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ORIGINAL ARTICLE

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Mammosomatotroph and mixed somatotroph-lactotroph adenoma in acromegaly: a retrospective study with long-term follow-up

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Abstract

Purpose Although well-documented from pathological aspect, the clinical features and outcomes of acromegaly with mammosomatotroph (MSA) and mixed somatotroph-lactotroph adenoma (MSLA) are seldom reported. Thus, in this study, we analyzed and reported the clinical data about MSAs and MSLAs.

Methods We retrospectively reviewed medical records of patients with acromegaly in our institution during 2008–2017. Growth hormone (GH)-secreting adenomas were categorized into pure somatotroph adenoma (PSA), MSA and MSLA based on inclusion and exclusion criteria. Clinical information and treatment outcomes during follow-up were analyzed by univariate and multivariate methods.

Results Among 94 patients within this cohort, PSAs, MSAs, and MSLAs accounted for 53, 28 and 13 cases, respectively. MSAs often had smaller size, lower frequency of cavernous sinus invasion and higher gross total resection (GTR) rate. MSLAs were characterized by bigger tumor size, higher frequency of preoperative hyperprolactinemia, and lower GTR rate. Thus, MSLAs had worse long-term biological remission rate than MSAs and PSAs (15.4% vs. 50.0% and 26.4%, $p = 0.0371$). Gender (male, OR = 0.784, $p = 0.011$) and tumor volume (OR = 0.784, $p = 0.020$) were independent predictors for long-term biological remission in binary logistic regression. Subgroup analyses indicated that postoperative nadir GH level (GH-7, HR = 1.242, $p = 0.001$) was the only risk factor for tumor recurrence for patients with GTR.

Conclusions Our results provide valuable insights into clinicopathological features of acromegaly. MSAs were relatively smaller lesions with better prognosis. MSLAs were more aggressive with massive size, invasiveness and preoperative hyperprolactinemia. Tumor size and GH-7 were significantly associated with biological remission and tumor relapse after GTR, respectively.

Keywords Acromegaly · Mammosomatotroph adenoma · Mixed somatotroph-lactotroph adenoma · Remission

Introduction

Acromegaly is a rare but severe systematic disease characterized by excess growth hormone (GH) and insulin-like factor 1 (IGF-1), which is predominantly caused by a GH-secreting pituitary adenoma (GHPA). Acromegalic patients suffer from acral overgrowth, soft tissue swelling and high mortality [1] which is mainly resulted from the development of cardiovascular and respiratory disease, arthropathy and diabetes mellitus [2–4]. Surgery, medication, and radiotherapy are available treatment options at present. Transsphenoidal adenomectomy (TSA) is the first-line option particularly for patients with microadenoma and non-invasive macroadenoma. Biological remission rate ranges from 35 to 75% after surgery, but decreased to 40–60% for macroadenomas and 10–20% for invasive macroadenomas [5–7]. Medical treatment is often indicated as adjuvant therapy for patients failed to be biological remission after surgery. Somatostatin analogue (SSA) is usually the first choice [8]. Sustained treatment by SSA is an efficient approach to control disease but disease recurrence is a possible consequece of SSA withdrawal [9–11]. Other drugs, like GH antagonist and dopamine agonist, are also

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recommended [8]. Radiotherapy, especially stereotactic radiosurgery, is reserved for tumor residual. However, primary stereotactic radiosurgery for selected patients is recently investigated and present comparable efficiency with postoperative stereotactic radiosurgery with respect to remission rate [12].

From the pathological aspect, GHPA covers a wide spectrum of pathological subtypes. Acidophil stem cell adenoma and plurihormonal adenomas could result in acromegaly [8, 13]. However, somatotroph adenoma is the most common type of GHPA, which could be categorized into sparsely granulated somatotroph (SGSA), densely granulated somatotroph (DGSA), mammosomatotroph (MSA) and mixed somatotroph-lactotroph adenoma (MSLA) [14, 15]. SGSAs and DGSAs are pure somatotroph adenomas (PSAs) which positively stain for GH. It is reported that SGSA is more invasive and therefore has a poorer prognosis than DGSA [16, 17]. MSA and MSLA could be differentiated from PSA for positive staining for both GH and prolactin (PRL). Recent study indicates that MSA and MSLA consist of ~25% of somatotroph adenomas [18]. MSA is originated from a common progenitor which produces GH and PRL. But MSLA is a dimorphous tumor which is composed of somatotrophic and mammotrophic components. These distinctive somatotroph adenomas are well-documented in the literature from the pathological aspect. However, the clinical features of MSA and MSLA are poorly illustrated.

Hence, to address this knowledge gap, we retrospectively reviewed and analyzed the endocrinological, radiological and pathological studies of MSA and MSLA by comparing to PSA. We reported the clinicopathological features and treatment responses of these patients and hoped to facilitate the understanding of MSA and MSLA.

Patients and methods

Patients' selection

We retrospectively reviewed medical records of patients operated for acromegaly via transsphenoidal microscopic approach from January 2008 to December 2017 at West China Hospital of Sichuan University. Inclusion criteria were (1) newly diagnosed cases by endocrinological, radiological and pathological clues; (2) sufficient medical records, including pre- and postoperative endocrinological and radiological studies, well-documented hospital course and comprehensive preoperative note; (3) more than one year's postoperative outpatient follow-up; Exclusion criteria included (1) patients who received preoperative radiosurgery; (2) adenomas stained for adrenocorticotropic hormone (ACTH), thyrotropin (TSH), luteinizing hormone (LH), and follicle-stimulating hormone (FSH); (3) pathologically confirmed acidophil stem cell tumor; (4) multiple tumors.

Neuroradiological studies

Magnetic resonance images (MRIs) were acquired using standard 3.0-T scanner with contrast enhancement preoperatively and within 72 h postoperatively. Serial MRIs were acquired 3, 6, and 12 months after surgery and annually thereafter. Knosp Grade 3 and 4 were regarded as cavernous sinus (CS) invasion [19]. Suprasellar tumor growth was considered significant in cases with optic chiasm compression [20]. Lesion grew into the sphenoid sinus was classified as sphenoid sinus extension [20, 21]. Gross total resection (GTR) of GHPA was verified through MRI examinations within 3 days or on 3 months postoperatively. Tumor size was measured by the MRI system and tumor volume was verified using the Region of Interest (ROI) function and calculated as the sum of all tumor area measured on each tumor slice multiplied by slice thickness [22]. Accordingly, tumors were categorized into microadenoma (<1 cm), macroadenoma (<4 cm) and giant adenoma (≥4 cm).

Endocrinological evaluation and biological remission

Preoperative endocrine assessments including cortisol, ACTH, free tetraiodothyronine (FT4), free triiodothyronine (FT3), TSH, LH, FSH, estradiol, testosterone, PRL, GH, and IGF-1 at 7 am~9 am. Oral glucose tolerance test (OGTT) was preoperatively employed in each patient and 1 week (GH-7), 3, 6, and 12 months after surgery, and annually thereafter. Serum GH and IGF-1 levels were measured by commercial electro-chemiluminescence kits (Roche, Mannheim, Germany). Short-term or long-term biological remission was verified when the serum GH nadir after an OGTT was <0.4 ng/mL and normal serum IGF-1 level adjusted by age and gender at 3 and 12 months after surgery, respectively [23]. To standardize the IGF-1 values for comparison across the gender and age, we calculated IGF-1 z-scores using the formula: z-score = (IGF-1 value–mean)/SD [24]. Central hypothyroidism was diagnosed based on low serum FT4 in the presence of low or normal TSH concentration [25, 26]. Central hypoadrenalism was verified by low serum cortisol level [27]. The diagnosis of central hypogonadism was based on low estradiol/testosterone level with normal or low FSH/ LH level and low or normal FSH/ LH level in postmenopausal women [28].

Pathological study

Surgical specimens were verified by routine H&E staining and further immunohistochemistry (IHC) for GH, PRL,

ACTH, TSH, LH, FSH, and Ki67 in the Department of Pathology of our institution. PSA was negative staining for all these hormones but GH. MSA was positive staining for GH and PRL in the same cells whereas MSLA was composed of a dual cell population that was respectively positive for GH and PRL [15]. Sparsely granulated adenoma was defined as focal immunoreactivity with GH and juxtanuclear globular immunoreactivity with low molecular weight keratin (LMWK), but densely granulated adenoma was defined as diffuse immunoreactivity with GH and perinuclear staining with LMWK [14, 29].

Statistical analysis

Data were displayed in the form of mean ± standard deviation (SD) or median. Chi-square or Fisher's exact tests were used for comparison of categorical variables whereas Student's *T*, Mann–Whitney, one-way ANOVA, and Kruskal–Wallis tests were used for continuous variables. Spearman's rank correlation analyses were conducted for correlations among preoperative GH level and clinicopathological results. Receiver-operating characteristic (ROC) curve was performed to verify the predictive ability or optimal cutoff point of tumor volume, gender, and postoperative GH level by comparing the area under the ROC curve (AUC). Linear regression model was employed for preoperative GH level and tumor volume (after normal transformation). Binary logistic regression was employed for analyzing independent predictors of biological remission. Cox hazard regression and Kaplan–Meier tests were used for recurrence-free survival. When *p*-values were <0.05, the differences were considered statistically significant. Statistical analyses were performed with SPSS version 17.0 (SPSS Chicago IL, USA) and GraphPad Prism (GraphPad Software, Inc., La Jolla, CA, USA).

Results

Patients' clinicopathological characteristics

We retrospectively reviewed the medical record system of our institution and identified 94 patients who met the inclusion and exclusion criteria. Initially, according to the pathological findings, 53, 28, and 13 patients were subdivided into PSA, MSA, and MSLA groups, respectively (Table 1). There was no difference in gender and age across subtypes. Females accounted for 60.0%, 50.0,% and 53.8% of cases in PSA, MSA, and MSLA groups, respectively ($p = 0.5208$). The median age at diagnosis were 42, 44, and 46 years in each group ($p = 0.7656$). Pre-surgical SSA was applied in 24 patients (13 PSA, 9 MSA, and 2 MSLA).

Preoperative neuroradiological evaluation revealed that macroadenoma was the most common entity and accounted for 86.2% of the whole cohort. MSAs were relatively smaller than PSAs and MSLAs from the aspects of tumor anteroposterior (AP) diameter (1.75 cm vs. 2.00 cm and 2.60 cm, $p = 0.0021$), height (1.743 ± 0.945 cm vs. 2.245 ± 0.910 cm and 2.708 ± 1.080 cm, $p = 0.0077$) and width (1.70 cm vs. 2.00 cm and 2.80 cm, $p = 0.0286$). Accordingly, the tumor volume of MSAs was also smaller than PSAs and MSLAs (2.47 cm^3 vs. 4.95 cm^3 and 9.10 cm^3, $p = 0.0033$). Parasellar extension was identified in the majority of cases. 59.6% ($n = 56$) and 30.9% ($n = 29$) cases presented suprasellar growth and sphenoid sinus extension, respectively. A part of lesions invaded the CS, but the frequency differed by subtype: 32.1% of PSA, 7.1% of MSA, and 7.7% of MSLA for left CS invasion ($p = 0.0145$) and 7.5% of PSA, 0.0% of MSA, and 38.5% of MSLA for right CS invasion ($p = 0.0003$).

Preoperative hormones studies revealed remarkable increasing of GH and IGF-1 levels in these patients. The baseline nadir GH and IGF-1 levels were 25.68 ng/ml and 367.3 ± 360.6 ug/l, respectively. There was no difference in baseline nadir GH and IGF-1 *z*-scores across subtypes. Preoperative hyperprolactinemia was identified in 38 cases (40.4%) and the baseline PRL level was significantly higher in MSLAs than PSAs and MSAs (45.41 ng/ml vs. 19.86 ng/ml and 19.25 ng/ml, $p = 0.0203$). Pituitary function assessments also revealed different degrees of hypopituitarism. Hypoadrenalism, hypothyroidism, and hypogonadism were identified in 11.7%, 26.6%, and 37.2% of patients, respectively and there was no statistical discrepancy about the frequency of hypopituitarism among three subgroups.

All of these patients underwent microscopic TSA and GTR rate was 61.7%. MSA group possessed of higher GTR rate than PSA and MSLA (85.7% vs. 54.7%, and 38.5%, $p = 0.0043$). At the meantime, after surgery, patients with MSAs had lower GH concentration than PSA and MSLA patients (GH-7, 1.27 ng/ml vs. 2.90 ng/ml and 4.81 ng/ml, $p = 0.0110$). Postoperative histopathological studies revealed that 59.6% of cases were sparsely granulated subtype and the median Ki67 index was 1.45%. There was no difference in above-mentioned pathological features across subtypes.

In addition, Spearman's rank correlation analyses indicated that preoperative GH level was correlated with tumor volume (correlation coefficient (r_s) = 0.301, $p = 0.003$), granulation pattern ($r_s = 0.394$, $p = 0.001$), GH positive area ($r_s = 0.387$, $p = 0.001$) and suprasellar growth ($r_s = 0.239$, $p = 0.02$). Further linear regression analysis revealed that there was a quantitative association between GH level and tumor volume ($r^2 = 0.07206$, $p = 0.0089$, Fig. 1a). Also, the median preoperative GH level was 36.23 ng/ml for

Table 1 General characteristics of whole series

Patient characteristics[a]	PSA	MSA	MSLA	*P*-value
No. of patients	53	28	13	
Short-term remission (%)	13.2	28.6	0.0	**0.0476**
Long-term remission (%)	26.4	50.0	15.4	**0.0371**
Gender (female, %)	60.0	50.0	53.8	0.5208
Age at diagnosis (year)	42 (17–58)	44 (23–64)	46 (23–70)	0.7656
Preoperative SSA injection (%)	24.5	32.1	15.4	0.5026
MRI performances				
Tumor AP diameter (cm)	2.00 (0.80–3.80)	1.75 (0.60–3.00)	2.60 (0.70–4.10)	**0.0021**
Tumor height (cm)	2.245 ± 0.910	1.743 ± 0.945	2.708 ± 1.080	**0.0077**
Tumor width (cm)	2.00 (1.00–4.90)	1.70 (0.50–3.10)	2.80 (0.80–4.50)	**0.0286**
Tumor volume (cm^3)	4.95 (0.30–33.37)	2.47 (0.11–18.06)	9.10 (0.22–25.56)	**0.0033**
Macroadenoma (%)[b]	86.8	92.9	69.2	0.2881
Left CS invasion (Knosp 3/4, %)	32.1	7.1	7.7	**0.0145**
Right CS invasion (Knosp 3/4, %)	7.5	0.0	38.5	**0.0003**
Suprasellar extension (%)	67.9	42.9	61.5	0.0905
Sphenoid sinus extension (%)	11.3	7.1	23.1	0.3331
Preoperative hormones studies				
Baseline nadir GH (ng/ml)	19.61 (1.33– 366.00)	27.49 (2.14– 147.60)	34.43 (4.28– 240.00)	0.4936
Baseline IGF-1(ug/l)	363.3 ± 333.7	382.2 ± 340.6	344.1 ± 549.9	0.9799
Baseline IGF-1 z-score	3.778 ± 6.427	4.361 ± 6.788	2.736 ± 9.063	0.9078
Baseline PRL (ng/ml)	19.86 (1.12–113.40)	19.25 (4.97–110.40)	45.41 (15.41–694.60)	**0.0203**
Baseline PRL >200 ng/ml (%)	0.0	0.0	23.1	**<0.0001**
Hypoadrenalism (%)	*13.2*	*3.6*	23.1	0.3394
Hypothyroidism (%)	*28.3*	*14.3*	46.2	0.0907
Hypogonadism (%)	35.8	28.6	61.5	0.1207
Gross total resection (%)	54.7	85.7	38.5	**0.0043**
GH-7 (ng/ml)	2.90 (0.30 – 134.20)	1.27 (0.23– 22.82)	4.81 (0.46–48.44)	**0.0110**
Pathological studies				
Sparsely granulated (%)	66.0	57.1	38.5	0.1832
GH positive area (%)	40(8– 95)	45(15– 90)	30(15–90)	0.1723
Ki67 index (%)	1.30 (0.0–5.00)	1.25 (0.0–5.00)	2.10 (0.1–7.0)	0.3200

Positive results were highlighted in bold

PSA pure somatotroph adenoma, *MSA* mammosomatotroph adenoma, *MSLA* mixed somatotroph-lactotroph adenoma, *SSA* Somatostatin analogue, *AP* anteroposterior, *CS* cavernous sinus, *GH-7* nadir GH level in 1 week after surgery

[a]Data were presented as mean ± standard deviation (SD) or median (range)

[b]Microadenoma was detected by MRI in 3, 1 and 1 patients from PSA, MSA, and MSLA groups, respectively

densely granulated subtype and 14.48 ng/ml for sparsely granulated subtype ($p = 0.0001$, Fig. 1b).

Treatment outcomes

During a median follow-up of 35 months (range, 13–129 months), the short-term and long-term biological remission rates were 16.0% and 31.9%. MSAs had higher short-term and long-term biological remission rate than PSAs and MSLAs (Table 1). More detailed analyses about biological remission rate were listed in Table 2 and Supplementary Table 1.

Patients with long-term biological remission were less likely to be female (30.0% vs. 71.9%, $p = 0.0003$). Tumor volume was a predictor for long-term remission that median volume was 1.31 cm^3 in remission group whereas 6.71 cm^3 in patients with persistent disease ($p < 0.0001$). By contrast, patients without biological remission were more likely to had left CS invasion (28.1% vs. 6.7%, $p = 0.0283$) or suprasellar extension (73.4% vs. 30.0%, $p < 0.0001$). Besides, patients in biological remission had significantly lower preoperative (20.05 ng/ml vs. 30.95 ng/ml, $p = 0.0194$) and postoperative GH level (GH-7, 0.69 ng/ml vs. 3.47 ng/ml, $p < 0.0001$). Tumor residual was another relevant factor. None of the patient with biological remission harbored tumor residual, but postoperative residual was detected in 56.3% of the counterparts ($p < 0.0001$). Other factors, like age at diagnosis, preoperative SSA application, right CS invasion, sphenoid sinus extension, and Ki67 index had no impact on long-term biological remission.

Further binary logistic regression analyses demonstrated that gender (male, odds ratio (OR) = 0.784, $p = 0.011$) and

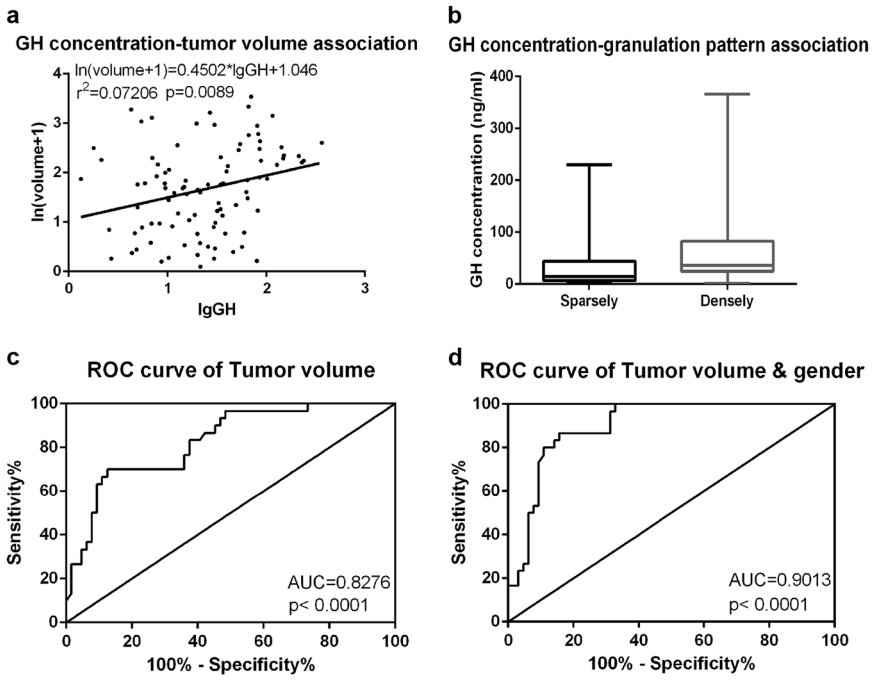

Fig. 1 **a** Linear regression model indicated a correlation between preoperative GH level and tumor volume (after normal transformation, $r^2 = 0.07206$, $p = 0.0089$); **b** preoperative GH level also correlated with granulation pattern. Densely granulated subtype had higher GH level than sparsely granulated subtype (36.23 ng/ml vs. 14.48 ng/ml, $p = 0.0001$); **c** ROC curve of tumor volume identified that the cutoff point was 2.12 cm^3 (AUC = 0.8276, $p < 0.0001$); **d** combination of tumor volume and gender had better predictive ability (AUC = 0.9013, $p < 0.0001$)

Table 2 Clinicopathological factors associated with long-term biological remission

	Persistent disease	Biological remission	*P*-value
No. of patients	64	30	
Gender (female, %)	71.9	30.0	**0.0003**
Age at diagnosis (year)	44 (17–70)	44 (21–64)	0.4326
Preoperative SSA injection (%)	21.9	33.3	0.3105
Tumor volume (cm^3)	6.71 (0.30–33.37)	1.31 (0.11–11.16)	**<0.0001**
Left CS invasion (Knosp 3/4, %)	28.1	6.7	**0.0283**
Right CS invasion (Knosp 3/4, %)	10.9	6.7	0.7138
Suprasellar extension (%)	73.4	30.0	**<0.0001**
Sphenoid sinus extension (%)	15.6	3.3	0.1649
Preoperative nadir GH (ng/ml)	30.95 (2.14–366.00)	20.05 (1.33–84.92)	**0.0194**
Preoperative PRL (ng/ml)	23.99 (1.12–694.60)	19.16 (5.62–316.30)	0.0887
GH-7 (ng/ml)	3.47 (0.46–134.20)	0.69 (0.23–9.01)	**<0.0001**
PSA/ MSA/ MSLA (No. of patients)	39/14/11	14/14/2	**0.0371**
Ki67 index (%)	1.45 (0.00–7.00)	1.35 (0.00–5.00)	0.3365
Tumor residual (%)	56.3	0.0	**<0.0001**

Data were presented as mean ± standard deviation (SD) or median (range)

Positive results were highlighted in bold

SSA Somatostatin analogue, *CS* cavernous sinus, *GH-7* nadir GH level in 1 week after surgery, *PSA* pure somatotroph adenoma, *MSA* mammosomatotroph adenoma, *MSLA* mixed somatotroph-lactotroph adenoma

tumor volume (OR = 0.784, $p = 0.020$) were independent predictors for long-term biological remission. ROC curve of tumor volume revealed that the optimal cutoff point was 2.12 cm^3 and the AUC was 0.8276 ($p < 0.0001$, Fig. 1c). Compared with tumor volume alone, the combination of tumor volume and gender had better predictive ability for long-term remission (AUC = 0.9013, $p < 0.0001$, Fig. 1d).

Tumor recurrence in cases with GTR

After surgery, GTR was achieved in 58 patients (61.7%). However, 51.7% of these patients were in long-term remission during the follow-up. More importantly, 6 out of cases with GTR suffered from disease recurrence (Table 3).

Table 3 Clinicopathological factors associated with recurrence in patients with GTR

	Recurrence	Recurrence-free	*P*-value
No. of patients	6	52	
Gender (female, %)	50.0	46.2	1.0000
Age at diagnosis (year)	43 (27–53)	46 (21–64)	0.4799
Preoperative SSA injection (%)	33.3	26.9	0.6637
Tumor volume (cm^3)	4.98 (0.30–22.38)	2.12 (0.11–11.16)	0.3626
Left CS invasion (Knosp 3/4, %)	0.0	3.8	1.0000
Right CS invasion (Knosp 3/4, %)	0.0	3.8	1.0000
Preoperative nadir GH (ng/ml)	10.36 (2.70–230.00)	20.05 (1.33–127.5)	0.9325
GH-7 (ng/ml)	3.19 (2.08–13.78)	0.89 (0.11–12.86)	**0.0006**
PSA/MSA/MSLA (No. of patients)	3/2/1	26/22/4	0.7381
Ki67 index (%)	1.35 (0.60–5.00)	1.35 (0.00–5.00)	0.6303

Data were presented as mean ± standard deviation (SD) or median (range)

Positive results were highlighted in bold

SSA Somatostatin analogue, *CS* cavernous sinus, *GH-7* nadir GH level in 1 week after surgery, *PSA* pure somatotroph adenoma, *MSA* mammosomatotroph adenoma, *MSLA* mixed somatotroph-lactotroph adenoma

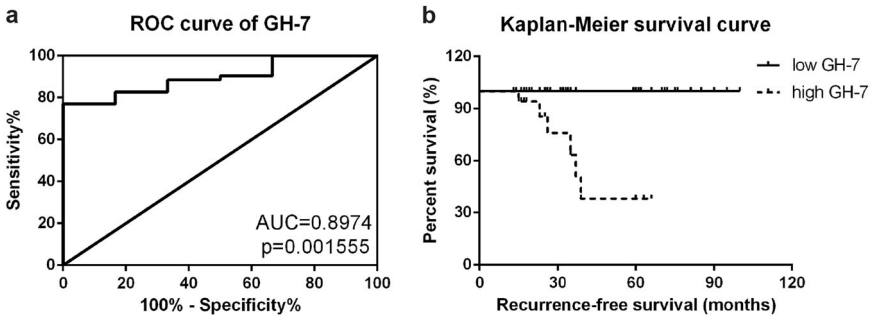

Fig. 2 **a** ROC curve revealed that the optimal cutoff point of GH-7 was 1.945 ng/ml (AUC = 0.8974, $p = 0.001555$); **b** high Gh-7 group (>1.945 ng/ml) had higher recurrence rate ($p < 0.0001$). The recurrence-free survival rate was 100.0% for low GH-7 group during the follow-up, but the recurrence-free survival rates were 85.6%, 50.7%, and 38.0% for high GH-7 group at 2, 3, and 4 years, respectively

Compared with patients in recurrence-free survival, relapsed patients had higher postoperative GH level (GH-7, 3.19 ng/ml vs. 0.89 ng/ml, $p = 0.0006$). Other clinicopathological factors, including gender and age of patients, preoperative SSA injection, tumor volume, CS invasion, preoperative nadir GH level, pathological subgroup, and Ki67 index, were consistent in two groups of patients.

Further Cox proportional hazard regression analysis indicated that postoperative GH level (GH-7) was the only independent risk factor for tumor recurrence (Hazard ratio (HR) = 1.242, $p = 0.001$). ROC curve analysis identified that the optimal cutoff point of GH-7 to predict recurrence was 1.945 ng/ml (Fig. 2a). Accordingly, patients with GTR were divided into high GH-7 and low GH-7 groups. Further Kaplan–Meier survival analysis demonstrated that high GH-7 group had significantly higher recurrence rate ($p < 0.0001$). None of the cases in low GH-7 group relapsed during the follow-up. However, the recurrence-free survival rates were 85.6%, 50.7%, and 38.0% at 2, 3, and 4 years, respectively (Fig. 2b).

Discussion

GHPA is a heterogeneous entity composed of several distinctive pathological subtypes. More importantly, clinical characteristics vary among different subtypes. Compared with DGSAs, SGSAs are more resistant to SSA and more invasive and bigger on imaging performance [30]. Acidophil stem cell adenomas are characterized by mild elevated GH level in addition to hyperprolactinemia with more aggressive prognosis [13, 31]. Thus, in this study, we analyzed the clinicopathological features of MSA and MSLA and identified a number of significant differences among PSA, MSA, and MSLA. It is reported that MSAs are more common in young patients with gigantism [14]. However, there was no difference in gender and age of

patients among somatotroph adenomas for only acromegaly was enrolled in the current study. MSAs were smaller tumors with lower frequency of CS invasion. MSLAs were relatively big and invasive tumor with higher level of preoperative PRL level. Tumor size and invasiveness prominently affect the biological remission after surgery [5–7]. Therefore, MSLAs had lower GTR rate and higher postoperative GH level and consequent lower biological remission rate during follow-up. Wang et al. reports that GHPAs with hyperprolactinemia often are larger lesions and have relatively low preoperative GH level than GHPAs without hyperprolactinemia. However, mild hyperprolactinemia is usually secondary to stalk effect [32]. Radiological features including tumor size are relevant factors for stalk effect [33, 34]. Thus, bigger tumor size observed in GHPAs with hyperprolactinemia may be the cause rather than the consequence for hyperprolactinemia. In our cohort, 40.4% of patients presented hyperprolactinemia before surgery. But obvious hyperprolactinemia (>200 ng/ml) was detected merely in MSLAs ($n = 4$). So, it seemed that MSLAs could produce and secret PRL to the circulation. But allowing for the small sample size of MSLAs, it should be inspected by further studies. Except for the study of serum PRL level in GHPAs, Rick et al. investigates GH and PRL staining tumors in acromegalic patients [18]. They found that dual-staining adenomas (positive for GH and PRL) presented with significantly higher serum PRL and IGF-1 levels, poorer response to medical therapy and higher risk for recurrence, despite similar tumor size with single-staining adenomas. In our study, we also employed pathological methods to categorized somatotroph adenomas, but dual-staining adenomas were further subdivided into MSAs and MSLAs, which was more consistent with the classification of pituitary adenoma released by world health organization (WHO) [17]. Actually, we identified that MSLAs were responsible for the aggressive clinical course of dual-staining adenoma presented by Rick et al. MSAs were innocent for reason that they were usually small lesion with better biological remission rate.

We also intended to identify independent predictors for long-term remission. Short-term and long-term biological remission rates were 16.0% and 31.9%, respectively. Gender, tumor size and invasiveness, pre- and postoperative GH level, pathological subtype and tumor residual were significantly associated with long-term biological remission in univariate analyses. Binary logistic regression indicated that gender and tumor volume were independent predictors for biological remission. The association between tumor size and biological remission has been reported in the literature [5–7]. Tumor size also has a significant relationship to invasiveness and GTR rate in functional and non-functional pituitary adenomas (PAs) [19, 35]. Besides, we identified a quantitative correlation between tumor size and preoperative GH level. So, the vast majority of aforementioned clinicopathological factors were associated with tumor size, which highlighted tumor volume as an independent predictor for long-term biological remission. Additionally, we also believed that bigger tumor size of MSLAs made them an aggressive subtype of somatotroph adenomas. But there was no different about Ki67 index across subtypes. Therefore, instinct differences, perhaps molecular alterations [36, 37], were likely to be the reason for the bigger tumor size and worse prognosis of MSLAs.

Regardless of tumor size, the basic goal of surgical intervention for acromegaly is tumor debulking as much as possible. However, only 51.7% of patients were in long-term remission after GTR. It is reported that GH level would rapidly decline after surgery and postoperative GH level shows significant association with resection degree and long-term outcomes [38–40]. That's why nadir GH level in OGTT is assigned as one of the criteria for biological remission. The cutoff point of nadir GH level for remission criteria is 1 ng/ml but revised to a more stringent value (0.4 ng/ml), which was employed in this study. Except for the application of ultrasensitive GH assays, the long-term mortality rate of acromegalic patients is taken into account in this revision [41, 42]. Although it is in lower priority than mortality, tumor recurrence is one of the major causes for therapeutic failure. Thus, in this study, we analyzed the relationship of clinicopathological factors and tumor recurrence in patients with GTR. We concluded that postoperative GH level (GH-7) was the only risk factor for tumor recurrence in univariate and multivariate analyses. The cutoff point of GH-7 for relapse prediction was 1.945 ng/ml. At present, GTR for PA is defined through intraoperative inspection and postoperative radiological studies. It is not true GTR from the biological aspect for functional and non-functional PAs [43]. It is also the reason for tumor recurrence in patients after radiological GTR. Sustained GH excess assessed by OGTT is a clue for invisible residual in GHPA. Therefore, postoperative GH level is important in early identification of cases with high risk of recurrence. Perhaps, a nadir GH cutoff point of 1.945 ng/ml in OGTT is helpful.

The current study had several limitations: (1) as a retrospective study, it was subject to the common limitations of retrospective analysis; (2) data about the clinical presentations of elevated GH and PRL were not analyzed for reason that male patients usually were shamed to claim symptoms like decreased libido and erectile dysfunction in mainland China, which may lead to underestimation of hyperprolactinemia-associated symptoms; (3) stimulation tests for hypoadrenalism were not employed in this study; (4) accounting for the small number of relapsed cases ($n = 6$) after GTR, we could not get strong conclusion about the association of GH-7 and tumor recurrence, which should be further verified.

In conclusion, MSAs were relatively small lesions with higher biological remission rate. MSLAs were aggressive tumors characterized by bigger tumor size, higher frequency of CS invasion and preoperative hyperprolactinemia. Tumor size was a predictor for biological remission whereas postoperative GH level was significantly associated with tumor relapse after GTR. These data may prompt further understanding of the heterogeneity of somatotroph adenoma and benefit for further investigation of the biological behavior of GHPA.

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Compliance with ethical standards

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

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This study was approved by Biomedical Research Ethics Committee of West China Hospital of Sichuan University.

Informed consent For this type of study formal consent is not required.

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