Relevance of high Ki-67 in pituitary adenomas

Case report and review of the literature

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Pituitary adenomas are heterogeneous in growth rate, invasiveness, and recurrence. To understand the biological behavior of the individual adenoma more fully, cell proliferation markers such as monoclonal antibodies targeted against the Ki-67 antigen have been applied. The Ki-67 antigen is a protein related to cell proliferation and is expressed in cell nuclei throughout the entire cell cycle. The authors report the case of an extremely rapidly growing pituitary adenoma with cavernous sinus invasion. The lesion, which displayed a high Ki-67 labeling index (LI; 22%), was found in a 54-year-old woman who presented with diplopia and headaches. The patient underwent three transsphenoidal operations in less than 6 months and, ultimately, was treated with fractionated intensity-modulated radiation therapy. The relationships between high Ki-67 LIs and tumor recurrence, invasiveness, and growth velocity in pituitary adenomas are reviewed.

KEY WORDS • Ki-67 labeling index • pituitary adenoma • tumor invasiveness • tumor recurrence • tumor growth velocity • transsphenoidal approach • radiotherapy

CASE REPORT

History. This 54-year-old woman was referred to the University of Virginia hospital for the evaluation and further treatment of a known pituitary macroadenoma in January 2005.
She initially presented to an emergency department in July 2004 with new onset of very severe headaches; a CT scan was obtained and was reported to be normal. The headaches were controlled with pain medications until the end of July. In August 2004, the patient was evaluated by her primary care physician for return of the headaches, and at that time an MR imaging examination revealed the presence of a 13 × 8 × 8-mm pituitary adenoma. The woman was referred to an endocrinologist, who ordered a dedicated pituitary MR imaging study in September 2004; that study revealed the presence of a 15 × 12 × 12-macroanoma abutting the optic chiasm. The patient had normal visual fields. Laboratory tests given September 30, 2004, showed normal pituitary function with the following hormone levels: thyroid-stimulating hormone 2.57 mIU/L (normal 0.4–4.5 mIU/L); cortisol 19.5 μg/dl (normal 4.3–22.4 μg/dl); FSH 29.1 μIU/mL (normal > 23 μIU/mL, postmenopausal); luteinizing hormone 24.6 μIU/mL (normal 15.9–54 μIU/mL, postmenopausal); prolactin 19.8 ng/ml (normal 1.8–20.3 ng/ml); free thyroxine 0.93 ng/dl (normal 0.7–2.1 ng/dl); and insulin-like growth factor–I 117 ng/ml (normal 109–284 ng/ml). In October, the patient experienced another intense headache, this time associated with diplopia. She was referred to a neurologist, who repeated the MR imaging study. This time the MR images revealed a significant enlargement of the mass, now measuring 22.5 × 14 × 15 mm. At that time she was given dexamethasone and was seen by a neurosurgeon who scheduled surgery. Her formal visual field testing was normal.

The patient underwent transsphenoidal surgery in October 2004. The operation was complicated by an intraoperative CSF leakage and approximately 1.2 L of blood loss. The operation was terminated early and only three quarters of the tumor was reported to have been removed. The pathological findings were consistent with those of a pituitary adenoma with extensive infarction, and there was weak staining for FSH and prolactin. Postoperatively, the woman’s vision normalized.

The patient experienced another significant headache in December and was reevaluated with MR imaging, which showed a residual tumor on the right side of the sella turcica, measuring 10 × 5 × 4 mm. In January 2005 she again noted blurry and double vision, and repeated MR imaging revealed that the mass had doubled in size in less than 1 month; it now measured 20 × 16 × 13 mm with a mild elevation of the left optic nerve and deviation of the stalk to the right side.

**Presentation and Examination I.** The patient presented to the University of Virginia hospital with partial hypopituitarism; she had been receiving steroid replacement and treatment for diabetes insipidus since her first operation. The general physical examination detected no abnormalities. The neurological and ophthalmological examinations revealed a subtle left third cranial nerve palsy.

We performed preoperative CT angiography because of an unclear source of excessive bleeding requiring transfusion, which had occurred in the previous operation. This ruled out previous damage to the carotid artery and subsequent aneurysm formation (Fig. 1).

**Operation I (January 2005).** A repeated transsphenoidal exploratory surgery was performed with the aid of Stealth computerized neuronavigational guidance. A fibrotic gray pituitary lesion was encountered. An intraoperative consultation confirmed the diagnosis of a pituitary adenoma. The lesion had a cartilaginous consistency and was adherent to the walls of the sella turcica and to the diaphragm. The latter was ultimately violated, producing a moderate CSF leak. The intrasellar contents were thoroughly removed, and there was no sign of tumor in the region of the diaphragm or in the region of the left cavernous sinus. An abdominal fat graft was taken from the subumbilical region and placed to occlude the sella turcica. The sellar floor was carefully reconstructed. There was little, if any, normal pituitary tissue remaining in the sella after removal of the tumor.

**Pathological Findings I (January 2005).** A microscopic examination showed a pituitary adenoma exhibiting sheet-like growth. The tumor cells appeared clear to chromophobic with a lightly eosinophilic cytoplasm; a few enlarged nuclei were also present. The nuclei were round to oval with some more irregular forms; there were fine chromatin and small nucleoli. Rare mitotic figures were present, but the mitotic activity did not appear to be increased. The adenoma displayed extensive fibrosis with prominent macrophage infiltration, old hemorrhage, hemosiderin deposition, and necrosis—findings consistent with the history of recent surgical intervention in the area. No normal pituitary gland tissue was identified.

Wilder reticulin staining revealed disruption of the normal acinar pattern throughout the neoplasm, with areas of fibrosis both around and within the adenoma. A panel of immunohistochemical stains for pituitary hormones (growth hormone, prolactin, adrenocorticotropic hormone, FSH, luteinizing hormone, α-subunit, and thyroid-stimulating hormone) was performed using the automated Ventana Nexes IHC stainer (Ventana Medical Systems, Tucson, AZ). The hormone markers were essentially nondiagnostic, with only rare α-subunit positive cells. In addition, CD68 (a macrophage marker) demonstrated extensive macrophage infiltration. Overall, the findings were consistent with a pituitary adenoma that was immunonegative for hormone markers and displayed recent changes at surgery.

The Ki-67 LI was obtained by performing an immunohistochemical analysis with the monoclonal antibody MIB-1, which recognizes the antigen Ki-67. The antigen retrieval technique was used, and immunostaining was performed using the automated Ventana Nexes IHC stainer. From 1000 to 2000 nuclei were counted and the percentage of positive Ki-67 nuclei was assessed. The Ki-67 LI in this case was 22% (Fig. 2).

**Postoperative Course I and Presentation II.** The patient did well for 1 month following surgery with resolution of her diplopia. She then began to experience recurrent severe headaches and subsequent recurrent diplopia in March 2005.

**Examination II.** A neuroophthalmological examination confirmed that she had mild left-sided sixth and third cranial nerve palsies.

A new MR imaging study was ordered because of the recurrent symptoms. The MR images revealed a 16 × 13 × 2-mm left cavernous sinus lesion (Fig. 3), and a repeated transsphenoidal operation was recommended.
**Operation II (March 2005).** A new transsphenoidal exploratory surgery was performed with the aid of Stealth computerized neuronavigational guidance. The sphenoid sinus was entered and the fat that had been placed previously was carefully removed along with some early scar tissue. The sella turcica was identified and the fat was differentiated from recurrent tumor. In fact, there was obvious tumor within the left cavernous sinus, which was completely reconstituted and very tense. It was a blue structure and was carefully explored using a micro-Doppler technique to be certain that the CA was not at risk. Blunt dissection was used to enter the cavernous sinus where the surgeon encountered a firm, rubbery purple tumor. The lesion had to be removed very carefully because significant force was required to detach small pieces of the tumor. Eventually, the cavernous sinus was again cleared of tumor back to the posterior dura of the sella and the posterior clinoid. The dorsum sellae was visualized and its position was confirmed with the aid of the intraoperative neuronavigational system. There was a nodule of tumor extending superiorly, which was very carefully brought down and stripped away from the diaphragm, but in the process of doing this, a CSF leak was produced. As much of the tumor as possible was removed from the posterior and lateral reaches of the left cavernous sinus, but some tumor remained firmly attached to the dura and adjacent to the carotid artery, which was left undisturbed. After a satisfactory decompression of the cavernous sinus portion of the tumor had been carried out and no further tumor was visualized anywhere else within the sella, a fat graft was placed within the sella and the sellar floor was reconstructed.

**Pathological Findings II (March 2005).** A microscopic examination showed a pituitary adenoma composed of small cells with eosinophilic to slightly basophilic cytoplasm and small, round nuclei. Areas of tumor necrosis were identified. There was marked fibrosis and hemosiderin deposition. The findings were similar to those of the previous operation.

Immunohistochemical stains for α-subunit and Ki-67 were performed. The tumor cells displayed focal, weak immunoreactivity for α-subunit. The Ki-67 LI at this time was identical to that of the previous resection specimen, which was 22%.

**Postoperative Course.** Although the patient’s vision returned to normal after surgery, she again experienced headaches, and a new MR image obtained in April 2005 revealed that the residual tumor in the left cavernous sinus was rapidly recurring, reaching larger dimensions than indicated on the preoperative MR images (Fig. 4).

The case was discussed and the lesion was interpreted as an atypical adenoma with a high proliferation rate associated with an invasive and rapidly recurring pattern. The woman underwent 54 Gy intensity-modulated radiation therapy divided into 30 fractions of 1.8 Gy each. Chemotherapy was reserved for the possibility of eventual radiation failure.

At her last visit (July 2005), 2 months after completion of radiation therapy, the patient was asymptomatic and the MR images demonstrated moderate shrinkage of the tumor (Fig. 5).

**DISCUSSION**

**Ki-67 Antigen and Its Use in Human Cancers**

The eukaryotic cell cycle consists of four phases: G₁, S, G₂, and M. The two main phases are DNA synthesis (S), in which DNA replication takes place, and mitosis (M), in which the replicated genome is divided equally between two new daughter cells. Quiescent cells may again enter
the cell cycle from this reversible state in response to growth stimuli; however, the vast majority of cells in the human body exist in a metabolically active state outside the cell cycle called quiescence (G0). Cycling cells are only found regularly in a minority of sites such as bone marrow and epithelial tissues or in abnormal neoplastic tissues.

The Ki-67 antigen is a protein present in the nuclei of cells in the G1, S, and G2 phases of the cell cycle as well as in mitosis. It is not expressed in quiescent or resting cells in the G0 phase, in which many proteins involved in proliferation are degraded. A recent study showed that Ki-67 has a dynamic expression and can be weakly detected in the early G1 phase. Nevertheless, this fact does not interfere with the reliability of the method in demonstrating the proliferation rate of a determinate tissue. The presence of Ki-67 antigen is measured by a monoclonal antibody called MIB-1. The MIB-1 immunoreactive nuclear index, also known as the MIB-1 index or the Ki-67 LI, is expressed as a percentage of Ki-67 antigen-positive nuclei among total nuclei.

Although the Ki-67 LI reflects the growth fraction of a given cell population, there is no association between this index and the mitotic count per se, as shown in the present case report. The mitotic count merely reflects a small proportion of the entire cell population’s growth fraction, whereas the Ki-67 LI determination identifies cells through the entire period of proliferative activity.

Because the Ki-67 antigen is present in basically all proliferating cells—both normal and tumor—it is an excellent marker for determination of the growth fraction of a given cell population. Because of its special characteristics, the Ki-67 antigen has been extensively measured to analyze the proliferation rate of many different tumors since its discovery in 1983.

The Ki-67 LI and Pituitary Adenomas

The Ki-67 LI was first reported in pituitary adenomas in 1986, and the percentage of stained cells varied between 0.2 and 1.5%. Initial series did not list significant variations in this range, with the mean Ki-67 LI reported to be approximately 1% and the highest LIs 2.8%, 3.7%, and 4.6%. Subsequent series reported by Zhao, et al., and Mastronardi and colleagues have shown the mean positive reaction to MIB-1 to be 1.4 and 2.64%, respectively. Authors of some recent series have reported the same low mean Ki-67 LI for pituitary adenomas; however, they have shown that in some cases the index can be high, reaching 15.48%, 17.45%, or 23%. The relevance of these high levels is further discussed in this article.

The Ki-67 LI and the Age of Patients With Pituitary Adenomas

In a series of 87 pituitary adenomas, Yonezawa and associates reported a significantly higher Ki-67 LI in nonfunctioning adenomas found in patients younger than 30 years than in those lesions found in patients older than 40 years. Similarly, Jaffrain-Rea and colleagues reported a significantly higher index in patients younger than 30 years of age than in older patients. The opposite was found in one study, in which high Ki-67 LIs were found in...
elderly patients with nonfunctioning adenomas. In another study, however, different age groups (< 25 years, 25–50 years, and > 50 years) were compared and no significant difference in the Ki-67 LI was found.

Ki-67 LI and the Growth of Pituitary Adenomas

Some groups of researchers have directly compared growth velocity and Ki-67 expression in nonfunctioning adenomas. Ekramullah and colleagues assessed tumor-doubling time in 14 recurrent adenomas. The doubling time varied from 200 to 2550 days and exhibited a significant inverse correlation with Ki-67 LIs; the higher the Ki-67 LI the more rapid was the growth velocity. Honegger, et al., determined the growth velocity of 23 adenomas in patients by performing serial imaging studies. Tumor growth was described by a linear growth model in the majority of cases. The growth rate was expressed as the daily percentage of increase in the size of the adenomas. The results of that study demonstrated a highly significant correlation between Ki-67 expression and the tumor growth rate. All rapidly growing adenomas with a daily growth rate exceeding 0.07%, which corresponds to a yearly increase larger than 25% of the adenoma volume, were found to have Ki-67 LIs greater than 1.5%.

Although many reports have demonstrated no relationship between the size of pituitary adenomas and the Ki-67 LI, particularly for nonfunctioning adenomas, some studies have shown that there is a relationship only when secreting tumors are analyzed. Losa, et al., demonstrated that macroadenomas had a significantly higher Ki-67 LI (9.3%) than microadenomas (2.8%) in patients with Cushing’s disease. Other series in which prolactinomas were studied have demonstrated that higher Ki-67 LIs are related to higher prolactin levels and larger macroprolactinomas, particularly in men.

A similar case of a rapidly growing pituitary adenoma was previously reported. Jaffrain-Rea and colleagues described the case of a patient with an FSH-secreting tumor, which a Ki-67 LI of 24% and evolved with early recurrent symptoms of cavernous sinus compression after surgery. Their patient underwent a repeated operation; however, she died 10 days afterward as a result of complications.

The Ki-67 LI and the Invasiveness of Pituitary Adenomas

Pituitary adenomas frequently invade surrounding structures such as the cavernous sinus, sphenoid sinus, and even the brain. Invasive adenomas are not considered malignant; their biological behavior lies between noninfiltrative adenomas and pituitary carcinomas. The reported frequency of invasive pituitary adenomas has varied greatly from 10 to 85%, a reflection of different criteria for the definition of invasiveness. Scheithauer and associates reported a frequency of 35%. Meij, et al., reported dura mater invasion in 41% of 291 patients who underwent primary pituitary surgery. Residual pituitary disease postsurgery was identified in 20% of the patients and it was significantly more frequent in patients with invasive adenomas.

Since initial reports on the range of Ki-67 LI, a correlation of high levels of Ki-67 LI with more aggressive and invasive pituitary adenomas has been detected. Initially the studies demonstrated the invasiveness of a pituitary adenoma based on its capability to invade the dura mater of the floor of the sella turcica, which was easily and con-
sistently collected during the transsphenoidal approach and sent for pathological analysis. Various publications have shown that pituitary adenomas with higher Ki-67 LIs are more prone to present with dura mater invasion.19,20,22

On the other hand, many studies assessing the capability of Ki-67 LI to predict invasiveness in pituitary adenomas have been published, with contradictory results. The reason for this lies in the lack of criteria to define an adenoma that is invasive. Some studies focus on the surgeon’s impression of tumor invasiveness during surgery as the most important factor, whereas others base their criteria on tumor location and configuration in relation to the cavernous sinus on magnetic resonance imaging. Knosp and colleagues21 created a classification based on coronal MR images in an attempt to standardize the level of cavernous sinus invasion in pituitary adenomas. Their classification is determined by the relationship between the lateral aspect of the tumor and the cavernous sinus. Grades 0, 1, 2, and 3 are distinguished from each other by a medial tangent, the intercarotid line through the cross-sectional centers, and a lateral tangent based on the intra- and supra-cavernous internal CAs. Grade 0 represents the normal condition and Grade 4 corresponds to total encasement of the intracavernous CA.21 Although this classification constitutes a good attempt to systematize the data on invasion of the cavernous sinus, it is impossible to differentiate adenomas that are merely pushing against the cavernous sinus from those definitely invading it. Some researchers have used this classification to analyze the relation of the Ki-67 LI to invasion of the cavernous sinus. They consider Grades 3 and 4, which consist of pituitary adenomas present beyond the CAs in the cavernous sinus, to be invasive pituitary adenomas, and these lesions have shown higher levels of Ki-67 expression in comparison with non-invasive pituitary adenomas.14,15,61

In their report on a series of 77 pituitary lesions, Thapar and associates53 demonstrated statistically significant differences among the Ki-67 LIs of pituitary adenomas (mean Ki-67 LI 1.37%), invasive adenomas (mean Ki-67 LI 4.66%), and pituitary carcinomas (mean Ki-67 LI 11.91%). Tumor invasion was defined as a gross infiltration of dura mater or bone observed intraoperatively or on imaging studies. Besides the fact that these authors showed significantly elevated Ki-67 LIs in invasive adenomas, they established a threshold LI of 3% to distinguish invasive from noninvasive adenomas, with 97% specificity and 73% sensitivity associated with positive and negative predictive values of 96 and 80%, respectively.54 Various studies have confirmed this correlation of higher Ki-67 LIs present in invasive pituitary adenomas by using multiple criteria to define invasive as opposed to noninvasive pituitary adenomas.16,27,31,42,45,55,62

On the other hand, several investigators argue against the reliability of the Ki-67 LI, in determining tumor invasiveness. Some reports of series have not shown the same correlation between Ki-67 LI and invasiveness.12,28,59,60 Reductions in E-cadherin and β-catenin expression, complexes that regulate cellular adhesion and motility,
have also been related to tumor invasiveness. Polysialylated neural cell adhesion molecules, which have been implicated in the regulation of cell growth and migration, were studied in 82 pituitary lesions. They were not found in the normal pituitary gland, but were expressed in 46.3% of typical pituitary tumors and 85% of tumors selected as highly aggressive, including one carcinoma and three tumors with histological characteristics that raised the suspicion of malignancy. These changes were independent of Ki-67 LIs.

The Ki-67 LI and Recurrence of Pituitary Adenomas

Because the Ki-67 LI represents the proliferative rate of tumors, many studies have been performed to correlate this LI with tumor recurrence. Shibuya, et al., compared the Ki-67 LIs of primary and recurrent pituitary adenomas and demonstrated that recurrent adenomas have a higher Ki-67 LI than primary ones. Subsequent studies have contained follow up of patients over time to verify if the rate of recurrence would be influenced by the Ki-67 LI. Abe and colleagues reported significantly more tumor re-growth in patients with a Ki-67 LI higher than 1.5%. Miyagami, et al., periodically observed 97 patients with pituitary adenomas for longer than 5 years and showed that recurrent tumors had higher Ki-67 LIs (2.5%) than nonrecurrent tumors (1%). Confirming these data, high Ki-67 LIs also have been correlated with shorter progression-free survival rates, as well as with tumor recurrence and tumor-related visual defects. Among secreting pituitary adenomas, adrenocorticotropic hormone-secreting tumors reportedly tend to have higher Ki-67 LIs and are more prone to recur. On the other hand, in many series no correlation between Ki-67 LI and recurrence has been demonstrated.

We understand that adequate follow up is necessary to identify the predicted recurrence of a tumor as early as possible. Although the Ki-67 LI does not seem to provide independent information to predict tumor recurrence, it does appear to provide valuable prognostic information. A high Ki-67 LI might suggest the need for more frequent clinical and neuroimaging follow up, and may guide other aspects of the overall therapeutic strategy.

The Ki-67 LI and Pituitary Carcinomas

Pituitary carcinomas are defined as pituitary tumors with subarachnoid, brain, or systemic metastasis. Thapar and colleagues have demonstrated in two consecutive studies that malignant and invasive tumors exhibit much higher Ki-67 LIs than benign adenomas and also exhibit a strong correlation with p53. Analysis of metastases from pituitary carcinomas has shown that these lesions usually have a much higher Ki-67 LI than the original pituitary lesion. A study of 15 cases of pituitary carcinomas has shown that the mean Ki-67 LI was 2.6% in primary and 11% in metastasizing lesions.

Pituitary carcinomas have significantly higher mean Ki-67 LIs, but there are exceptions and the LIs vary from 0 to 21.9%. This suggests that pituitary carcinomas are heterogeneous with respect to proliferative activity and, although assessment of proliferation helps predict a tendency toward invasiveness and/or malignant potential, growth rate is probably not the only major determinant of tumor behavior and carcinogenesis.

CONCLUSIONS

We agree that the Ki-67 LI represents an additional piece of information that is helpful for clinical decision making. An adenoma with a high Ki-67 LI has an-
creased risk of early recurrence, and may need to be care-
fully periodically observed or treated with radiotherapy.
Because of the overlap of Ki-67 LI s, particularly in those
adenomas with moderate growth velocity, the prognosis
cannot be predicted on the basis of the Ki-67 LI alone.

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