Oct	Combined/ STR	SS3/ 1.8	Oct	No	Yes
13	19/ M	+/ -	31.6/ 861	UA	Rec	27.1/ 4	No	Oct	Combined/ STR	SG/ 4	Oct, Peg	No	No
14	16/ F	+/ +	47.1/ 1050	+/+	Prim	23.8/ 1	*AIP* mutation	None	TSS/ GTR	PH/ 3.3	None	No	No
15	17/ M	+/ -	4.8/ 767	UA/+	Prim	7.5/ 0	No	None	TSS/ GTR	PH/ 3.8	None	Yes	Yes
16	17/ M	+/ +	10.9/ 750	+/+	Prim	9.3/ 0	No	None	TSS/ GTR	PH/ 0.3	None	Yes	Yes
17	18/ M	+/ -	124.8/ 849	+/+	Prim	20.2/ 3	No	Lan, Cab	TSS/ GTR	PH/ 0.2	None	Yes	Yes
18	17/ F	+/ +	8.9/ 636	+/+	Prim	19.5/ 2	*PRKAR1A* mutation	SSA	TSS/ GTR	SG/ 0.5	None	No	No
19	18/ M	+/ +	8.35/ 533	UA	Prim	9.9/ 0	*PRKAR1A* mutation	None	TSS/ GTR	PH/ 3.4	Oct	No	No
20	19/ F	+/ +	172.4/ 836	+/+	Prim	18.8/ 2	No	Lan	TSS/ GTR	DG/ 2.3	None	Yes	Yes
21	17/ M	+/ -	8.37/ 677	-/+	Prim	19.8/ 2	No	Oct	TSS/ GTR	PH/ 8	None	Yes	Yes
22	16/ M	+/ -	47.8/ 600	+/-	Prim	46.2/ 2	No	Oct	TSS/ GTR	SG/ 0.6	None	Yes	Yes
23	14/ F	+/ +	33.8/ 732	+/+	Prim	28.4/ 3	No	Oct	TSS/ GTR	DG/ 0.5	None	Yes	Yes
24	14/ M	+/ +	37.9/ 614	+/+	Prim	29.3/ 2	*AIP* mutation	Oct	TSS/ GTR	SG/ 2.5	None	Yes	Yes
25	18/ F	+/ -	3.27/ 689	+/+	Prim	82/ 4	No	Oct	Combined/ PR	SS3/ 0.2	Oct	No	Yes

UA: unavailable, Oct: Octreotide, Brom: Bromocriptine, Prim: primary, Rec: recurrence, Cab: Cabergoline, Lan: Lanreotide, SSA: somatostatin analog, TSS: transsphenoidal surgery, eTSS: extended transsphenidal surgery, combined: simultaneous combined transsphenoidal and transcranial surgery, GTR: gross total resection, STR: subtotal resection, PR: partial resection, SG: sparsely granulated adenoma DG: densely granulated adenoma, PH: plurihormonal adenoma, SS3: silent subtype 3 adenoma, SRT: stereotactic radiotherapy, Peg: pegvisomant

Table 2. The tumor characteristics and clinical outcomes of each pathological group of GH-producing adenomas

	SG	DG	PH	SS3
Number of cases (%)	5 (20)	6 (24)	9 (36)	5 (20)
Preoperative serum GH level (ng/mL)	28.4	150.8	32.2	29.2
Preoperative serum IGF-1 level (ng/mL)	653	1155	827	811
Mean maximum tumor diameter (mm)	29.2	29.0	14.5	43.2
Knosp grade ≥ 3 (N (%))	1 (20)	3 (50)	1 (11.1)	3 (60)
Mean Ki67 labeling index (%)	1.82	0.82	3.26	3.36
GTR (N (%))	4 (80)	4 (66.7)	9 (100)	0 (0)
Endocrinological remission by surgery alone (N (%))	3 (60)	3 (50)	7 (77.8)	1 (20)
Overall endocrinological control (N (%))	3 (60)	5 (83.3)	7 (77.8)	4 (80)

GTR: gross total resection, SG: sparsely granulated adenoma, DG: densely granulated adenoma, PH: plurihormonal adenoma, SS3: silent subtype 3 adenoma

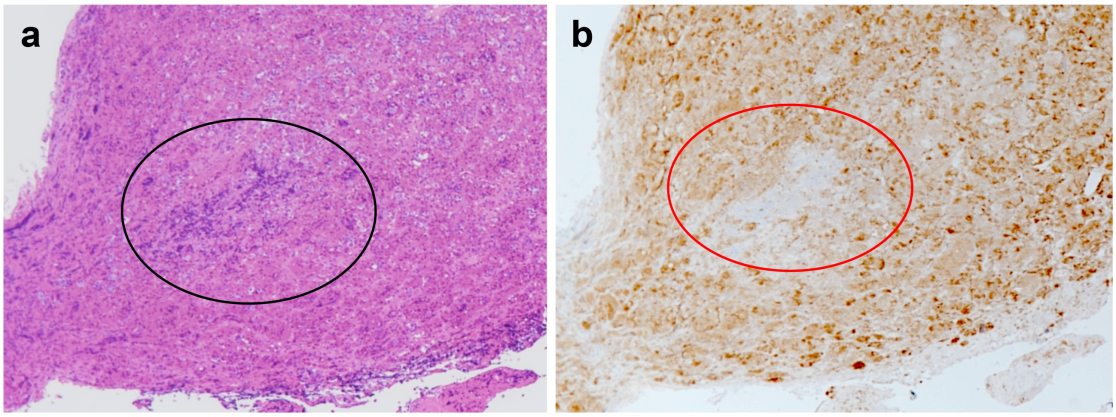

Fig.1