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Cavernous Sinus Invasion and Effect of Immunohistochemical Features on Remission in Growth Hormone Secreting Pituitary Adenomas

Büyüme Hormonu Salgılayan Hipofiz Adenomlarında Kavernöz Sinüs İnvazyonu ve İmmünohistokimyasal Özelliklerin Remisyona Etkisi

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ABSTRACT

AIM: We examined the cavernous sinus invasion and tumor biological markers that influence the remission rate. Cavernous sinus (CS) invasion was evaluated radiologically. Tumor biological markers consisting of the tumor cell growth parameter Ki-67 and the cancer cell vasculature marker of vascular endothelial growth factor (VEGF) were evaluated.

MATERIAL and METHODS: We examined 28 immunohistochemically proven GH secreting pituitary adenoma patients who had been operated via endoscopic transsphenoidal surgery at Department of Neurosurgery, Kocaeli University Hospital between 2003 and 2008. Pathology preparations were stained with Ki-67 and VEGF. We evaluated remission at the postoperative 6th week. The basal GH level, nadir GH level and IGF-1 levels were evaluated to determine remission.

RESULTS: Remission was achieved in 6 of 18 patients (33%) who had cavernous sinus invasion. Remission was achieved in 7 of 10 patients (70%) who did not have cavernous sinus invasion. There was no correlation between the Ki-67 proliferation index and cavernous sinus invasion (p=0.593). There was a positive correlation between VEGF expression and cavernous sinus invasion (p=0.03).

CONCLUSION: The remission rate found less in the cavernous sinus invasion group. No association was found between Ki 67 proliferation index and cavernous sinus invasion. We found that a positive correlation between VEGF expression and cavernous sinus invasion. VEGF expression can therefore indirectly affect remission via cavernous sinus invasion.

KEYWORDS: GH adenoma, VEGF, Ki-67, Cavernous sinus invasion, Remission

ÖZ

AMAÇ: Çalışmada remisyona etkisi olduğu öngörülen faktörlerden; kavernöz sinüs invazyonu ve tümör biyolojisi ile ilgili özellikler gözden geçirildi. Bu amaçla kavernöz sinüs invazyonu radyolojik olarak değerlendirildi. Ayrıca tümör biyolojisini gösteren; tümör büyüme potansiyelinde etkili Ki-67 ve tümör damarlanmasını gösteren VEGF immünohistokimyasal olarak incelendi.

YÖNTEM ve GEREÇLER: Çalışmaya 2003-2008 tarihleri arasında Kocaeli Üniversitesi Hastanesi Nöroşirürji Kliniği'nde endoskopik transfenoidal yolla ameliyat edilen 28 büyüme hormonu (GH) adenomu hastası dahil edildi. Doku örneklerine Ki-67 ve VEGF immünohistokimyasal boyamaları uygulandı. Kısa dönem remisyon değerlendirmesi için postoperatif 6. haftada IGF-1 ve OGTT sonrası GH düzeyleri ölçümlerine bakıldı.

BULGULAR: Kavernöz sinüs invazyonu olan hastalarda kısa dönem remisyon oranı 6/18 (%33) idi. Kavernöz sinüs invazyonu olmayan 10 hastanın 7'sinde remisyon sağlandı (%70). Ki-67 proliferasyon indeksi ile kavernöz sinüs invazyonu arasında anlamlı bir korelasyon olmadığı (p=0,593), VEGF ekspresyonunun kavernöz sinüs invazyonu açısından önemli bir gösterge olduğu (p=0,03) saptandı.

SONUÇ: Kavernöz sinüs invazyonu gösteren GH adenomu olgularında kısa dönem remisyon oranlarının daha düşük görüldüğü, Ki-67'nin kavernöz sinüs invazyonu ve remisyonu etkilemediği, VEGF ekspresyonunun kavernöz sinüs invazyonunu artırarak indirekt yolla remisyon üzerinde etkili olabileceği sonucuna varıldı.

ANAHTAR SÖZCÜKLER: GH adenomu, VEGF, Ki-67, Kavernöz sinüs invazyonu, Remisyon

INTRODUCTION

Pituitary adenoma is the third most common primary brain tumor after the gliomas and meningiomas. This tumor type makes up 10-15% of primary brain tumors.

GH (Growth Hormone) secreting pituitary adenoma patients come to hospital with symptoms of acromegaly, gigantism or tumor mass effect. Surgery is the first choice treatment method for acromegaly (34,54). These tumors are histologically benign and treatment outcome depends on tumor size and invasion to nearby structures. If cavernous sinus invasion is present in GH secreting pituitary adenomas, endocrinological remission cannot be achieved with surgery alone. Adjuvant radiosurgery or medication modalities can be used in these patients (28,41,44). Being aware of cavernous sinus invasion in the preoperative period is important for surgery and adjuvant therapy planning.

There are some arguments about the method of cavernous sinus invasion in pituitary gland adenomas. Cavernous sinus invasion can be seen because of tumor biology or a cavernous sinus medial wall defect (25,39,55). Some authors believe there is an effect of a medial wall defect on cavernous sinus invasion (32,55) while some other studies report that cavernous sinus invasion can be seen because of the nature of pituitary adenoma (18,38,39).

Various growth, invasion and recurrence patterns can be seen in pituitary adenomas. Proliferation markers, growth factors and genetic analyses are used to understand these biological differences.

In this study, we examined 28 GH secreting pituitary adenoma patients who underwent endoscopic transsphenoidal surgery at Kocaeli University Hospital. We evaluated the cavernous sinus invasion and tumor biological markers that influence the remission ratio. Tumor biological markers are tumor cell growing parameter Ki-67 and the cancer cell vasculature marker of vascular endothelial growth factor (VEGF).

MATERIAL and METHODS

Patient Group

In this study, we examined 28 immunohistochemically-proven GH-secreting pituitary adenoma patients who had undergone endoscopic transsphenoidal surgery at Kocaeli University Hospital between 2003 and 2008. There were 13 female patients and 15 male patients aged 29 to 71 years, with a follow-up time from 6 to 69 months and a mean duration of 27.6 months. There were 4 patients who were positive for prolactin (PRL) immunohistochemical staining and 3 who were positive for ACTH immunohistochemical staining also. All patients were followed up with endocrinology department preoperatively and postoperatively.

Cavernous Sinus Invasion and Radiological Evaluation

Cavernous sinus (CS) invasion was evaluated radiologically. In the preoperative period, MRI findings were evaluated. Knosp grade 4, 3 or more venous or lateral venous compartment compression and encasement of internal carotid artery (ICA) of more than 45% were accepted as indicating cavernous sinus invasion. Intraoperative findings were taken into consideration to determine cavernous sinus invasion of pituitary adenomas precisely.

We used a 30 cm diameter head coil and 1.5 Tesla Philips MRI device for examination. T1, T2 and postcontrast T1 coronal and sagittal 3 mm slice images were examined with the radiology department selecting midsellar coronal MRI images. In this plane, we can see the intracavernous and supracavernous segments of ICA easily. In the preoperative period, cavernous sinus invasion was evaluated according to the Knosp classification, cavernous sinus venous compartment compression, and percentage of intracavernous ICA encasement.

Knosp Classification and Cavernous Sinus Venous Compartment

CS invasion was classified into 5 grades according to Knosp's grading system as follows: Grade 0, adenomas with no CS invasion; Grade 1, adenomas not pass the intercarotid line; Grade 2, adenomas pass the intercarotid line but not extending beyond the lateral aspects of the internal carotid arteries (ICAs); Grade 3, adenomas pass the lateral aspects of the ICAs but not encasing the ICAs; and Grade 4, adenomas with total encasement of the intracavernous ICAs. CS invasion evaluation was made as follows: for Grade 0 cavernous sinus invasion is absent and for Grade 4 cavernous sinus invasion is present. For Knosp grade 1, 2 and 3 we used other parameters for cavernous sinus invasion.

In this study, the cavernous space was divided into four venous compartments with regard to the ICA (Figure 1): The medial compartment, which is between the ICA and the pituitary fossa; the superior compartment, which is above the ICA; the lateral compartment, which is the venous group lateral to the ICA; and the inferior compartment, which is below the ICA. If there was compression of 3 or more venous compartments or the lateral venous compartment, we accepted cavernous sinus invasion to be present (27).

The presence of 45% or more encasement of ICA was evaluated as cavernous sinus invasion and 25% or less encasement of ICA was evaluated as absence of cavernous sinus invasion.

Tumor size and volume calculation

Tumor size more than 1cm was classified as macroadenoma and less than 1cm was classified as microadenoma. The volume of the adenomas was calculated by the formula for an ellipsoid: height x width x thickness x 1/2 cm^3 (32).

Laboratory Examination and Biochemical Remission Evaluation

In the preoperative period, basal GH and IGF-1 serum levels of the patients were evaluated. At the postoperative 6^{th} week we evaluated remission analyses. The basal GH level, nadir GH level and IGF-1 levels were evaluated to determine remission. In this study, biochemical cure was accepted if nadir GH level

was under 1 ng/mL and IGF-1 level was normal for age and sex (18).

Histopathology Examination

GH (DAKO, Denmark), PRL (DAKO, Denmark), ACTH (DAKO, Denmark), Ki-67 (DAKO, Denmark), and VEGF (Neomarkers, USA) antibodies were applied to the pathology specimens. Sections were placed on Poly-L-Lysin covered glass and then kept for 1 night at the 56°C incubator.

Sections are placed sequentially in xylol (30 minutes), absolute alcohol (15 minutes), and 96% alcohol (15 minutes). All sections were washed with water. Pathology specimens that were examined for GH, PRL, Ki-67 and ACTH antibody were boiled in pH6 citrate buffer. Pathology specimens that were examined for VEGF antibody were boiled in pH8 EDTA buffer. After cooling of these specimens, they were kept in 3% hydrogen peroxide solution for 15 minutes.

Specimens that were stained with GH, PRL, Ki-67 and ACTH were kept with the antibody for 30 minutes. For VEGF antibody staining, overnight incubation was performed.

All specimens were placed sequentially in biotinylated antibody for 15 minutes, streptovidin antibody for 15 minutes, and AEC chromogen for 15 minutes. The specimens were stained with Mayer's hematoxylin and then closed with a water-based closure item.

All stained preparations were examined by same pathologist who did not know the patients' clinical data. Both immunolabeled and unlabeled nuclei were evaluated and the percentage of positive cells was calculated. For VEGF, we graded cases with diffuse and dense staining as (++), with diffuse but thin staining, or dense but only focal staining as (+), and without staining as (-). For comparison, preparations were grouped as VEGF positive stained and VEGF negative stained specimens.

Statistical Analysis

Statistical analysis was performed using SPSS (Statistical Package for Social Sciences) for Windows 16.0. Results were analysed for statistically significant differences using the Mann-Whitney test or the Chi-square test where appropriate. A P value < 0.05 was considered significant.

RESULTS

Cavernous Sinus Invasion

In the preoperative period, cavernous sinus invasion was evaluated with MRI and tumor volumes were calculated. Knosp grade 4, the compression of 3 or more venous compartments and cavernous ICA encasement above 45% were grouped as the cavernous sinus invasion present group. 18 patients (64.3%) had cavernous sinus invasion and 10 patients (35.7%) did not have cavernous sinus invasion (Figure 2).

For comparison of cavernous sinus invasion with tumor volume, the Mann-Whitney U test was used and the p value

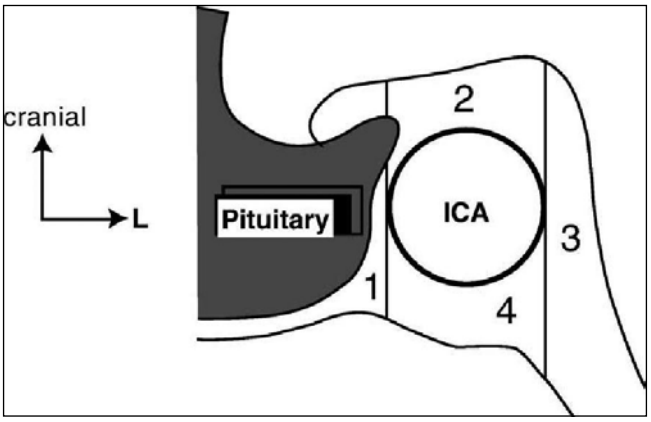

Figure 1: Cavernous sinus venous compartments: medial (1), superior (2), lateral (3), and inferior (4).

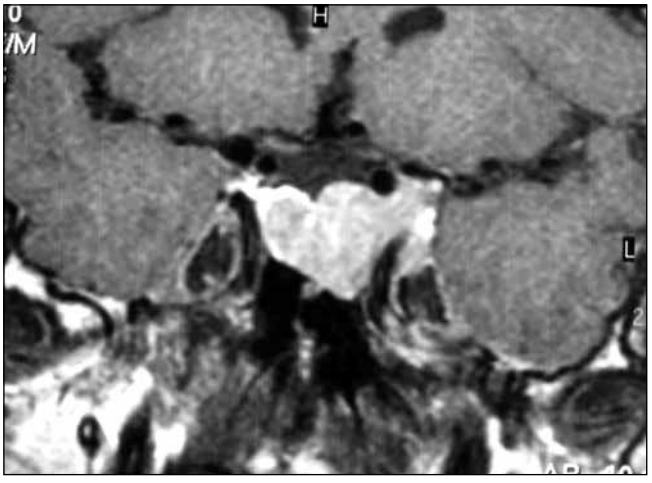

Figure 2: Left ICA total encasement, lateral venous compartment compression.

was found 0.014 ($p<0.05$). There was a significant correlation between tumor volume and cavernous sinus invasion. If tumor volume increased, the cavernous sinus invasion ratio increased.

A microadenoma was found in 7 patients (25%) and a macroadenoma in 21 patients (75%) macroadenoma. Two microadenoma patients had cavernous sinus invasion. The median tumor volume was 1.68 cm^3 and the mean tumor volume was 5.93 cm^3 (±13.54) (Table I).

Laboratory and Remission Results

Remission results were evaluated at the postoperative 6th week. Patient groups were classified as remission positive and remission negative. 13 patients (46.4%) had endocrine remission and 15 patients (53.6%) did not have endocrine remission.

Remission was achieved in 6 of 18 patients (33%) who were cavernous sinus invasion positive. Remission was achieved in 7 of 10 patients (70%) who did not have cavernous sinus invasion.

Remission was not achieved in 2 patients who had cavernous sinus invasion and were grouped as microadenoma. Remission was achieved in 3 of the 7 microadenoma patients (43%). The Mann-Whitney U test was used for the evaluation of relationship between tumor volume and remission. The p value was 0.201 and there was no correlation between tumor volume and remission (p>0.05) (Table II).

Ki-67 Proliferation Index and VEGF Staining Results

Twenty-eight patients' pathology preparations were examined by staining with Ki-67 monoclonal antibody (Figure 3, 4). The mean Ki-67 proliferation index was 0.85 (±0.78). The mean Ki-67 proliferation index in cavernous sinus invasion positive cases was 0.94 (±0.74). The mean Ki-67 proliferation index without cavernous sinus invasion was 0.68 (±0.87).

The Mann-Whitney U test was used for the evaluation of the relationship between the Ki-67 proliferation index and cavernous sinus invasion. The p value was 0.332 and there was no correlation between Ki-67 and cavernous sinus invasion (p>0.05).

The Mann-Whitney U test was used for the evaluation of the relationship between the Ki-67 proliferation index and remission. The p value was 0.745 and there was no correlation between Ki-67 and remission (p>0.05).

For comparison, preparations were classified as VEGF staining positive and negative (Figure 5). Staining was not observed in 18 (64.3%) preparations and observed in 10 (35.7%) preparations.

Table I: Radiological Classification, Tumor Volume, Invasion, VEGF and Ki-67 Staining Properties

Case	Knosp grade	Micro or Macroadenoma	Tumor volume (cm^3)	Compression of three venous compartments or the lateral venous compartment	Cavernous sinus invasion	Remission	VEGF staining	Ki-67
1	4	Macro	2.64	+	+	-	+	1.4
2	3	Macro	1.70	+	+	-	-	0.2
3	2	Macro	1.32	-	-	+	-	0.1
4	3	Macro	13.67	+	+	-	+	0.9
5	3	Macro	1.53	+	+	+	++	0.07
6	4	Macro	23.13	+	+	+	++	1.2
7	4	Micro	0.94	+	+	-	+	0.2
8	2	Macro	2.79	+	+	+	+	2
9	0	Micro	0.05	-	-	-	-	0.4
10	3	Macro	3.56	+	+	-	++	1.2
11	2	Macro	0.81	-	-	+	+	0.4
12	2	Micro	0.48	+	+	-	-	0.6
13	1	Micro	0.38	-	-	+	-	0.2
14	1	Macro	0.64	-	-	+	-	1
15	4	Macro	16.31	+	+	-	-	2
16	4	Macro	3.78	+	+	-	-	0.4
17	0	Micro	0.10	-	-	+	-	0.05
18	1	Macro	1.94	-	-	+	-	3
19	0	Micro	0.29	-	-	+	-	0.4
20	2	Macro	1.18	+	+	-	-	2
21	2	Macro	1.70	+	+	+	+	0.2
22	2	Micro	0.36	-	-	-	-	0.8
23	2	Macro	5.46	+	+	+	-	1.2
24	2	Macro	0.83	+	+	+	+	1.2
25	1	Macro	2.86	-	-	-	-	0.4
26	4	Macro	6.86	+	+	-	++	0.1
27	2	Macro	1.67	+	+	-	-	0.04
28	4	Macro	69.30	+	+	-	-	2

Table II: Laboratory Results and Remission

Case	Preoperative GH (ng/mL)	Preoperative IGF-1 level (ng/mL)	Postoperative IGF-1 level (ng/mL)	Postoperative GH level (ng/mL)	Cavernous sinus invasion	Remission
1	11.1	820	632	0.73	+	-
2	15.3	980	142.7	2.07	+	-
3	91.0	1840	210	0.74	-	+
4	30.5	1106	475	8.3	+	-
5	5.3	465	305	0.705	+	+
6	29.9	580	216	0.512	+	+
7	6.77	490,9	277.3	2.13	+	-
8	35.0	2150	304	0.415	+	+
9	20.5	677	425	4.56	-	-
10	32.1	1470	244	1.89	+	-
11	1.11	360	262.6	0.17	-	+
12	3.90	750	300	4.5	+	-
13	9.95	401.7	172.9	0.05	-	+
14	16.7	120	184.1	0.93	-	+
15	34.0	921	496.6	1.97	+	-
16	40.0	2504	560	2.47	+	-
17	1.20	557	366.25	0.301	-	+
18	40.0	830.7	176.51	0.981	-	+
19	4.21	650	278.31	0.721	-	+
20	40.0	890	550	1.63	+	-
21	40.0	1800	270	0.484	+	+
22	30.6	2350	1300	8.51	-	-
23	12.3	435	294.81	0.507	+	+
24	6.51	988	268.3	0.60	+	+
25	58.3	698.7	800	3.19	-	-
26	64.1	860	448.24	3.13	+	-
27	20.1	970	865	3.25	+	-
28	11.5	713	510.57	7.33	+	-

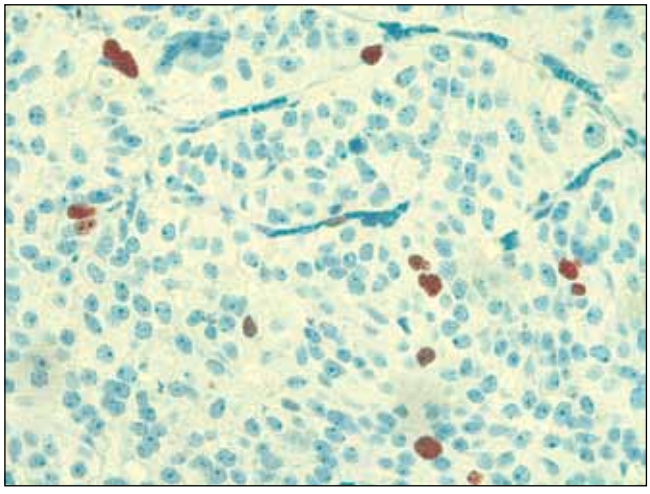

Figure 3: Ki-67 monoclonal antibody strongly positive staining.

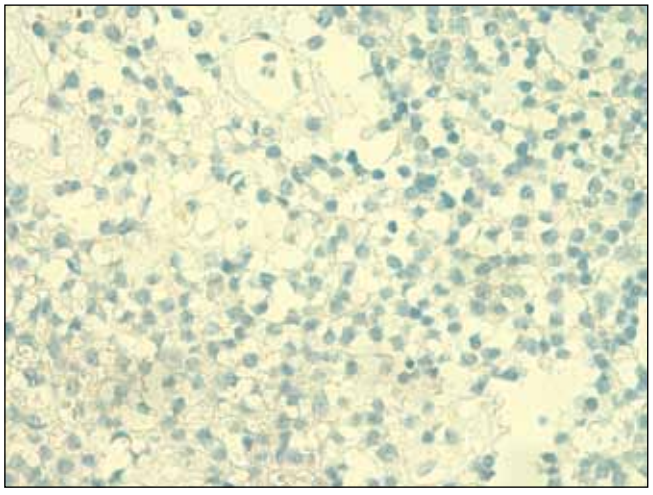

Figure 4: No staining with Ki-67 monoclonal antibody staining.

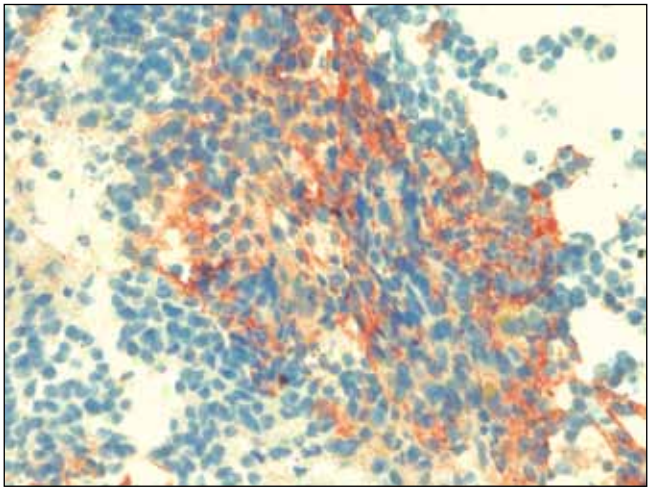

Figure 5: Strongly VEGF staining positive preparation.

The Chi-Square test was used for determining the correlation between VEGF expression and cavernous sinus invasion. A statistically positive correlation was found (p=0.03) (Table I). Patients who had VEGF expression had a higher cavernous sinus invasion rate.

The Chi-square test was used for determining the correlation between VEGF expression and remission. No statistically significant correlation was found (p=0.910).

DISCUSSION

Acromegaly is an important problem in GH-secreting pituitary adenoma. If we look at retrospective cohort studies, there is increased risk of mortality compared with the normal population in the acromegaly patient group (38). Decreasing serum GH level to the normal level can decrease the mortality rate (2). Normalisation of serum GH level is the primary goal for treatment of acromegaly. In recent studies, surgery alone or with radiosurgery and medical treatment is the first-choice treatment modality for acromegaly patients (34).

Pituitary gland adenomas are slowly growing tumors but can cause chiasm compression and can invade the cavernous sinus or sphenoid sinus. Invasive adenomas can infiltrate the bone and rarely the brain (8). There is no parameter for treatment options and behavior pattern of this type of invasive pituitary adenoma.

Immediate decreasing of growth hormone levels for acromegaly patiens can be achived by surgery. For patients with microadenomas, normalization of growth hormone secretion can be achieved in approximately 70% of patients with acromegaly (15,28,42). In macroadenomas, the results are less satisfactory with regard to full normalization in that only approximately 50% of such patients achieve those goals (3,5,10,28). Remission cannot be achieved with only surgery and thus we have to perform radiosurgery or medical treatment as adjuvant therapy. GH values and invasion of the cavernous sinus were independent predictors of surgical failure. Many studies indicate that such patients usually require a multidisciplinary and more aggressive approach to control GH hypersecretion (28,30,41). In our group, we found that cavernous sinus invasion is important for achieving remission. Remission was achieved in 6 of 18 patients (33%) who had cavernous sinus invasion. Remission was achieved in 3 of 7 microadenoma patients (43%). We concluded that cavernous sinus invasion is an important factor for remission.

Six to ten percent of pituitary adenomas involve the cavernous sinus (1,12). These rates are found more frequently in radiological publications. Vieira et al. examined 103 pituitary adenoma patients and 206 cavernous sinuses and found cavernous sinus invasion in 25%. Cavernous sinus invasion was evaluated as positive if encasement of ICA was more than 45% and compression of 3 or more venous compartments was present in their study. Cavernous sinus invasion was evaluated as absent if the medial venous compartment is intact or the gland is pushed toward the cavernous sinus wall in their study (51). Cottier et al. examined 106 pituitary adenoma patients and 212 cavernous sinuses and cavernous sinus invasion was found in 44% (94 patients). In their study, cavernous sinus invasion was uncertain for 21 patients (10%) at surgery. An encasement percentage of the intracavernous ICA by adenoma greater than or equal to 67% was the most specific sign; if the median intercarotid line was not crossed, the superior venous compartment was visible, the cavernous sinus was normal size, or there was no bulging of its lateral dural wall, then invasion of the cavernous sinus space could be excluded reliably (9). Nakasu et al. examined 80 pituitary gland adenoma patients and found no cavernous sinus invasion in microadenoma patients. Also in their study, cavernous sinus invasion was found in 21.5% of macroadenoma patients (36). In our study, we found that most of cavernous sinus invasion present patients were macroadenoma patients.

There is disagreement about the cavernous sinus invasion theory. Some studies support a medial wall defect and others support tumor biology (25,39,55). Why some tumors have cavernous sinus invasion present is unclear. Two different concepts are present in the literature. Some authors argue that a pituitary fossa lateral wall defect or weakness can be responsible for cavernous sinus invasion (11,55). Some other authors argue that tumor biological behavior can be responsible for cavernous sinus invasion (25,33,45).

The sella wall thickness can vary from person to person as well as in the right and left sides of the same person. Sometimes the lateral wall can be seen as loose fibrous band (9). Difference of lateral wall thickness can be responsible for growing of tumor into the cavernous sinus. As an example, if there is a single-sided lateral wall defect, one side cavernous sinus invasion can be seen. If we look at collagen immunochemistry, there are collagen type I, II, III and IV in the pituitary capsule unlikely there is only collagen type I and II in lateral wall. Matrix metalloproteinases (MMPs) are a family of zinc-containing endopeptidases that are able to degrade the extracellular matrix (39). MMP-9 is a type IV collagenase. Kawamoto et al. published the first document relationship between MMP-

9 expression in pituitary adenomas and cavernous sinus infiltration (25). The pituitary capsule is very rich in collagen type IV. Considering this, one would expect that a pituitary tumor cell that expresses MMP-9 would degrade the capsule. As a result, cavernous sinus invasion in a pituitary adenoma can occur because of lateral wall weakness or biochemically collagen degrading enzyme secretion. Ki-67 is found in the cell nuclei and can be seen only if the cell cycle is in the G1, S, G2 or M phase. It cannot be seen in the G0 phase (17). Ki-67 is good indicator for growth rate and neoplasia process. Thapar et al. used 3% Ki-67 proliferation index as an invasion and not differentiation indicator and also found this cut-off point to be 97% specific and 73% sensitive (43). As the Ki-67 proliferation index was used as an indicator of cell proliferation, many studies were conducted about pituitary gland adenoma invasion (21,22,24,26,33,55). Mastronardi et al. examined 103 pituitary gland adenoma patients and found the Ki-67 proliferation index to be a useful marker for the invasion character of pituitary tumors (33). There are some other studies that support this study (21,22,26,40). Kawamato et al. managed another study regarding the relationship between invasion and Ki-67 proliferation index and found no correlation (24). Tugan et al. found no correlation between the Ki-67 proliferation index and invasion or recurrence in a 44-patient study group (46). In our study, the mean Ki-67 proliferation index was 0.85 (±0.78). The mean Ki-67 proliferation index mean in cavernous sinus invasion positive cases was 0.94 (±0.74). The mean Ki-67 proliferation index without cavernous sinus invasion was 0.68 (±0.87). There was no correlation between the Ki-67 proliferation index and cavernous sinus invasion.

Angiogenesis is complex biological mechanism and related to various growth factors associated with vascular proliferation (4,14,19). Angiogenesis was found to be associated with a poor prognosis, metastases, high recurrence and high mortality in tumor groups (6,52,53). The role of angiogenesis has not been understood in endocrine tumors (16,47). The relationship between angiogenesis and a pituitary adenoma is not adequately known (23,48,49). VEGF-A is a polypeptide and can be secreted from normal or tumor cells (13,20). VEGF can especially be found in the vascular endothelial cell and has an important role regarding angiogenesis, increasing cell proliferation, migration and vascular permeability (20,29). VEGF expression was found to be related with prognosis in breast, lung and gastrointestinal tract cancers (7,13,20,29). There is less vascular structure in pituitary adenoma tissue compared with normal pituitary gland tissue. The reason of this difference could be the presence of angiogenesis inhibiting factors (7,14,47). On the other hand, vasculature of pituitary adenoma tissue is completely or incompletely from the extraportal system (7). There is some controversy about the effect of VEGF in pituitary adenoma. Viacava et al. found no difference in VEGF expression between normal pituitary gland tissue and pituitary adenoma tissue. They also found no correlation between VEGF expression and tumor size, age, sex, recurrence rate and histological type (49). Niveiro et al. found high VEGF expression in elderly patients and those with nonfunctional tumor. We also found no correlation between VEGF and proliferative activity and extracellular growth (37). Vidal et al. examined the Flk-1 receptor, normal pituitary gland and VEGF receptor found in GH3 (GH- and PRL-secreting rat pituitary tumor cell) on 6 rat pituitary gland tissues. They concluded that Flk-1 had an important role in the neoplasia process as a receptor of VEGF. GH-secreting pituitary adenomas had more VEGF expression because of less vasculature than in other types of pituitary gland tumors (50). Lloyd et al. found VEGF expression to be highest in GH-secreting pituitary adenoma and less in PRL-secreting pituitary adenoma in 148 patients (31). Less staining was observed with VEGF in the octeotide treatment group. Iuchi et al. found a positive correlation between VEGF expression and cavernous sinus invasion (22). We found a positive correlation between VEGF expression and cavernous sinus invasion (p=0.03).

Remission is an important problem for GH-secreting pituitary adenoma. If remission is achieved, there is a lower mortality rate. Remission criteria have changed in past 2 decades (18). A basal GH level less than 2.5 ng/mL, nadir GH level less than 1 ng/mL and IGF-1 levels have been used to determine remission. Serum hormone levels have to be evaluated to determine early remission. A GH level of less than 5 ng/mL has been used as a reference point for remission, leading to higher remission rates in previous studies. Ross and Wilson published a 79.4% remission rate in 214 transsphenoidal surgery patients (41). With the same remission criteria, Tindall et al. found a remission rate of 81.3% in 103 patients (44). The remission rate is now lower with the new criteria. Laws et al. published a remission rate of 52% in 86 patients (30). Kreutzer et al. found a 51.4% remission rate in 57 acromegaly patients. In our study, we found a 46.4% remission rate. Kreutzer et al. also found a lower remission rate with cavernous sinus invasion (28). Minniti et al. found a 38% remission rate in the invasion present group and 81% remission rate in the microadenoma group (35). In our study, we found a 70% remission rate without cavernous sinus invasion and 33% remission rate with cavernous sinus invasion present. We conclude that cavernous sinus invasion is an important factor regarding the remission rate.

CONCLUSION

We found a high cavernous sinus invasion rate (64%) in GH-secreting pituitary adenoma patients. The remission rate was found to be lower in the cavernous sinus invasion present group. The Ki-67 proliferation index was not associated with remission or cavernous sinus invasion. A correlation was found between VEGF and cavernous sinus invasion. To summarize, we found that GH-secreting pituitary adenoma patients with cavernous sinus invasion have a lower remission rate and VEGF expression can be used to determine the behavior of pituitary adenomas.

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