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Original Article

Clinico-radio-pathological predictors of outcomes in patients with acromegaly undergoing endoscopic transsphenoidal surgery

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ABSTRACT

Background: Acromegaly is a rare chronic endocrine disorder with variable biochemical remission rates from 40% to 85%. Hence, understanding the factors predicting biochemical cures helps in planning targeted and personalized treatment. We aimed to study the various clinico-radio-pathological predictors of outcomes in patients with pituitary neuroendocrine tumor (PitNET) who underwent transsphenoidal surgery (TSS) at 3 months follow-up.

Methods: Our cohort included 61 consecutive patients with acromegaly treated at an institute in northwest India between January 2019 and June 2021. The outcomes of TSS were assessed at the end of 3 months postoperatively as defined by Endocrine Society Guidelines 2014.

Results: The mean age at diagnosis was 38 ± 12 years, with the majority being females (67.2%). The median tumor volume was 2376 mm^3 with high insulin-like growth factor-1 levels (3.12 ± 1.76 times the upper reference limit). Forty-two patients (68.8%) had radiological evidence of cavernous sinus invasion. Overall, the biochemical remission rate at 3 months was 34.4%. Unlike preoperative Knosp grading, T2-hypointensity was not predictive of biochemical remission. The granularity of PitNET, as well as immunohistochemical (IHC) markers such as Ki-67 index somatostatin receptor subtype (SSTR2/5) and low-molecular-weight cytokeratin (CAM5.2) expression, failed to show any significant correlation with remission.

Conclusion: Overall, bulky tumors, higher hormone burden, and advanced Knosp grades translated to lower rates of biochemical remission in the present study cohort. Contrary to earlier studies, conventional IHC markers such as Ki-67, SSTR2/5, and CAM5.2 were not useful for predicting biochemical remission at 3 months.

Keywords: Acromegaly, Histopathology, Pituitary neuroendocrine tumor (PitNET), Radiology, Remission, Transsphenoidal surgery

INTRODUCTION

Acromegaly is a chronic endocrine disorder characterized by hypersecretion of growth hormone (GH), most often secondary to a functioning pituitary neuroendocrine tumor (PitNET).

Early diagnosis and timely personalized management of acromegaly are required for alleviating morbidity and financial burden.[9,16] The current gold standard in the management of acromegaly is selective excision of PitNET. Hence, the biochemical cure following surgery is determined by the completeness of resection, which, in turn, depends on inherent tumor characteristics such as tumor size and microinvasion, as well as the expertise of the treating surgeon. The proportion of patients achieving biochemical cure following surgery is highly variable, >85–90% for microadenomas and 40–50% for macroadenomas.[9] There are various clinical, radiological, and histopathological markers, Ki-67 index, and somatostatin receptor subtype (SSTR2/5 expression) proposed to predict biochemical remission.[1,7] We sought to analyze the utility of various clinical, radiological, and histopathological parameters in predicting the biochemical remission of acromegaly. This information aids in not only prognosticating the surgical outcomes but also helps in the timely initiation of adjuvant therapy in high-risk candidates.

MATERIALS AND METHODS

The study cohort consists of 61 patients with acromegaly, diagnosed based on Endocrine Society guideline 2014,[9] treated at our institute with endoscopic transsphenoidal surgery (TSS) between January 2019 and June 2021. The study was approved by ethical approval from the Institutional Research Committee, and written informed consent was obtained from all participants before enrollment. All patient's baseline data were collected at the time of inclusion, consisting of detailed clinical features, including comorbidities, visual field assessment, and anthropometry. Preoperative hormonal assessments, including thyroid function test, prolactin (PRL), GH, adrenocorticotropic hormone (ACTH), cortisol, luteinizing hormone (LH), and follicle-stimulating hormone (FSH) were done by electrochemiluminescence using COBAS 600 (Roche) while insulin-like growth factor-1 (IGF-1) was done by COBAS 801 (Roche). We defined hypopituitarism by comprehensive assessment of clinical features along with hormonal analysis. Hypocortisolism was defined biochemically by basal cortisol <100 nmol/L or peak cortisol post synacthen test <550 nmol/L.[17,18] Hypogonadism was defined by considering both clinical features as well as a hormonal picture of low-sex steroids (Testosterone <9 nmol/L and estrogen <30 pg/mL) with inappropriately low gonadotropins.[4] An oral glucose tolerance test (OGTT) was performed for all the patients at diagnosis and at follow-up at 3 months. The biochemical remission was defined by random GH <1 ng/mL with IGF-1 in the age-appropriate normal range.[9] In case of discordant GH and IGF-1 results, nadir GH <0.4 ng/mL is said to have controlled disease. Gadolinium-enhanced magnetic resonance imaging (MRI) of the sella turcica region (3T) with T1- and T2-weighted sequences was performed at diagnosis and follow-up at 3 months. All the MRI images were reviewed by a single neuroradiologist (CKA). The imaging characteristics included maximum tumor size (expressed as maximum diameter in mm), tumor volume, intensity of PitNET in T2 weighted images, and extrasellar extension, including parasellar invasion. Immunohistochemical (IHC) assessments were done using monoclonal antibodies to anterior pituitary hormones (GH 1:400; Dako hGH, ACTH 1:70; Dako 02A3, thyroid-stimulating hormone 1:50; Dako 0042, PRL 1:200; Dako polyclonal, FSH 1:50; Dako C10, LH 1:50; Dako C93, SSTR2, SSTR5 – Abcam, CAM5.2 [Diagnostic biosystem], and Ki-67 [1:300; Cell marque sp6]).

All patients were reevaluated at 3 months to assess biochemical, clinical, and radiological remission following TSS. The composite clinical remission was defined by the resolution of four clinical features, which include subjective improvement in acral enlargement and a decrease in headache, sweating, and seborrhea, while the complete absence of tumor residue defined radiological remission. We also calculated the global SAGIT score.[9] SAGIT score comprises of following parameters with individual scores: Symptoms (0–4), associated comorbidities (0–6), GH status (0–4), IGF-1 levels (0–3), and tumor (0–5). Preoperative clinical imaging and histopathological determinants were then analyzed to assess their predictive nature for biochemical remission at 3 months.

Statistical analysis

The outcome groups were compared using the Chi-square or Fischer exact test. Univariate, followed by multivariate logistic regression, was applied to find significant predictors of remission in TSS. All tests were carried out at a 5% level of significance; that is, $P < 0.05$ was considered significant. All analyses were carried out using IBM-Statistical Package for the Social Sciences Statistics version 21 software (IBM Corporation, Armonk, New York, USA).

RESULTS

Clinical features

The mean age at diagnosis of patients in the study cohort was 38 ± 12 years with a female-to-male ratio of 2:1. The mean lag period (from first symptom to diagnosis) was 39 ± 33 months. The observed clinical features were as follows (in decreasing order of prevalence): acral enlargement (97%), coarse facial features (97%), sweating (75%), headache (75%), menstrual irregularities in females (36%), arthralgia (21%), obstructive sleep apnea (17%), and self-reported visual symptoms (5%). However, formal visual field assessment (n = 49) revealed field defects in the right eye (n = 18/49: 36.7%) and left eye, respectively (n = 22/49; 44.9%). Among comorbidities,

14 (23%) of the participants had diabetes mellitus, while 20 (33%) had hypertension.

Preoperative hormonal analysis revealed hypogonadism in 40%, hypocortisolism in 21%, concomitant hypothyroidism in 10%, and panhypopituitarism in 5%. Postoperatively, the proportion of patients with subjective resolution of observed clinical features was as follows (in decreasing order): headache (58%), acral enlargement (57%), seborrhea (52%), and sweating (51%). Composite clinical remission defined by resolution of the above four clinical features was 42%. The postoperative remission rates of diabetes and hypertension were 86% and 33%, respectively. The mean global SAGIT score (n = 51) in our study cohort was 13 + 2.6.

Radiological findings

Preoperative

Tumors were classified into microadenoma and macroadenoma based on the maximum tumor diameter in any dimension. The summary of radiological findings is listed in Table 1. The majority of subjects had macroadenoma (n = 55; 90%). Interestingly, only 6 (10%) participants had microadenoma. The median tumor diameter and volume were 21 ± 11.5 mm and 2376 mm^3 (microadenoma: 240 mm^3 and macroadenoma: 2688 mm^3), respectively. Thirteen (21%) of the participants had hypointensity in T2-weighted MRI sequences. Twenty-eight (46%) participants had cavernous sinus invasion defined by a knosp grade greater than or equal to two [Figure 1a,b]. Three participants (5%) had radiological features of apoplexy, while 4 (7%) had cystic adenoma.

Postoperative

Even though only 20 patients among 61 subjects (36%) had radiological remission at 3 months, 30 (60%) participants (n = 55; follow-up) had radiological remission on long-term follow-up with a median duration of 49 ± 30 months. The increase in remission rates is due to the cumulative effect of adjuvant therapy. There was no mortality in our study cohort. The relative percentage of patients with cerebrospinal fluid rhinorrhea, carotid artery injury, and postoperative epistaxis was not assessed in the present study, as similar studies have already been done from our center.

Table 1: Summary of preoperative MRI.

Preoperative MRI	Mean±SD||Median (IQR)||Range
Lesion	
Microadenoma	6 (9.8)
Macroadenoma	55 (90.2)
Giant adenoma (Yes)	7 (11.5)
Maximum tumor diameter (mm) (preoperative)	22.49±11.50 (15.00–29.00) || 1.00–50.00
Median tumor volume (mm≥) (preoperative)	2376±7571.97 (962.00–7800.00) || 49.00–36750.00
Lesion location	
Left/Right/Center	24 (39.3)/18 (29.5)/19 (31.1)
Signal intensity T1	
Hypointense	8 (13.1)
Isointense	49 (80.3)
Hyperintense	4 (6.6)
Signal intensity T2	
Hypointense	13 (21.3)
Isointense	39 (63.9)
Hyperintense	9 (14.8)
Knosp grade	
Grade 0	4 (6.6)
Grade 1	15 (24.6)
Grade 2	14 (23.0)
Grade 3A	6 (9.8)
Grade 3B	5 (8.2)
Grade 4	17 (27.9)
Cavernous sinus invasion (Yes)	42 (68.8)
Suprasellar extension (Yes)	34 (55.7)
Infrasellar extension (Yes)	17 (27.9)
Retrosellar extension (Yes)	2 (3.3)
Apoplexy (Yes)	3 (4.9)
Cystic change (Yes)	4 (6.6)

MRI: Magnetic resonance imaging, SD: Standard deviation, IQR: Interquartile range

Biochemical remission at 3 months

The median preoperative random GH and IGF-1 were 23.22 ng/mL (interquartile range [IQR]: 10.00–46.25) and 750.00 ng/mL (IQR: 499.50–1059.75), respectively. The mean nadir GH following the OGTT (n = 54) was 33.18 ± 43.20 ng/mL, and eight patients had a paradoxical rise of GH following OGTT. Overall, 21 (34.4%) had biochemical remission at 3 months. The remission rates were 83.3% (n = 5/6) and 29% (n = 16/55) among microadenoma and macroadenoma, respectively. Ten subjects had discordant GH- IGF-1 levels, of which five had high GH with low IGF-1, and the remaining five had high IGF-1 with low GH.

Follow-up and adjuvant therapy

We followed up on patients' serial GH and IGF-1 at regular intervals. Redo surgery was done in 5 (8%) subjects who were not in remission. Patients with persistent disease were subsequently offered various adjuvant therapies. Till the last follow-up data available, 35 (58%) had received adjuvant treatment. Radiotherapy, in the form of either Gamma Knife radiosurgery or intensity-modulated radiotherapy (IMRT), was offered to 52% of the study subjects. The most provided drugs were somatostatin receptor ligands (SRLs) – octreotide-LAR (32%), cabergoline (27%), and temozolomide (7%). Thirty-eight (n = 38/53; 72%) study subjects on long-term follow-up achieved biochemical remission with the aid of adjuvant therapy akin to surgery.

Histopathological analysis

On IHC, 58 specimens (95%) showed GH positivity [Figures 2 and 3], of which 16 (26%) showed both GH and PRL positivity [Table 2], while three tumors were negative for anterior pituitary hormone expression. Pituitary transcription factor-1 (PIT-1) expression was not assessed. A total of 17 cases (17/47, 36%) had histopathological evidence of invasion defined by invasion of bone, dura, or sphenoid mucosa. Due to paucity of good quality specimens, tissue distortion and limited availability of IHC stains during the study setting, IHC assessment for CAM5.2, SSTR2, and SSTR5 was not performed in all specimens. The granularity of the adenoma and IHC staining with CAM5.2, SSTR2, and SSTR5 was assessed in 41, 40, 39, and 29 specimens, respectively. Based on GH staining characteristics, 83% (n = 34/41) were densely granulated [Figure 2a-d], while (n = 7/41) 17% were sparsely granulated [Figure 3a-d]. Immunoreactivity for CAM5.2 was detected in 26 tumors out of 40 cases (65%; n = 26/40). All the sparsely granulated adenomas based on the GH staining pattern showed CAM5.2 positivity (100%; P = 0.073). Ki 67 labeling index <3% in 85% (n = 32/39)). Only eleven (28%; 11/39) tumors yielded positivity for SSTR2

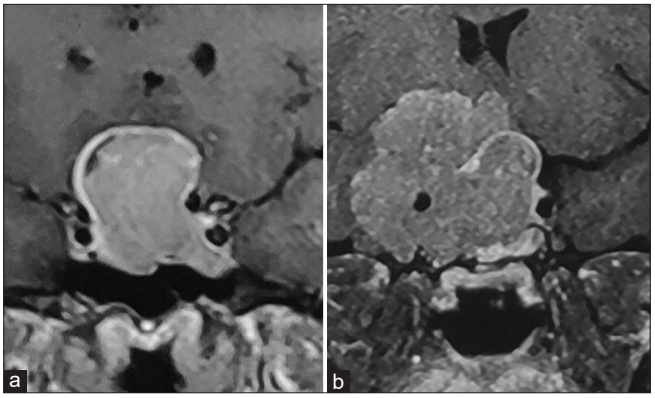

Figure 1: (a) Gadolinium-enhanced T1 magnetic resonance imaging (MRI) images in coronal section showing pituitary adenoma with Knosp grade 3B. Gadolinium-enhanced T1 MRI images in coronal section showing pituitary adenoma with (b) Knosp grade 4.

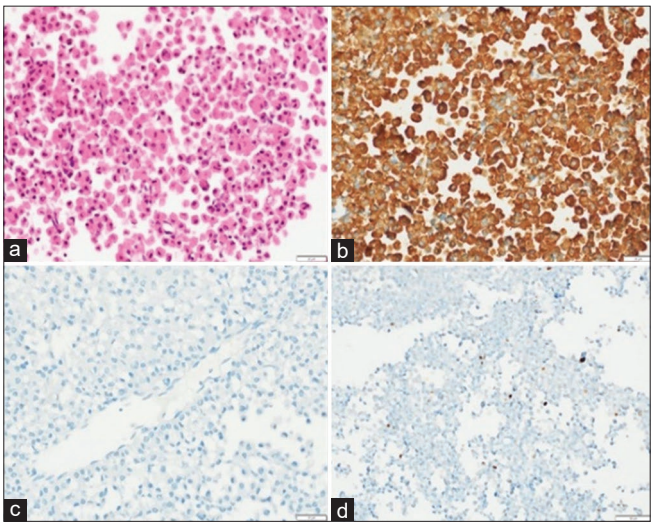

Figure 2: Densely granulated pituitary neuroendocrine tumor (a) sheets of small round cells with abundant eosinophilic cytoplasm (Hematoxylin and eosin, scale bar 20 μm); (b) strong and diffuse immunoreactivity for growth hormone (GH) (anti-GH, scale bar 20 μm); (c) tumor cells were negative for prolactin, thyroid-stimulating hormone, follicle-stimulating hormone, luteinizing hormone and adrenocorticotropic hormone (immunoperoxidase, scale bar 20 μm); and (d) Ki-67 labeling index is low <3% (immunoperoxidase, scale bar 50 μm).

[Figure 4a-d]. Sparsely granular adenoma had more intense SSTR2 staining than densely granular adenoma (P = 0.035). Out of 29 tumors, only 15 cases (52%; 15/29) showed SSTR5 positivity [Figure 5a-d].

Predictors of biochemical remission

The parameters that had a significant association with biochemical remission at 3 months were younger age at diagnosis, higher tumor diameter and volume, preoperative

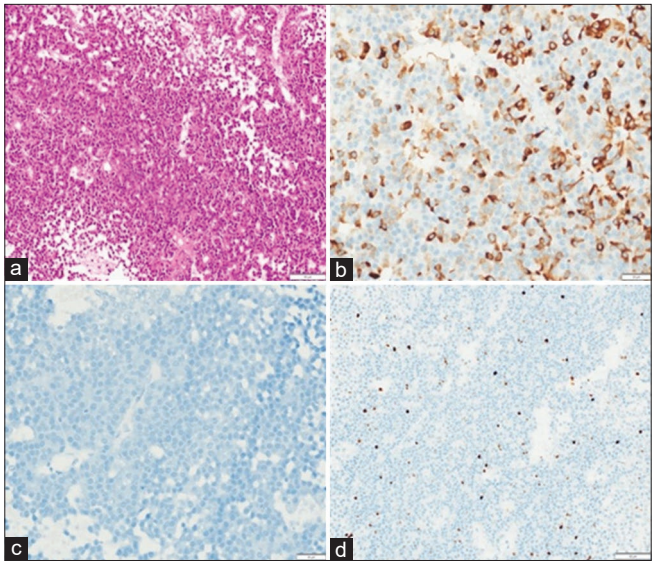

Figure 3: Sparsely granulated Pituitary neuroendocrine tumor. (a) Low magnification depicting small round cells arranged in sheets interrupted by fine capillaries (Hematoxylin and eosin, scale bar 50 μm); (b) patchy immunoreactivity for growth hormone (GH) (anti-GH, scale bar 20 μm); (c) tumor cells were negative for Prolactin, thyroid-stimulating hormone, follicle-stimulating hormone, luteinizing hormone and adrenocorticotropic hormone (immunoperoxidase, scale bar 20 μm); and (d) Ki-67 labeling index <3% (immunoperoxidase, scale bar 50 μm).

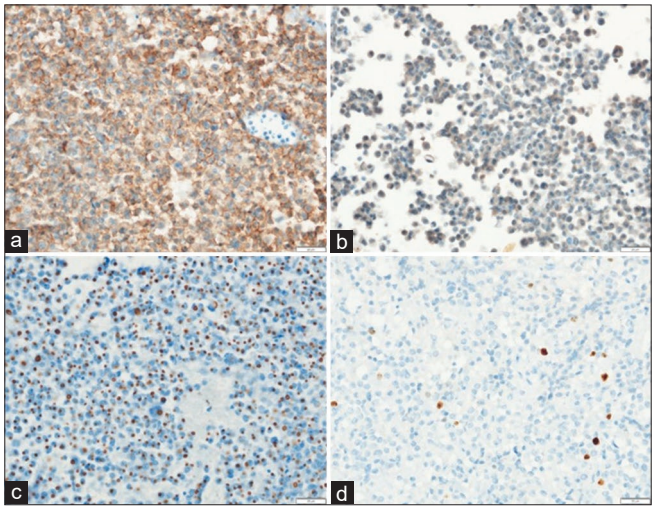

Figure 4: (a) Pituitary neuroendocrine tumor showing diffuse and strong membranous immunoreactivity for somatostatin receptor subtype (SSTR2) (anti-SSTR5, scale bar 20 μm); (b) focal immunoreactivity for SSTR2a (anti- SSTR2a, scale bar 20 μm); (c) Low-molecular weight cytokeratin (CAM5.2) reveals characteristic fibrous bodies in vast majority of tumor cells (anti-CAM5.2, scale bar 20 μm); and (d) Ki-67 labeling index <3% (immunoperoxidase, scale bar 20 μm).

Knosp grading, radiological evidence of cavernous sinus invasion, composite clinical remission, higher preoperative GH and IGF-1, and percentage change in tumor volume post-TSS. In univariate regression analysis with biochemical remission as dependent variable, variables such as GH nadir (odds ratio [OR] = 0. 93; P = 0.011), age at diagnosis (OR = 1.05, P = 0.050), and preoperative maximum tumor diameter OR = 0.88 (P = 0.004) were found to be significant. Further, logistic regression analysis was done using GH nadir on OGTT, age at diagnosis, and preoperative maximum tumor diameter. On multivariate analysis, GH nadir on OGTT (OR = 0.94, confidence

Table 2: Summary of histopathology.

HPE	Frequency (%)
GH (Positive)	58 (95.1)
PRL (Positive)	16 (26.2)
Granularity	
Densely granular	34 (82.9)
Sparsely granular	7 (17.1)
Necrosis	
No necrosis	41 (100.0)
Necrosis	0 (0.0)
Mitosis/HPF	
<2/HPF	41 (100.0)
>2/HPF	0 (0.0)
Ki67	
<3%	39 (84.8)
>3%	7 (15.2)
SSTR2 (Positive)	11 (28.2%)
SSTR2 positivity	
Focal positive	4 (36.4)
Positive	7 (63.6)
Strongly positive	0 (0.0)
SSTR5 (positive)	15 (51.7)
SSTR5 positivity	
Focal positive	6 (40.0)
Positive	8 (53.3)
Strongly positive	1 (6.7)
CAM5.2 (Positive)	26 (65.0)
CAM5.2 positivity	
Focal positive	5 (19.2)
Positive	13 (50.0)
Strongly positive	8 (30.8)
Bone	
Involved	2 (6.5)
Free	29 (93.5)
Dura	
Involved	15 (39.5)
Free	23 (60.5)
Mucosa	
Involved	4 (9.3)
Free	39 (90.7)
Histopathological invasion	
Involved	17 (36.2)
Free	30 (63.8)

SSTR2/5: Somatostatin receptor subtype, GH: Growth hormone, PRL: Prolactin, HPE: Histopathological examination, CAM 5.2: Cytokeratin

interval [CI] 0.89–1, $P = 0.037$) and preoperative maximum tumor diameter (OR = 0.90, CI 0.82–0.99, $P = 0.029$) stood significant [Tables 3 and 4].

There was no statistical significance between remission and gender, lag period before diagnosis, comorbidities, or visual acuity. Giant adenoma, T2 signal intensity, and tumor extension other than parasellar invasion did not show statistical significance in predicting outcomes at 3 months. None of the histopathological features, including immunoreactivity for SSTR2, SSTR5, CAM5.2, and Ki67 index, had any significant association in predicting biochemical remission.

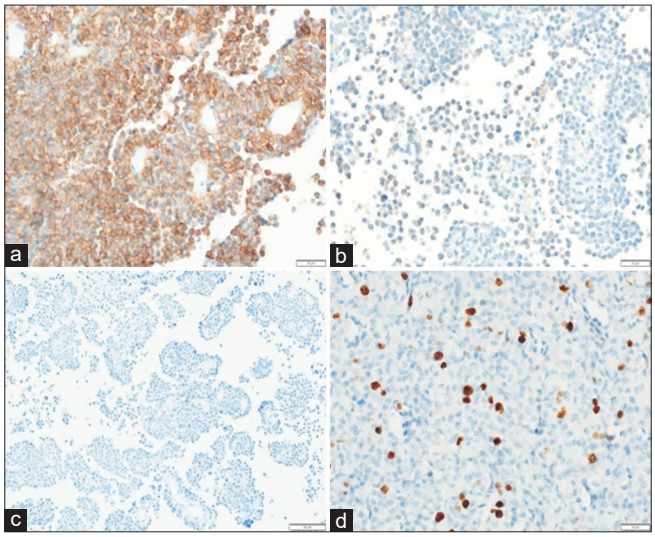

Figure 5: (a) Pituitary neuroendocrine tumor showing diffuse and strong membranous immunoreactivity for somatostatin receptor subtype (SSTR5) (anti-SSTR5, scale bar 20 μm); (b) focal and weak immunoreactivity for SSTR 5 (Anti -SSTR 5, scale bar 20 μm), scale bar 20 μm); (c) absence of immunoreactivity with cytokeratin (CAM5.2) (anti-CAM5.2, scale bar 50 μm); and (d) Ki-67 labeling index =5% (immunoperoxidase, scale bar 20 μm).

Table 3: Summary of IHC markers and patient in remission at 3 months.

Pattern	Biochemical remission	Not in remission	*P*-value
SSTR2 (*n*=39)			
Negative	12	16	0.368
Positive	3	8	
SSTR5 (*n*=29)			
Negative	5	7	0.550
Positive	9	8	
CAM 5.2 (*n*=40)			
Negative	3	13	0.079
Positive	11	13	

SSTR2/5: Somatostatin receptor subtype, IHC: Immunohistochemistry, CAM 5.2: Cytokeratin

DISCUSSION

This is one of the largest single-center studies from Southeast Asia exploring predictors of remission at 3 months following TSS. In this study, bulky tumors, higher hormone burden, and advanced Knosp grades translated to lower rates of biochemical remission. Contrary to earlier studies, conventional IHC markers such as Ki-67, SSTR2/5, and CAM5.2 were not useful for predicting biochemical remission at 3 months.

The present study cohort includes young patients with lesser lag periods and large somatotropinoma with high hormone burden.[18] In contrast to various European registries, our study participants had florid clinical features with very high preoperative random GH and IGF-1 levels, higher tumor volume, and cavernous sinus invasion (69%), irrespective of age and gender.[4-6] The discordance between clinical features and lesser lag time might be due to recall bias rather than due to the inherent hyperfunction of the tumor, considering the higher rate of locoregional invasion at diagnosis. Interestingly, though a significant fraction of PitNET was macroadenoma, the self-reported visual deficit was only 5%. However, formal visual field assessment revealed visual field defects in about one-third of patients contrary to self-reported symptoms. In the Indian setting, patients quite often present late to a point where the deficits are incapacitating. Since these visual field defects were not restricting them from their day-to-day occupation, patients failed to notice these deficits.

The overall biochemical and radiological remission rates were 34.4% and 36.1%, respectively. The relative remission rates among microadenoma and macroadenoma were 83.3% ($n = 5/6$) and 29% ($n = 16/55$), respectively.

Ten subjects had discordant GH- IGF-1 levels, of which five had high GH with low IGF-1, and the remaining five had high IGF-1 with low GH. Such discordance between GH and IGF-1 is not unknown and is usually reported in about one-third of patients. This is said to be due to the disruption of a neural or anatomical network of regulation of GH secretion after surgery. Those with elevated IGF-1, irrespective of GH status, are considered to have active disease. Four patients (4/5) with low IGF-1 but elevated random GH were subjected to GH-GTT and were found to be in biochemical remission. Overall, the lower biochemical remission rate at 3 months might be due to the dominance of macroadenoma as well as higher rates of cavernous sinus invasion. The functional status of somatotropinoma, determined by nadir GH post-OGTT and IGF-1 levels, positively correlated with size and parasellar invasion predicted by Knosp grading, which translated to lower biochemical and radiological remission. T2 hypointensity predicts densely granulated somatotropinoma, which has better remission rates and response to SRLs.[14] However, in our study, T2 hypointensity did not show any significant association with the granularity of the tumor as

Table 4: Summary of radiological markers and patient in remission at 3 months.

	Biochemical remission (*n*=21)	Not in remission (*n*=40)	*P*-value
Microadenoma	5	1	0.016
Macroadenoma	16	39	
Preoperative MRI: Knosp	Frequency (%)		0.001
Grade 0	3 (14.3)	1 (2.5)	
Grade 1	9 (42.9)	6 (15.0)	
Grade 2	7 (33.3)	7 (17.5)	
Grade 3A	1 (4.8)	5 (12.5)	
Grade 3B	0 (0.0)	5 (12.5)	
Grade 4	1 (4.8)	16 (40.0)	
Preoperative MRI: Cavernous sinus invasion (Yes)	9	33	<0.001
Preoperative MRI: Signal intensity T2			0.387
Hypointense	4 (19.0)	9 (22.5)	
Isointense	12 (57.1)	27 (67.5)	
Hyperintense	5 (23.8)	4 (10.0)	

MRI: Magnetic resonance imaging

well as biochemical remission. This might be due to overall higher locoregional invasion, cystic changes, and apoplectic, which might have obscured the objective assessment. On both univariate and multivariate analysis, remission rates had a significant association with the age at diagnosis, tumor size, GH nadir, and cavernous sinus invasion. In recent times, the Global SAGIT score has been validated in various studies as a comprehensive score useful in predicting adverse surgical outcomes. However, we found no correlation between the Global SAGIT score (n = 51) and biochemical remission.

Histologically, Pit-NETs are classified based on the tumor cell lineage, cell of origin, secretory nature, and granularity. Somatotropinomas are histologically characterized by the expression of PIT1, GH immunostaining, alpha-subunit of glycoprotein hormones, and cytokeratin staining.[2,3] Acromegaly may also be a result of plurihormonal adenohypophyseal tumors such as mammosomatotropinoma, acidophil cell adenoma, mixed somatotroph lactotroph lineage pituitary tumors and PIT1 lineage, immature and mature, and pituitary tumors. Due to their aggressive nature and poor response to medical treatment, plurihormonal pituitary tumors are associated with poor surgical and medical outcomes.[13] On histological analysis, 95% (n = 58/61) of specimens showed GH immunostaining, and among GH-positive PitNET, 26% of tumors showed both GH and PRL positivity. However, plurihormonal nature of PitNET was not useful in predicting remission (clinical and biochemical) or tumor invasion (radiological or based on histopathology) in our study. In three patients, GH staining was negative. Although rare, acromegaly with GH immunostaining has been reported.[13] One of the most possible explanations for this phenomenon is technical failure, that is, either due to inadequate pituitary tissue or faulty histopathological assessment.[12,13] The second mechanism is loss of antigenicity during the fixative procedure.[12] However, in our case, a repeat assessment did not change initial histopathological findings, negating the former two possibilities. The third reason in this regard is sparsely granulated Ghoma with low-level expression of GH and Pit-1 expression missed by immunostaining.[13] Unfortunately, we could not perform PIT-1 immunostaining in these samples.

Based on the secretory granule pattern, somatotropinomas can be further classified into densely granulated and sparsely granulated PitNET.[16] The most common subtype, *densely granulated somatotroph tumor,* is composed of strongly acidophilic cells with characteristic perinuclear keratin staining resembling parent non-neoplastic somatotroph.[8] They are often hormonally active, hence, are comparatively detected at a young age and relatively smaller in size with less extrasellar extension and better chances of remission. On the other hand, the *sparsely granulated somatotroph tumor*s are constituted by chromophobe cells with sparse secretory granules with negative or focally weak positive GH expression.[11] This subtype is characterized by cytoplasmic globules called fibrous bodies that can be visualized on hematoxylin and eosin staining and are delineated by stains for cytokeratins such as CAM5.2, CK18, and AE1/AE3.[15] Further, the somatostatin receptor expression with SSTR2/SSTR5 immunostaining is helpful in predicting treatment response to SRLs. The relative distribution of densely granular and sparsely granular somatotroph tumors based on cytokeratin was 65% and 35%, respectively. Contrary to previous observations, the granularity of the tumor failed to show any consistent trends in remission rates in the present study. These results might be partly due to a higher rate of locoregional invasion, irrespective of the granularity of the tumor, thus resulting in incomplete resection.

All the sparsely granulated somatotroph tumors showed CAM5.2 positivity and avid SSTR2 expression as compared to

densely granulated adenoma, though not meeting statistical significance. A previous study by Brzana *et al.* showed that sparsely granular tumors had less staining for SSTR2 as compared to densely granular tumors.[4,10] However, no such significant association was observed in our current study. The tumors with a high Ki67 proliferation index ≥3% were observed to have higher rates of cavernous sinus invasion and suprasellar extension. However, these immunostaining characteristics, Ki 67 index, SSTR2/5, or CAM5.2 expression, failed to predict overall biochemical remission.

We also followed this patient with periodic random GH and IGF-1. Redo surgery was offered to only 5 (8%) patients who were not in biochemical remission. Redo surgery rates are lower in our study cohort due to the following reasons: (1) lack of acceptance of repeat surgery, (2) as majority of our patients had macroadenoma with parasellar extension; hence, patients mainly opted out for IMRT or SRL, and (3) due to financial burden, our center prefer combined IMRT with SRL therapy as a second line therapy after failed surgery in patients with macroadenoma with parasellar invasion rather than SRL alone. The biochemical remission was sustained in only 29.5% without any adjuvant therapy in the present study cohort. Although mechanistically, SSTR2 expression predicts response to SRLs, we did not observe any association with the said parameters. A significant fraction of our patients did not attain biochemical remission even with adjuvant therapy. This underlines the baseline aggressive and resistant nature of PitNET in our study cohort compared to the Western literature. Hence, the larger study might be required to arrive at a definite conclusion regarding ethnic differences in the tumor nature and heterogeneity in response to SRLs.

Strengths and limitations

The major strength of our study was the single-center study cohort, with all radiological and histopathological analyses done by a single experienced neuroradiologist and pathologist, respectively. The limitations of our study were the small sample size. Due to technical limitations and paucity of tissue for processing, SSTR2, SSTR5, and CAM5.2 staining could not be performed in all the study participants. This could have affected the lower sensitivity of histological parameters for predicting remission. The unavailability of pharmacological agents might have affected the overall long-term remission rate at long-term follow-up with adjuvant therapies.

CONCLUSION

The clinic-radiological predictors of biochemical remission at 3 months were as follows: younger age of presentation, higher tumor diameter and volume, higher preoperative GH and IGF-1 levels, Knosp grade, and radiological evidence of cavernous sinus invasion. T2-hypointensity on MRI and IHC markers such as SSTR2/5 and CAM5.2 failed to reveal a correlation with biochemical remission.

Ethical approval

The research/study approved by the Institutional Review Board at Post Graduate Institute of Medical Education and Research, number NK/5923/MD/456, dated January 30, 2020.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Nil.

Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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