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Pituitary tumors: Update on histopathological diagnosis

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Abstract

The majority of pituitary tumors are benign noninvasive adenomas. However, aggressive behavior is not uncommon, and the tumor often extends beyond the sellar region. Recently, the classification of pituitary adenoma (PA) in relation to aggressive lesions has been amended. The new edition of the World Health Organization recommends that major changes be made to the current classification of tumors of the adenohypophysis. It is thus the purpose of this review to provide the reader with a general overview of the changes that have been suggested. This includes a novel approach to classifying pituitary neuroendocrine tumors, the revision of the histological grading (in which the term "atypical" PA is discontinued), the redefinition of old entities and the introduction of new ones.

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Introduction

Tumors of the pituitary gland and sellar region constitute approximately 10–15% of all intracranial tumors. The majority of pituitary tumors are adenomas, benign neuroendocrine neoplasms confined to the sella turcica. Yet many types of lesions, including pseudotumoral and tumoral, may influence the pituitary gland and the sellar region, thus providing evidence that the anatomy of this area is quite complex.

Recently, the World Health Organization (WHO) published the updated fourth edition of tumor classification with regard to the pituitary gland [1]. This new edition presents several important changes, of which the most important are a revision in the classification of the tumors of the anterior pituitary gland, a redefinition of old entities, and a redescription of the new ones.

The goal of the present article is to provide a summary of these recommended changes along with a discussion of themes of particular importance. This review is not meant to be exhaustive. It does not touch upon histomorphological details of all kinds of tumors found in the WHO classification or of particular tumors that involve the region (since many of the latter have been the subject of the recent revised edition of the WHO Classification of Central Nervous System Tumors). The reader who wishes a broader discussion of these issues is referred instead to the "blue books" and other specialized literature on said topic.

Cornerstones of the new classification

The majority of tumors arising in the pituitary gland are pituitary adenomas (PA). For years, these have been classified based on their histopathological features, pituitary hormone content of the tumor cells determined by immunohistochemistry, and ultrastructural features [2]. According to the new WHO classification, the most significant revision concerns the pituitary adenohypophyseal cell lineage, which from now on is considered as the main framework guiding the classification of adenomas into the acidophilic lineage, the corticotroph lineage, and the gonadotroph lineage [3,4]. The main transcription factors with significance for pathologists' practice are the PIT1 (for acidophilic lineage), the TPIT (for corticotroph lineage) and the SF1 (for gonadotroph lineage). Given that the localization pattern of these transcription factors in human PA is similar to that of the normal pituitary cell differentiation, these factors have served as diagnostics tools for the characterization of PA [5–8]. However, with the introduction of this new concept, the organization of adenomas in the new 2017 WHO classification is now governed by their pituitary cell lineage rather than a hormone-producing PA. Using the main cell lineages of differential as a guiding framework, the designations for adenomas are the following: lactotroph adenomas, somatotroph adenomas, thyrotroph adenomas, corticotroph adenomas, gonadotroph adenomas, and finally null-cell adenomas (the type of adenomas for which the cell lineage is still not established). A more detailed subclassification in morphological variants is based on specific histological and immunohistochemical features. This newly introduced classification is valuable not only as a source of clear information for diagnosis

implementation, but also as an additional prognostic value for a treating clinical team.

Relevant features of some specific types of PA

The introduction of markers such as, for example, transcription factors, which are capable of more specific cell lineage differentiation led to new evidence for better discrimination of "weakly immunoreactive" or "hormone-immunonegative" adenomas from adenomas with lack of cellular differentiation (i.e., null-cell adenomas). This, in turn, gave rise to a new definition of null-cell adenomas in the 2017 WHO classification. More specifically, these adenomas are now defined as adenomas that have no immunohistochemical evidence whatsoever of cell-type-specific differentiation when adenohypophyseal hormones and pituitary transcription factors are used. Of note, when adopting these new criteria, the number of adenomas diagnosed as null-cell adenoma decreased substantially, and only relatively few remained diagnosed as such [9]. Thus, these tumors are likely candidates for a diagnosis of exclusion from other rare neuroendocrine tumors that can be found in the sellar region, including paragangliomas (indistinguishable from a nonfunctioning PA on imaging) or secondary tumors (metastatic neuroendocrine tumors), with addition of other more specific immunomarkers, including tyrosine hydroxylase and dopamine beta-hydroxylase [10–12]. The use of tyrosine hydroxylase is particularly noteworthy when distinguishing a keratin-negative null-cell adenoma.

A recommended change in plurihormonal adenomas by the new classification (an adenoma displaying more than one pituitary hormone expression, with exception of synchronous GH and PRL or β-FSH and β-LH expression) is the introduction of a new entity, the plurihormonal PIT1-positive adenoma, previously called silent subtype 3 adenoma. The diagnosis of these adenomas is of great significance due to their intrinsic aggressive behavior and high degree of invasiveness, low rates of disease-free survival, and high propensity for recurrence [13,14].

Histological grading of pituitary neuroendocrine tumors

A great deal of attention in the new classification is devoted to histological grading of pituitary neuroendocrine tumors. The 2004 WHO classification suggests classifying adenomas into three categories that did not prove be effective for assessment of tumor behavior. Neuroendocrine tumors were split into typical adenoma, atypical adenoma, and carcinoma [2]. The diagnosis of pituitary carcinomas (extremely rare), whose process is based on the presence of cerebrospinal fluid and/or systemic metastasis (there are no histological features that can distinguish carcinoma from ordinary typical adenomas prior to metastasis), did not suffer any changes.

The question causing significant controversy in the 2004 WHO classification had to do with the so-called atypical adenomas as these were defined very vaguely; based on the detection of mitoses or expression of Ki-67 or p53 has proven to lack reproducibility and does not accurately predict recurrence or resistance to medical therapy [15]. For this reason, the incidence of atypical adenoma in the literature is relatively variable, ranging from 2.7% to 18% [15–21]. In light of the above, the term "atypical adenoma" was dropped in the 2017 WHO classification [22]. In addition, the new WHO classification of tumors does not provide a new classification by tumor grading as the emphasis now is on the evaluation of such tumor features as proliferation and invasion that both demonstrated a high degree of correlation with a more aggressive clinical behavior of tumors [15,19,23,24]. However, in this new classification no specific number of mitosis and Ki-67 cutoff value is recommended; it remains clear that just as there is no evidence that p53 immunostaining on a regular basis is useful, there are no specific recommendations for the practicing pathologist as to how to report these findings to the treating physician.

Following the WHO endocrine bluebook preparation, in November 2016 (in Annecy, France) the International Pituitary Pathology Club (a group of expert pathologists, endocrinologists, neurosurgeons and scientists created in 1981) suggested a reclassification of these tumors in line with the terminology already widely accepted in other neuroendocrine tumors (NETs). In particular, it was proposed to use the term "pituitary neuroendocrine tumors (PitNET)" [25], term that had previously been suggested by other authors [26].

After a great deal of discussion during WHO meetings as to whether tumor invasion should be included in the clinicopathological classification of neuroendocrine tumors or not, the consensus was not to include it in the pathological grading and classification of PA on the following grounds: (a) the definition of invasion can still be controversial and imprecise; and (b) pathologists often have no access to the invasion-related data derived from neuroimaging studies or surgeon's impression [27].

Another important recommendation from the updated WHO guidelines with regards to "grading" is to recognize adenomas that are more aggressive in their behavior no matter their histological grading [22]. Lactotroph adenoma in men [28,29], sparsely granulated somatotroph adenoma [30,31], the silent corticotroph adenoma [32–34], the Crooke's cell adenoma (a corticotroph adenoma variant composed in >60% of cells with ring-like deposition of cytokeratin called Crooke's change) [35,36] and the plurihormonal PIT1-positive adenoma (formerly known as silent subtype III pituitary adenoma) [13,14] represent these special variants of adenomas for which clinical behavior was shown to be more