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Pituitary Neuroendocrine Tumor: Is It Benign or Malignant?

Chae Heuck Lee

Department of Neurosurgery, Ilsan Paik Hospital, College of Medicine, Inje University, Goyang, Korea

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Correspondence
Chae Heuck Lee
Department of Neurosurgery,
Ilsan Paik Hospital,
College of Medicine, Inje University,
170 Juwha-ro, Ilsanseo-gu,
Goyang 10380, Korea
Tel: +82-31-910-7730
Fax: +82-31-915-0885
E-mail: chleens@paik.ac.kr

The World Health Organization (WHO) updated the classification of pituitary tumors in 2022. The new classification presents detailed histological subtyping of a pituitary neuroendocrine tumor (PitNET) based on the tumor cell lineage, cell type, and related characteristics. The immunohistochemistry for pituitary transcription factors (PIT1, TPIT, SF1, GATA3, and ERα) is routinely needed in this classification. The controversy regarding the change of behavior code of all PitNET/pituitary adenoma from "0" for benign tumors to "3" for primary malignant tumors is a topic of debate among experts, nowadays. Some authors represent that pituitary adenoma has a tendency for hemorrhage and necrosis and frequent invasion of the cavernous sinus. However, most small PitNET/pituitary adenoma do not need any treatment because of benign biologic behavior or less than 5% recurrence after gross total removal. Pituitary apoplexy is also benign nature but has a tendency of cranial nerve compression or panhypopituitarism. Most of cavernous invasion is compression of the cavernous sinus. Aggressive PitNET/pituitary adenoma with malignant biological behavior is less than 1%.

Keywords Pituitary gland; Neuroendocrine tumor; Pituitary adenoma.

INTRODUCTION

The 5th edition of the World Health Organization (WHO) classifications—2021 World Health Organization Classification of Central Nervous System Tumors and 2022 World Health Organization Classification of Endocrine and Neuroendocrine Tumors—has made significant changes to the classification of pituitary adenomas, the most common type of pituitary gland tumor as determined by expression of transcription factors, hormones, and other biomarkers [1,2]. In this paper, we will discuss the clinical, histopathological, and radiological disease character.

DEFINITION AND NOMENCLATURE CHANGE

Pituitary neuroendocrine tumor (PitNET)/pituitary adenoma is defined as a clonal neoplastic proliferation of the anterior pituitary hormone-producing cells [2], and the third most common tumor after meningiomas and diffuse glial tumors [3]. A major nomenclature change from the previous edition of the WHO classification is the transition from "pituitary adenoma" to "pituitary neuroendocrine tumor" (PitNET) [1]. Adenomas are benign, and it means a mass of cells (tumor) that does not invade neighboring tissue or metastasize (spread throughout the body). Compared to malignant (cancerous) tumors, benign tumors generally have a slower growth rate and relatively well-differentiated cells.

NEW (5TH EDITION) WHO CLASSIFICATIONS

A classification of the pituitary tumor has been changed to neuroendocrine tumors, rather than organ-specific classification [4]. In the WHO Classification of Central Nervous System Tumors, 5th edition released in 2021, "pituitary adenoma" was incorporated under the same entry as "PitNET." In the WHO Classification of Endocrine and Neuroendocrine Tumors 5th edition released in 2022, it is listed as "PitNET/pituitary adenoma." The adenohypophysis is composed of at least six normal cell types: somatotrophs, lactotrophs, mammosomatotrophs, and thyrotrophs are of PIT1 lineage, corticotrophs are of TPIT lineage, and gonadotrophs are of SF1 lin-

eage (Table 1) [1,5]. The pathological diagnosis should include pituitary neuroendocrine tumor, transcription factor (PIT1, TPIP, SF1), and the name of the cell from which it differentiated, such as "A well-differentiated pituitary neuroendocrine tumor composed of PIT1-lineage adenohypophysial cells with mammosomatotroph differentiation."

In the 5th edition, the behavior code for International Classification of Diseases for Oncology (ICD-O) was revised from "0" for benign tumors to "3" for primary malignant tumors as same to neuroendocrine tumors in other organs [1,2]. In the 3rd edition of ICD-O released in 2001, morphology code of pituitary adenoma was M8272/0 and pituitary carcinoma

Table 1. The 2022 WHO classification of PitNETs, 5th edition

PitNET type	Subtype	Transcription factors	Hormones	LMWK
PIT1-lineage PitNETs				
Somatotroph tumors	Densely granulated	PIT1	GH, α-subunit	Perinuclear
	Sparsely granulated	PIT1	GH	Fibrous bodies (>70%)
Lactotroph tumors	Sparsely granulated	PIT1, ERα	PRL (paranuclear dot-like)	Weak or negative
	Densely granulated		PRL (difuse cytoplasmic)	Weak or negative
Mammosomatotroph tumor		PIT1, ERα	GH (predominant), PRL, α-subunit	Perinuclear
Thyrotroph tumor		PIT1, GATA3	α-subunit, βTSH	Weak or negative
Mature plurihormonal PIT1-lineage tumor		PIT1, ERα, GATA3	Monomorphic tumor cells with predominant GH expression and variable PRL, βTSH, and α-subunit	Perinuclear
Immature PIT1-lineage tumor		PIT1, ERα, ATA3	Monomorphic tumor cells with focal/variable staining for no hormones, or one or more of GH, PRL, βTSH, and/or α-subunit	Focal/variable
Acidophil stem cell tumor		PIT1, ERα	Monomorphic tumor cells with PRL (predominant) and GH (focal/variable)	Scattered fibrous bodies
Mixed somatotroph and lactotroph tumor*		PIT1, ERα†	Somatotroph tumor component: GH±α-subunit depending on tumor subtype; lactotroph tumor component: PRL (diffuse or paranuclear depending on the subtype)	Tumor subtype characteristics
TPIT-lineage PitNETs				
Corticotroph tumors	Densely granulated	TPIT, NeuroD1(β2)	ACTH and other POMC Derivates	Strong, always diffuse
	Sparsely granulated			Variable (often diffuse)
	Crooke cell tumor			Intense ring-like perinuclear
SF1-lineage PitNETs				
Gonadotroph tumor		SF1, ERα, GATA3	α-subunit, βFSH, βLH, or none	Variable or negative
PitNETs without distinct cell lineage				
Plurihormonal tumor		Multiple combinations	Multiple combinations in a monomorphous tumor population	Variable
Null cell tumor		None	None	Variable

*These tumors are composed of two morphologically and immunohistochemically distinct tumor cell populations; †Positive in the lactotroph tumor component. PitNET, pituitary neuroendocrine tumor; LMWK, low molecular weight cytokeratin; PIT1, pituitary-specific positive transcription factor 1; GH, growth hormone; ERα, estrogen receptor α; PRL, prolactin; GATA3, GATA-binding protein 3; SF1, steroidgenoic factor 1; GATA, binding protein 3; TPIT, T-box family member TBX19; ACTH, adrenocorticotropic hormone; POMC, pro-opiomelanocortin; FSH, follicle-stimulating hormone; LH, luteinizing hormone

was M8272/3. In ICD-11 code released on January 2023, pituitary neuroendocrine tumor is classified into three different codes: 1) 2F37.Z benign neoplasm of endocrine glands, unspecified (pituitary gland); 2) 2F7A.Z neoplasm of uncertain behavior of endocrine glands, unspecified (pituitary gland); and 3) 2D12Z malignant neoplasm of other endocrine glands or related structures, unspecified (pituitary gland).

CONTROVERSY OF PitNET/PITUITARY ADENOMA

The WHO classification of pituitary tumors was updated in 2022. The new classification provides detailed histological subtyping of a PitNET based on the tumor cell lineage, cell type, and related characteristics [5]. The immunohistochemistry for pituitary transcription factors (PIT1, TPIT, SF1, GATA3, and ERα) is routinely needed in this classification.

The controversy regarding the change of behavior code of all PitNET/pituitary adenoma from "0" for benign tumors to "3" for primary malignant tumors is a topic of debate among experts, nowadays [6]. We neurosurgeons all know that there are few patients with multiple recurrences with malignant tendency or aggressive nature. Some authors noted that pituitary adenoma has a tendency for hemorrhage and necrosis, frequent invasion of cavernous sinus, and rare metastasis [7]. However, the biology of pituitary adenoma is clinically benign. An average prevalence of pituitary adenoma was reported to be 10% in a comprehensive review of 16 studies, more than 21,000 autopsies [8]. There are several studies that 10%−40% of normal volunteers have discrete pituitary lesions with brain MRI scan [9,10]. It means overall population prevalence of pituitary adenoma is about more than 10%. Recurrence rates were approximately 20%−50% after surgical resection of nonfunctioning pituitary adenoma over 10 years of follow-up periods but no mortality or overall survival was discussed because of benign biology of pituitary adenoma [11]. Most small PitNET/pituitary adenoma do not need any treatment because of benign biologic behavior or less than 5% recurrence after gross total removal. Pituitary apoplexy is also benign nature but has a tendency of cranial nerve compression or panhypopituitarism. Most of cavernous invasion is compression of the cavernous sinus. Melmed et al. [12] reported that fewer than one-thousandth of all pituitary adenomas cause clinically significant disease and cellular senescence acts as a mechanistic buffer protecting against malignant transformation, an extremely rare event. As a personal experience, I had only two (<1%) malignant progression cases over two hundred pituitary tumors in twenty years periods and no metastasis. Aggressive PitNET/pituitary adenoma with malignant biological behavior is less than 1%. Meningiomas also have a frequent invasion to cavernous sinus and venous sinus but behavior code of benign meningioma is M9530/0. Cranial schwannoma has a tendency for hemorrhage and invasion of cavernous sinus, but behavior code is M9560/0. So pituitary adenoma is more suitable for defining this disease since it originated from the anterior lobe of the pituitary gland and a large majority of the tumors are well-differentiated and benign neoplasms that do not adversely impact life expectancy [13,14].

Patients who have incidentally found tumor without symptoms might have a great psychological burden for the naming of malignant tumor. That malignant behavior code will occur many social, medical, educational, and legal problems especially with the insurance company in medical fields. And this classification system provides no additional treatment policy for neurosurgeons in clinical practice, especially in determining the treatment strategies, such as deciding the follow-up plans and adjunctive treatment.

CONCLUSIONS

The PitNET/pituitary adenoma is the most common pathology of the sellar lesion. The new classification from pituitary adenoma to PitNET based on the tumor cell lineage, cell type, and related characteristics is adjustable. The clinical biology of pituitary adenomas is particularly benign nature and very different from other tumors of the endocrine system, such as thyroid and other neuroendocrine tumors. So, the change of behavior code of all PitNET/pituitary adenoma from "0" for benign tumors to "3" for primary malignant tumors seems debatable. That malignant behavior code will occur many social, medical, educational, and legal fields.

Ethics Statement

Not applicable

Availability of Data and Material

Data sharing not applicable to this article as no datasets were generated or analyzed during this study.

ORCID iD

Chae Heuck Lee https://orcid.org/0000-0002-6008-1557

Conflicts of Interest

The author has no potential conflicts of interest to disclose.

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Comments to the editor

Yeon-Soo Lee
Department of Pahtology, The Catholic University of Korea, Seoul, Korea

Pituitary adenomas/PitNET arising in adenohypophysis express neuroendocrine proteins such as synaptophysin, chromogranin A, and CD56. Pituitary adenomas may be locally invasive and can metastasize. However, there are no morphologic features that distinguish locally invasive and metastatic lesions from benign tumor.

WHO unifies the pituitary adenomas to neuroendocrine tumors (NET) and change the nomenclature. This change in nomenclature is accompanied by a change in behavior coding that aligns with other NET such as gastrointerstinal tract.

The revolution of NET nomenclature and behavior code is proceeding according to WHO policy. All kinds of NET in the whole body have malignant potential, categorized as behavior code /3.