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Immunohistochemical Subtypes of Growth Hormone-Secreted Pituitary Adenoma and Association with the Clinical Course and Secondary Malignancy

Growth Hormon Sekrete Eden Adenomlarda Subtip Tayininin Klinik Takip ve Akromegali İlişkili Sekonder Malignansi Gelişiminde Rolü

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Abstract

Objective: Most of the acromegaly cases are caused by growth hormone-secreting pituitary adenoma. Pituitary adenomas are classified histologically into sparsely granulated adenoma (SGA) and densely granulated adenoma (DGA). SGAs have been reported to elicit a more aggressive clinical course and therapy resistance. The aim of this study was to investigate the immunohistochemical subtype of patients with pituitary adenoma and their relationship with the clinical course of the disease. **Material and Methods:** In the period between 2000 and 2016, about 40 (F21, M19) patients with acromegaly who were diagnosed and operated for pituitary adenoma at our university hospital were included in this study. The medical history of patients, duration of the disease, and comorbidities were assessed. Based on current guidelines for acromegaly management, we determined the serum growth hormone [with 75 g "oral glucose tolerance test" (OGTT)], insulin-like growth factor 1 (IGF-1) levels, as well as computed tomography (CT) or magnetic resonance imaging of the pituitary gland. Immunohistochemical staining of postoperative tissue materials and subtypes of pituitary adenomas were evaluated by an experienced cytopathologist. **Results:** Of the 40 acromegaly patients included in the study, 25 patients were evaluated as sparsely granulated and the remaining 15 patients were evaluated as densely granulated. The mean age of SG adenomas (40.6±9.7 vs. 48.6±5.7, p=0.04) was significantly lower. At the first visit, 64% of SG adenomas were macroadenoma while only 35% of DG adenomas were macroadenoma and the difference was not statistically significant (p=0.43). SG adenomas' pre-treatment GH, IGF1 values (29.2 ng/mL, 800 ng/mL versus 8.4 ng/mL, 445 ng/mL, p=0.02) and post-treatment GH, IGF1 values (4.1 ng/mL, 440 ng/mL versus 0.4 ng/mL, 152 ng/mL, p=0.03) were significantly higher. While endocrine remission is more common in DG adenomas; organomegaly, abnormal echocardiographic findings (left ventricular hypertrophy) and multinodular goiter were more common in SG adenomas. Malignancy (renal cell Ca, thyroid Ca, larynx Ca) was detected in four patients and histopathological diagnosis of these patients was detected as SG adenoma. **Conclusion:** The immunohistochemical subtype of the pituitary adenoma may have the potential to affect the clinical course and therapy of acromegaly. SGA is more prone to cavernous sinus invasion, comorbidity and resistance to therapy. Carcinogenesis associated with malignancy was more common in patients with SGA. However, further studies are needed to confirm our findings.

Keywords: Acromegaly; carcinogenesis; sparsely granulated adenoma

Özet

Amaç: Büyüme hormonunu [growth hormone (GH)], sekrete eden adenomlar immünohistokimyasal olarak boyanma paternlerine göre yoğun granüllü (DG) ve seyrek granüllü (SG) olarak gruplandırılmaktadır. Klinik takipte seyrek granüllü adenomlar daha genç hastalarda görülmek ile birlikte, tedaviye daha dirençli olarak bilinirler. Biz bu çalışmada, yoğun granüllü ve seyrek granüllü adenomların akromegali ile ilişkili komorbiditeler (tedavi yanıtı, hipertansiyon, kardiyopulmoner hastalıklar, organomegali, malignansi) açısından ilişkisi olup olmadığını inceledik. **Gereç ve Yöntemler:** Çalışmaya, 2000-2016 yılları arasında tanı alan 40 (Kadın=21, Erkek=19) akromegali hastasını retrospektif olarak dâhil ettik. Çalışmaya alınan tüm hastaların klinik öykü, fizik muayene bulgusu, tanı anındaki ve tedavi sonrasındaki hormonal, biyokimyasal parametreleri ve görüntüleme (hipofiz manyetik rezonans görüntüleme) bulguları kayıt edildi. Hastaların aldığı tedavi yöntemi (cerrahi, cerrahi+medikal, cerrahi+medikal+radyoterapi) kayıt edildi. Cerrahi sonrası 75 g oral glukoz tolerans testi (OGTT) testine göre GH değerleri kayıt edildi. Hastaların patoloji spesmenleri uzman 2 patolog tarafından tarafsız olarak boyanma paternlerine (DG, SG) göre tekrar değerlendirildi. **Bulgular:** Çalışmaya alınan 40 akromegali hastasının 25'i seyrek granüllü geriye kalan 15 hasta yoğun granüllü olarak değerlendirildi. SG adenomların yaş ortalaması (40,6±9,7'ye karşı 48,6±5,7, p=0,04) anlamlı olarak daha düşüktü. SG adenomların %64'ü ilk gelişte makroadenom iken, DG adenomların sadece %35'i makroadenom olup istatistiksel olarak anlamlı değildi (p=0,43). SG adenomların tedavi öncesi GH, IGF1 (29,2 ng/mL, 800 ng/mL'ye karşı 8,4 ng/mL, 445 ng/mL, p=0,02) ve tedavi sonrası GH, IGF1 (4,1 ng/mL, 440 ng/mL'ye karşı 0,4 ng/mL, 152 ng/mL, p=0,03) değerleri anlamlı olarak daha yüksek olarak saptandı. Endokrin remisyon DG adenomlarda daha fazla görülürken; organomegali sıklığı, anormal ekokardiyografik bulgular (sol ventrikül hipertrofisi) ve multinodüler guatr SG adenomlarda daha fazla olarak görülmekte idi. Dört hastada malignansi (Renal cell Ca, tiroid Ca, larinks CA) saptanmış olup bu hastaların histopatolojik tanısı SG adenom olarak saptanmıştır. **Sonuç:** Çalışmamızda, SG adenomlar literatüre uygun olarak daha genç yaşta görülmekle birlikte, tedaviye yanıtları daha az olarak saptandı. Eşlik eden komorbid durumlar (organomegali, kardiyak bulgular, multinodüler guatr) daha fazla eşlik etmekte idi. İstatistiksel olarak anlamlı olmasa da maligniteye eşlik eden 4 akromegali hastasının histopatolojik tanısı seyrek granüllü olarak saptandı. Bu konu ile ilgili yapılacak daha fazla hasta sayısının olduğu çalışmalara ihtiyaç vardır.

Anahtar kelimeler: Akromegali; karsinogenez; seyrek granüllü adenom

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Introduction

Acromegaly is a rare systemic disease caused by excess growth hormone secretion (1). Increased growth hormone (GH) and insulin-like growth factor (IGF-1) levels lead to somatic overgrowth, along with multiple comorbid disorders including hypertension, diabetes mellitus, respiratory disturbances, and secondary malignancy. The estimated prevalence of acromegaly is estimated to be 40 to 480 cases per million (2).

Based on the histological, immunohistochemical and electron microscopic studies, growth hormone-secreting adenomas can be subdivided in sparsely (SGA) and densely granulated (DGA) adenomas (3,4).

In the clinical course of the disease, SGAs are more aggressive and resistant to treatment (5,6). Major differences between SGA and DGA are the intensity and size of secretory granules and the distribution of cytokeratin filament. SGAs are composed of cytokeratin filament called fibrous bodies and an eccentric nucleus. DGAs have large secretory granules and its nucleus is located centrally. Immunohistochemical stainings of the DGA show strong growth hormone secretion (7,8).

It has been suggested that immunohistochemical subtypes of these adenomas could determine the clinical outcomes of the therapy. SGAs are commonly seen in young patients and presented with large size of the pituitary mass and more invasive to adjacent tissues such as cavernous sinuses and optic chiasm (9). In this study, we evaluated the postoperative immunohistochemical pituitary adenoma subtypes and their relationship with the clinical course of the disease.

Material and Methods

Forty patients with acromegaly who had been referred to our endocrinology clinic between January 2000 and December 2016 were retrospectively included in the study. The diagnosis of acromegaly was assessed based on the clinical findings and hormone analysis according to the endocrine guidelines (10). We obtained data of demographical, hormonal and radiological reports from patient files. There were 40 patients with acromegaly who were eligible based on the pathological reports. In our study, the disease duration was defined as the time between the initial diagnosis of acromegaly and the current time of performing this study. The inclusion criteria were as follows: (a) confirmed acromegaly diagnosis, (b) a pituitary mass on MRI, (c) patients who had pituitary surgery and quantitatively enough specimen for histopathological diagnosis, (d) those who had colonoscopy to screen colon neoplasm at initial diagnosis of acromegaly, and (e) those who had at least one follow-up clinical evaluation after the pituitary surgery. The follow-up screening criteria and postoperative tests were as follows: (a) random GH and IGF-1 value at 12 weeks or nadir GH value after a 75 g-glucose tolerance test (GH ≤1 mcg/L) (b) MRI of the pituitary at least after 12 weeks (c) thyroid ultrasonography was performed if there was a palpable thyroid nodule and/or a positive family history of thyroid malignancy. (d) abdominal ultrasonography was performed on those patients given somatostatin receptor analogs for gallstone disease (10).

The endocrine remission criteria were as follows: (a) Patients who had serum IGF-1 within normal ranges considering age and gender, and GH levels <1.00 mcg/L with 75 g oral glucose load (OGTT); (b) Patients who had unsuccessful pituitary surgery and continuing active disease, and growth hormone suppressive therapy including somatostatin analogs and cabergoline have been administered (10).

Serum GH levels were measured as a chemiluminescence immunometric assay using the Immulite 2000, Siemens; ng/mL. Serum IGF-1 measurements were performed with a solid phase enzyme-labeled chemiluminescence immunometric assay using the Immulite 2000, Siemens; ng/mL. Calibration was up to 1600 ng/mL (WHO National Institute for Biological Standards and Control first International Reference Reagent [NIBSC first IRR] 87/518). The serum levels of prolactin, thyroid-stimulating hormone (TSH), free thyroxin, adrenocorticotropic hormone (ACTH), follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol, testosterone were analyzed using an immunoassay kit (DxI 800, Beckman Coulter; ng/mL).

Radiological Evaluations

Magnetic resonance imaging of the pituitary was performed before and after intravenous contrast administration. Tumors were classified as macroadenomas (>10 mm) or microadenomas (<10 mm) as consistent with the clinical guidelines. Parasellar extensions of pituitary tumors were classified into five grades according to the Knosp classification (11). Grades 0, I and II were considered as noninvasive and grades III/IV as invasive.

We assessed the pre- and post-operative MRI/BT scans of the pituitary gland as follows: a change in the residual mass size below 10% was defined as the stabilized mass and an increase of >10% as unstabilized mass. Ultrasonographic examinations were conducted by the same experienced radiologist by using static grayscale and real-time B mode ultrasonography. Both ultrasonographic examinations (thyroid and abdomen) were performed after 8-h of fasting. Sonographic measurements for hepatomegaly were determined according to the criteria of Gosink et al (12).

Pathological Evaluation and Immunohistochemistry

Immunohistochemical stainings were performed on tissues of 5-mm sections which had been formalin-fixed and paraffin-embedded using human growth hormone antibody (GH) (1/100, Zymed Laboratories), low molecular weight keratin (LMWK) (1/70, Leica) and Ki-67 (clone MIB-1, Dako). BenchMark XT with heat-induced epitope retrieval (CC1 solution) and iView DAB detection kit (Ventana, Tucson, AZ) were used for the visualization system. Cytoplasmic staining was regarded as positive for GH. Dot-like globules of keratin staining called as a fibrous body at LMWK and fibrous bodies were defined for SGA. Granular cytoplasmic staining with LMWK was considered as DGA. Nuclear staining was accepted as positive for Ki-67 and the percentage of its staining was evaluated. Examples of different immunostaining patterns are shown in Figure 1. This study was conducted in accordance with the Declaration of Helsinki. The Local Ethics Committee of Cukurova University approved the study (No:87, 2019).

Statistical Analysis

Statistical analyses were performed using the Shapiro-Wilk, Mann-Whitney U and Chi-squared tests. For correlations between the groups, Pearson's correlation was used for the parameters with the normal distribution, and Spearman's tests were used for the parameters without normal distribution. The results for categorical variables were presented as n (%), while quantitative variables were expressed as mean±SE mean or median (min, max). SPSS-19 software (IBM, Armonk, NY, USA) was used for all statistical analyses.

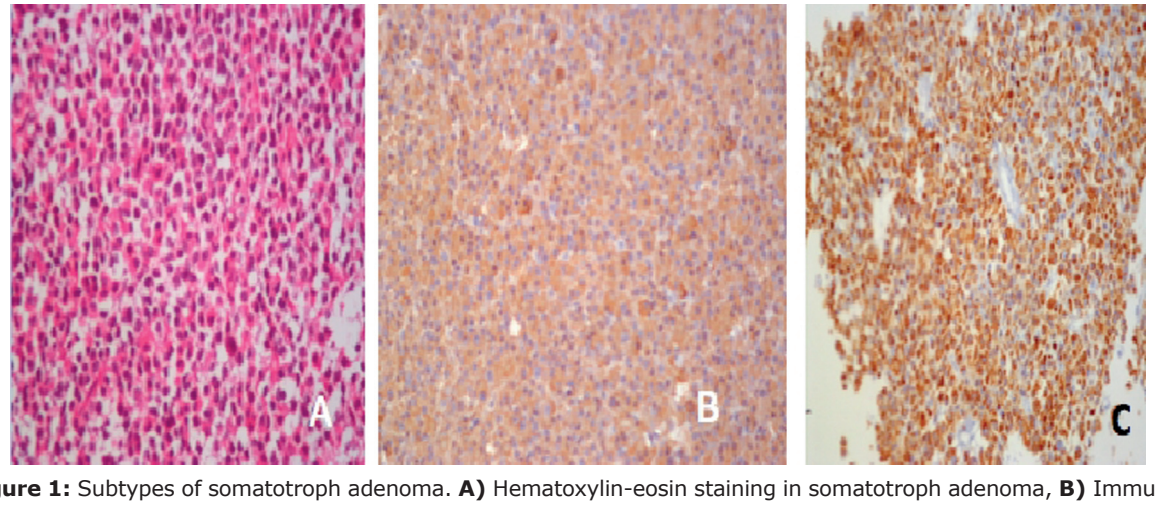

Figure 1: Subtypes of somatotroph adenoma. **A)** Hematoxylin-eosin staining in somatotroph adenoma, **B)** Immunohistochemical positivity of growth hormone (GH) in somatotroph adenoma, **C)** Distinct paranuclear fibrous bodies typical of sparsely granulated somatotroph adenoma.

Results

There were 21 female and 19 male patients. The median age of patients was 48 years (range, 30 to 66). The mean duration of the disease was 12-years (range, 12 to 192 months). Of the 40 patients, 30 had macroadenoma (tumor size >10 mm) and 10 had microadenoma (tumor size <10 mm).

Twenty-five of the total 40 patients (62.5%) had SGA, while 15 (37.5%) had DGA. Ki-67 proliferation index was found to be 1% in the specimens of 38 patients and 2% in the specimens of two patients. The SGA was found to be higher in females than in males (15 vs. 10, $p<0.05$), respectively.

The preoperative mean serum GH value of the patients with DGA was 8.4 ng/mL. The median IGF-1 values of the patients with DGA were two times higher than the upper limit of the normal range (median 445 ng/mL).

The preoperative mean GH value of the patients with SGA was 29 ng/mL and the median IGF-1 levels of the patients with SGA were four times higher than the upper limit of normal (median 800 ng/mL).

The remission rate after primary surgery in all patients with acromegaly was 9/40. Of the nine patients, two had SGA (2/25) and the remaining seven patients had a subtype of DGA (7/15) ($p=0.001$, SGA vs. DGA).

The postoperative MRI scans of the pituitary revealed that 31 patients had residual lesions, 7 patients had no residual lesions, and 2 had empty sella. While 20 of 25 patients with SGA were found to have macroadenomas using MRI of the pituitary, only ten patients with DGA had macroadenomas.

Seventy percent of adenomas (28/40) were found to have cavernous sinuses invasion (CSI) at grade III (n=16) and grade IV (n=12) levels.

When compared for the cavernous sinus invasion in both adenoma types, SGA (n=18) showed a higher rate of invasion than that of the DGA, which was not significant (18 vs. 10, $p=0.05$), respectively.

Of the 40 patients, 10 (25%) had only diabetes mellitus as a comorbid disease, 5 (12.5%) only hypertension and the remaining 25 (62.5%) had no other disease.

The patients' data including demographic, CT/MRI, serum GH/IGF-1, and histopathological characteristics are summarized in Table 1.

Complete endocrine remission (defined as the serum GH level <1 ng/mL with OGTT) was seen in 15 of 40 (37.5%) patients. Among patients with endocrine remission, nine patients had only transsphenoidal surgery (TSS) and the remaining six patients were administered somatostatin analogs (Octreotide) and gamma-knife radiotherapy in addition to TSS. The median duration to remission was 36 months considering the serum IGF-1 normalization (range, 12-192 months). When compared to the histopathological subtypes of 15 patients who achieved endocrine remission, 11 had DGA, and only four patients presented with SGA ($p<0.05$). There were total 25 (25/40) patients showing no endocrine remission after TSS, who were followed with chemotherapy (Octreotid: 16, Lanreotid LAR:5, Cabergolin:2) and/or gamma-knife radiotherapy. Of them, 21 were SGA and 4 were DGA. The outcomes of surgical or combination therapy with respect to immunohistochemical subtypes of adenomas (SGA, DGA) are shown in Table 2.

Surveillance Findings

The results of the 31 patients who were treated with GH suppressive medical therapy and screened by abdominal ultrasonography are shown in Table 1. All patients with SGA (100%) had abnormal ultrasound findings including hepatomegaly (n=10), hepatosteatosis (n=2), splenomegaly (n=5), hepatomegaly and splenomegaly (n=4), polycystic renal diseases (n=2), and cholelithiasis (n=2).

The thyroid ultrasonography of the 40 patients indicated that 19 were with normal observations, 21 showed multinodular goiter, and of these 21 cases, most (n=14) were associated with SGA. In the diagnostic fine needle aspirations (FNA) of the patients with nodular goiter, there was only one case with thyroid follicular neoplasia. The echocardiographic findings of the 40 patients were normal in 24 cases; however, in 10 patients, it showed left ventricular hypertrophy, and in 6 patients, left ventricular diastolic dysfunction and pericardial effusion were observed. Regarding the adenoma subtypes, all patients with abnormal cardiac findings including left ventricular hypertrophy (n=10), left ventricular diastolic dys-

Table 1. The patient data including demographics, hormonal parameters, imaging findings and comorbidities with respect to immunohistochemical subtypes of GH secreting adenomas.

	DGA (n=15)	SGA (n=25)	P-value
Duration of Disease (year)	14	4	0.002
Age	48.6±5.7	40.6±9.7	0.04
Sex			0.04
Male	9/40	10/40	
Female	6/40	15/40	
Cavernous Sinus invasion	10 (%35.8)	18 (%64.2)	0.05
Macroadenoma	10 (%33.4)	20 (%66.6)	0.43
Microadenoma	5 (%70)	5 (%30)	
GH*(ng/mL)	8.4	29.2	0.02
IGF1* (ng/mL)	445	800	
GH**(ng/mL)	0.4	4.1	0.03
IGF1** (ng/mL)	152	440	
Post operative residual mass	9 (%31.1)	20 (%68.9)	0.01
Endocrine Remission***	11 (%64.7)	4 (%35.5)	0.02
Hepatomegaly	2	10	
Splenomegaly	2	5	
Cholelithiasis	2	2	
Abnormal echocardiography ∞	2	14	0.04
Nodular goiter	7	14	0.04
Malignant disease δ	-	4	0.91

DG, densely granulated; SG, sparsely granulated, * Preoperative value; **Postoperative value; ***Endocrine Remission, Growth hormone (GH) <1ng/mL with 100 g OGTT; ∞, Abnormal echocardiography including left ventricular hypertrophia, left ventricular diastolic dysfunction, pericardial effusion. δ, Malignant disease including larynx, renal, thyroid neoplasia.

Table 2. Outcomes of surgical and medical treatment in patients with DGA or SGA.

	Surgical Treatment	Combination Therapy+	Endocrine Remission***	Without Endocrine Remission
SGA	2	2	4	21
DGA	7	4	11	4
Total	9	6	15	25

+: Surgical, Medical and/or Gamma knife RT; ***: Growth hormone (GH) <1 ng/mL with 100 g OGTT.

function (n=5) and pericardial effusion (n=1) were carrying SGA, while those with DGA had normal echocardiographic findings (SGA vs. DGA, $p<0.05$). The colonoscopic findings were normal in all patients. The results of thyroid ultrasonography, echocardiography, and their relevance with the immunohistochemical subtypes of the adenomas are shown in Table 1.

Secondary malignancies associated with acromegaly

We found four secondary malignant diseases including renal cell cancer (n=2), thyroid follicular neoplasia (n=1), and larynx cancer (n=1) in our patients with acromegaly. These four patients were operated and were clinically followed postoperatively. The different types of cancer immunostaining are shown in Figure 2. All patients with malignancy had SGA but with no statistical significance.

Discussion

It is well known that the primary treatment for acromegaly patients with pituitary adenoma is transsphenoidal surgery to control the growth hormone excess and to prevent the acromegaly related comorbidities. An unsuccessful surgery requires the other

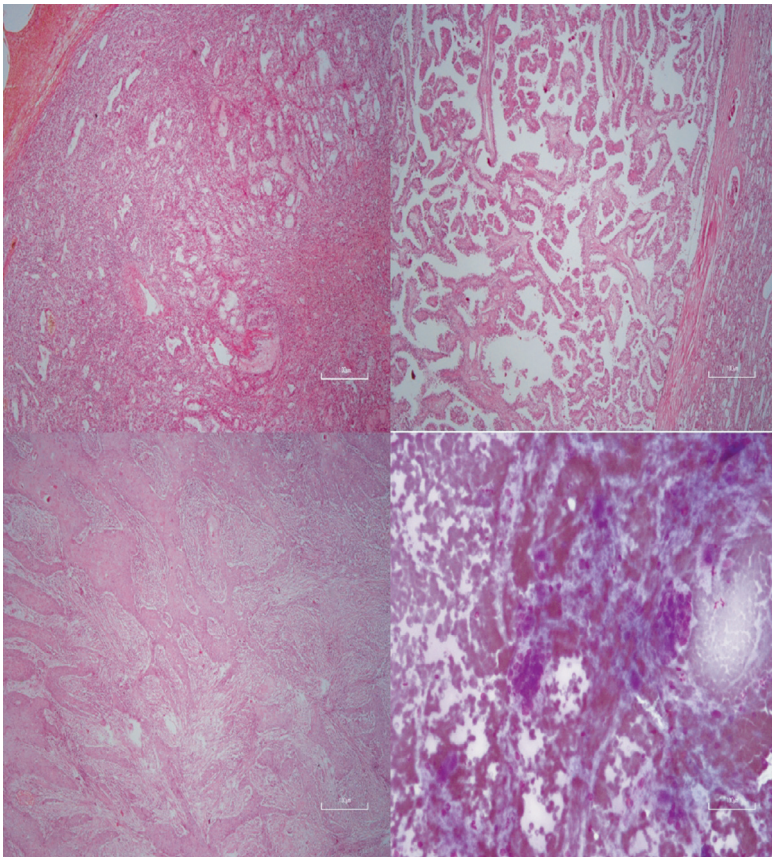

Figure 2: Patient 1 (Upper left side, x40 Hematoxylin and Eosin staining)Cystic dilated blood spaces were intermingled with large polygonal cells with clear cytoplasmic uniform round nuclei and inconspicuous nucleoli, **Patient 2** (Upper right side, x 100 Hematoxylin and Eosin staining) Papillary and tubulocystic areas were lined by large polygonal cells with clear cytoplasm, **Patient 3** (Lower left side, X40 Hematoxylin and Eosin staining) Atypical squamous cell shaped tumor segments in the samples of thyroid fine-needle aspiration, **Patient 4** (Lower right side, x100 May Grünwald Giemsa) Pleomorphic atypical follicular segments bearing rough chromatin in the samples of thyroid fine-needle aspiration.

known treatment options such as medical therapy and pituitary radiotherapy (13).
Recent studies (14-17) have shown that immunohistochemical subtypes of GH-secreting adenomas (DGA, SGA) have a significant relationship with treatment response, aggressiveness, and clinical and hormonal features of acromegaly. It has been reported that the SGA subtype has a larger tumor volume, higher incidence of suprasellar extension, cavernous sinus invasion and is more common in females than the DGA subtype (5,18-20).
Similarly, we observed that the clinical course and outcomes of acromegaly treatment were related to the immunohistochemical subtypes of the GH-secreting adenoma. Among the 40 patients with acromegaly, 25 had SGA while 15 had DGA. Of the total 40 patients who had acromegaly treatment, 15 were in endocrine remission, and 11 of them (11/15) were due to DGA.
Although it did not reach the statistical significance, pituitary macroadenomas were found to be higher in patients with SGA than in patients with DGA (20 vs. 10; p=0.435), respectively. In addition, the cases with SGA showed more frequent invasion of the cavernous sinuses than those with DGG (18 vs. 10; p=0.05, respectively). As reported in the other studies, SGA was found to be more common in females.
Although in a few studies (20-22), the baseline serum GH and IGF-1 levels were high in patients with DGA, in most of the other studies (5,16,21-23), the baseline serum

GH and IGF-1 levels were reported to be higher in patients with SGA than the patients with DGA subtypes. Consistent with the later reports, we found higher baseline (pretreatment) serum GH and IGF-1 levels in patients with SGA than the patients with DGA (29 ng/mL and 800 ng/mL vs. 8.4 ng/mL and 445 ng/mL; p=0.03), respectively.

Several studies (21,23,24) reported that the surgical response rate of patients with DGA was higher than patients with SGA. Kiseljak et al. (20) reported that acromegaly caused by DGA showed a higher remission rate than acromegaly by SGA (65.7% vs. 14.3%; p<0.001). Bakhtiar et al. (16) reported that patients with SGA (n=30) had a higher tumor volume and a lower surgical cure rate (42.3%) compared to patients with DGA (n=111, 60.4%). Similarly, we found a significant correlation between the postoperative remission rate (47%) and DGA (p=0.001).

Another aspect of the study is to investigate acromegaly related comorbidities such as morbidity and mortality (25-27). Hypertension, impaired glucose metabolism, sleep apnea, osteoarthritis, visceromegaly, multinodular goiter, and malignancy elsewhere in the body are the most common concomitant diseases (28-30). The most frequent disorders in the cardiovascular system are left ventricular hypertrophy, decreased ventricular diastolic filling, and reduced left ventricular ejection fraction (31). Acromegaly related cardiomyopathy is found in most of the patients at initial diagnosis. Although hypertension is the best-known causative factor in cardiac hypertrophia, several studies have suggested that cardiac hypertrophia was an initial finding in the heart, even in patients without hypertension (32). In this study, we found left ventricular hypertrophy in ten patients (25%), left ventricular diastolic dysfunction in five patients and pericardial effusion in one patient using echocardiography. When compared to the patients with DGA, all cases with abnormal cardiac findings belonged to SGA (SGA vs. DGA, p<0.005).

Previous studies, with respect to the intra-abdominal morbidities of acromegaly, reported that the higher serum GH/IGF1 levels and the higher visceromegaly incidence including of hepatomegaly, splenomegaly, cystic renal disease in patients were due to SGA (12,33-36). Consistent with these studies, we found that all our patients with SGA (25/40; 100%) had hepatomegaly (n=10), splenomegaly (n=5), hepato-splenomegaly (n=4), cholelithiasis (n=2) and cystic renal disease (n=2). However, there were only six patients (n=15, 40%) with abnormal abdominal findings due to DGA (Table 1).

Several preliminary studies have reported that patients with acromegaly have three times increased risk of the corresponding type of tumor. However, it is still under debate whether the cancer risk increases or not. In some retrospective studies, nearly 15% to 24% of deaths of acromegaly were attributed to various types of cancer including colon, thyroid, breast, hematopoietic and renal cell (37,38). In order to understand the underlying mechanisms of pathogenesis, GH/IGF-1 pathways are considered as the key factor in the induction of mitosis and predisposition to malignancy (39-41). In line with the reported observation of increased secondary malignancy in patients with acromegaly, we found four (4/40) patients with renal cell carcinoma, laryngeal carcinoma, and thyroid neoplasia, which were due to SGA. Although we could not find a statistically significant difference due to the small sample size, our results should not be neglected in the management of acromegalic patients for secondary malignancies.

In conclusion, an immunohistochemical subtype of pituitary adenoma whether SGA or DGA seems to affect the clinical course, comorbidities, and therapy responses. SGA was revealed as more prone to cavernous sinus invasion, comorbidity and resistance to therapy. Moreover, all patients with malignancy had SGA. Hence, to perform immunohistochemical staining of the pituitary adenoma, it is important to predict the clinical course of the patients with acromegaly.

Study Limitations

This is a retrospective study based on collected data. The sample size is very small since some of the patients underwent surgery in other tertiary centers and we could not collect pathologic specimens from these centers.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: Gamze Akkuş; Design: Gamze Akkuş, Sinem Şengöz; Control/Supervision: Murat Sert; Data Collection and/or Processing: Nuri Eralp Çetinalp, Gamze Akkuş, Emine Kılıç Bağır; Analysis and/or Interpretation: Mehtap Evran; Literature Review: Murat Sert, Gamze Akkuş; Writing the Article: Gamze Akkuş; Critical Review: Murat Sert, Tamer Tetiker, Suzan Zorludemir; Materials: Gamze Akkuş, Nuri Eralp Çetinalp.

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