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Pituitary Adenoma to Pituitary Neuroendocrine Tumor (PitNET): An IPPC Proposal

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Pituitary Adenoma to Pituitary Neuroendocrine Tumor (PitNET): An International Pituitary Pathology Club Proposal

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Abstract

The classification of neoplasms of adenohypophysial cells is misleading because of the simplistic distinction between adenoma and carcinoma based solely on metastatic spread and the poor reproducibility and predictive value of the definition of atypical adenomas based on detection of mitoses or expression of Ki-67 or p53. In addition, the current classification of neoplasms of the anterior pituitary does not accurately reflect the clinical spectrum of behavior. Invasion and regrowth of proliferative lesions, and persistence of hormone hypersecretion cause significant morbidity and mortality. We propose a new terminology, pituitary neuroendocrine tumor (PitNET), which is consistent with that used for other neuroendocrine neoplasms and which recognizes the highly variable impact of these tumors on patients.

Since the early work of Minkowski who attributed acromegaly to a pituitary tumor (1), neoplasms composed of pituitary adenohypophysial cells have been recognized as the cause of significant illness. However, Harvey Cushing attributed the term "adenoma" even to patients who died of their disease (2).

We now recognize that these neoplasms are complex and heterogeneous; they present multiple clinical manifestations, including a wide range of proliferative and invasive behaviors (3). Some are slowly-growing small lesions that are clinically insignificant, some are small or large hormonally active lactotroph tumors that respond to medical therapy with shrinkage and reduced hormone secretion, while other small and minimally proliferative lesions cause the severe metabolic dysfunction of Cushing's disease or acromegaly. Many are large and invasive neoplasms that cause significant morbidity due to mass effects, with or without hormone excess syndromes. Traditional classifications only recognize malignancy, denoted as pituitary carcinoma, when there is evidence of distant metastasis or cerebrospinal spread (4). The attempt to classify a subgroup as "atypical adenomas" based on detection of mitoses or expression of Ki-67 or p53 (4) has proven to lack reproducibility and does not accurately predict recurrence or resistance to medical therapy (5). Recently, a clinicopathological classification with five grades identified Grade 2b tumors as those with a high risk of recurrence or progression (6;7). However, prediction of clinical aggressive behavior of these neoplasms, which occurs in approximately 10% of these tumors, remains debatable (8). The term "adenoma", which defines a tumor as benign, does not seem appropriate to define aggressive and invasive pituitary tumors that cannot be resected and are refractory to therapy.

Patients and healthcare providers have long expressed frustration that these lesions are considered rare, benign, and inconsequential. In most jurisdictions they are not reported in cancer

registries. Pituitary patients are often denied access to and/or health insurance coverage for therapies that would be provided for "cancers".

The International Pituitary Pathology Club, created in 1981, is a group of expert pathologists, endocrinologists, neurosurgeons and scientists who meet on a regular basis to discuss challenges and advances in the pituitary field. At the14th meeting in Annecy, France in November 2016, the subject of classification of these lesions was, as usual, controversial. However, there was consensus on one important aspect: pituitary endocrine neoplasms exhibit a spectrum of behaviors that are not entirely benign and can cause significant morbidity, even when they are not metastatic.

We therefore propose a reclassification of these tumors to apply terminology that has been widely accepted in other neuroendocrine tumors (NETs) (4). Pituitary hormone-producing cells are members of the family of neuroendocrine cells, similar to those of pancreatic islets, as well as dispersed endocrine cells of the gastrointestinal and respiratory tracts. Over the last two decades, there have been terminology shifts that reflect the potential for malignant behavior of even the most bland of those neuroendocrine neoplasms. They evolved from "adenoma" to 'tumor" to recognize the lack of predictability. We therefore propose that neoplasms of adenohypophysial cells be termed "pituitary neuroendocrine tumors".

Like other neuroendocrine neoplasms, many primary adenohypophysial tumors are indolent; they may be controlled by long-term pharmacologic treatment (e.g. dopamine-agonist therapy in the case of lactotroph tumors) or are non-invasive and cured by surgery. However, a variable proportion may recur despite remission. In addition, a large proportion (40%) is invasive into the cavernous or sphenoid sinuses or cranial bones and cannot be totally removed by surgery. Moreover, some are resistant to the multiple medical treatments available, and are

considered to be clinically "aggressive". The features distinguishing these behaviors are not entirely clear at this time and there is still no consensus on this matter. Moreover, there is no biomarker that can reliably predict malignancy as defined by metastatic spread. There is evidence that morphologic subtypes of pituitary neoplasms of the various cell lineages exhibit more aggressive behavior (8). It is also clear that invasive lesions which cannot be surgically resected are likely to result in considerable morbidity (7); some may require radiotherapy or are rapidly proliferative despite surgery, radiotherapy and/or medical therapy, requiring chemotherapy, for example temozolomide, or molecular targeted therapies. Accordingly, indications for novel therapies require elucidation of biomarkers that can guide personalized strategies.

This revision of nomenclature is not intended to negate the classification by morphologic cell type, but instead is intended to change the classification to "tumor" rather than "adenoma", for example, a "sparsely granulated somatotroph tumor" rather than "sparsely granulated somatotroph adenoma". The classification by morphologic cell type has been adopted by the World Health Organization (WHO) (4) and will remain in the next WHO classification that is underway. Although the new terminology of "tumor" replacing "adenoma" will not be incorporated in the 2017 WHO book, this change, as with previous terminologies that transitioned to "NETs", will be gradually adopted in order to be included in the next edition. We hope that clarification of additional appropriate biomarkers will ultimately allow further refinement of the classification of pituitary neuroendocrine tumors.

The authors of this statement feel strongly that the time has come to reclassify clonal adenohypophysial proliferations under the umbrella of "pituitary neuroendocrine tumor" (PitNET), a term that emphasizes the biological spectrum of these common endocrine

neoplasms. Importantly, by analogy with other NETs, we encourage tumor registries to capture data on these tumors, thereby assisting efforts to clarify clinical and pathological features that can appropriately guide patient management. Pituitary neuroendocrine tumors are not simply endocrine diseases, but should be considered as tumors with endocrine manifestations within the context of oncology.

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References

1. Minkowski O. Ueber einen Fall von Akromegalie. Berl Klin Wochenschr 1887; 24:371-374.
2. Cushing H. The basophil adenomas of the pituitary body and their clinical manifestations (pituitary basophilism). Bull Johns Hopkins Hosp 1932; 50:137-195.
3. Asa SL. Tumors of the Pituitary Gland. AFIP Atlas of Tumor Pathology, Series 4, Fascicle 15, Silverberg SG, editor. Silver Spring, MD, ARP Press, 2015.
4. DeLellis RA, Lloyd RV, Heitz PU, Eng C. Pathology and Genetics of Tumours of Endocrine Organs. Lyons, France: IARC Press, 2004.
5. Miermeister CP, Petersenn S, Buchfelder M et al. Histological criteria for atypical pituitary adenomas - data from the German pituitary adenoma registry suggests modifications. Acta Neuropathol Commun 2015; 3:50.
6. Trouillas J, Roy P, Sturm N et al. A new prognostic clinicopathological classification of pituitary adenomas: a multicentric case-control study of 410 patients with 8 years post-operative follow-up. Acta Neuropathol 2013; 126(1):123-135.
7. Raverot G, Vasiljevic A, Jouanneau E, Trouillas J. A prognostic clinicopathologic classification of pituitary endocrine tumors. Endocrinol Metab Clin North Am 2015; 44(1):11-18.
8. Asa SL, Ezzat S. Aggressive Pituitary Tumors or Localized Pituitary Carcinomas: Defining Pituitary Tumors. Exp Rev Endocrinol Metab 2016; 11(2):149-162.