Turk J Endocrinol Metab. 2021;25:227-231

A Case of Plurihormonal Pituitary Giant Macroadenoma

Plurihormonal Hipofizer Dev Makroadenomu Olan Olgu Sunumu

Hatice ÖZIŞIK, Banu SARER YÜREKLİ, Yeşim ERTAN*, Cenk ERASLAN**, Erkin ÖZGİRAY***, Füsun SAYGILI

Department of Endocrinology and Metabolic Diseases, Ege University Faculty of Medicine, İzmir, TURKEY
*Department of Pathology, Ege University Faculty of Medicine, İzmir, TURKEY
**Department of Radiology, Ege University Faculty of Medicine, İzmir, TURKEY
***Department of Neurosurgery, Ege University Faculty of Medicine, İzmir, TURKEY

Abstract

We would like to draw the attention of the readers to Pit-1 positive giant macroadenomas in this work. A 62-year-old male patient was admitted to the hospital due to his vision loss and blurred vision in the left eye. His pituitary magnetic resonance imaging revealed the presence of a diffuse and homogeneous mass lesion originating from the pituitary gland having grade 4 invasion into the bilateral cavernous sinus and eroding the base of the sella. He consulted our department before his operation in 2016. Laboratory examination revealed that pituitary hormone levels were within normal ranges while the testosterone level [total testosterone 0.27 ng/mL (2.8-8)] was low. Pathological findings revealed a pituitary adenoma that displayed focal immunoreactivity to thyrotrophin, growth hormone, and prolactin. While the main prevalence and the basic mechanism of plurihormonal pituitary adenomas are not clear, one of the hypotheses is based on the role of divergent transcription factors such as Pit-1. According to this condition, we should perform a complete biochemical and histologic evaluation in patients with pituitary adenomas.

Keywords: Plurihormonal adenoma; pituitary diseases;growth hormone-secreting pituitary adenoma;lactotrophs

Özet

Bu çalışmada, Pit-1 pozitif dev makroadenomlara dikkat çekmek istedik. Altmış iki yaşında erkek hasta, sol gözde görmede azalma ve bulanık görme nedeniyle hastaneye başvurdu. Hipofiz manyetik rezonans görüntülemesinde, hipofiz bezinden kaynaklanan yaygın homojen kitle lezyonunun, bilateral kavernöz sinüse 4. derece invazyonunun olduğu ve sella tabanını aşındırdığı izlendi. Preoperatif dönemde, endokrinoloji bölümümüze konsülte edilmişti. Laboratuvar incelemesinde hipofiz hormon düzeyleri normal sınırlarda, total testosteron düzeyi 0,27 ng/mL (2,8-8) düşüktü. Operasyon sonrası patoloji sonucu, fokal tirotropin, büyüme hormonu ve prolaktin immünoreaktivitesi gösteren bir hipofiz adenoma olarak raporlandı. Plurihormonal hipofiz adenomlarının prevalansı ve temel mekanizması net değildir; hipotezlerden biri, Pit-1 gibi farklı transkripsiyon faktörlerinin rolüne bağlı olabileceği yönündedir. Hipofiz adenomlu hastalarda, tam bir biyokimyasal ve histolojik değerlendirme yapmalıyız.

Anahtar kelimeler: Plurihormonal adenom; hipofizer hastalıklar; büyüme hormonu salgılayan hipofizer adenom; laktotroplar

Introduction

Pituitary adenomas producing more than one pituitary hormone are defined as plurihormonal pituitary adenomas (PPA) according to the 2017 World Health Organization (WHO) classification of pituitary tumors (1). While the majority of functioning pituitary adenomas produce a single hormone, an im-

Address for Correspondence: Hatice ÖZIŞIK, Division of Endocrinology and Metabolic Diseases, Ege University Faculty of Medicine, İzmir, TURKEY
Phone: :+90232 3904612 **E-mail:** drhaticege@hotmail.com

Peer review under responsibility of Turkish Journal of Endocrinology and Metabolism.

Received: 15 Sep 2020 **Received in revised form:** 07 Dec 2020 **Accepted:** 31 Dec 2020 **Available online:** 23 Mar 2021

DOI: 10.25179/tjem.2020-78997

munohistochemical examination has also shown pituitary adenomas that produce multiple hormones (2). A feature of these adenomas is the expression of Pit-1 (pituitary-specific transcription factor-1) (3,4). PPAs are classified into 2 subtypes: Pit-1 positive PPAs (Pit-1+PPAs) and plurihormonal adenomas with unusual immunohistochemical combinations (PAwUIC) (5). PAwUICs are described as PPAs derived from divergent pituitary cell lineages. This subtype displays symptoms associated with either nonfunctioning pituitary adenoma symptoms or with the clinical characteristics of a hormone-secreting pituitary adenoma (6,7). Pit-1+PPAs display an aggressive phenotype, high recurrence ratios, and persistence post-surgery (8,9). Pit-1 is a transactivator of the prolactin (PRL), growth hormone (GH), and TSH-β (thyrotrophin) genes during anterior pituitary development. It also plays a significant role in the development of plurihormonality in these pituitary adenomas (10). Nevertheless, only the expression of Pit-1 mRNA is not enough to account for plurihormonality in pituitary adenomas (11). This makes it challenging for the classification of these tumors. Furthermore, according to the European Pituitary Pathology Group algorithm, plurihormonal adenomas are classified into functioning and nonfunctioning tumors. Functioning plurihormonal adenomas are further inclusive of three groups; somatotroph, plurihormonal, thyrotroph plurihormonal, and double/triple tumors. Nonfunctioning tumors show no hormone secretion and are defined as silent plurihormonal/poorly differentiated Pit-1 tumors (12).

In the clinical pathology of pituitary adenomas, the Pit-1 family is the most complicated and diverse. So we present the plurihormonality of pituitary adenomas with a case report.

Case Report

A 62-year-old male patient complaining of visual loss and blurred vision in the left eye consulted our department before his operation in 2016. The neurosurgery department scheduled his operation because of a giant macroadenoma that was detected in the magnetic resonance image (MRI) of the brain. Besides, he also had suffered from sexual dysfunction for two years. The preoperative pituitary MRI revealed a diffuse and homogeneous mass lesion originating from the pituitary gland. It displayed grade 4 invasion into the bilateral cavernous sinus along with the erosion of the base of the sella (Figure 1). The lesion extended to the anterior temporal convexity on the left side. Laboratory examination revealed that while the levels of pituitary hormone and cortisol were within the normal range, testosterone levels were low [total testosterone was 0.27 ng/mL (2.8-8)]. The patient underwent an endonasal endoscopic transsphenoidal surgery. Pathological findings revealed the presence of a pituitary adenoma that displayed immunohistochemically focal TSH, rare GH, and focal PRL positivity. While the adenoma was negative for follicle-stimulating hormone (FSH), luteinizing hormone (LH), and adrenocorticotropic hormone (ACTH), the ki-67 score was 1% (Figure 2A-C). Postoperatively, pituitary MRI demonstrated the component of the adenoma extending in the anterior to temporal convexity and the component extending toward the suprasellar area to be operated, but the rest of the tumor remained. While the levels of the hormones fT4 and total testosterone were low, the level of prolactin was high with other hormones in the normal ranges. The patient received cabergoline for hyperprolactinemia and L-thyroxine for central hypothyroidism. A pituitary MRI in the 2017-follow-up demonstrated pressure on optic chiasma while there was no difference in the size of the adenoma. He underwent a second operation via an endonasal endoscopic transsphenoidal method in 2018. Immunohistochemical examination revealed that the tumor was diffusely positive for Pit-1 and focal for prolactin, while GH, TSH, ACTH, FSH, LH were negative, and ki-67 was 1%. Assessment of the tumor using the primary pathology material was done and reported as plurihormonal adenoma. After the second surgery, pituitary MRI detected an operation-related defect in the central parts of the macroadenoma that invaded the cavernous sinus, the sphenoid bone, and the anterior section of the left temporal lobe. Laboratory examination revealed that the level of pro-

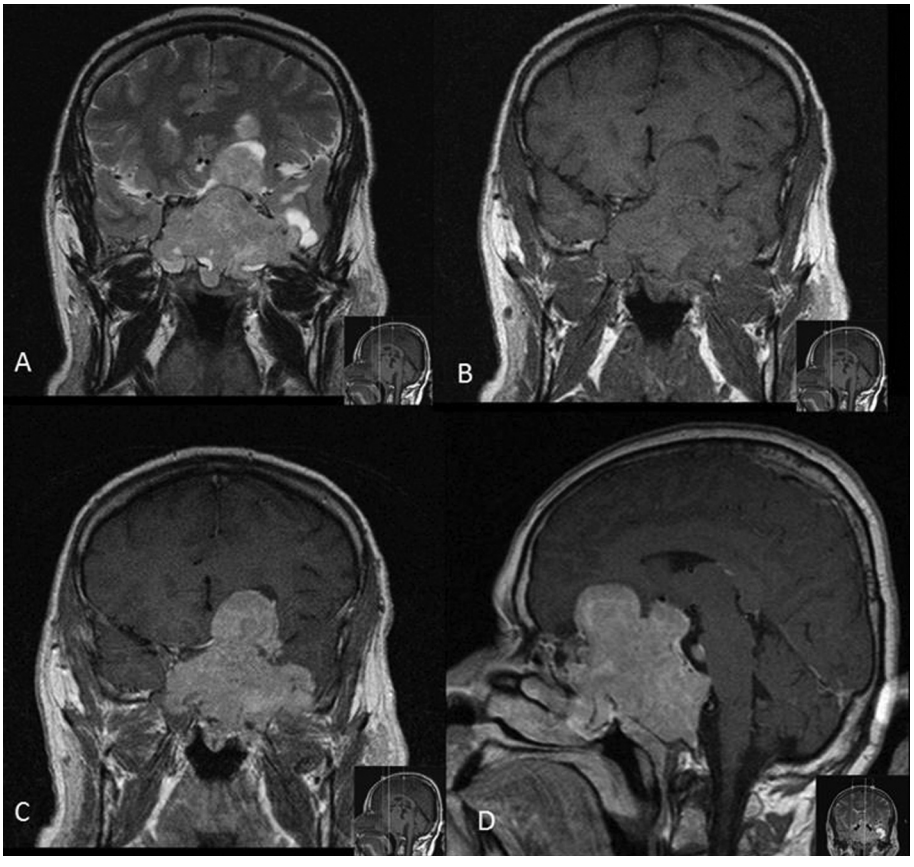

Figure 1. A) Coronal T2 image, B) Coronal T1 image, C) Postcontrast coronal T1 image, D) Postcontrast sagittal T1 image. Giant pituitary adenoma, enlarged sellar cavity, optic chiasm compression, and bilaterally cavernous sinus invasion.

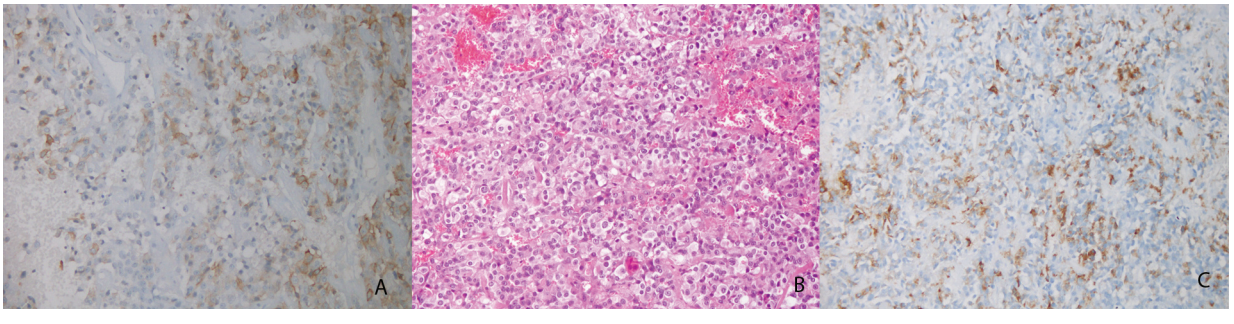

Figure 2. A) Microscopic finding of the plurihormonal adenoma showing sheets of tumor cells (H&E, x20). B) Thyrotrophin immunopositivity of scattered tumor cells immunohistochemistry (x20). C) Prolactin immunopositivity of scattered tumor cells immunohistochemistry (x20).

lactin was 163.6 µg/L (4.04-15.2), total testosterone was 55.6 ng/dL (280-800), GH was 1.06 µg/L, insulin-like growth factor (IGF)-1 was 216 (44.7-210), and other hormones were in the normal range. Although the IGF-1 level was high, physical examination revealed no signs of features of acromegaly. Despite the initiation of cabergoline treatment, the prolactin level did not normalize. The cabergoline dose was increased to 3 tablets twice a week. Radiotherapy was applied due to the size of the adenoma. After radiotherapy and dopamine agonist treatment, the IGF-1 level was normalized, but that of prolactin was not normalized.

Discussion

The main prevalence and the basic mechanism of PPAs are not clear; one of the hypotheses points out the role of divergent transcription factors such as Pit-1 (3). Pit-1 plays a significant role in the differentiation of thyrotroph, lactotroph, and somatotroph cell lineages and is expressed from embryonic day 13.5 (3,4).

Plurihormonal adenomas often display varied different immunohistochemical staining patterns characterized by dispersed or focal positivity for one or more of the hormones GH, PRL, and TSH when compared to differentiated Pit-1 lineage adenomas (13). Pathological examination of our patient displayed focal TSH, GH, and PRL immunoreactivity.

Although the 2017 WHO classification discusses Pit-1 positive plurihormonal adenomas (formerly known as silent subtype 3 adenomas), we should keep in mind that a small fraction of these Pit-1 positive pituitary tumors may be negative for adenohypophysial hormones. Therefore, these tumors have been recommended to be described as poorly differentiated Pit-1 lineage pituitary adenomas (13). Three such cases have been reported by Mete et al. (13).

Plurihormonal adenomas expressing GH, TSH, and PRL are rare (7). Nearly 30% of TSHomas are plurihormonal, and the most commonly associated hormones are GH and PRL. This can be explained by the fact that they share mutual transcription factors such as Prop-1, Pit-1, and HESX-1 (14,15). Furthermore, Azzalin et al. have reported that besides βTSH, TSHomas were also found to have the immunohistochemical expression of at least one pituitary hormone. The positivity for βTSH, GH, and PRL combined was the most commonly seen (16). On the other hand, 13% of GH secreting pituitary tumors displayed immunopositivity for TSH (17).

In addition, plurihormonality does not always convert into the clinical features of hormonal excess (18). There is no correlation between peripheral blood hormone levels and immunohistochemical reactivity. Hence, hormone levels are not used for the diagnosis of PPAs (19). In some Pit 1+PPAs, hyperprolactinemia can be seen as a result of the mass effect. Our patient did not show any clinical features except blurred vision. Inadequate peptide synthesis by the tumor tissue may determine the deficiency of the corresponding clinical and biochemical symptoms (20). In order to control high levels of prolactin after the second operation and the size of adenoma, cabergoline treatment was initiated, and radiotherapy was applied.

Plurihormonal adenomas are usually huge and invasive; therefore, surgical treatment cannot be seen in patients with Pit-1+PPAs (13).

Moreover, according to the Congress of Neurological Surgeons Systematic Review, surgical resection is the best method for symptomatic nonfunctioning pituitary adenomas in patients with symptoms of visual field defects, compression symptoms, and endocrine dysfunction (21).

In conclusion, Pit-1 positive plurihormonal adenomas are monomorphous and usually express one or more hormones of the Pit-1 lineage, with only a small portion of them being hormone negative (22). We should perform a complete biochemical and histologic evaluation in patients with pituitary adenomas.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: Hatice Özışık; Design: Hatice Özışık, Banu Sarer Yürekli; Control/Supervision: Füsun Saygılı; Data Collection and/or Processing: Yeşim Ertan, Cenk Eraslan;

Analysis and/or Interpretation: Erkin Özgiray, Füsun Saygılı; Literature Review: Hatice Özışık; Writing the Article: Hatice Özışık; Critical Review: Banu Sarer Yürekli; Materials:Yeşim Ertan, Hatice Özışık, Banu Sarer Yürekli.

References

1. Mete O, Lopes MB. Overview of the 2017 WHO Classification of Pituitary Tumors. Endocr Pathol. 2017;28:228-243. [Crossref] [Pubmed]
2. Ho DM, Hsu CY, Ting LT, Chiang H. Plurihormonal pituitary adenomas: immunostaining of all pituitary hormones is mandatory for correct classification. Histopathology. 2001;39:310-319. [Crossref] [Pubmed]
3. Osamura RY, Tahara S, Kurotani R, Sanno N, Matsuno A, Teramoto A. Contributions of immunohistochemistry and in situ hybridization to the functional analysis of pituitary adenomas. J Histochem Cytochem. 2000;48:445-458. [Crossref] [Pubmed]
4. Roche C, Rasolonjanahary R, Thirion S, Goddard I, Fusco A, Figarella-Branger D, Dufour H, Brue T, Franc JL, Enjalbert A, Barlier A. Inactivation of transcription factor pit-1 to target tumoral somatolactotroph cells. Hum Gene Ther. 2012;23:104-114. [Crossref] [Pubmed]
5. Kontogeorgos G KK, Lloyd RV, Righi A. Plurihormonal and double adenomas. In: Lloyd RV, Osamura RY, Klöppel G, Rosai J, eds. World Health Organization Classification of Tumours of Endocrine Organs (4th ed). Lyon; IARC Press; 2017:39-40. [Link]
6. Rasul FT, Jaunmuktane Z, Khan AA, Phadke R, Powell M. Plurihormonal pituitary adenoma with concomitant adrenocorticotropic hormone (ACTH) and growth hormone (GH) secretion: a report of two cases and review of the literature. Acta Neurochir (Wien). 2014;156:141-146. [Crossref] [Pubmed]
7. Lopes MBS. The 2017 World Health Organization classification of tumors of the pituitary gland: a summary. Acta Neuropathol. 2017;134:521-535. [Crossref] [Pubmed]
8. Horvath E, Kovacs K, Smyth HS, Cusimano M, Singer W. Silent adenoma subtype 3 of the pituitary-immunohistochemical and ultrastructural classification: a review of 29 cases. Ultrastruct Pathol. 2005;29:511-524. [Crossref] [Pubmed]
9. Erickson D, Scheithauer B, Atkinson J, Horvath E, Kovacs K, Lloyd RV, Young WF Jr. Silent subtype 3 pituitary adenoma: a clinicopathologic analysis of the Mayo Clinic experience. Clin Endocrinol (Oxf). 2009;71:92-99. [Crossref] [Pubmed]
10. Pellegrini I, Barlier A, Gunz G, Figarella-Branger D, Enjalbert A, Grisoli F, Jaquet P. Pit-1 gene expression in the human pituitary and pituitary adenomas. J Clin Endocrinol Metab. 1994;79:189-196. [Crossref] [Pubmed]
11. Yamada S, Takahashi M, Hara M, Hattori A, Sano T, Ozawa Y, Shishiba Y, Hirata K, Usui M. Pit-1 gene expression in human pituitary adenomas using the reverse transcription polymerase chain reaction method. Clin Endocrinol (Oxf). 1996;45:263-272. [Crossref] [Pubmed]
12. Trouillas J, Jaffrain-Rea ML, Vasiljevic A, Raverot G, Roncaroli F, Villa C. How to classify the pituitary neuroendocrine tumors (PitNET)s in 2020. Cancers (Basel). 2020;12:514. [Crossref] [Pubmed] [PMC]
13. Mete O, Gomez-Hernandez K, Kucharczyk W, Ridout R, Zadeh G, Gentili F, Ezzat S, Asa SL. Silent subtype 3 pituitary adenomas are not always silent and represent poorly differentiated monomorphous plurihormonal Pit-1 lineage adenomas. Mod Pathol. 2016;29:131-142. [Crossref] [Pubmed]
14. Kirkman MA, Jaunmuktane Z, Brandner S, Khan AA, Powell M, Baldeweg SE. Active and silent thyroid-stimulating hormone-expressing pituitary adenomas: presenting symptoms, treatment, outcomes, and recurrence. World Neurosurg. 2014;82:1224-1231. [Crossref] [Pubmed]
15. Yamada S, Fukuhara N, Horiguchi K, Yamaguchi-Okada M, Nishioka H, Takeshita A, Takeuchi Y, Ito J, Inoshita N. Clinicopathological characteristics and therapeutic outcomes in thyrotropin-secreting pituitary adenomas: a single-center study of 90 cases. J Neurosurg. 2014;121:1462-1473. [Crossref] [Pubmed]
16. Azzalin A, Appin CL, Schniederjan MJ, Constantin T, Ritchie JC, Veledar E, Oyesiku NM, Ioachimescu AG. Comprehensive evaluation of thyrotropinomas: single-center 20-year experience. Pituitary. 2016;19:183-193. [Crossref] [Pubmed]
17. Mori R, Inoshita N, Takahashi-Fujigasaki J, Joki T, Nishioka H, Abe T, Fujii T, Yamada S. Clinicopathological features of growth hormone-producing pituitary adenomas in 242 acromegaly patients: classification according to hormone production and cytokeratin distribution. ISRN Endocrinol. 2013;2013:723432. [Crossref] [Pubmed] [PMC]
18. Beck-Peccoz P, Persani L, Mantovani S, Cortelazzi D, Asteria C. Thyrotropin-secreting pituitary adenomas. Metabolism. 1996;45:75-79. [Crossref] [Pubmed]
19. Felix I, Asa SL, Kovacs K, Horvath E, Smyth HS. Recurrent plurihormonal bimorphous pituitary adenoma producing growth hormone, thyrotropin, and prolactin. Arch Pathol Lab Med. 1994;118:66-70. [Pubmed]
20. Vora TK, Karunakaran S. Thyrotropic pituitary adenoma with plurihormonal immunoreactivity. Neurol India. 2017;65:1162-1164. [Crossref] [Pubmed]
21. Lucas JW, Bodach ME, Tumialan LM, Oyesiku NM, Patil CG, Litvack Z, Aghi MK, Zada G. Congress of Neurological Surgeons Systematic Review and Evidence-Based Guideline on Primary Management of Patients With Nonfunctioning Pituitary Adenomas. Neurosurgery. 2016;79:E533-E555. [Crossref] [Pubmed]
22. Drummond J, Roncaroli F, Grossman AB, Korbonits M. Clinical and pathological aspects of silent pituitary adenomas. J Clin Endocrinol Metab. 2019;104:2473-2489. [Crossref] [Pubmed] [PMC]