Research Article

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Prognostic Value of Proliferation Markers Ki-67 and p53 in Patients with Recurrent Macro- and Giant Non-Functional Pituitary Tumors

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Introduction

Non-functional pituitary adenomas (NFPA) are the most common type of pituitary macroadenomas, accounting for 25–35% of all cases [1]. They are usually benign, but many infiltrate the sphenoid sinus, cavernous sinus, or dura mater and cannot be completely removed by surgical resection. Because residual cells retain the ability to proliferate, residual tumors may re-proliferate, requiring new therapeutic interventions [2]. Most relapses occur within five years after surgery. Due to the high rate of distant relapses, the prognosis for patients is not always favorable: surgery is the main treatment for NFPA, and there is currently no effective pharmacological treatment for NFPA [3,4]. Various histological biomarkers of NFPA have been 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 to detect 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 for pituitary adenomas, but its prognostic value is controversial [8]. In previous studies, the incidence of Ki-67 positivity was 2.7–15% [9-11]. Several studies have examined the use of Ki-67 as a prognostic marker for tumor recurrence or repopulation [12]. One study reported that tumor development correlated with Ki-67 LI >2% [13]; in other studies, LI >2.2% was associated with residual tumor growth, and LI >3% was a strong prognostic factor for recurrence/progression of pituitary adenoma [14]. However, some researchers have not found a correlation between Ki-67 expression and postoperative tumor behavior [15]. The authors found that a Ki-67 LI of 0–12.4% was associated with moderate staining intensity (2+), with no difference between primary/recurrent adenomas and relapsed/recurrent adenomas. Other authors have found that elevated Ki-67 values showed a strong correlation, suggesting that Ki-67 plays a role in adenoma progression [16]. Some authors have reached similar conclusions. Micko ASG found a strong trend between invasive and non-invasive adenomas, with

no statistically significant correlation with higher MIB-1 in invasive cases [17]. Indeed, no association was found between Ki-67 LI and Knosp classification of pituitary adenomas, which was the same for completely and partially resected adenomas [17]. All of the above emphasizes the relevance of this area. Therefore, this study assessed the expression of p53, Ki-67 in 20 NFPA cases with primary and recurrent tumors to identify a suitable marker for NFPA progression. The purpose of the study is to study the prognostic value of proliferation markers Ki-67 and p53 in patients with recurrent macro and giant non-functional pituitary adenomas.

Material and Research Methods

We studied 20 patients with NFPA (group 1 - 10 pituitary macroadenomas and group 2 - 10 giant pituitary adenomas) who underwent transnasal pituitary adenomectomy in the Department of Pituitary Neurosurgery of the Republican Specialized Scientific and Practical Medical Center of Endocrinology, in the period 2020 - 2022. Of these, 12 (60%) are men, 8 (40%) are women. Average age: men were 48.12 years, women - 46.15 years. 20 healthy individuals of the corresponding gender and age formed the control group.

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 sella turcica and adrenal glands.
4. Ultrasound of the internal and genital organs, etc.

Hormonal blood tests (GH, IGF-1, LH, FSH, PRL, TSH, ACTH, prolactin, testosterone, estradiol, progesterone, cortisol (ICL method). In addition, postoperative material was subjected to histological diagnostics at the Republican Scientific and Practical Medical Center of the Ministry of Health of the Republic of Uzbekistan named after academician Y. Kh. Turakulov (histology office, candidate of medical sciences Issaeva S.S.). Immunohistochemical studies (IHS) were performed according to the contract in the pathomorphological laboratory of OOO IPSUM Pathology (Tashkent, Bogiston str., building 1). Ready-made paraffin blocks with confirmed diagnoses of "pituitary adenoma" were used. Serial sections 3 μm thick were deparaffinized, dehydrated, unmasked, and stained with antigens using a specialized automated system Ventana Benchmark XT, Roche, Switzerland. The study was carried out with antibodies ki-67 (30-9), P53 (Bp53-11). Ki67. IHS assessment of sections: the proliferative activity of tumor cells in the nuclear compartment was assessed. P53. IHS assessment of sections: to verify abnormal (mutant) p53 expression, it was accepted that expression was present in more than 75% of the cells in the affected area. Negative expression or weak staining of the nuclear locus up to 70% was interpreted as natural (wild type). The obtained data were processed using Microsoft Excel and STATISTICA_6 computer programs. The arithmetic mean (M) was calculated, standard deviation of the arithmetic mean, or error of the arithmetic mean from all n repetitions (m). The reliability of differences in levels between groups was assessed by the confidence interval and Student's test (p). Differences were considered statistically significant at $p<0.05$.

Research Results

Table 1 shows the distribution of patients by gender and age. The maximum mean tumor diameter determined by MRI diagnosis was 44.7 ± 13.6 mm in 10 patients with giant NFPA, 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). Infrasellar invasion was observed in 80%/71.9% of all cases. Suprasellar extension of any degree was observed with an incidence of 62%/69.8% of the cohort. Table 2 shows the immunohistochemical characteristics of the study groups. The observed frequency of immune expression of proliferation markers was 20%/- for p53 (≥3+), 70%/40% for Ki-67 (≥2+). Tumors with immune expression of at least 2 markers with a high proliferation index were observed in 20% of the cohort and were regarded as proliferative adenomas. In Figures 1 & 2 give examples of IHC patterns of patients with macro- NFPA and giant NFPA. Thus, IHC studies performed in patients with recurrent NFPA made it possible to confirm the risk of continued tumor growth 11 patients (55%) with Ki-67 expression (>2%).

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

Age, years	Number of men, n = 12		Number of women n = 8	
	1 gr	2 gr	1 gr	2 gr
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

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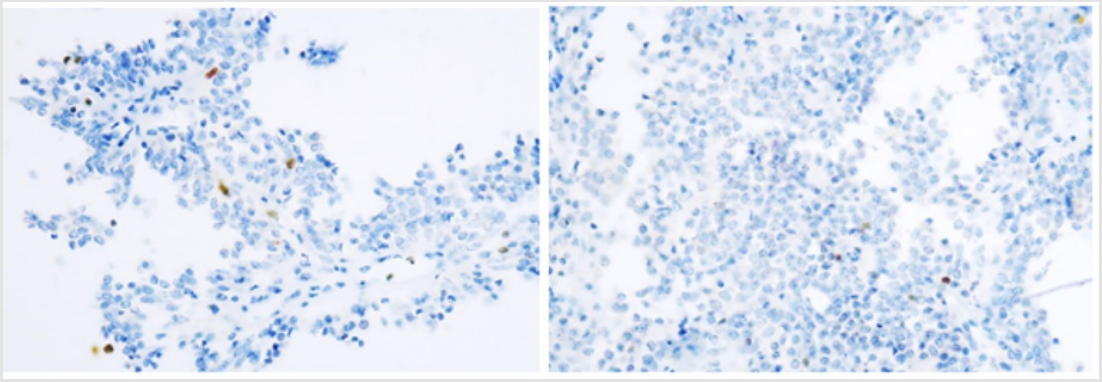
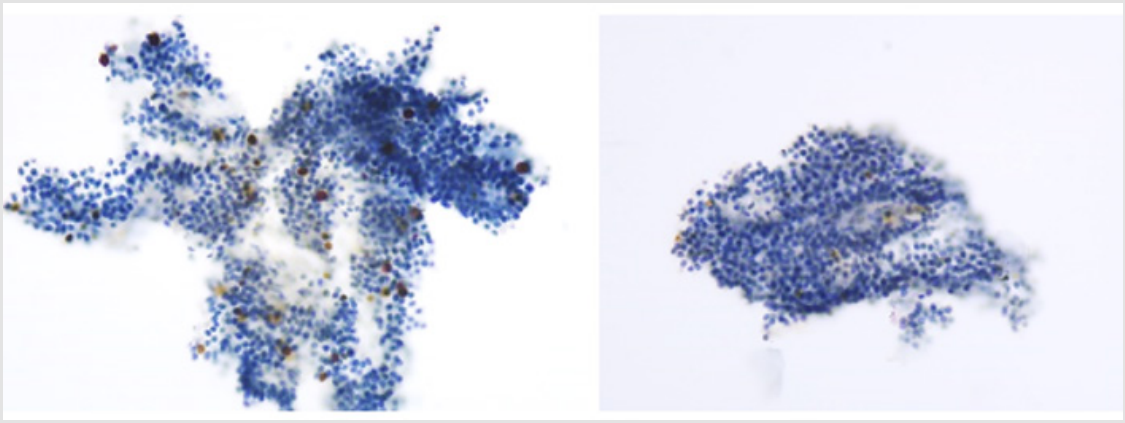
Table 2: Immunohistochemical characteristics of the study groups.

Markers	1 group –patients with macro-NAG – 10 persons	Group 2 –patients with giant NAG – 10 persons
P53		
Expression up to 70%	8 (80%)	10 (100%)
Expression > 75%	2 (20%)	-
Ki 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%)	-



Note: Ki67 (30-9) 3-4% P53, wild type.
Figure 1: Immunohistochemical picture of a patient with macro- NFPA.



Note: Ki67 (30-9) 9-10% P53, wild type.
Figure 2: Immunohistochemical picture of a patient with giant NFPA.

Conclusion

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 extension of any degree was observed with an incidence of 62%/69.8% of the cohort.
2. The observed frequency 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. Of the 20 patients with NFPA, in 11 patients (55%) with Ki-67 expression (> 2%) studied, the risk of continued tumor growth in the postoperative period was identified due to an IHC study.

References

1. Giustina Andrea (2012) Keep an eye on nonfunctioning pituitary adenomas. Clinical Endocrinology 77(5): 656-657.
2. Cury ML, Fernandes JC, Machado HR, Elias LL, Moreira AC, et al. (2009) Non-functioning pituitary adenomas: clinical feature, laboratorial and imaging assessment, therapeutic management and outcome. Arq Bras Endocrinol Metabol 53(1): 31-39.
3. Berkmann S, Schlaffer S, Nimsky C, Fahlbusch R, Buchfelder M (2014) Follow-up and long-term outcome of nonfunctioning pituitary adenoma operated by transsphenoidal surgery with intraoperative high-field magnetic resonance imaging. Acta Neurochir 156(12): 2233-2243.
4. Rubinfeld H, Shimon I (2012) PI3K/Akt/mTOR and Raf/MEK/ERK signaling pathways perturbations in non-functioning pituitary adenomas. Endocrine 42(2): 285-291.
5. Mohammed AA, Rotondo F, Munoz DG, Kovacs K, Bilbao JM, et al. (2015) Diagnostic and prognostic biomarkers of a sellar melanocytic tumor mimicking pituitary adenoma: case report and literature review. Pathol Res Pract 211(9): 682-687.
6. Monsalves E, Larjani S, Loyola GB, Juraschka K, Carvalho F, et al. (2014) Growth patterns of pituitary adenomas and histopathological correlates. J Clin Endocrinol Metab 99(4): 1330-1338.
7. Righi A, Morandi L, Leonardi E, Farnedi A, Marucci G, et al. (2013) Galectin-3 expression in pituitary adenomas as a marker of aggressive behavior. Hum Pathol 44(11): 2400-2409.
8. De Aguiar PH, Aires R, Laws ER, Isolan GR, Logullo A, et al. (2010) Labeling index in pituitary adenomas evaluated by means of MIB-1: is there a prognostic role? A critical review. Neurol Res 32(10): 1060-1071.
9. Saeger W, Ludecke DK, Buchfelder M, Fahlbusch R, Quabbe HJ, et al. (2007) Pathohistological classification of pituitary tumors: 10 years of experience with the German Pituitary Tumor Registry. Eur J Endocrinol 156(2): 203-216.
10. Yildirim AE, Divanlioglu D, Nacar OA, Dursun E, Sahinoglu M, et al. (2013) Incidence, hormonal distribution and postoperative follow up of atypical pituitary adenomas. Turk Neurosurg 23(2): 226-231.
11. Zada G, Woodmansee WW, Ramkissoon S, Amadio J, Nose V, et al. (2011) Atypical pituitary adenomas: incidence, clinical characteristics, and implications. J Neurosurg 114(2): 336-344.
12. Šteňo A, Bocko J, Rychlý B, Chorváth M, Celec P, et al. (2014) Nonfunctioning pituitary adenomas: association of Ki-67 and HMGA-1 labeling indicators with residual tumor growth. Acta Neurochir 156(3): 451-461.
13. Urso L, Calabrese F, Favaretto A, Conte P, Pasello G (2016) Critical review about MDM2 in cancer: Possible role in malignant mesothelioma and implications for treatment. Crit Rev Oncol Hematol 97: 220-230.
14. Righi A, Agati P, Sisto A, Frank G, Faustini-Fustini M, et al. (2012) A classification tree approach for pituitary adenomas. Hum Pathol 43(10): 1627-1637.
15. Dubois S, Guyétant S, Menei P, Rodien P, Illouz F, et al. (2007) Relevance of Ki-67 and prognostic factors for recurrence/progression of gonadotropic adenomas after first surgery. European Journal of Endocrinology 157(2): 141-147.
16. Yao X, Gao H, Li C, Wu L, Bai J, et al. (2017) Analysis of Ki67, HMGA1, MDM2, and RB expression in nonfunctioning pituitary adenomas. J Neurooncol 132(2): 199-206.
17. Micko ASG, Wöhrer A, Wolfsberger S, Knosp E (2015) Invasion of the cavernous sinus space in pituitary adenomas: endoscopic verification and its correlation with an MRI-based classification. J Neurosurg 122(4): 803-811.

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