บทความพิเศษ

Pituitary adenomas : current classification*

Vira Kasantikul**

Kasantikul V. Pituitary adenomas : current classification. Chula Med J 1989 Aug; 33(8) : 569-574

The current functional classification of pituitary adenoma based on the immunohistochemical and electron microscopic investigation is reveiwed. Prolactinomas are found to be the most common pituitary adenomas while thyrotropic-cell adenoma is the rarest type. Growth hormone secreting adenomas are often associated with elevated serum growth hormone level and acromegaly or gigantism. Corticotropic-cell adenomas are usually microadenoma, in patients with Cushing's disease or Nelson's syndrome. Silent corticotroph adenomas are rare, often large and invasive. For the pathologists, gonadotropic adenomas are not as rare as for clinicians because tumors may be associated with normal or low serum gonadotropin level. The most common variant of plurihormonal adenoma produces GH and PRL. One morphologic cell type may secrete several hormones. The tumors are generally large and often demonstrate gross invasion. Nonfunctioning tumors show no immunostaining, although they are positive for chromogranin. Most tumors are large, often growing beyond the sella turcica. The recurrence rate is high.

Reprint request : Kasantikul V, Department of Pathology, Faculty of Medicine, Chulalongkorn University, Bangkok 10330, Thailand.
Received for publication. May 8, 1989.

* ได้รับทุนส่งเสริมอาจารย์ผู้อุทิศตนเป็นนักวิชาการของคณะแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย

** Department of Pathology, Faculty of Medicine, Chulalongkorn University.

วีระ กสานติกุล. อเดโนมาของต่อมใต้สมอง : การแบ่งชนิดในปัจจุบัน. จุฬาลงกรณ์เวชสาร 2532 สิงหาคม; 33(8) : 569-574

ได้ทบทวนการแบ่งชนิดอเดโนมาของต่อมใต้สมอง โดยวิธีการอิมมิวโนฮิสโตรเคมี และกล้องจุลทรรศน์อิเลคตรอน โปรแลคตินโนมา พบได้บ่อยที่สุดในขณะที่ไทโรโทรบิน อเดโนมาพบได้น้อยที่สุด. อเดโนมาที่สร้างโกรธฮอร์โมนมักพบในผู้ป่วยที่มีลักษณะของอโครเมกาลี หรือไจแกนติสม์ คอร์ติโคโทรป อเดโนมา มักมีขนาดเล็กในผู้ป่วยที่มีกลุ่มอาการของคุชิงหรือเนลสัน เนื้องอกชนิดนี้ในผู้ป่วยที่ไม่มีกลุ่มอาการดังกล่าว พบได้น้อย มักมีขนาดใหญ่และมักจะลุกลามไปยังเนื้อเยื่อข้างเคียง สำหรับพยาธิแพทย์แล้วเนื้องอกชนิดโกนาโดโทรปิค อเดโนมา มักพบได้บ่อยกว่าอายุรแพทย์ เนื่องจากเนื้องอกกลุ่มนี้อาจพบในผู้ป่วยที่มีระดับโกนาโดโทรบินในเลือดปกติหรือต่ำกว่าปกติได้ ชนิดเนื้องอกที่พบบ่อยที่สุดในกลุ่มเนื้องอกที่สร้างฮอร์โมนหลาย ๆ อย่าง ได้แก่ พวกที่สร้างโกรธฮอร์โมน และโปรแลคตินเซลล์เนื้องอกชนิดเดียวจึงอาจสร้างฮอร์โมนหลาย ๆ ชนิดได้ ในกลุ่มอเดโนมาที่ไม่ให้ฮอร์โมนใด ๆ มักจะมีขนาดใหญ่และลุกลามออกนอกแอ่งเซลลาเตอร์ซิกา อัตราการเป็นใหม่ของเนื้องอกชนิดนี้สูง

Pituitary adenoma is the most common tumor of the sellar region and often results from the localized growth of one, or less frequently, more than one type of cells from the anterior lobe. Most pituitary adenomas arise spontaneously. Exceptionally, they may be secondary to the absence or hyposecretion of the target organs such as thyroid or adrenal glands.[1,2] The previously established classification was based on the tinctorial characteristic of cell cytoplasm and categorized the tumors into chromophobic, acidophilic, and basophilic adenomas. Although simple, this classification has only limited value and is not satisfactory because it does not provide informations concerning structure-function relationship, as well as composition of tumors. The introduction of radioimmunoassay, electron microscopy (EM) and immunohistochemistry have resulted in striking progress, opening new avenues in clinical medicine as well as in pathology related to the pituitary adenomas. Both EM and immunocytochemistry have unravelled the ultrastructural characteristic and the specific localization of different hormones in the cell cytoplasm. A new classification thus has been developed that divided pituitary adneomas on the basis of their immunocytological and ultrastructural findings (Table).[3,6] This system has permitted correlation between morphology and endocrinological activity.

Table. Current Classification of Pituitary Adenomas.

Prolactin cell adenoma
densely granulated
sparsely granulated
Growth hormone cell adenoma
densely granulated
sparsely granulated
Corticotropic cell adenoma
endocrinologically active
endocrinologically inactive
Gonadotropic cell adenoma
FSH - cell adenoma
LH - cell adenoma
Thyrotropic cell adenoma
Plurihormonal adenoma
Nonfunctioning adenoma

Prolactin (PRL)-Cell Adenomas.

PRL-cell adenoma has become the most common adenoma in recent reports and in the author's experience of 90 cases at the Chulalongkorn Hospital.[3-6] The frequency ranges from 28% to 31%. The majority of PRL-cell adenomas in young women are often small while those in postmenopausal women and men are more likely to be large with parasellar extension and invasion[5] It can be explained by the fact that symptoms of amenorrhea, galactorrhea and infertility in young women will impel the patients to seek medical attention in the early phase of disease while in postmenopausal patients, such clinical features as well as impotence and libido in men may not be conspicuous until the tumors begin to cause compression symptoms such as visual disturbances or cranial nerve dysfunction. Histologically, the tumors are generally chromophobic, or slightly acidophilic. Ultrastructural, there are two variants including the rare densely granulated and the common sparsely granulated type. The large secretory granules (400-700 nm) occupy a considerable part of the cytoplasm in the former group.[5,6] In immunohistochemistry, two patterns of immunostaining can be distinguished. Densely granulated cells show a strong granular positivity. In sparsely granulated cells the positivity is restricted to the Golgi sacculi filled with an immunoreactive substance.

The malignant counterparts is extremely rare, although local invasion is fairly common. The latter is not indicative of malignancy and the diagnosis of PRL-cell carcinoma is justified only if subarachnoid and brain invasion or distant metastases are present.[7] Pituitary carcinomas may produce other hormones or may be clinically silent.[8,9]

Growth hormone (GH)-Cell Adenomas.

Tumors that produce GH represent approximately 10% to 14% of all pituitary adenomas.[10] They are often associated with elevated serum GH, acromegaly or gigantism. Large tumors are also accompanied by local symptoms such as visual disturbance, nausea and headaches. Grossly, the most characteristic finding is a well demarcated adenoma, frequently located in one of the lateral wing which is the main site for GH-cells. In rare instances, the adenoma is ectopic and can be detected in the sphenoid sinus or parapharynx which reflects the path of cell migration from Rathke's pouch in the pharynx to sella during embryogenesis.[11] Histologically GH-cell adnomas consist of densely granulated cells and sparsely granulated cells. The former tumor is acidophilic adenoma The cytopalsm shows intense staining with acidic dyes such as eosin, and orange G. The immunostaining demonstrates diffuse GH reactivity. By EM, the secretory granules, (300-600 nm) are numerous. The sparsely granulated cells are chromophobic tumors. By EM, the secretory granules (100-300 nm) are sparse. Some authors

have suggested that the sparsely granulated tumors exhibit a more rapid growth, are often operated on at an earlier age, and their recurrence rate appears to be somewhat higher.[12]

Corticotropic-Cell Adenomas.

This adenoma has long been described by Cushing as the cause of hypercortisolism.[13] Generally, correlation is excellent between the results of immunohistochemical study and clinical manifestations of functioning corticotroph adenomas. The tumors are often associated clinically with Cushing's disease or Nelson's syndrome. Several authors have reported the strong prevalence of microadenomas producing ACTH.[14,15] Microscopically, the tumor cells are often basophilic. Occasionally, some chromophobic adenomas have been described.[15] Most tumors display secretory granules not exceeding 400 to 500 nm. Immunohistochemical study reveals the presence of B-LPH. It should be noted that eucorticoid patients have been recently described. The data concerning such endocrine inactive are still insufficient. However in agreement with the findings of other investigators, the silent corticotroph adenomas are often large, and invasive.[3,10]

Gonadotropic-Cell Adenomas.

For the clinician, gonadotropic-cell adenomas associated with increased serum levels of gonodotropins are rare, but for the pathologist, the frequency of such tumors is higher than for the endocrinologist. From in vitro study, Mashiter has stated that 66% of functionless tumors secrete gonadotropin.[16] The systemic search for gonadotropin immmunoreactivity enables the pathologic diagnosis to be made in many nonfunctional adenomas.[10] Hence this type of adenoma does not seem as rare as the small number of clinical cases might suggest. The incidence varies from 4.1% to 10%.[10,13] This tumor makes up 11.1% of 90 pituitary adenomas obtained from Department of Pathology, Chulalongkorn Hospital.[3] The tumor has been reported most often in elderly men with a 2:1 male: female ratio.[10] Several authors have suggested that the tumor may be associated with normal or low serum level.[17,18] The tumors are often large, presenting with visual symptoms and inconstant secondary hypogonadism.

Histologically, the cells are often chromophobic and the arrangement is more often in cords but it may also be diffuse. Ultrastructurally, the secretory granules (50-250 nm) are usually scattered sparsely in the cytoplasm. Immunohistochemical study reveals that the tumor cells may secrete both FSH and LH, α and B FSH, or α -subunit alone. Tumor recurrence following previous external radiotherapy or craniotomy is noted with a frequency of 12%.[18]

Thyrotropic-Cell Adenomas.

This type of pituitary adenomas is the rarest tumor. Its frequency varies from 0.2% to 1.2%[19]. The lesion occurs more often in women than in men and the majority of reported examples are associated with either hypo-or hyperthyroidism.[10] More rarely it can occur in euthyroid patients.[20] The tumors are usually large with suprasellar extension but may be microadenomas.[21,22] Microscopically the cells are slightly basophilic, arranged in cords or diffuse. The ultrastructural secretory granules are small (60 to 110 nm).[19] The pathological diagnosis is supported by immunoreactivity with anti-thyrotropin antiserum.

Plurihormonal adenomas.

Early immunohistochemical studies have suggested that most pituitary adenomas produce single hormone. Current investigations have recognized that some tumors may engage in the elaboration of two or more hormones.[3,10,20] The application of immunocytochemical batteries directed towards the full spectrum of anterior pituitary hormones has resulted in the increasing recognition of plurihormonal tumors. The incidence varies from 10% to 15% of all pituitary adenomas.[23] The most common forms produce GH and PRL. There are three variants of GH-PRL cell adenomas which comprise a spectrum from biologically benign to aggressive lesions.[12] Firstly, the mixed GH cell-PRL cell adenoma is a bimorphic tumor composed of mature somatotrophs and lactotrophs, each secreting its respective hormone. Secondly, the mammosomatotroph adenoma is monomorphic tumor and consists of cells that produce both hormones. Thridly, the acidophil stem cell adenoma, the aggressive form, is a monomorphic-bihormonal tumor presumably derived from a common precursor cell of lactotrophs and somatotrophs. Most patients presents with either acromegaly or hyperprolactinemia or both. Occasionally authors have reported adenomas showing variable reactivity for gonadotropic, lactotropic, and thyrotropic components.[20,22] It should be noted that plurihormanal adenomas are more often macroadenomas and frequently demonstrate gross invasion.[10] The lesions may be ultrastructurally monomorphous, bimorphous, or trimorphous.[23] However, one morphologic cell type may elaborate several hormones.

Nonfunctioning Adenomas.

This term is applied to the pituitary adenomas that are not capable of producing detectable known hormones. They are also known as undifferentiated or null-cell adenomas. The incidence provided by various

series ranged from 15% to 50% of all pituitary adenoma.[3,4,24] Most tumors are large causing compression symptoms such as visual disturbance, headaches, or even seizures. Some tumors may provoke endocrine abnormalities such as hypopituitarism secondary to compression and/or destruction of the remaining pituitary gland. At surgery they have often shown evidence of extrasellar extension.[10] Histologically, the tumors are chromophobic or slightly acidophilic. They fail to demonstrate any known pituitary hormone in their cytoplasm. Martinez, however,has reported that most of the nonfunctioning adenomas are positive for chromogranin.[24] The tumors tend to recur. In a series of 100 cases, Ebersold et al have reported 17% of combined rate of clinical and radiographic recurrence over a 10-year-follow-up period.[25]

Acknowledgement

The author is in reciept of fund from Chulalongkorn University Faculty of Medicine, China Medical Board Scholar Development Fund.

References

1. Fatourechi V, Gharib H, Scheithauer BW, Meybody NA, Gharib M. Pituitary thyrotropic adenoma associated with congenital hypothyroidism. Am J Med 1984 Apr; 76(4) : 725-8
2. Scheithauer BW, Kovacs K, Randall RV. The pituitary gland in untreated Addison's disease : a histologic and immunocytologic study of 18 adenohypophyses. Arch Pathol Lab Med 1983 Sep; 107(9) : 484-7
3. Kasantikul V, Shuangshoti S. Pituitary adenomas : immunohistochemical study of 90 cases. J Med Assoc Thai (in press)
4. Mukai K. Pituitary adenomas. Immunocytochemical study of 150 tumors with clinicopathogic correlation. Cancer 1983 Aug; 52(4) : 648-53
5. Horvath E, Kovacs K. Pathology of prolactin cell adenomas of the human pituitary. Semin Diagn Pathol 1986 Feb; 3(1) : 4-17
6. Martinez AJ, Lee A, Moossy J, Maroon JC. Pituitary adenomas: Clinicopathological and immunohistochemical study. Ann Neurol 1980 Jan; 7(1): 24-36
7. Scheithauer BW, Randall RV, Law ER, Kovacs KT, Horvath E, Whitaker MD. Prolactin cell carcinoma of the pituitary; clinicopathologic, immunohistochemical and ultrastructural study of a case with cranial and exteranial metastases. Cancer 1985 Feb; 55(3) : 598-604
8. McCarty KS, Bredesen DE, Vogel FS. Neoplasms of the anterior pituitary. Neurosurgery 1978 Jul-Aug; 3(1) : 96-104
9. Queiroz L de S, Facure NO, Facure JJ, Modesto NP, de Faria JL. Pituitary carcinoma with liver metastases and Cushing Syndrome: report of a case. Arch Pathol Lab Med 1975 Jan; 99(1) : 32-5
10. Scheithauer BW, Kovacs KT, Laws ER, Randall RV. Pathology of invasive pituitary tumors with special reference to functional classification. J Neurosurg 1986 Dec; 65(6) : 733-44
11. Corenblum B, LeBlanc FE, Watanabe M. Acromegaly with an adenomatous pharyngeal pituitary. JAMA 1980 Apr 11; 243(14) : 1456-7
12. Kovacs K, Horvath E. Pathology of growth hormone-producing tumors of the human pituitary. Semin Diagn Pathol 1986 Feb; 3(1) : 18-33
13. Cushing H. The basophil adenomas of the pituitary body and their clinical manifestations (pituitary basophilism).Bull Johns Hopkins 1932 Mar;50: 137-95
14. Bigos ST,Somma M, Rasio E, Eastman RC, Lanthier A, Johnston HH, Hardy J. Cushing's disease: Management by transphenoidal pituitary microsurgery. J Clin Endorcinol Metab 1980 Feb; 50(2) : 348-54
15. Robert F, Hardy J. Human corticotroph cell adenomas. Semin Diagn Pathol 1986 Feb; 3(1) : 34-41
16. Mashiter K. Gonadotropin-Secreting Adenomass: In vitro Studies, Clinical Aspects and Treatment. 3rd Eur Workshop on Pituitary Adenomas. Amsterdam, 1983. (abstr)
17. Trouillas J, Girod C, Sassolas G, Claustrat B. The human gonadotropic adenoma: pathologic diagnosis and hormonal correlations in 26 tumors. Semin Diagn Pathol 1986 Feb; 3(1) : 42-57
18. Horvath E, Kovacs K. Gonadotroph adenomas of the human pituitary; sex-related fine-structural dichotomy: a histologic, immunocytochemical and electron microscopic study of 30 tumors. Am J Pathol 1984 Dec; 117(3) : 429-40
19. Girod C, Trouillas J, Claustrat B. The human thyrotropic adenoma: pathologic diagnosis in five

cases and critical review of the literature. Semin Diagn Pathol 1986; Feb; 3(1) : 58-68

20. Horvath E, Kovacs K, Scheithauer BW, Randall RV, Laws ER, Thorner MO, Tindall GT, Barrow DL. Pituitary adenomas producing growth hormone, prolactin, and one or more glycoprotein hormones: a histologic, immuohistochemical, and ultrastructural study of four surgically removed tumors. Ultrastruct Pathol 1983 Sep-Oct; 5(3): 171-83
21. Horn K, Erhardt E, Fahlbusch R, Pickardt CR, Werdork, Scriba PC. Recurrent goiter, hyperthyroidism, galactorrhea and amenorrhea due to a thyrotropin and prolactin-producing pituitary tumor. J Clin Endocrinol Metab 1976 Jul; 43(1): 137-43
22. Kellett HA, Wyllie AH, Dale BAB, Best JJK, Toft AD. Hyperthyroidism due to a thyrotropin-secreting microadenoma. Clin Endocrinol 1983 Jul; 19(1) : 57-65
23. Scheithauer BW, Horvath E, Kovacs K, Laws ER, Randall RV, Ryan N. Plurihormonal pituitary adenomas. Semin Diagn Pathol 1986 Feb; 3(1): 69-82
24. Martinez AJ. The pathology of nonfunctional pituitary adenomas. Semin Diagn Pathol 1986 Feb; 3(1): 83-94
25. Ebersold MJ, Quast LM, Scheithauer B W, Randall RV. Long-term results in transphenoidal removal of nonfunctioning pituitary adenomas. Neurosurgery 1986 May; 64(5) : 713-9