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The coexistence of infundibular pituicytoma and Cushing's disease due to pituitary adenoma: A case report

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Objectives. Pituicytomas are rare, solid, well-circumscribed, low grade (grade I), non-neuroendocrine, and noninfiltrative tumors of the neurohypophysis or infundibulum, which appear in the sellar/suprasellar regions. Herein, we present a case with Cushing's disease (CD) caused by an ACTH-secreting pituitary adenoma in association with an infundibular pituicytoma.

Subject and Results. A 37-year-old male patient presented to the hospital with a six-month history of blurry vision. Physical examination demonstrated plethora, excessive sweating, weight gain, moon facies, and acne. Basal serum cortisol and ACTH levels were 16 μg/dl and 32 pg/ml, respectively. The results of screening tests were suggestive of Cushing syndrome. It was also 1.97 μg/dl following 8 mg dexamethasone suppression test which was consistent with CD. Pituitary MR imaging revealed a single lesion measuring 6x6.5 mm on the pituitary stalk. Infundibular mass excision and pituitary exploration by extended endoscopic endonasal approach were applied. On immunohistochemistry, strong diffuse immunolabeling for both S100 and TTF-1 was noted for the cells of infundibular mass, diagnosed as pituicytoma. Because the developed panhypopituitarism postoperatively, patient was discharged with daily desmopressin, levothyroxine, hydrocortisone, and intramuscular testosterone, once a month.

Conclusions. Pituicytoma is an uncommon noninvasive tumor of the sellar and suprasellar regions. In this case report, we described a patient with Cushing's disease to whom MRI displayed only an infundibular well-circumscribed lesion, but not any pituitary adenoma. Despite the absence of any sellar lesion, awareness of other undetected possible lesion and exploring hypophysis during the transsphenoidal surgery is mandatory for the correct diagnosis.

Key words: pituicytoma, Cushing's disease

Pituicytomas were added to the international classification of human tumors in 2007 by World Health Organization (WHO) as rare, solid, well-circumscribed, low grade (grade I), non-neuroendocrine, and noninfiltrative tumors of the neurohypophysis or infundibulum, which appear in the sellar/suprasellar regions. They are derived from the specialized glial cells called "pituicytes" (Louis et al. 2007). These non-adenomatous tumors can be asymptomatic or symptomatic due to local tumor-mass effects. While there are few case reports describing pituicytomas with hormone hypersecretion (Chakraborti et al. 2013; Feng et al. 2018), they are generally considered as non-secretory pituitary tumors. Herein, we present a case with Cushing's disease (CD) caused by an ACTH-secreting pituitary adenoma in association with an infundibular pituicytoma.

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Case report

A 37-year-old male patient presented to the hospital with a six-month history of blurry vision. Retrobulbar edema was detected during eye examination causing the blurred vision. The patient applied to our clinic for further examination of a possible mass in the sellar region. He had no past medical history of any disease. His heart rate was 84 beats per minute and blood pressure was 150/95 mmHg. Physical examination demonstrated plethora, excessive sweating, weight gain, moon facies, and acne. Visual field examination was normal. Body mass index was 29 kg/m^2 and waist circumference was 128 cm. Impaired glucose tolerance was detected by oral glucose tolerance test and HbA1c was found to be 5.7%. Basal serum cortisol and ACTH levels were 16 μg/dl and 32 pg/ml, respectively. Midnight plasma cortisol was elevated (13.5 μg/dl) and 24-h urinary free cortisol was 425 μg/day (<403). The plasma cortisol level was not suppressed (9.7 μg/dl) after 2-day dexamethasone suppression test. It was also 1.97 μg/dl following 8 mg dexamethasone suppression test which was consistent with CD.

Pituitary MR imaging revealed an isointense (in both T1 and T2-weighted images) lesion measuring 6×6.5 mm, which showed contrast enhancement on the pituitary stalk. Additionally, the stalk was enlarged and the height of the pituitary gland was 7.3 mm (Figure 1). Therefore, as differential diagnosis of hypophysitis, lymphoma-leukemia, granulomatous diseases, and pituicytoma were considered. The urine acid resistance bacteria (ARB) was negative and there was no pathological finding in the thorax computed tomography. During purified protein derivative of tuberculin test (PPD) 10 mm induration was detected. Thus, tuberculosis was excluded. Serum angiotensin-converting enzyme, calcium, and 24-h urinary calcium excretion were in normal limits. Physical examination revealed no evidence of any organ involvement including skin; therefore, sarcoidosis was excluded. Similarly, histiocytosis was excluded due to the absence of diabetes insipidus, any skin lesion or organ involvement in thorax and abdominal computed tomography. There was no B symptom and physical examination showed no pathological lymphadenopathy. Complete blood count and routine biochemical tests were within normal range. Thus, leukemia-lymphoma was excluded, as well.

Table 1
Postoperative laboratory parameters

Parameter	Result	Reference range
TSH (mIU/l)	0.05	0.38–5.33
fT4 (ng/dl)	0.45	0.61–1.20
GH (ng/ml)	1.15	>8
IGF-1 (ng/ml)	140	72–233
ACTH (pg/ml)	<5	0–45
Cortisol (μg/ml)	1.44	6.7–22.6
FSH (mIU/l)	2.6	1.27–19.26
LH (mIU/l)	1.2	1.24–8.62
Testosterone (ng/ml)	<0.1	1.75–7.81
Prolactin (ng/ml)	0.5	2.64–13.13

Abbreviations: TSH – thyroid-stimulating hormone; fT4 – free thyroxine ; GH – growth hormone; IGF-1 – insulin-like growth factor 1; ACTH – adrenocorticotropic hormone; FSH – follicle-stimulating hormone; LH – luteinizing hormone.

The patient refused surgical treatment, because of high possibility the pituitary stalk damage during surgery and medical treatment was initiated for CD. Subcutaneous Pasireotide 0.6 mg/ml twice daily was initiated. Complaints of dry mouth, increased plasma glucose level, and mild diarrhea were appeared during the first month, deteriorating the quality of life. His morning adrenocorticotropin hormone (ACTH) and cortisol levels were 16.6 pg/ml and 12.5 μg/dl, respectively and 24-h urinary cortisol level was 236 μg/day. Pasireotid dose could not be increased due to described side effects and cabergoline 2 mg/week was added. At the sixth month follow-up; plethora, facial and supraclavicular swelling were found to be exacerbated. The patient ceased his treatment due to excessive diarrhea and morning ACTH, cortisol and 24-h urinary cortisol levels were 14 pg/ml, 11.5 μg/dl and 1015 μg/day, respectively. No significant difference was observed in pituitary MR images compared to previous imaging. The patient was re-evaluated by the multidisciplinary council.

Infundibular mass excision and pituitary exploration by extended endoscopic endonasal approach were planned. Postoperative laboratory parameters are listed in Table 1.

Immunohistochemistry revealed a strong diffuse immunolabeling for both S100 and TTF-1, no immunoreactivity for GFAP, and 1% Ki 67 proliferation index were noted for the cells of infundibular mass (Figure 2). Even though, the neurosurgeons reported that they excised an adenoma besides the infundibular lesion (Figure 1), which could not be detected during pathological examination. Because the panhypopituitarism was developed postoperatively, patient was discharged with desmopressin 120 mg tablet twice a day, levothyroxine 75 mg/day, hydrocortisone 30 mg/day and intramuscular testosterone once a month.

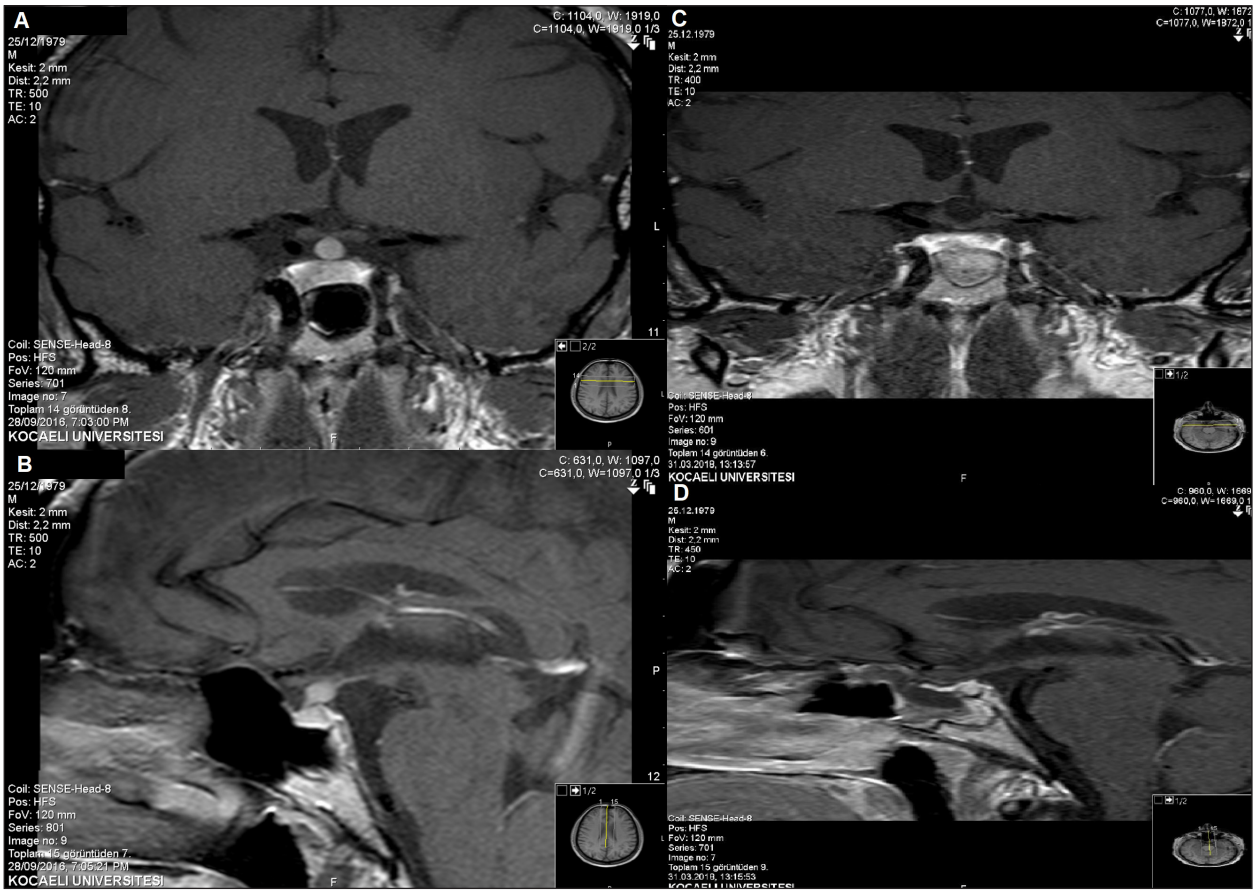

Figure 1. Preoperative T1-weighted gadolinium-enhanced dynamic coronal (**A**) and sagittal (**B**) MR images, single infundibular lesion measuring 6×6.5 mm. Postoperative T1-weighted gadolinium-enhanced dynamic coronal (**C**) and sagittal (**D**) MR images.

Discussion

The term "pituicytoma", also previously known as "infundibuloma" or "posterior pituitary astrocytoma", was first described in 1958 as a tumor arising from neurohypophysis (Liss and Kahn 1958). After some specific pathological criteria for the diagnosis of pituicytoma, it was defined by Brat in 2000 (Brat et al. 2000), WHO changed "pituicytoma" term to a new standalone entity, distinct from astrocytomas (Louis et al. 2007). Pituicytoma is histologically composed of bipolar spindle-shaped glial cells rich in Golgi apparatus occupying perivascular zones of the neurohypophysis and they contribute to the regulation of the release of hypothalamic hormones (Pirayesh Islamian et al. 2012).

Histological and immunohistochemical examinations are the cornerstones for the diagnosis of pituicytoma, because clinical and radiological findings for this type of tumor are nonspecific. Major cells, dark cells, oncocytes, ependymal cells, and granular cells are five different types of pituicytes, of which first two are the most common (Zygourakis et al. 2015). All of them are supposed to give rise to a distinct tumor type. Pituicytomas display a clear immunoreactivity for S100 protein and vimentin, whereas the expression of glial fibrillary acidic protein (GFAP) is variable and generally show negative or focal and weak expression of epithelial membrane antigen (EMA).

The clinical manifestations can be various such as visual disturbances, headache, symptoms of hyperprolactinemia, hypopituitarism, central diabetes insipidus (DI) and cavernous sinus syndrome (Secci et al. 2012). Since pituicytomas are thought to arise from neurohypophysis, DI is expected to be a common finding however, only 5% of all reported cases presented with DI (Guo et al. 2016). Hyperprolactinemia, secondary to "stalk effect", is the most commonly seen endocrinological abnormality accounting for 25%. The clinical presentation of our case was only Cushing syndrome, which was due to an ACTH-secreting pituitary adenoma and it is

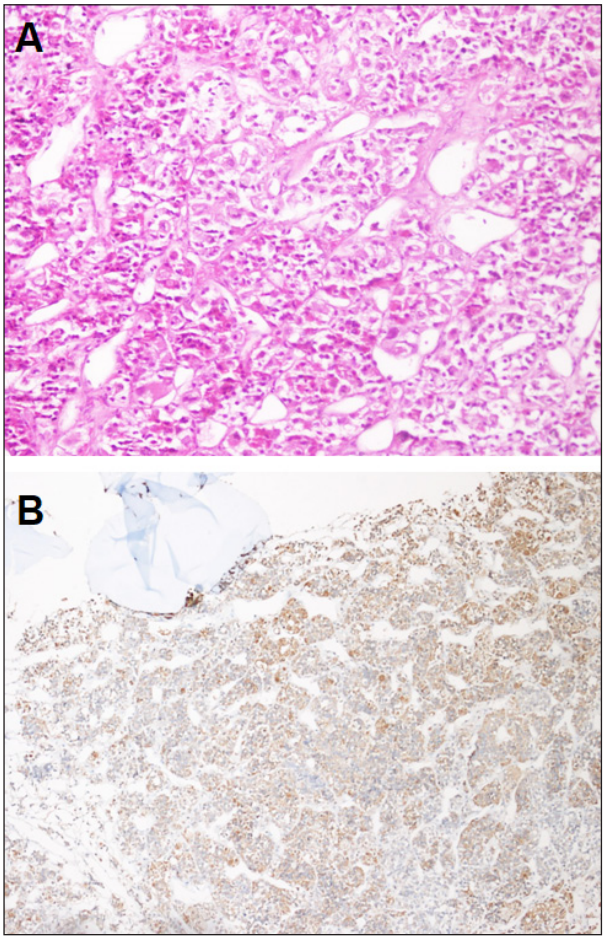

Figure 2. Histopathological examination of the tumor showed a spindle cell lesion [H&E, ×200] (**A**) and strong and diffuse positivity for S-100 of cytoplasm and uniform nuclei [S-100, ×100] (**B**).

obvious that pituicytoma per se caused no symptom.

Besides the mainly accepted theory arising from the neurohypophysis and proximal infundibulum, some authors propose that they are derived from the folliculostellate cells (FSCs) of the adenohypophysis. There are few cases of pituicytomas that reveal focal expression of B-cell lymphoma-2 (Bcl-2), an oncoprotein that inhibits apoptosis and induces the progression of various tumor types and in a normal pituitary gland, FSCs are the only cells expressing that protein. In addition, these cases show some ultrastructural transitional features between a pituicytoma and pituitary adenoma, which is also suggestive of adenohypophyseal origin (Cenacchi et al. 2001; Ulm et al. 2004). If this hypothesis is accepted, then the development of different subtypes of pituitary tumors are eventual and the coexistence of pituicytoma and a pituitary adenoma should not be considered a mere coincidence (Cambiaso et al. 2015). In contrast to this hypothesis, the pituitary tumor in our case expressed thyroid transcription factor-1 (TTF-1) which is significantly immunoreactive in pituicytes, but not in FSCs.

The association of Cushing's disease and pituicytoma is uncommon and to our knowledge, there are only 5 cases reported so far. Two of them were similar to our case and they have described the coexistence of an ACTH-secreting pituitary adenoma and pituicytoma (Schmalisch et al. 2012; Cambiaso et al. 2015). In one case of the pituicytoma, Cushing's disease was due to ACTH-secreting pituitary hyperplasia (Guo et al. 2016). In the last two cases, the pathological mechanisms of Cushing's disease were uncertain. The clinical symptoms were disappeared after the resection of pituicytomas by transsphenoidal route and histologically. No other lesion has been described beside pituicytoma (Chakraborti et al. 2013; Feng et al. 2018), which can be interpreted as hormone secretion of pituicytes. One of two possible explanations for this situation is the coexistence of a non-adenomatous tumor and a hypersecretory adenoma, which cannot be demonstrated histopatologically. The latter is the production of some chemical substances, such as cytokines, by the adenohypophysis induced non-adenomatous tumor hormone secretion. Beyond these explanations, the consensus on them is still a matter of debate.

In conclusion, pituicytoma is an uncommon noninvasive tumor of the sellar and suprasellar regions. If symptomatic, the common ones are visual disturbances, headache, hypopituitarism, and endocrinological abnormality, such as hyperprolactinemia. Gross total resection is the mainstay treatment. In this case report, we described a patient with Cushing's disease of whom MRI displayed only an infundibular well-circumscribed lesion, but not any pituitary adenoma. Despite the absence of any sellar lesion, awareness of any other undetected possible lesion and exploring hypophysis during the transsphenoidal surgery is mandatory for the correct diagnosis.

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References

Brat DJ, Scheithauer BW, Staugaitis SM, Holtzman RNN, Morgello S, Burger PC. Pituicytoma: A distinctive low-grade glioma of the neurohypophysis. Am J Surg Pathol 24, 362–368, 2000.

Cambiaso P, Amodio D, Procaccini E, Longo D, Galassi S, Camassei FD, Cappa M. Pituicytoma and Cushings Disease in a 7-Year-Old Girl: A Mere Coincidence? Pediatrics 136, e1632–e1636, 2015.

Cenacchi G, Giovenali P, Castrioto C, Giangaspero F. Pituicytoma: Ultrastructural evidence of a possible origin from folliculo-stellate cells of the adenohypophysis. Ultrastruct Pathol 25, 309–312, 2001.

Chakraborti S, Mahadevan A, Govindan A, Sridhar K, Mohan NV, Satish IR, Rudrappa S, Mangshetty S, Shankar SK. Pituicytoma: Report of three cases with review of literature. Pathol Res Pract 209, 52–58, 2013.

Feng Z, Mao Z, Wang Z, Liao B, Zhu Y, Wang H. Non-adenomatous pituitary tumours mimicking functioning pituitary adenomas. Br J Neurosurg 2018.

Guo X, Fu H, Kong X, Gao L, Wang W, Ma W, Yao Y, Wang R, Xing B. Pituicytoma coexisting with corticotroph hyperplasia: Literature review with one case report. Medicine (Baltimore) 95, e3062, 2016.

Pirayesh Islamian A, Buslei R, Saeger W, Fahlbusch R. Pituicytoma: Overview of treatment strategies and outcome. Pituitary 15, 227–236, 2012.

Liss L, Kahn EA. Pituicytoma, tumor of the sella turcica; a clinicopathological study. J Neurosurg 15, 481–488, 1958.

Louis DN, Ohgaki H, Wiestler OD, Cavenee WK, Burger PC, Jouvet A, Scheithauer BW, Kleihues P. The 2007 WHO classification of tumours of the central nervous system. Acta Neuropathol 114, 97–109, 2007.

Schmalisch K, Schittenhelm J, Ebner FH, Beuschlein F, Honegger J, Beschorner R. Pituicytoma in a patient with Cushing's disease: case report and review of the literature. Pituitary 15, 10–16, 2012.

Secci F, Merciadri P, Rossi DC, D'Andrea A, Zona G. Pituicytomas: radiological findings, clinical behavior and surgical management. Acta Neurochir (Wien) 154, 649–657, 2012.

Ulm AJ, Yachnis AT, Brat DJ, Rhoton AL Jr. Pituicytoma: report of two cases and clues regarding histogenesis. Neurosurgery 54, 753–758, 2004.

Zygourakis CC, Rolston JD, Lee HS, Partow C, Kunwar S, Aghi MK. Pituicytomas and spindle cell oncocytomas: modern case series from the University of California, San Francisco. Pituitary 18, 150–158, 2015.