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COMMENTARY

From Benign to Malignant: The Arrival of Pituitary Neuroendocrine Tumors (PitNETs)

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Pituitary adenomas were recently reclassified as "neuroendocrine tumors," and are now considered to be cancers. The evolution and justification for this change are described.Critical illness policies, which currently provide coverage of pituitary adenomas under the "Benign Brain Tumor" provision must now be modified to reflect this new taxonomy. This change also prompts questions about the use of the words 'benign' and 'tumor' in critical illness policies.

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WHY THE CHANGE?

In 1932, Cushing proposed the term "pituitary adenoma" to explain acromegaly. It still features in both the International Classification of Diseases (ICD) and the International Classification of Diseases-Oncology (ICD-O), and so clearly has withstood the test of time. However, expert groups have increasingly questioned its accuracy.[1,2] They point out that some adenomas are aggressive in nature, may invade local structures, and may recur, behavior that is uncharacteristic of adenomas. The experts also point out that the cells of the anterior pituitary are neuroendocrine cells. Thus, their neoplasms are more accurately described as pituitary neuroendocrine tumors (PitNETs). They propose that pituitary adenoma be abandoned in favor of PitNETs. And given their propensity to invade, PitNETs should be considered as cancers rather than benign tumors. Neuroendocrine neoplasias in other locations, such as the intestine, lung, and pancreas, are now called neuroendocrine tumors, replacing older terms such as carcinoids and islet cell tumors. The logic for these changes should extend to the pituitary. A more accurate classification of pituitary tumors will improve understanding of tumor behavior and will lead to improved diagnoses and outcomes.

THE CHANGE IS NOT UNIVERSALLY ACCEPTED

Not everyone agrees with this change.[4–6] Critics point out that pituitary adenomas are common, affecting 10% of the population. Fewer than 1% of these come to medical attention. Of those that do, most do not require surgical removal. They argue that the concern about aggressive pituitary adenomas is overstated; most pituitary adenomas are localized and do not invade adjacent structures. Of those surgically removed, a minority demonstrate aggressive behavior. Thus, to consider all PitNETs as cancerous lesions belies the benign nature of the majority. Lastly, they point out that neuroendocrine tissues in organs such as thyroid, parathyroid and ovary have not been reclassified in the same manner, as the advantages are unclear, a situation identical to that of the pituitary. Of further note, a recent clinical review of pituitary adenomas in a major medical publication made no mention of pituitary neuroendocrine tumors, suggesting that mainstream clinical medicine is not yet ready to adopt the new nomenclature.[7]

CLASSIFICATION CONFUSION

Further clouding the matter, there is inconsistency between disease classification systems. ICD-11 (2023) lists both "pituitary adenomas" and "pituitary neuroendocrine tumors." The former are classified under "adenomas, benign," whereas the latter appear under "adenocarcinomas, malignant."[8] This is an interesting dichotomy, given that the same pathology is being described. In ICD-Oncology (ICD-O-3, 1st revision) pituitary adenomas are listed under "adenomas" and are assigned a behavior code 0, signifying a benign process; pituitary neuroendocrine tumors are not listed.[9] In the WHO Classification of Tumors of the Central Nervous System (5th edition, 2021), both pituitary adenomas and pituitary neuroendocrine tumors appear under a single entry, "Pituitary adenoma/PitNET."[10] Both are assigned a behavior code of 3, indicating a malignant process, which is odd, as an adenoma, by definition is a benign tumor. Finally, in the WHO Classification of Endocrine and Neuroendocrine Tumors (5th edition 2022) the entry "PitNET/adenomas" appears under a category "anterior pituitary neuroendocrine tumors (PitNETs)," also with a behavior code of 3.[11]

TIME WILL SORT THIS OUT

At first flush, this seems chaotic and suggests widespread dissension amongst authorities. However, the likely explanation is that nomenclature changes are not widely adopted at the same time. In the world of oncologic pathology, new terms are introduced first in The WHO 'Blue Books' (the popular name for the volumes that contain the WHO Classification of Tumours), and are eventually incorporated into a version of ICD and ICD-O. This may take many years. However, of most relevance to critical illness insurers, pathologists—who are guided by the Blue Books—are now abandoning the term "pituitary adenoma" in pathology reports, in favor of "PitNET." And PitNETs are, by definition, cancers.

WHAT ARE THE IMPLICATIONS?

At present, a pituitary adenoma >10mm (ie, a macroadenoma) is eligible for payment under the Benign Brain Tumour category, if it requires surgery, or if it has caused a neurological deficit. In the future, a PitNET, being cancer while ineligible in the Benign Brain Tumour category, could be considered in the Cancer category. The definitions for both Benign Brain Tumour and Cancer will require modification to accommodate this change. In the interim, a claim for a PitNET <10mm could be submitted in the Cancer category, as no exclusion based simply on size currently exists in the latter. Nor is there a requirement for surgery or residual neurological deficit. This situation exemplifies the challenge of future-proofing critical illness definitions to avoid an unexpected increase in claims that result from updated diagnostic criteria.

BAFFLING TERMINOLOGY

The terminology problems in the category 'Benign Brain Tumour' do not stop here. Indeed, both "benign" and "tumor" cause confusion. A tumor that is histologically benign (WHO behavior code 0) yet invades the optic nerve or the cavernous sinus, is hardly benign. Likewise, a tumor that causes a permanent neurological deficit hardly merits such a label. The word tumor is also problematic. The National Cancer Institute describes it as "an abnormal mass of tissue that forms when cells grow and divide more than they should…"[12] A large arachnoid cyst or arteriovenous malformation would fit this description, yet it was never the intention of "Benign Brain Tumour" to include either of these processes. Not surprisingly, these nuances are lost on all but the most knowledgeable and lead to endless discussions during the adjudication of claims.

CONCLUSION

Changes in disease nomenclature are a constant challenge for the designers of critical illness policies. The PitNET one will not be the last. Diagnostic methods for cancer are undergoing momentous changes, as molecular techniques take hold. Repeated changes to the Cancer definition are inevitable. Awkward medical terminology will also continue to frustrate the refining of critical illness definitions. To minimize contentious claims, definitions should be in lockstep with medical progress and use terminology that is as unambiguous as possible. The updating of definitions is arduous work, and their widespread acceptance is far from assured. Critical illness insurance remains very much a work in progress.

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