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EDITORIAL

Agressive pituitary tumours: A diagnostic and therapeutic challenge for multidisciplinary pituitary units☆

Tumores adenohipofisarios agresivos: Reto diagnóstico y terapéutico para las Unidades Multidisciplinares de Excelencia en Patología Hipofisaria

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Iglesias P et al.[1] recently published a review of the multimodal treatment of aggressive pituitary tumors. After introducing the concept of aggressiveness based on clinical, radiographic, and histological criteria, they identified the subtypes of pituitary tumors most commonly related to an aggressive behavior and analyzed the pathological pathways involved in their development that justify the different therapeutic strategies used. They finally emphasized the need for multidisciplinary treatment of these tumors in centers of excellence that have the resources and experience to ensure the best possible results.

But are aggressive pituitary tumors well defined? Are they amenable to a therapeutic approach different to that for other pituitary tumors?

Adenopituitary tumors usually exhibit a benign behavior and have therefore been considered as adenomas. It has recently been proposed that they are called pituitary neuroendocrine tumors[2] because they share histological characteristics with extrapituitary neuroendocrine tumors. But clinical sectors in the neuroendocrinology field do not agree with this proposal of the International Pituitary Pathology Club by just because of their indolent behavior.[3] However, some of these tumors relapse, compress adjacent anatomical structures, and metastasize. This raises two problems: 1. There must be specific criteria defining the concept of ''aggressiveness'' in pituitary tumors, and 2. An action plan for them should be established.

The 2004 WHO classification stratified three subcategories of pituitary adenomas based on the aggressiveness of their behavior: typical adenoma, atypical adenoma, and carcinoma. Atypical adenomas were defined based on pathological criteria only: high mitotic index, a Ki-67 proliferation rate greater than 3%, and strong staining for p53. Over the subsequent 10 years, these criteria were shown to be inadequate because their prognostic significance could not be established. The 2017[4] WHO classification therefore excluded the atypical adenoma subtype. It admitted however the existence of high-risk pituitary tumors and maintained the recommendation to measure tumor prolif-

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eration markers as indicators of aggressiveness. But are these markers equally applicable to all subtypes of pituitary tumors? Are pathological criteria sufficient to define a pituitary tumor as aggressive?

Poorly granulated somatotropic tumors, lactotropic tumors in males, Crooke cell tumors, silent corticotropic tumors, and PIT-1 plurihormonal tumors are known to have a more aggressive behavior than all other subtypes of adenopituitary endocrine tumors. In fact, in 2014 Trouillas et al.[5] proposed a clinical-pathological prognostic classification based on tumor subtype and size and on a grading that considered the presence of radiographic invasion (magnetic resonance imaging) and tumor proliferation based on mitotic count and the strength of staining for Ki-67 and p53. A little later, Kovacs et al.[6] replied that the clinical-pathological classification proposed by Jacqueline Trouillas was not applicable to all tumors, stressing the need for a standardized and simplified classification that would allow pathologists not specialized in pituitary morphology to make a faithful diagnosis of pituitary tumors. The authors suggested that hematoxylin and eosine staining and immunostaining for adenopituitary hormones, low molecular weight cytokeratins, and the Ki-67 nuclear index were not sufficient. Finally, in 2018 the European Society of Endocrinology clinical guidelines[7] on aggressive pituitary tumors stated that the definition of aggressiveness of these tumors should be based on their clinical and radiographic presentation and on their behavior during follow-up (rapid growth, refractoriness to treatment, and tendency to relapse).

While the proposal to introduce clinical variables in the aggressiveness diagnostic equation is reasonable, the concept of ''rapid growth'' should be quantified. In the absence of consensus in the literature, it may be appropriate to use the RECIST criteria[8] to assess the growth of a pituitary tumor. According to this classification, an increase in tumor size of 20% or greater should be considered significant, and a 5 mm increase would have clinical and therapeutic connotations. However, 5 mm is excessive in the case of pituitary adenomas, and 2 mm increases appear more appropriate. To define ''growth'', the RECIST criteria use the lowest sum of tumor diameters at baseline. However, the irregular shape of pituitary tumors makes it difficult to identify the three smallest diameters. Luckily, it has recently been shown that the response of the largest diameter of a pituitary tumor to treatment correlates with volumetric response, and can be used in clinical practice.[9]

The concept of invasion should also be defined as accurately as possible. The invasion and aggressiveness criteria are sometimes mistakenly exchanged. On the one hand, there are widely invasive tumors with an indolent behavior. On the other hand, all aggressive tumors are invasive, and invasion is the most important clinical feature because it conditions complete surgical resection of the tumor and is associated to a greater likelihood of recurrence or relapse.[10] Invasion has historically been defined based on pathological, radiological, and surgical evidence. However, microscopic invasion of dura mater is present in most macroadenomas, as well as in some microadenomas, and is not correlated to tumor behavior after surgery. By contrast, there appears to be a good correlation between the invasion detected during endoscopic surgery and that established radiographically,[11] with these two parameters being possibly sufficient to define a pituitary tumor as invasive.

Finally, pathological markers of proliferation should be clearly established. The criteria in the 2004 WHO classification (Ki-67 > 3%, strong p53 staining, and increased mitotic activity) have not been prospectively validated in the clinical setting. In fact, different Ki-67 thresholds ranging from 3% and 10% have been proposed. However, although there are pituitary tumors with low Ki-67 indices showing an aggressive behavior, most of these have Ki-67 ratios greater than 10%, as compared to the Ki-67 levels of 1%–3% seen in slowly growing tumors. The recommendation to continue using this marker is therefore maintained. However, attention should be paid to the type of antibody used for its detection and the method to fix the preparation, and the estimate should be replaced by the absolute count, using for this the appropriate programs. The other proliferation indices, a mitotic count >2 and p53 staining intensity >10 nuclei per 10 fields, also have observer-related methodological limitations. A recent European Endocrine Society survey of 93 aggressive pituitary tumors and 34 carcinomas found Ki-67 values $\geq$3% in 81% and 85%, strong (>10) positivity for p53 in 73% and 78%, and mitotic counts >2 mitoses per 10 fields in 63% and 90% respectively.[12] Based on these findings, routine assessment of Ki-67 and the other two markers is recommended only when the index is $\geq$3%7.

The second question is whether aggressive tumors are amenable to a different therapeutic strategy than other pituitary tumors. Surely, yes. The presence of invasion and the tendency to relapse of these tumors makes it highly advisable that they be operated on by surgical teams of proven experience, and that repeat surgery is performed as often as required to reduce local compression symptoms. Adjuvant radiotherapy should not be delayed when tumor growth or hormone hypersecretion cannot be controlled by surgery. Finally, other medical treatments should be used, as these tumors are usually refractory to somatostatin analogues or dopamine agonists. Although specific cases of response to systemic chemotherapy, to inhibitors of the vasoendothelial growth factor (bevacizumab), the mTOR pathway (everolimus), or tyrosine kinase (lapatinib), and to peptide receptor radionuclide therapy agents (^{111}In-DTPA-octreotide, ^{177}Lu-DOTATATE, ^{177}Lu-DOTATOC,[13] 90Yttrium-DOTATE) have been reported, it is still recommended to use temozolamide alone as first-line chemotherapy.[7] Temozolamide was first used in 2006, and subsequent series have confirmed its efficacy, reporting disease stabilization rates in aggressive adenomas and carcinomas of 29% and 17.4% respectively after 5.5–120 months of follow-up.[14] These results have been supported by a recent survey by the European Endocrine Society.[12] However, it will be necessary to wait for the results with the immune checkpoint inhibitors CTLA-4 and PD-1, for which there have already been some reports.

In conclusion, according to Pedro Iglesias et al.,[1] not all pituitary tumors have an indolent behavior, and some of them pose a significant diagnostic and therapeutic challenge. This justifies the positioning of the Pituitary Society,[15] which recommends that a condition of such low prevalence but very high complexity be treated by units of excellence with proven experience in pituitary disease.

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