

## Correlation of Clinical and Immunohistochemical Diagnosis in Patients with Pituitary Adenomas

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**Objective :** Pituitary adenomas are common neurological lesions believed to account for 10% to 15% of all primary brain tumors. There can be diagnostic confusion due to discordance of the preoperative endocrine and the postoperative immunohistochemical diagnosis. In this study, the rate of discordance between preoperative and postoperative findings and their clinical implications were investigated.

**Methods :** From March 2005 to March 2006, 26 patients who underwent surgery for a pituitary adenoma were enrolled in this study. The preoperative pituitary hormone level and postoperative immunohistochemical results were compared and analyzed.

**Results :** The median age of the patients was 38 years (range 15-66 years). The male to female ratio was 8 to 18. The endocrine evaluation showed 16 hormonally-active and 10 hormonally-inactive adenomas. The immunohistochemical findings showed : 13 prolactin-positive, 1 GH-positive, 1 FSH-positive, 8 pleurihormone-positive and 3 stain-negative adenomas. The percentage of discordance observed between the preoperative endocrine and postoperative immunohistochemical diagnosis was 54%. Nine of 10 endocrine non-functioning adenomas showed : 3 PRL positive, 1 GH positive, 2 PRL+GH positive, 1 TSH+FSH positive, 1 FSH+ACTH+PRL positive and 1 FSH+LH+PRL positive adenomas by immunohistochemistry. Three endocrine PRL+GH secreting adenomas showed 2 PRL positive and 1 FSH+GH positive by immunohistochemistry. One endocrine PRL secreting and 1 GH secreting adenoma showed 1 PRL+TSH positive and 1 GH+PRL positive by immunohistochemistry, respectively. The diagnosis of the other 12 pituitary adenomas showed concordance.

**Conclusion :** The results of this study showed 54% discordance rate between the preoperative endocrine and postoperative immunohistochemical diagnosis for pituitary adenomas.

**KEY WORDS :** Pituitary adenoma · Pituitary hormone · Immunohistochemistry · Correlation.

### Introduction

Pituitary adenomas are common neurological lesions and have been reported to account for 10% to 15% of all primary brain tumors<sup>1,6,12</sup>. They present with symptoms associated with the secretion of hormones as well as the mass effect itself. Surgery for such tumors is approached with either the transcranial or the transsphenoidal technique based on the size, shape, extrasellar extension, age and general condition of the patients.

The normal adenohypophysis is composed of five different cell types : lactotrophs, somatotrophs, corticotrophs, thyrotrophs and gonadotrophs, each functionally distinguished by their capacity to secrete prolactin (PRL), growth hormone (GH), insulin-like growth factor-1 (IGF-1), adenocorticotrophic

hormone (ACTH), thyroid-stimulating hormone (TSH) and gonadotrophins (luteinizing hormone, LH and follicle-stimulating hormone, FSH). Pituitary adenomas potentially develop from any of these cell types; the adenoma will have the histopathological characteristics of the origin cell type as well as the hormone secretion of that cell type.

The diagnosis of adenomas has demonstrated discordance between clinical and pathological findings. For example, clinically non-secretory pituitary adenomas have at times been diagnosed as hormone-secreting pituitary adenomas by pathologic, immunohistochemical and electron microscopic examination. It has been suggested that treatment should be determined based on clinical symptoms rather than immunohistochemical results. However, there are limited studies of this discordance and the implication for clinical management.

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Therefore, this study was undertaken in order to better understand the rate of discordance between preoperative clinical and postoperative immunohistochemical diagnosis and thereby improve patient management.

### Materials and Methods

From March 2005 to March 2006, we recruited 26 patients who underwent surgery for pituitary adenomas. We evaluated age, gender, clinical manifestations, preoperative and postoperative hormone levels, surgical technique, the extent of removal, immunohistochemical findings and clinical outcome.

Preoperatively, the laboratory study of hormones by enzyme immunoassay (EIA) was performed and the tumors were divided endocrinologically into active and inactive pituitary adenomas. Endocrinologically active pituitary adenomas were classified into : prolactin, GH, ACTH, TSH and FSH/LH secreting adenomas. Postoperatively, immunohistochemical analysis is a standard step in the pathological evaluation and classification of every pituitary adenoma. The immunohistochemistry was performed using the battery of antisera directed against all anterior pituitary hormone products (GH, PRL, ACTH, TSH, FSH, LH)<sup>6,12</sup>.

### Results

Twenty-six patients with pituitary adenoma underwent surgery. The median age of the patients was 38 years (range 15-66 years). The male to female ratio was 8 to 18. Surgery via the transsphenoidal approach was performed in 23 patients and via the transcranial approach in 3. Tumors were totally removed except for three patients who had cavernous sinus encasement.

There were 10 patients with inactive and 16 with active pituitary adenomas by endocrine assessment. Among the endocrinologically active pituitary adenomas, there were 9 patients with PRL secreting, 3 with GH secreting, 1 with FSH secreting, and 3 pleurihormone secreting adenomas (Table 1).

There were 3 patients with negative and 23 with positive

**Table 1.** Preoperative endocrine status of 26 pituitary adenomas

Secreting hormone	No. of Patient
Hormonally inactive	10
Hormonally active	
PRL	9
GH	3
FSH	1
Pleurihormone(PRL+GH)	3
Total	26

PRL : prolactin, GH : growth hormone, FSH : follicle-stimulating hormone

immunohistochemical staining pituitary adenomas. Among the positive staining tumors there were 13 patients who were PRL positive, 1 GH positive, 1 FSH positive and 8 pleurihormone positive adenomas (Table 2).

There were 14 out of 26 (54%) patients discordant for endocrine and immunohistochemical study. The discordant cases were characterized by 9 endocrinologically non-functioning, 1 GH secreting and 1 PRL secreting and 3 PRL+GH secreting adenomas (Table 3, Fig. 1, 2).

Patients were followed for a mean of four months for hormone levels. Preoperatively elevated hormone levels were normalized except in four patients after 23 operations with total removal (87%) and in two patients after three operations with subtotal removal (33%).

### Discussion

The pituitary gland is a common anatomical substrate for neoplastic transformation, giving rise to approximately

**Table 2.** Immunohistochemistry of pituitary adenomas

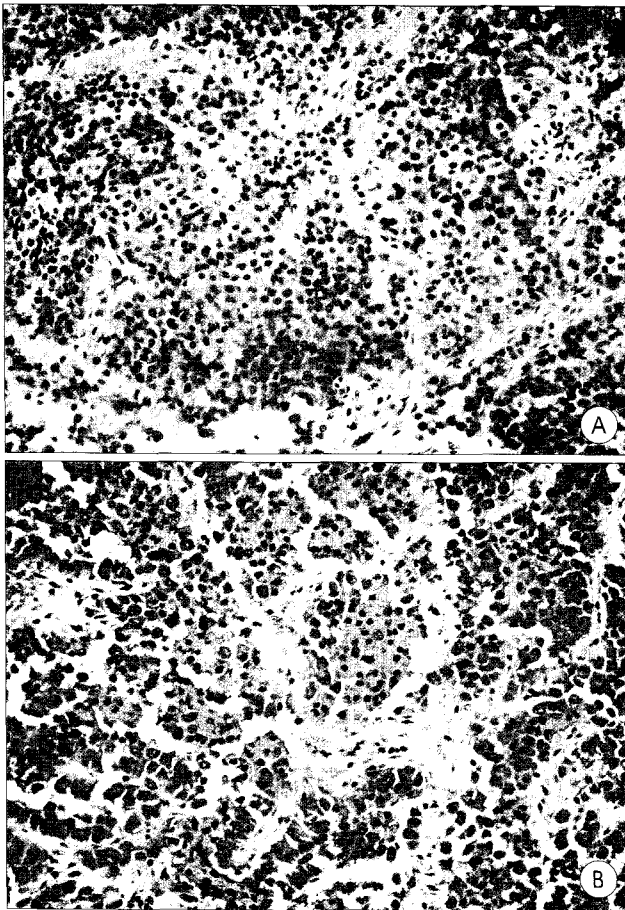
Immunohistochemical stain	No. of Patient
Negative stain	3
Positive stain	23
PRL	13
GH	1
FSH	1
PRL+GH	3
PRL+TSH	1
GH+FSH	1
TSH+FSH	1
PRL+FSH+ACTH	1
PRL+FSH+LH	1
Total	26

PRL : prolactin, GH : growth hormone, FSH : follicle-stimulating hormone, TSH : thyroid-stimulating hormone, ACTH : adenocorticotrophic hormone, LH : luteinizing hormone

**Table 3.** Discordance of diagnosis between endocrine study and immunohistochemical evaluation

Endocrinologic diagnosis	Immunohistochemical diagnosis	No. of patient
Hormonally inactive	PRL	3
	PRL+GH	2
	GH	1
	TSH+FSH	1
	FSH+ACTH+PRL	1
	FSH+LH+PRL	1
PRL	PRL+TSH	1
	GH+PRL	1
	PRL+GH	2
	PRL+GH	1
	FSH+GH	1
	Total	14

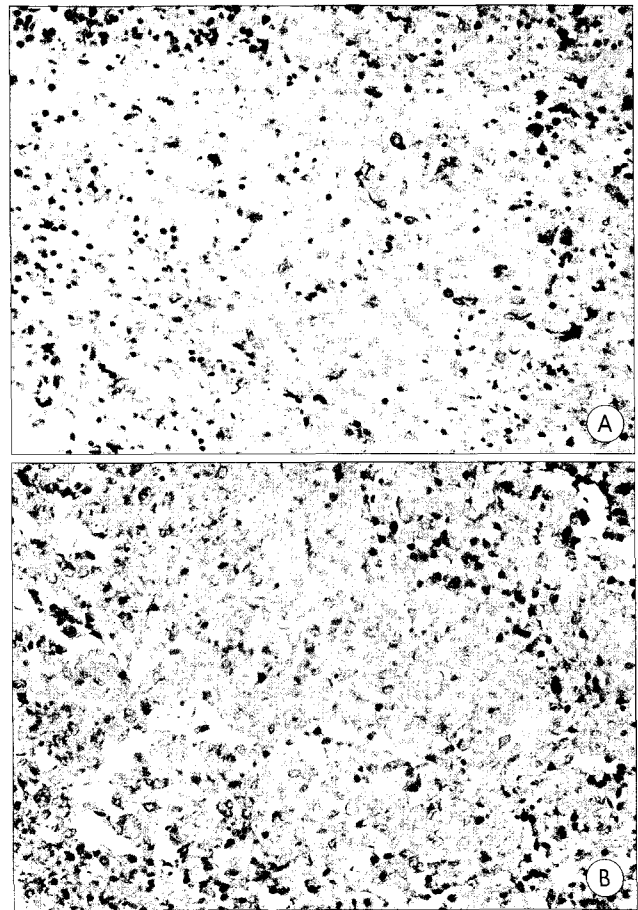
PRL : prolactin, GH : growth hormone, TSH : thyroid-stimulating hormone, FSH : follicle-stimulating hormone, ACTH : adenocorticotrophic hormone, LH : luteinizing hormone



**Fig. 1.** Immunohistochemistry of illustrative case : Positive immunohistochemical stains for growth hormone (A) and prolactin (B) in hormonally inactive pituitary adenoma (Original magnification x 100).

10-15% of all primary intracranial tumors<sup>6,12</sup>. Developing from the hormone-secreting cells of this anterior lobe of the pituitary, the overwhelming majority of pituitary tumors are histologically benign adenomas. Although many pituitary adenomas exhibit varying degrees of local invasiveness, few demonstrate the metastatic capacity needed to merit a diagnosis of pituitary carcinoma<sup>4,12</sup>.

Pituitary adenomas have been classified histologically on the basis of cytoplasmic staining affinities into categories of acidophilic, basophilic and chromophobic<sup>10,11</sup>. Although this classification is appealing because of its simplicity and availability, it provides little information concerning the function of a pituitary adenoma as an endocrine tumor<sup>10</sup>. Immunohistochemistry provides valuable information on hormone content; 60% of surgical specimens of pituitary adenomas contain one hormone, about 15% are bihormonal, 15% are plurihormonal and less than 15% are hormone negative<sup>9</sup>. Although immunohistochemistry has been shown to be useful for classification it should be used in the context of other information as it does not reflect the structure of the tumor<sup>6</sup>. Immunohistochemical analysis is an essential



**Fig. 2.** Immunohistochemistry of illustrative case : Positive immunohistochemical stains for follicle-stimulating hormone (A) and growth hormone (B) in hormonally prolactin and growth hormone secreting pituitary adenoma (Original magnification x 100).

step in the pathological classification for all pituitary adenomas<sup>12</sup>. Using a battery of antisera directed against all anterior pituitary hormone products (GH, PRL, ACTH, TSH, FSH, LH), immunohistochemistry is both a reliable and powerful method for determining the hormonal content of tumor cells. Generally a positive correlation exists between the tumor immunoprofile and the type of hormones produced by the tumor<sup>5,12</sup>.

However, there are reports where immunohistochemical evaluations have not been helpful. There are a variety of clinical and pathological situations where pituitary lesions may result in discordance between the clinical and pathological findings. In this study we identified discordance in 54% of patients. There are several possible causes for the discordance; where the tumor was positive by immunohistochemistry, but not found to secrete hormone; non-PRL secretion when the tumor showed positive immunohistochemistry due to a focal positive stain and cross reactivity to immunohistochemistry is possible. In cases with high prolactin levels and negative immunohistochemistry, PRL cell hyperplasia and a stalk

effect should be considered. Glycoprotein alpha-subunit production in corticotroph tumors and somatostatin receptor subtype in nonfunctioning adenomas may be the cause of the discordance<sup>3,8)</sup>.

Hormonal effects are reflected by patient symptoms not by immunohistochemistry. Therefore, for clinical management the endocrine diagnosis may be more important than the pathological diagnosis including immunohistochemistry. Thorough analysis of individual cases with diagnostic discordance may provide useful information for better understanding of endocrine disease and for appropriate treatments<sup>2,7,10)</sup>.

## Conclusion

In this study, we identified a discordance of 54% in the preoperative and postoperative findings of patients undergoing surgery for pituitary adenoma. Because patient's symptoms are results from hormones, the most useful data needed for patient treatment is preoperative hormonal study. Immunohistochemistry results may be less important in this regard. Therefore, precise endocrine evaluation is needed preoperatively due to the relatively high rate (54%) of discordance identified in this study.

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