Atypical adenoma

The 2017 World Health Organization classification of tumors of the pituitary gland, changes include the following: (1) a novel approach for classifying pituitary neuroendocrine tumors according to pituitary adenohypophyseal cell lineages; (2) changes to the histological grading of pituitary neuroendocrine tumors with the elimination of the term atypical adenoma.

The 2004 World Health Organization classification introduced atypical pituitary adenoma (aPA), which was equivocally defined as invasion with increased mitotic activity that had a Ki67 labeling index (LI) greater than 3%, and extensive p53 immunoreactivity. However, aPAs that exhibit all of these features are rare and the predictive value for pituitary adenoma recurrence remains uncertain.

Atypical pituitary adenomas were relatively more malignant lesions defined by WHO criteria. However, not all of them show clinically aggressive behavior. Thus, the current WHO criteria of atypical adenoma didn't seem to be enough to distinguish clinically aggressive adenoma.

One hundred and sixty-seven cases of surgically resected PA or aPA were retrieved from 2011 to 2013 in Seoul St. Mary's Hospital. Among them, 28 cases were confirmed to be recurrent, based on pathologic or radiologic examination. The pathologic characteristics including mitosis, invasion, Ki-67 LI and p53 immunoreactivity were analyzed in relation to recurrence.

Analysis of the pathologic features indicated that only Ki-67 LI over 3% was significantly associated with tumor recurrence (p=.02). The cases with at least one pathologic feature showed significantly higher recurrence rates (p<.01). Analysis indicated that cases with two pathologic features, Ki-67 LI over 3% and extensive p53 immunoreactivity 20% or more, were significantly associated with tumor recurrence (p<.01).

Based on these results, PA tumor recurrence can be predicted by using mitosis, invasion, Ki-67 LI (3%), or extensive p53 immunoreactivity (≥20%). Assessment of these features is recommended for PA diagnosis for more accurate prediction of recurrence [1)].

Based on a case-control study using a representative cohort of typical pituitary adenomas and APAs selected from the German Pituitary Tumor Registry, Miermeister et al. aimed to obtain reliable cut-off values for both p53 and the mitotic index. In addition, we analyzed the impact of all four individual parameters (invasiveness, Ki67-index, p53, mitotic index) on the selectivity for differentiating both adenoma subtypes.

Of the 308 patients included in the study, 98 were diagnosed as APAs (incidence 2.9 %) and 10 patients suffered from a pituitary carcinoma (incidence 0.2 %). As a control group, we selected 200 group matched patients with typical pituitary adenomas (TPAs). Cut-off values were attained using ROC analysis.

They determined significant threshold values for p53 (≥2 %; AUC: 0.94) and the mitotic index (≥2 mitosis within 10 high power fields; AUC: 0.89). The most reliable individual marker for differentiating TPAs and APAs was a Ki-67-labeling index ≥ 4 % (AUC: 0.98). Using logistic regression analysis (LRA)

we were able to show that all four criteria (Ki-67) ($p < 0.001$); OR 5.2 *p53 ($p < 0.001$); OR 3.1* mitotic index ($p < 0.001$); OR 2.1 invasiveness ($p < 0.001$); OR 8.2)) were significant for the group of APAs. Furthermore, we describe the presence of nucleoli as a new favorable parameter for TPAs ($p = 0.008$; OR: 0.4; CI95 %: 0.18; 0.77).

Here we present a proposed rectification of the current WHO classification of pituitary tumors describing an additional marker for TPA and specific threshold values for p53 and the mitotic index. This will greatly help in the reliable diagnosis of APAs and facilitate further studies to ascertain the prognostic relevance of this categorization [2].

Case series

26 cases were identified as clinically aggressive pituitary adenoma. Clinically aggressive lesions were more likely to be functional (46.2% vs. 17.4%, $p = .0388$) and be detected in males (65.4% vs. 21.7%, $p = .0037$). Clinically aggressive adenomas also had higher Ki-67 index [5.0 (5.3)% vs. 4.1 (1.3)%, $p = .0011$] and presented bigger tumor size [11.83 (11.95) cm3 vs. 5.39 (6.08) cm3, $p = .0174$]. In multivariate analysis, gender ($p = .017$), functional status ($p = .009$) and Ki-67 index ($p = .024$) were independent predictors of clinical aggressiveness. Further analysis revealed that Ki-67 index of more than 4.45% was associated with worse progression-free survival.

Gender, functional status, tumor size and Ki-67 index ≥4.45% were associated with clinical aggressiveness. A clinicopathological classification of pituitary adenomas may be useful to determine who should be under closer radiological follow-up or followed multimodal treatment strategy [3].

Atypical pituitary adenomas: clinical characteristics and role of Ki-67 and p53 in prognostic and therapeutic evaluation. A series of 50 patients [4].

1)
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