Diagnostic Controversies in Pituitary Tumor Pathology

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M. Beatriz S. Lopes, MD, PhD

Division of Neuropathology

Department of Pathology

University of Virginia School of Medicine

Charlottesville, VA, U.S.A.
INTRODUCTION

Tumors of the pituitary gland and sellar region represent approximately 10–15% of all brain tumors [1]. Numerous types of tumors may involve the sellar region, reflecting its complex anatomy. Table 1 lists the most frequent tumors arising in the sellar and parasellar region. The most common tumors are, by far, the pituitary adenomas, benign epithelial tumors derived from cells of the adenohypophysis. In fact, pituitary adenomas represent the third most common primary intracranial tumor in neurosurgical practice, outnumbered only by gliomas and meningiomas [1]. Pituitary adenomas predominantly affect females between the third and sixth decades; however, no age group is spared [1]. Adenomas are uncommon in the pediatric population, but most tumors of childhood are clinically functioning adenomas and thought to be more aggressive [2]. Rates for pituitary tumors in the USA are slightly higher among blacks than whites [1]. Incidental adenomas can be found in nearly 10% of autopsied patients [3, 4].

Comparatively, primary tumors of the neurohypophysis are rare and in general are similar to primary tumors of the central nervous system. The neurohypophysis, however, is a common site for metastases [5].

In addition to tumors, a variety of non-neoplastic lesions may affect the pituitary gland, bringing a number of processes into the differential diagnosis of tumors involving this region.
TABLE 1 – Tumors and Tumor-Like Lesions of the Pituitary Gland and Sellar Region

| TUMORS OF THE ANTERIOR PITUITARY | - Pituitary Adenoma  
|                                  | - Atypical Adenoma  
|                                  | - Pituitary Carcinoma  
|                                  | - Spindle Cell Oncocytoma  |
| TUMORS OF THE POSTERIOR PITUITARY | - Pituicytoma  
|                                   | - Gangliocytoma  
|                                   | - Granular Cell Tumor  |
| TUMOR OF NON-PITUITARY ORIGIN     | - Craniopharyngioma  
|                                   | - Meningioma  
|                                   | - Chordoma  
|                                   | - Langerhans Cell Histiocytosis  
|                                   | - Metastases  |
| CYSTIC LESIONS                    | - Rathke’s Cleft Cyst  
|                                   | - Arachnoid Cyst  
|                                   | - Epidermoid/Dermoid Cyst  |
| INFAMMATORY LESIONS               | - Lymphocytic Hypophysitis  
|                                   | - Granulomatous Hypophysitis  
|                                   | - Sarcoidosis  |

TUMORS OF THE ANTERIOR PITUITARY GLAND

Pituitary Adenomas

1. Classification

Pituitary adenomas are classified clinically into two main groups: the *clinically functioning adenomas* and the *clinically non-functioning adenomas*, according to whether or not an endocrine syndrome is present. Most adenomas are functioning tumors and include PRL-
producing, GH-producing, ACTH-producing, and TSH-producing adenomas [6]. However, about a third of all pituitary adenomas are unassociated with either clinical or biochemical evidence of hormone excess [7]. In this group are included the gonadotroph-adenomas that produce FSH and LH, the less differentiated null-cell adenomas, and the silent adenomas. These clinically non-functioning adenomas commonly present with symptoms related to local mass effect such as headaches, neurologic deficits in the cranial nerves including visual field disturbances, and mild hyperprolactinemia due to pituitary stalk compression (the so-called stalk effect).

According to tumor size and gross anatomic features, adenomas are divided into microadenomas (tumors < 1cm in diameter) and macroadenomas (tumors ≥ 1cm in diameter). Giant adenomas (tumors > 4cm) rarely occur. Macroadenomas show an increased tendency toward suprasellar extension, gross invasion, and recurrence. A radiologic classification proposed by Hardy [8], is the most used in clinical practice.

A number of attempts to histologically classify pituitary adenomas have been made over the years. From the first morphologic classification proposed by Cushing in 1912 to the present time, pituitary adenomas classifications have aimed to combine the tumor morphologic aspects with the clinico-endocrinologic presentation of the patients. The recommended World Health Organization (WHO) classification from 2004 [9], which is now used by most laboratories, incorporates the clinical and radiological presentation of the tumor with its morphologic features, immunohistochemical profile, and ultrastructural appearance (Table 2). This classification has helped not just to understand further the cytogenesis of pituitary adenomas, but also to identify different tumor types that may present clinically with similar symptomatology.
Pituitary adenomas are classified according to the hormone content of the tumor cells as assessed by immunohistochemical stains. The immunohistochemical classification provides significant information for clinical practice [10]. However, immunohistochemistry alone does
not discriminate a number of specific subtypes of tumors which have prognostic clinical significance and, in these instances, analysis of the ultrastructure of adenomas is necessary [11].

The WHO classification employs updated lineage studies that result in new and appropriate clustering of a variety of tumor subtypes. This has changed our understanding not only of the pathogenesis of these tumors but also opens new avenues of pharmacological treatment, which hopefully will result in increasing levels of hormonal control. Additionally, potentially useful data with regard to oncogenes and the loss of tumor suppressor genes as pathogenic mechanisms for these tumors are provided, and continue to accumulate based on molecular biology studies, which extend to signal transduction processes and to the influence of a variety of transcription factors.

A few highlights of the new WHO classification include enhanced evidence that many of the non-secreting tumors that were formally classified as “null cell” tumors are actually derived from the gonadotroph family. There is continuing evidence that morphological features, including ultrastructure, e.g., the sparsely granulated growth hormone adenoma, the mammosomatotroph adenoma, the acidophil stem cell tumor and a variety of silent subtypes, may correlate with aggressive tumor behavior.

2. Grading

Perhaps the most controversial aspect of the new WHO classification is the introduction of a grading system for pituitary endocrine tumors. These tumors are now categorized in typical adenoma (8272/0), atypical adenoma (8272/1), and pituitary carcinoma (8272/3).
The majority of pituitary adenomas are typical with bland histological features, infrequent mitotic figures, and a Ki-67 proliferative index less than 3%. The designation of *atypical adenoma* is reserved for tumors that show histological features suggestive of aggressive clinical behavior. These adenomas are characterized by “atypical morphologic features suggestive of aggressive behavior such as invasive growth” [12]. In addition, other features seen in these tumors include elevated mitotic index, a Ki-67 labeling index greater than 3%, and extensive nuclear staining for the p53 protein by immunohistochemistry [12]. Close follow-up of patients with atypical adenomas is recommended.

Pituitary carcinomas are very rare, comprising less than 1% of all pituitary neoplasms [12-14]. By definition, pituitary carcinomas are characterized by demonstration of either craniospinal dissemination or systemic metastases [12]. The majority of cases are endocrinologically functioning tumors; the most common are PRL-secreting tumors, followed by ACTH-secreting [13, 14]. Non-functioning carcinomas constitute about 15-20% of the cases including gonadotroph, silent corticotroph, and rarely null cell carcinomas [13, 14].

There are no morphologic criteria to distinguish locally aggressive or even markedly atypical adenomas from carcinomas when the tumor is confined to the sella turcica. Standard morphologic features associated with malignancy including hypercellularity, nuclear and cellular pleomorphism, increased mitotic activity, necrosis, and dural/bony invasion are commonly present but are not necessarily diagnostic of carcinoma. Ki-67 labeling indices are quite variable and show considerable overlap with ordinary pituitary adenomas. However, they are often higher in metastatic deposits. Additionally, unlike pituitary adenomas, carcinomas appear to show overexpression of the p53 protein by immunohistochemistry [13].
3. Invasiveness and proliferative potential of pituitary adenomas

Pituitary adenomas either grow expansively or invade adjacent structures. In the first case, the tumors are usually small, well demarcated, and restricted to the sella turcica. Invasive adenomas usually have a more rapid growth rate, spreading into neighboring tissues such as the sphenoid sinus, the cavernous sinus and, in some cases, the brain [15, 16].

The mechanisms of progression of pituitary adenomas to more aggressive, invasive tumors are not yet totally understood. A proliferative continuum from benign adenoma to invasive adenoma and carcinoma has not been demonstrated in the great majority of tumors. The propensity of pituitary adenomas to infiltrate locally and invade adjacent structures appears to be independent of the histologic features of the tumors. Invasive adenomas do not necessarily show histologic features of tumor aggressiveness, including pleomorphism, nuclear atypia, and mitotic activity, as seen in atypical adenomas. Although both clinically functioning and non-functioning adenomas may present as invasive tumors, gross invasion appears to be more frequent in functioning tumors [15, 16]. On the other hand, there is an apparent relationship between invasiveness and tumor size in that macroadenomas have a higher frequency of invasion than microadenomas [15].

Studies of proliferative potential of pituitary adenomas have been applied as an adjuvant tool for distinguishing aggressive pituitary adenomas from the most common benign tumors [17]. These studies have revealed that the majority of tumors show a low growth fraction, with most Ki-67 indices being less than 3%. The mean growth fractions are significantly higher among invasive adenomas and pituitary carcinomas when compared with non-invasive
adenomas [17, 18]. Although these data may suggest that a significant correlation exists between Ki-67 labeling index and pituitary tumor invasiveness, a significant correlation between proliferative index and tumor recurrence has not yet been demonstrated [18].

Conclusions

One of the most important prognostic features of pituitary adenomas remains their hormonal profile and pathological subtype classification. It appears that the recognition of specific subtypes of adenomas that have a higher propensity for aggressive clinical behavior, including the sparsely granulated growth hormone adenoma, the densely granulated lactotroph adenoma, the silent type 3 adenoma and the silent corticotroph adenoma, in a systematic grading designation may assist in clinical management and understanding of the epidemiology of these tumors.

Nevertheless, there remain a number of areas of controversy with regard to the classification of pituitary tumors. Controversy exists with regard to the phenomenon of invasion of tissues surrounding the tumor, including the brain, the cavernous sinuses and the skull base. Although some studies have shown that invasion in and of itself did not correlate with recurrence or with poor outcome, it is a fact that most of the patients who die from pituitary tumors have invasive adenomas.
References


