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ON THE ROLE OF KI-67 AND P53 PROLIFERATION MARKERS IN PATIENTS WITH RECURRENT MACRO AND GIANT INACTIVE PITUITARY TUMORS

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A B S T R A C T

The aim of the study was to study the prognostic value of the proliferation markers Ki-67 and p53 in patients with recurrent macro and giant inactive pituitary adenomas.

Material and methods of research. We studied 20 patients with NAG (group 1 - 10 pituitary macroadenomas and group 2 - 10 giant pituitary adenomas) who underwent transnasal pituitary adenomectomy in the Department of Pituitary Neurosurgery.

Results. A total of 76.4%/81.3% of all tumors had evidence of parasellar invasion (22% unilateral invasion, 62% bilateral invasion). Infrasellar invasion was observed in 80%/71.9% of all cases. Suprasellar spread of any degree was observed at a frequency of 62%/69.8% of the cohort.

The observed incidence of immunoexpression of proliferation markers was 20%/- for p53 (≥3+), 70%/40% for Ki-67 (≥2+). Tumors with immunoexpression of at least 2 markers with a high proliferation index were observed in 20% of the cohort and were regarded as proliferative adenomas.

Findings. Of the 20 patients with NAG, 11 patients (55%) with Ki-67 expression (> 2%) were at risk of continued tumor growth in the postoperative period due to immunohistochemical examination.

K E Y W O R D S

NGA, immunohistochemical research, Ki-67, p53

Introduction

Inactive pituitary adenomas (NAGs) are the most common type of pituitary macroadenomas, accounting for 25-35% of all cases [1]. They are usually benign, but many of them infiltrate the sphenoid sinus, cavernous sinus, or dura mater and cannot be completely removed by surgical resection. Since the residual cells retain the ability to proliferate, residual tumors can re-proliferate, requiring a new therapeutic intervention [2].

Most recurrences occur within five years of surgery. Due to the high incidence of distant recurrence, the prognosis for patients is not always favorable: surgery is the main treatment for NAG, and there is currently no effective pharmacological treatment for NAG.

Various histological biomarkers of NASH were studied, including the proliferative marker Ki-67, cell cycle factors such as p27 and galectin-3, and molecules such as p53, O-6-methylguanine-DNA methyltransferase, and matrix metalloproteinase-9. studied [5-7]. However, in the absence of reliable serum markers for the detection of residual tumor cells, the decision to recommend additional interventions is usually made on the basis of postoperative imaging.

Ki-67 is a widely used immunohistochemical marker of pituitary adenomas, however, its prognostic value is controversial [8]. In previous studies, the positivity rate of Ki-67 was 2.7-15% [9-11]. Several studies have investigated the possibility of using Ki-67 as a prognostic marker of tumor recurrence or repopulation [12]. One study reported that tumor development correlated with LI Ki-67>2% [13]; in other studies, LI>2.2% was associated with residual tumor growth, and LI>3% was a strong predictor for pituitary adenoma recurrence/progression [14]. However, some researchers have found no correlation between Ki-67 expression and postoperative tumor behavior [15]. The authors found that LI Ki-67 0-12.4% was associated with moderate staining intensity (2+), with no difference between primary/recurrent adenomas and recurrent/recurrent adenomas.

Other authors found that elevated Ki-67 scores showed a strong correlation, suggesting that Ki-67 plays a role in adenoma progression. [17]. Some authors have come to similar conclusions. Micko A.S.G. found a strong trend between invasive and non-invasive adenomas, with no statistically significant correlation with higher MIB-1 in invasive cases [16]. Indeed, no association was found between Ki-67 LI and the Knosp classification of pituitary adenomas, which was the same for fully and partially resected adenomas [16].

All of the above emphasizes the relevance of this direction. Therefore, in this study, the expression of p53, Ki-67 in 20 cases of NAH with primary and recurrent tumors was evaluated to identify a suitable marker of NAH progression.

The aim of the study was to study the prognostic value of the proliferation markers Ki-67 and p53 in patients with recurrent macro and giant inactive pituitary adenomas.

Material and Methods of Research

We studied 20 patients with NAG (group 1 - 10 pituitary macroadenomas and group 2 - 10 giant pituitary adenomas) who underwent transnasal pituitary adenomectomy Department of Pituitary Neurosurgery of the Republican Specialized Scientific and Practical Medical Center for Endocrinology, in the period for 2020 - 2022. Of these, 12 (60%) were men, 8 (40%) were women. The mean age was 48.12 years for males and 46.15 years for females. 20 healthy individuals of the corresponding sex and age made up the control group.

The research methods included: 1) general clinical (study of endocrine, neurological status), 2) instrumental (perimetry for all colors, fundus, visual acuity, 3) ECG, CT/MRI of the Turkish saddle and adrenal glands, 4) ultrasound of the internal and genital organs, etc.), 5) hormonal blood tests (GH, IGF-1, LH, FSH, PRL, TSH, ACTH, prolactin, testosterone, estradiol, progesterone, cortisol (ICLA

method). In addition, The postoperative material was subjected to histological diagnostics at the RSNMC E MZRUz named after Acad. E.Kh. Turakulova (histology room, Ph.D. Issaeva S.S.).
Immunohistochemical studies (IHC) were performed according to the contract in the pathomorphological laboratory of IPSUM Pathology LLC (Tashkent, Bogiston Street, 1). Ready-made paraffin blocks with confirmed diagnoses of pituitary adenoma were used. Serial sections with a thickness of 3 μm were dewaxed, dehydrated, unmasked, and stained with antigens using a specialized automated system Ventana Benchmark XT, Roche, Switzerland. The study was carried out with ki-67 (30-9) and P53 (Bp53-11) antibodies.
Ki67. IHC assessment of sections: the proliferative activity of tumor cells in the nuclear compartment was assessed.
P53. IHC Slice Assessment: To verify abnormal (mutant) p53 expression, it was assumed that more than 75% of cells in the affected area had expression. Negative expression or weak staining of the nuclear locus up to 70% was interpreted as a natural (wild) type.
The obtained data were processed using Microsoft Excel and STATISTICA_6. The arithmetic mean (M), the standard deviation of the arithmetic mean, or the error of the arithmetic mean of all *n* repetitions (m) were calculated.The significance of the differences between the groups was assessed by the confidence interval and the Student's test (p). The differences were considered statistically significant at $p<0.05$.

Results. Table 1. Distribution of patients by sex and age is given

Table 1. Distribution of patients by sex and age (n = 20)

Age, years	Number of males, n = 12		Number of women n = 8	
	1 gr	2 grams	1 gr	2 grams
13 years	-	-	-	-
16 – 29	-	-	-	-
30-44	4	1	1	3
45-59	3	4	2	3
60-74	-	-	-	-
75 and older	-	-	-	-
Total: n = 20	7	5	3	5

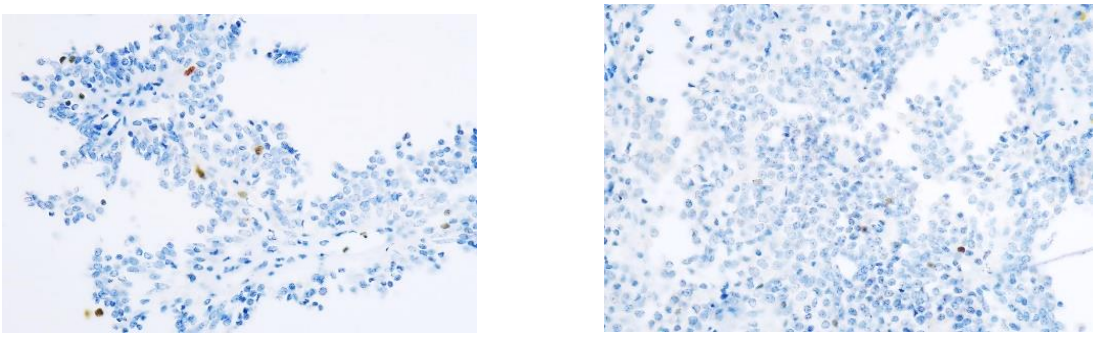
The maximum mean tumor diameter determined by MRI was 44.7 ± 13.6 mm in 10 patients with giant NAGs, and macroadenomas > 30 mm were present in 10 patients.
A total of 76.4%/81.3% of all tumors had evidence of parasellar invasion (22% unilateral invasion, 62% bilateral invasion).
Infracellular invasion was observed in 80%/71.9% of all cases.
Suprasellar spread of any degree was observed at a frequency of 62%/69.8% of the cohort.
Table 2 shows the immunohistochemical characteristics of the studied groups.

Table 2 Immunohistochemical characteristics of the studied groups

Markers	Group 1 – patients with macro NAG – 10 persons	Group 2 – patients with giant NAG – 10 persons.
R53		
Expression up to 70%	8 (80%)	10 (100%)
Expression > 75%	2 (20%)	-
To 67		
1-2%	1 (10%)	2 (20%)
2-3%	2 (20%)	3 (30%)
3-4%	2 (20%)	1 (10%)
4-5%	3 (30%)	-
5-6%	-	2 (20%)
6-7%	1 (10%)	-
7-8%	-	1 (10%)
9-10%	1 (10%)	-

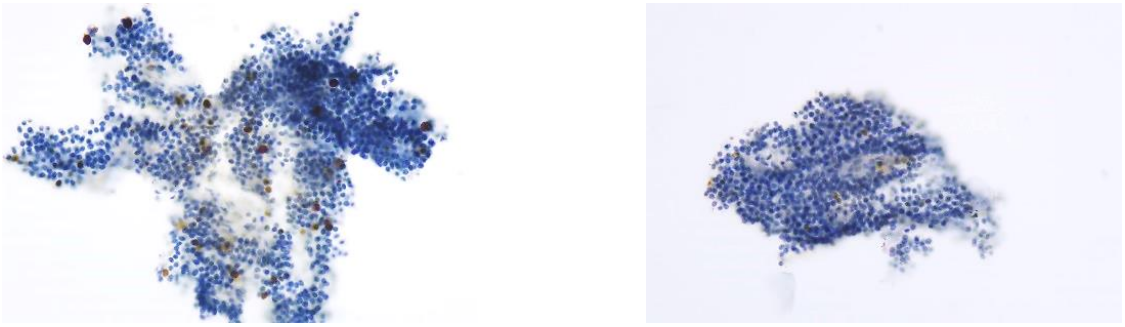
The observed incidence of immunoexpression of proliferation markers was 20%/- for p53 (≥3+), 70%/40% for Ki-67 (≥2+). Tumors with immunoexpression of at least 2 markers with a high proliferation index were observed in 20% of the cohort and were regarded as proliferative adenomas.

Fig. Figures 1 and 2 show examples of IHC pictures of patients with macro-NAG and giant NAG.



Ki67 (30-9) 3-4% P53, dicy type

Fig.1. Immunohistochemical picture of a patient with macro-NAG



Ki67 (30-9) 9-10% P53, dicy type

Fig.2. Immunohistochemical picture of a patient with gigantic-NAG

Thus, IHC studies in patients with recurrent NAG confirmed the risk of continued tumor growth in 11 patients (55%) with Ki-67 expression (> 2%).

Findings

1.A total of 76.4%/81.3% of all tumors had evidence of parasellar invasion (22% unilateral invasion, 62% bilateral invasion). Infrasellar invasion was observed in 80%/71.9% of all cases. Suprasellar spread of any degree was observed at a frequency of 62%/69.8% of the cohort.

2. The observed incidence of immunoexpression of proliferation markers was 20%/- for p53 (≥3+), 70%/40% for Ki-67 (≥2+). Tumors with immunoexpression of at least 2 markers with a high proliferation index were observed in 20% of the cohort and were regarded as proliferative adenomas.

3. Out of 20 patients with NAG, 11 patients (55%) with Ki-67 expression (> 2%) of the study patients were at risk of continued tumor growth in the postoperative period due to the IHC study.

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