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Pituitary Adenoma Characteristics in Patients Referred to Loghman Hospital in Seven Years

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ABSTRACT

Background and Aim: The classification of pituitary adenomas now includes an "atypical" variant, which can be defined as MIB-1 proliferative index greater than 3%, excessive p53 immunoreactivity, invasive growth pattern, and increased mitotic activity. In this study, we aimed to describe pituitary adenoma characteristics in patients referred to the Loghman Hakim hospital.

Methods: This article is a cross-sectional descriptive study. In this study, the authors reviewed the records of 300 patients, including 250 patients with typical pituitary adenoma and 50 patients with atypical pituitary who were referred to Loghman Hakim Hospital between 2011 and 2017. Statistical analyses were performed using Fisher's exact test and Mann-Whitney.

Results: In the APAs group, 47.8% and 52.2% of the tumors were microadenomas and macroadenomas, respectively. In the APA group, 91.3% of the patients had a Ki-67 labeling index of more than 3%, and the presence of p53 protein was observed in all the patients with APAs. The mean number of mitosis in the TPAs and APAs groups was 0.62 and 2.5, respectively. In addition, our results showed significant threshold values for mitotic index (>2 mitosis within ten high power fields). Also, there was no significant difference between the size of tumors and the type of secretion hormones in the APA and TPA groups (P> 0.05).

Conclusion: There was a relationship between tumor size and hormone secretion with types of pituitary adenoma.

INTRODUCTION

Pituitary adenomas constitute 10 to 25% of intracranial tumors and are considered the third most common intracranial neoplasms after meningiomas and astrocytomas, respectively. Recent studies have shown no gender or race difference in the prevalence of these adenomas(1, 2). The estimated prevalence of pituitary adenomas in the general population is between 10% and 17% (3). Moreover, Pituitary adenomas are very rare among children; however, the prevalence increases along with age, and its peak is at the age of 30-60 years old. Incidentally discovered pituitary masses have more than 27% incidence in autopsy studies and 10% incidence in MRI examinations (2).

Depending on pathologic features, radiological evidence, and clinical behaviors, pituitary adenomas can be classified into typical and atypical, invasive and non-invasive, and aggressive and non-progressive classes. As a synonym for invasive and atypical for pituitary adenomas, the term aggressive has resulted in various interpretations of their classes (4). According to a classification provided by World Health Organization (WHO), there are three pituitary neoplasms classes: typical pituitary adenomas, atypical pituitary adenomas, and pituitary carcinomas (4). In this classification, pituitary adenomas with at least three of the following parameters as excessive mitotic activity, Ki-67 index of >3% or extensive p53 immune response, and

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invasive growth pattern are categorized as atypical, and those that have none of the above-mentioned specifications are typical. If there is a metastasis, these tumors are called pituitary carcinomas, regardless of the presence or absence of histological features of malignancy (like high mitotic activity) (1).

The MIB-1 monoclonal antibody, which is one of the most common means of determining the Ki67 index and assessing the tissue samples of pituitary adenomas, has shown a good correlation with the growth of pituitary adenomas(5, 6). The high level of the tumor suppressor p53, which is widely recognized as an indicator of many cancers, is also known as a marker of atypical tumors in the pituitary gland. However, these markers have questionable values as a predictor of invasive behavior of pituitary adenomas (7). Evaluation of mitotic activity is one of the oldest and most common histopathologic methods of measuring the biological invasiveness in human tumors. However, for pituitary tumors, the accuracy of this approach as a way of evaluating tumor invasiveness remains doubtful. In fact, the practical value of this approach in evaluating tumor invasiveness has not been systematically analyzed(8). This study compared typical and atypical pituitary adenomas in terms of mitotic count per 10HPF, tumor size, secretory hormones, bone invasion, and the presence of Ki-67 and p53 markers and we described these parameters in typical and atypical pituitary adenomas.

METHODS

This study was approved by the ethical committee of Shahid Beheshti medical university (IR.SBMU.MSP.REC. 1396.654). We reviewed the records of 250 patients who underwent surgical evaluation for pituitary adenoma at the Loghman Hakim Medical Center affiliated to the Shahid Beheshti University of Medical Sciences between 2011 and 2017. The Shahid Beheshti University of Medical Sciences committee of ethics reviewed and approved this study.

Among these 250 patients, 100 adenomas exhibited mitotic activity on H & E staining; therefore, they underwent staining for mitotic index, p53, and Ki-67 institutional protocol; 50 of these tumors met diagnostic criteria for atypicality by showing positivity for all three features (5% of the total cohort and 30% of tumors stained for all three features of atypia).

Demographic data were collected through medical record review, including primary treatment modality, adjuvant medical or radiation-based therapies, recurrence rates, and treatment strategies for recurrent tumors.

Per institutional practice, all the patients underwent routine postoperative MRI within three months after primary surgery to assess the extent of resection. Atypical tumors were followed by annual MRI scans, whereas annual scans followed typical tumors for the first three years and were scanned every two years. Per the 2004 WHO designation, only the patients with adenomas meeting all three criteria for atypicality were included as having atypical pituitary adenomas: > 2 mitoses per 10 HPFs, positive p53 staining, and Ki-67 ≥ 3%. Three senior neuropathologists provided histological confirmation of atypicality and hormone functions in the Department of Pathology at Loghman Hakim Medical Center.

Then, Tumors were considered as microadenomas when their largest diameter was < 1 cm on MRI, and macroadenomas when ≥ 1 cm. Functionality (hormone hypersecretion) was determined based on histological staining in conjunction with laboratory evidence of an abnormal preoperative hormonal elevation. Pre- and postoperative hormone testing data were available for all the patients with functional adenomas.

All statistical analyses were performed using SPSS (IBM SPSS Statistics Developer 23.0), with a significance level defined as $p < 0.05$. Fisher's exact tests were used for categorical variables and the Student t-test for continuous variables.

RESULTS

From 2011 to 2017, 300 patients with pituitary adenoma underwent resection at our institution. Of these patients with adenomas, 50 exhibited increased mitotic activity; therefore, they underwent evaluation for all three markers of atypicality, with 50 tumors (50%) that were proved to be atypical. Among the patients with typical adenomas, there were 170 non-functional adenomas (68%) and 80 functional adenomas (32%). Also, there were 67 female patients (54%) and 183 male patients (46%) in the typical adenoma, and 37 male patients (73.9%) and 13 female patients (26.1%) in the atypical adenoma. The mean age of the patients in the typical cohort was 35.8 years old (ranging from 11 to 77 years old), which was significantly lower than the mean age of 43.66 years old (ranging from 20 to 76 years old) of the patients in typical cohort ($p < 0.0001$, Mann-Whitney).

Atypical adenomas were more likely to be functional (28 of 36 [53.2%]) rather than typical adenomas (80 of 300 [32%]) ($p < 0.0001$; Fisher's exact test). Table 1 compares tumor characteristics in both groups (Table 1).

The minimum and maximum numbers of mitosis in typical pituitary adenomas were 0 and 3, and in atypical pituitary adenomas were 1 and 6, respectively. Also, the mean number of mitoses in typical pituitary adenomas was 0.62 and in atypical pituitary adenomas was 2.5. The Mann-Whitney test showed that mitosis in atypical pituitary adenomas was significantly higher than in typical pituitary adenomas (Table 1 & Fig 1).

Table 1. Tumor Characteristics of the typical and atypical pituitary adenomas

		Typical	Atypical	P-values
Size	micro adenoma	64%	47.8%	0.242
	macro adenoma	36%	52.2%	
Ki-67	< 3%	86%	8.7%	*<0.05
	> 3%	14%	91.3%	
P53	Negative	60%	0%	*<0.05
	Focal	26%	26.1%	
	Diffuse	14%	73.9%	
Hormone Functionality	Non-Functional	68%	47.8%	0.72
	Prolactin	12%	21.7%	
	GH	12%	21.7%	
	ACTH	4%	4.3%	
	Plurihormone	2%	4.3%	
	TSH	2%	0%	
	LH	2%	0%	
	FSH	2%	0%	
Invasion	Yes	2%	21.7%	*<0.05
	No	81.3%	78.3%	

* **Fishers Exact's test**

GH= Growth hormone, ACTH= Adrenocorticotropic hormone, TSH= Thyroid-stimulating hormone, LH= Luteinizing hormone, FSH= Follicle-stimulating hormone

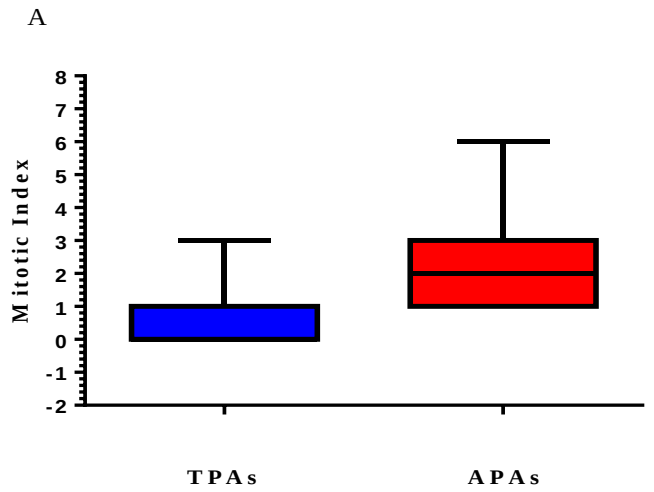

FIGURE 1. Mean number of mitosis in both groups

TPA= Typical Pituitary Adenoma, APA= Atypical Pituitary Adenoma

DISCUSSION

This study aimed to determine the histomorphologic and immunohistochemical parameters for diagnosing atypical pituitary adenoma (APA). Although the WHO classification of the typical and atypical pituitary adenomas was introduced more than ten years ago, the exact cut-off points for the "mitotic proliferative index" are yet to be defined. In this study, five proposed criteria were studied for the diagnosis of atypical pituitary adenomas (Ki-67, invasion, mitotic count, p53 level, and secretory hormone type) and then compared in both typical pituitary adenomas (TPA) and atypical pituitary adenomas (APA). For this purpose, the medical f of 300 patients were studied, including 50 patients with TPA and 250 patients with APA, who were registered in Loghman Hakim Hospital between 2011 and 2017.

In this study, the patients with APA had a mean age of 35.8 years old (ranging from 11 to 77 years old), while those with TPA had a mean age of 43.66 years old (ranged between 20-76 years old), which was significantly higher than the other group (P<0.05). These results are consistent with the results of a study by Rutkowski et al. (2017), in which the patients with APA (37 years old in the range of 10-65) had a significantly lower mean age (P<0.001) than those with TPA (49 years old in the range of 10-93) (9). In contrast, in a study by Zada et al. (2011), the APA patients had a mean age of 48 years old (ranged from 16 to 70 years old), and the TPA patients had a mean age of 47 years old (ranged between 16-81 years old), which were not significantly different (10).

In the present study, most of the typical pituitary adenomas (64%) were microadenomas. In comparison, most of the atypical pituitary adenomas (52.2%) were macroadenoma, but comparisons of tumor size in the two groups with the Mann-Whitney test showed no statistically significant difference in this respect (P=0.224). In the study by Zada et al. (2011), 94% of atypical pituitary adenomas were macroadenoma (10), and in a study by Yildirim et al. (2013), all atypical pituitary adenomas were macroadenoma (11). In a study carried out by De Caro et al. (2016), it was reported that 82% of atypical pituitary adenomas were macroadenoma (12). In another study, Chiloiro et al. (2015) found that 78.1% of atypical pituitary adenomas were macroadenoma; however, the comparison of typical and atypical pituitary adenomas showed no significant difference in terms of size (13).

P53 is considered a tumor suppressor gene on chromosome 17 that is involved in DNA regeneration, cell cycle arrest, and apoptosis. Overexpression of the mutated p53 is a common indicator of many human cancers. Although WHO classification (2004) has provided no exact cut-off point for p53 overexpression, it is generally agreed that a p53 expression of more than 2% in nuclei/HPF is a sign of atypicality. A study by Miermeister et al. (2015) found that p53 overexpression can diagnose atypical pituitary adenomas with 93% specificity, which suggests that it can be considered a good diagnostic criterion for atypical pituitary

adenomas (14). In the present study, all atypical pituitary adenoma cases showed p53 protein expression, of which 73.9% were diffused and 26.1% were focal. Statistical analysis using Fishers Exact test showed that atypical pituitary adenoma cases had significantly higher p53 protein expression than typical pituitary adenoma cases (P <0.05). In the study of De Caro et al. (2016), p53 expression was diffused in 54% of atypical pituitary adenomas, was poorly recognizable in 30% of these cases, and was focal in only 16% of these cases (12).

Regarding the WHO criteria, the Ki-67 index of >3% can diagnose atypical pituitary adenoma with 72.7% sensitivity, 97.3% specificity, 96% positive predictive value, and 80% negative predictive value. Out of the atypical pituitary adenomas examined in this study, 91.3% showed a Ki-67 index of >3%; however, among the examined typical pituitary adenomas, this ratio was only 14%. The comparison of these two groups showed that the Ki-67 index of >3% was significantly more frequent among APA cases than the TPA cases (P<0.05). The study by Miermeister et al. (2015) reported that the Ki-67 index of >4%, with 95% sensitivity and 97% specificity, is the only most reliable marker of the differentiation of APA from TPA. The mean Ki-67 index values reported in the studies by Rutkowski et al. (2017), De Caro et al. (2017), Saeger et al. (2016), Takibi et al. (2013), and Zada et al. (2011) are 4.1%, 5.6%, 9%, 4.7%, and 7%, respectively (9-12, 15).

Since the WHO guidelines have not specified an exact cut-off point for the mitotic index, there is plenty of room for discussion and interpretation regarding this index. The present study found that the APA cases had a significantly higher mitotic count than the TPA cases (P <0.05). Another study with comparable results is the study by Miermeister et al. (2015), where a cut-off of ≥2 mitoses per 10 HPF was found to have a 90% sensitivity and 74% specificity in the diagnosis of atypical pituitary adenomas(14).

Immunohistochemical analysis of atypical pituitary adenomas showed that 47.8% of APAs had no secretory hormone. In terms of secretory hormones, the groups with the highest frequency out of atypical pituitary adenomas were prolactin positive and GH positive adenomas (21.7%), followed by ACTH positive (4.3%), plurihormone positive (4.3%), and TSH positive (0%) adenomas, respectively. Of the examined typical pituitary adenomas, 66% lacked secretory hormone, 12% were prolactin positive, 12 were GH positive, 4% were ACTH positive, 2% were plurihormone positive, 2% were TSH positive, and 2% were FSH/LH positive. No significant difference was found between the two groups in terms of the type of secretory hormone (P=0.721). Also, in a study by Zada et al. (2011), 50% of the atypical pituitary adenomas were hormonally active (28% somatotroph, 11% corticotroph, and 11% prolactinoma) (10). However, out of silent tumors, 28% were null-cell adenomas, 17% were ACTH positive adenomas, and 6% were FSH positive adenomas(10). In another study, Saeger et al. (2007) reported that more than 70% of atypical pituitary adenomas were somatotropinoma, non-secretory adenomas, and ACTH adenomas (1).

The present study investigated the invasion of typical and atypical pituitary adenomas to surrounding tissues using an MRI examination. This examination showed local invasion in 21.7% of the APA cases and 2% of the TPA cases. The comparison of the two groups in this respect showed that atypical pituitary adenomas had significantly higher invasiveness than typical pituitary adenomas (P<0.05). In a study by Tortosa et al. (2016), 92.3% of the APA cases showed local invasion of the surrounding tissue (16). Moreover, in a study by Miermeister et al., more than 47% of the TPA cases and 87% of the APA cases had an invasive growth pattern (14).

CONCLUSION

For diagnosis of atypical pituitary adenoma, at least 3 out of 4 pathological criteria are required, including the increased mitotic index, p53 immunostaining, MIB-1 index ≥ 3%, and invasiveness. Compared with typical pituitary adenomas, atypical adenomas are more likely to be presented in younger patients, tend to invade surrounding tissues, and are associated with earlier recurrence.

These findings represent the first and the most comprehensive side-by-side comparison of atypical versus typical adenomas and for the first time, lend credence to the WHO designation of atypical adenoma as a unique pituitary tumor subtype.

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Not declared.

CONFLICT OF INTEREST

All authors declare no conflicts of interest.

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