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REVIEW ARTICLE

Novel aspects in histopathology of the pituitary gland☆

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Abstract The sellar and parasellar region is a complex anatomical area in which several diseases may develop. The pituitary gland may be affected by a wide range of conditions having similar clinical characteristics. Diagnosis of these lesions requires a multidisciplinary approach including, in addition to clinical, laboratory, imaging, and surgical findings, histological diagnosis of pituitary adenomas to guide therapeutic management. As the result of development in recent years of new immunohistochemical techniques, histopathological classification has become more complex and wide, and not only continues to be the gold standard in diagnosis, but also has prognostic implications. The aim of this review is to provide a clear and simple update of the main concepts of histological diagnosis of the most common pituitary conditions, especially for professionals in direct contact with such diseases.

PALABRAS CLAVE
Patología;
Tumor hipofisario;
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Aspectos novedosos en histopatología de la hipófisis

Resumen La región selar y paraselar es una área anatómica compleja en la que se pueden desarrollar una serie de enfermedades. La glándula hipofisaria puede verse afectada por una amplia gama de trastornos, que cursan con características clínicas similares. El diagnóstico de estas lesiones implica un enfoque multidisciplinar y, junto con la exploración clínica, analítica, radiológica y quirúrgica, el estudio histológico de los adenomas hipofisarios determina la conducta que tomará el médico especialista ante el paciente. Con la aparición, en los últimos años,

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de nuevas técnicas inmunohistoquímicas, la clasificación histopatológica se ha vuelto más compleja y amplia, ya que además de ser el *gold standard* del diagnóstico, tiene implicaciones pronósticas. El objetivo de esta revisión es actualizar conceptos del diagnóstico histológico de la patología hipofisaria más frecuente, de manera clara y fácil, especialmente para aquellos profesionales en contacto directo con este tipo de patología.

Introduction

The approach to the pathology of the pituitary gland and the sellar region is complex, because this area may be affected by many tumors and pseudotumoral lesions, and knowledge of multiple pathological conditions is therefore required. Tumors of the pituitary gland and sellar region account for approximately 15% of all brain tumors.[1] The vast majority of them are pituitary adenomas (PAs) (85%), followed by craniopharyngiomas (3%), Rathke cleft cysts (2%), meningiomas (1%), and metastases (0.5%). All other tumors are very rare lesions[2] that mimic PAs in neuroimaging studies, so that the final diagnosis should be made by the pathologist.

The development and widespread use of neuroradiological, computerized tomography, and magnetic resonance imaging studies has resulted in the increasingly frequent diagnosis of clinically silent pituitary lesions.[3–5] Magnetic resonance imaging (MRI) is currently considered the preferred modality for the diagnosis of pituitary lesions because of its capacity to examine multiple planes and because of the possibility of differentiating soft tissues based on contrast uptake. A focal hypointensity inside the pituitary gland is considered abnormal and suggests an adenoma.

Many pseudotumoral and tumoral types of lesions may affect the pituitary gland and the sellar region (developmental abnormalities, cysts, inflammatory, infectious, metabolic, and neoplastic diseases, and vascular disorders), reflecting the complex anatomy of this area. This review will focus on the histological diagnosis of the most common and relevant pituitary conditions.

Tumors of the adenohypophysis

General characteristics of pituitary adenomas

Incidental PAs may be found in approximately 10% of autopsies.[6–8] In a recent review of autopsy and MRI studies, the estimated overall prevalence of PA was 16.7%.[9] Primary tumors of the neurohypophysis are comparatively more uncommon, and usually similar to primary tumors of the central nervous system. However, the neurohypophysis is a common site for metastases.[10]

PAs are benign epithelial tumors derived from intrinsic cells of adenohypophysis. They occur in both sexes, predominantly between the third and sixth decades of life,[11] but may affect any age group.[1,12] Pediatric PAs are extremely rare, but when they do occur, they are usually ACTH-secreting adenomas.[13] PAs are not homogeneous; each subtype has its own clinical presentation, trend to invasion, hormone secretion pattern, histopathological characteristics, and treatment. The mechanisms involved in tumor genesis and progression are not yet well known.

Clinically, PAs are classified as functioning and non-functioning depending on whether or not there is a specific endocrine syndrome. Approximately one third of PAs are not associated with any clinical or biochemical evidence of excess hormones[14]; they are clinically non-functioning adenomas, usually presenting with signs and symptoms related to the local mass effect such as headache, neurological deficits of the cranial nerves (including visual field changes), and hyperprolactinemia. Hyperprolactinemia is due to pituitary stalk compression (the so-called ''stalk effect''), that prevents dopamine arrival to the adenohypophysis (and should not be misinterpreted by the pathologist as a prolactin-secreting adenoma).

Based on size and anatomical characteristics, adenomas are classified as microadenomas (<1 cm in diameter), macroadenomas (>1 cm to <4 cm), and giant adenomas (>4 cm). Radiographically, several classifications have been proposed to assess adenoma extension and local invasiveness. The Hardy and Knosp classifications are among those most commonly used.[15,16]

PAs are also classified histopatologically based on the hormonal content of tumor cells as shown by immunohistochemistry (IHC), which provides highly relevant information for clinical practice.[17] In this article, the classification of pituitary gland tumors published in 2004 by the World Health Organization (WHO) will be followed.[18]

Initial pathological assessment of pituitary lesions

The first decision to be taken when faced with a surgical specimen of the pituitary gland concerns whether the tissue submitted for analysis is a normal pituitary gland or a PA. For this, the most helpful histochemical stain after hematoxylin–eosin (HE) is the reticulin technique, which helps differentiate the preserved acinar pattern of normal adenohypophysis from the disruption of the reticulin network seen in PAs[19] (Fig. 1A). HE and other special histochemical procedures, such as the periodic acid-Schiff (PAS)-orange G technique (now considered obsolete and widely replaced by IHC), help visualize the variety of cell types with different cytoplasm staining characteristics (acidophilic, basophilic, or chromophobic) present in normal