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"IMMUNOHISTOCHEMICAL CHARACTERISTICS OF PATIENTS WITH MACRO AND GIANT INACTIVE PITUITARY TUMORS"

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ABSTRACT

The assessment of the KI-67 and P53 using immunohistochemistry, usually with monoclonal antibodies of MIB1, is mandatory for evaluating proliferation in patients subjected to transnasal adenomectomy of the pituitary gland.

Goal. *To study the prognostic significance of invasion and markers of proliferation in patients with macro and giant inactive pituitary tumors.*

Material and Methods

In total, 272 patients with macro and giant naga were examined. Of the 272 patients with the naga in the study, 151 patients (men and women) took part in the study)

Research methods included: 1) general clinical (study of endocrine, neurological statuses), 2) instrumental (perimetry for all colors, eye bottom, visual acuity, 3) ECG, CT/MRI of the Turkish saddle and adrenal glands, 4) ultrasound of the internal and genitals, etc.), 5) hormonal blood tests (STH, IFR-1, LG, FSG, PRL, TSL, ACTH, prolactin, testosterone, estradiol, progesterone, cortisol and immunohymph hand-chemical studies.

Results

The observed frequency of immunoexpression of proliferation markers was 40%/50% for P53 (≥3+), 50%/60% for Ki-67 (≥2+). Tumors with immunoexpression of at least 2 markers with a high proliferation index were observed in 54% cohorts and regarded as proliferative adenomas.

Conclusion

Giant inactive pituitary adenomas of the pituitary gland are often accompanied by invasive growth in the surrounding anatomical structures (more than 80% of cases), which is the main factor that limits the radicality of surgical intervention and increases the number of relapses.

KEYWORDS: *NFPA, Giant Pituitary Adenomas.*

INTRODUCTION

Non-functioning pituitary adenomas (NFPAs) are benign pituitary tumors arising from adenohypophyseal cells, accounting for one third of all pituitary adenomas [1].The widespread use of computed tomography (CT) and magnetic resonance imaging (MRI) for a variety of clinical conditions has led to a surge in incidentally diagnosed pituitary lesions, the so-called pituitary incidentalomas.[1].The clinical presentation of NFPA varies from an incidental finding to life-threatening apoplexy. Non-functioning pituitary adenomas are diagnosed in the absence of clinical and biochemical signs of tumor-related hypersecretion of hormones.[3].As a general rule, in patients with NFPA, mass effect symptoms are more common than insidious pituitary dysfunction.[4].

The principles of NFPA classification and grading are outlined in the recently published fourth edition of the World Health Organization (WHO) Classification of Endocrine Tumors, which established a more accurate and cell line-specific system.[5, 6].This novel approach is based on the expression of anterior pituitary (adenohypophysis) hormones and pituitary-specific transcription factors. Another change in the latest WHO classification is the elimination of the term "atypical adenoma" and the introduction of "high-risk pituitary adenoma", including tumors with defined histological subtypes, increased cell proliferation as assessed by mitotic rate, Ki-67 labeling index, and signs of invasive growth assessed with using imaging and/or histology

In patients with NFPA higher frequency of various types of neoplasms, the cause of which remains unknown; the hypothesis of genetic and/or epigenetic predisposition is still being studied[7].

While most NFPAs are benign, 45% to 55% are locally invasive and may show aggressive features. Proliferative markers such as Ki-67, mitotic rate, and p53 immunoreactivity are commonly used to assess the potential for aggressive behavior; at the same time, higher SSTR3 expression and low MGMT expression are also associated with more aggressive NFPAs.[8,9].Non-functioning pituitary carcinomas (NFPCs) are a very rare entity defined as tumors of adenohypophyseal origin with cerebrospinal, meningeal, or distant metastases along with no evidence of hormonal hypersecretion. [10].Fortunately, it is very rare and accounts for only 0.1 to 0.5% of all pituitary adenomas.[11, 12].About 38 cases have been registered to date. NFPA.[13].

Ki-67 is the most reliable marker of proliferation, with values ranging from 1.3% to 10% and greater than 10% associated with tumor recurrence and malignancy, respectively, while values greater than 3% are a reliable prognostic marker. Increased p53 immunoreactivity is another marker of proliferation; however, the lack of reliable quantification methods led to its removal from the 2017 WHO classification. Similarly, mitosis rates greater than 2 per 10 high power fields are commonly seen in pituitary carcinoma and are associated with increased recurrence rates [14].

The progression of benign to malignant pituitary tumors is not fully understood and remains largely unknown; however, it is generally accepted that it is due to genetic and epigenetic

abnormalities.[15].Activation of classical oncogenes such as Ras and p53 mutation are common in other types of cancer but rarely seen in pituitary carcinomas[16].The benign nature of most pituitary tumors, according to Lenders and McCormack, is thought to be the result of oncogene-induced aging with upregulation of cell cycle regulator genes such as p53, p21, and p16. Other factors that may play a role in the malignant transformation of benign NFPA include chromosomal instability with chromosomal changes including 14q, 5p and 7p.[17].Moreover, increased nuclear expression of the pituitary tumor transformation gene (PTTG) has been associated with tumor aggressiveness. Activation of certain micro RNAs has been shown to play a role in NFPF without evidence of over expression in the primary tumor.

Nonfunctioning pituitary carcinomas cannot be reliably distinguished from benign tumors by any clinical, biochemical, or radiographic features. In a review by Lenders et al., of 38 cases of NFPA observed, 23 were women with a mean age at diagnosis of 48 years. Non-functioning pituitary carcinoma usually develops from aggressive macroadenomas with a median latency of 6.6 years between initial tumor diagnosis and metastasis and initially presents with signs of mass effects; however, 5 cases showed extremely rapid progression, with metastases occurring within 1 month of only the initial presentation. Cerebrospinal metastases were more common than systemic ones, with intracranial metastases being the most common.[17].

All of the above emphasizes the relevance of this direction.

Target Explorenprognostic value of invasion and proliferation markers in patients with macro and giant inactive pituitary tumors.

Of 272 patients withNFPA. The study involved prospectively 151 patients (men and women) who received treatment at the Department of Neuroendocrinology of the Republican Specialized Scientific and Practical Medical Center of Endocrinology and applied to the outpatient clinic in the period for 2020-2022. Among them - men - 85 (56.3%), women - 66 (43.7%), who were constantly monitored in dynamics. Average age: A man was 48.12 years, women - 46.15 years. The duration of the disease ranged from 2 months to 5 years. 20 healthy individuals of the corresponding sex and age made up the control group.

According to the size of pituitary adenomas, patients of prospective (151 patients) observation were divided into 2 groups: group 1 - patients with macroscopicNFPA- 55 persons, group 2 - patients with giant NFPA- 96 persons.

Table 1 shows the distribution of patients by sex and age (data from a prospective study).

TABLE 1 DISTRIBUTION OF PATIENTS BY SEX AND AGE (PROSPECTIVE DATA, N = 151)

Age, years	Number of men, n = 85		Number of women n = 66	
	1 gr	2 gr	1 gr	2 gr
13 years	-	-	-	-
16 – 29	3	6	1	2
30-44	16	19	15	13
45-59	18	16	16	14

60-74	4	3	1	2
75 and older	-	-	1	1
Total: n=151	41	44	34	32

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 internal and genital organs, etc.), 5) hormonal blood tests (STH, 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 RSNPMC E MZRUz named after Academician Y.Kh.Turakulov (histology room).

The proliferation markers Ki-67 and p53 were obtained by a semi-quantitative method. Results were considered positive for cases where p53 ≥ 3+ (25 to 50% of cells immunoexpressed), Ki-67 ≥ 2+ (10 to 25% cells immune expressed), and c-erbB2 ≥ 2+ (more than 10% of cells positive).) according to local protocols [18, 19].

The obtained data were processed using computer programs Microsoft Excel and STATISTICA_6. The arithmetic mean (M), standard deviation of the arithmetic mean or error of the meanarithmetic of all n repetitions (m).The significance of differences in the level between groups was assessed by the value of the confidence interval and Student's test (p). Differences were considered statistically significant at $p<0.05$.

Results of Own Researches and their Discussion A total of 60 TAGs (transnasal pituitary adenomectomy) were performed (Ph.D. Akbutaev A.M., Prof. Michael Powell from the UK). Repeated operations on the pituitary gland were performed in 5 patients (7.3%). Radiation therapy was received by 5 (7.4%) patients and 1 - chemotherapy (1.5%).

Twenty immunohistochemical studies were analyzed in 10 patients with macro NAH and 10 patients with giantNFPA compared with MRI data of the pituitary gland.

Distribution of patients according to the topographic and anatomical classification of the growth side of the pituitary adenoma Kadashev B.A. (2007) showed that pituitary adenomas with a total growth variant were most often observed - 48 cases (17.6%), which is shown in Table 2.

TABLE 2 DISTRIBUTIONS OF PATIENTS ACCORDING TO TOPOGRAPHIC AND ANATOMICAL CLASSIFICATION OF THE SIDE OF GROWTH OF PITUITARY ADENOMA (ACCORDING TO KADASHEV B.A., 2007)

The nature of tumor growth:	
1) Endosellar:	**2) Endoextrasellar:**
a) microadenoma (endosellar)	a) endosuprasellar (with compression chiasma) - no
b) macroadenoma	b) tumors with invasion of the skull structures: - with supra, parasellar growth -101 - with infrasellar growth -113 - with parasellar growth - 120

	- totalgrowthoption (infra, latero, ante, retro) -48

Depending on the size of the pituitary adenoma detected on CT/MRI, the patients were divided into two groups: Group 1 -macroadenomas (from 20 to30 mm) - 17 (48.6%), and group 2 patients - giant - (more30 mm) – 18 (51.4%).

All sections of the MRI images were reviewed. Cavernous sinus invasion was considered in cases where the tumor volume occupied more than 2/3 of the internal carotid artery or grade 3 and 4 tumors according to Knosp et al. [20] and Edal et al. [21] classifications, respectively. Sphenoid sinus invasion was considered when MRI showed erosion of the sellar bone floor and/or tumor invasion of the sphenoid sinus (grade 1 and 2 by Edal et al. [21]. Tumors with significant suprasellar extension (grade 4, Edal et al. .[21]) causing obstructive hydrocephalus in close contact with the third ventricle and in close proximity to brain parenchymal tissue were also considered invasive.

Table 3 shows the distribution of patients according to the nature of the formation of the sellar region.

TABLE 3 DISTRIBUTIONS OF PATIENTS ACCORDING TO THE NATURE OF THE GROWTH OF THE FORMATION OF THE SELLAR AREA

Diagnosisofthedisease	1 group - patients with macro NFPA- 55 persons,	2 group - patients with giant NFPA - 96 persons.
hemorrhageinthestroma	5 (9.09%)	12 (12.5%)
parasellarinvasion	42 (76.4%)	78 (81.3%)
suprasellargrowth	34 (61.8%)	67 (69.8%)
infrasellarextension	44 (80%)	69 (71.9%)
expansion of the third ventricle	32 (58.2%)	57 (59.4%)
regrowth of residual tumor tissue after surgery	6 (10.9%)	9 (9.3%)

Note: NFPA - inactive pituitary adenoma

As can be seen from Table 3, hemorrhage into the pituitary stroma occurred in 5 (9.09%)/12 (12.5%) cases, parasellar invasion in 42 (76.4%)/78 (81.3%) cases, suprasellar growth - in 34 (61.8%) / 67 (69.8%), infrasellar expansion -44 (80%) / 57 (59.4%), expansion of the third ventricle - 32 (58.2%) / 57 (59.4%) observations in groups 1 and 2, respectively. Tumor recurrence after TAG occurred in 15 patients out of 60 (25%).

The maximum mean tumor diameter determined at diagnosis was 44.7 ± 13.6 mm, and macroadenomas >40 mm were present in 68% of patients. A total of 76.4%/81.3% of all tumors had evidence of parasellar invasion (22% unilateral, 62% bilateral). 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. Of these, the third ventricle and/or brain parenchymal tissue (Grade 4 according to Edal et al. [13]) were present in 58.2%/59.4% of all cases (Table 2).

Table 4 shows the immunohistochemical characteristics of the studied groups.The observed frequency of immunoexpression of proliferation markers was 40%/50% for p53 (≥3+), 50%/60% for Ki-67 (≥2+). Tumors with immunoexpression of at least 2 markers with a high proliferation index were observed in 54% of the cohort and were regarded as proliferative adenomas.

TABLE 4 IMMUNOHISTOCHEMICAL CHARACTERISTICS OF THE STUDIED GROUPS

Diagnosisofthedisease	1 group - patients with macro NFPA- 10 persons	2 group - Patients with giant NFPA - 10 persons.
Zero cell	8 (80%)	8 (80%)
R53		
>/3+	4 (40%)	5 (50%)
Ki 67		
>/2+	5 (50%)	6 (60%)
Clinicopathological classification		
1A	1 (10%)	1 (10%)
1B	1 (10%)	1 (10%)
2A	3(30%)	2 (20%)
2B	5 (50%)	6 (60%)

Next, all radiographic evaluations were reviewed, as well as images from the time of diagnosis and throughout the follow-up period. It was observed that over 80% of tumors were considered anatomically invasive by diagnosis. According to the clinicopathological classification, the relationship between anatomical and pathological classes revealed that 4% were non-invasive and non-proliferative tumors (grade 1A) and 2% were non-invasive and proliferative (grade 1B). In addition, 30%/20% of the tumors in the total sample were invasive and non-proliferative (level 2A), and 50%/60% were invasive and proliferative tumors (level 2B). Metastatic tumors were not observed.

A review of immunohistochemical analysis showed that of all cases, 76% were null-cell pituitary adenomas.

Next, we performed a correlation analysis of the relationship between MRI and immunohistochemistry parameters.Maximum tumor diameter was associated with stronger immunostaining for Ki-67 ($p = 0.009$), but no significant association was found for p53 ($p = 0.062$. Parasellar invasion was present in over 80% of cases; however, invasion was not associated with proliferative markers.

Suprasellar traction was observed to some extent in all patients, except for one, so it was not possible to compare groups in terms of the presence or absence of suprasellar traction. Although a statistical analysis was performed to test the effect of immunostaining intensity on proliferation markers in the suprasellar dilation group, no association was found. Extension to the third ventricle was present in 64% of tumors and was associated with p53 immunostaining ($p = 0.013$) but was not associated with Ki-67 immuno expression.

Thus, our results showed that in all patients with giant pituitary adenomas. The absence of parasellar invasion was associated with a higher rate of tumor stability after treatment (p = 0.0389; Pearson residual = +3). However, parasellar invasion was not associated with outcomes such as tumor regrowth/recurrence and cure/shrinkage. Infrasellar invasion and suprasellar extension have not been considered good predictors of clinical outcome. However, there was a trend to associate the lack of extension to the third ventricle with a greater likelihood of tumor stability after treatment. Proliferative tumors, but mostly those classified as Grade 2B (invasive proliferative), showed a significant association with tumor regrowth/recurrence (p = 0.0127),

CONCLUSIONS Giant inactive pituitary adenomas are often accompanied by invasive growth into the surrounding anatomical structures (more than 80% of cases), which is the main factor limiting the radicalness of the surgical intervention and increasing the number of relapses.

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