A RARE CASE OF A FUNCTIONING GONADOTROPH TUMOR ACCOMPANIED BY ERYTHROCYTOSIS IN AN ELDERLY MAN

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Functioning gonadotroph adenomas are rare pituitary tumors secreting one or two gonadotropins (follicle-stimulating hormone (FSH) and/or luteinizing hormone (LH)), which are hormonally active. In the majority of cases, gonadotroph tumors are endocrinologically "silent" and make up more than a half of non-functioning pituitary adenomas. In this article we describe a rare clinical case of LH/FSH-secreting pituitary macroadenoma with bitemporal hemianopsia in a 62-year-old man. The patient underwent transnasal transsphenoidal adenomectomy, leading to remission. The distinctive feature of this case is the presence of secondary erythrocytosis due to endogenous hyperandrogenism, which required several blood exfusions to normaliza the level of hematocrit before surgery. It is noteworthy that clinical signs of erythrocytosis were present long before visual impairment. This clinical case demonstrates difficulties in the early diagnosis of functioning gonadotroph adenomas.

KEYWORDS: pituitary adenoma; gonadotroph tumor; LH; FSH; hyperndrogenism; erythrocytosis.

РЕДКИЙ СЛУЧАЙ ГОРМОНАЛЬНО-АКТИВНОЙ ГОНАДОТРОПИНОМЫ, АССОЦИИРОВАННОЙ СО ВТОРИЧНЫМ ЭРИТРОЦИТОЗОМ, У МУЖЧИНЫ В ПОЖИЛОМ ВОЗРАСТЕ

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Гормонально-активные гонадотропиномы — это редкие опухоли гипофиза, секретирующие один или два гонадотропных гормона (фолликулостимулирующий гормон (ФСГ) и/или лютеинизирующий гормон (ЛГ)), которые обладают биологической активностью. В большинстве случаев гонадотропиномы являются «молчащими» и составляют более половины гормонально-неактивных аденом гипофиза. В статье представлено описание редкого клинического наблюдения: ЛГ/ФСГ-секретирующей макроаденомы гипофиза с развитием битемпоральной гемианопсии у 62-летнего мужчины. Пациенту была проведена трансназальная транссфеноидальная аденомэктомия, позволившая достичь ремиссии заболевания. Отличительной особенностью данного случая являлось наличие вторичного эритроцитоза, развившегося вследствие эндогенной гиперандрогении, что потребовало проведения процедур эксфузий крови с целью нормализации уровня гематокрита перед проведением оперативного вмешательства. Примечательно, что клинические признаки эритроцитоза у пациента были выявлены задолго до развития зрительных нарушений. Представленный клинический случай демонстрирует сложность ранней диагностики гормонально-активных гонадотропином.

КЛЮЧЕВЫЕ СЛОВА: аденома гипофиза; гонадотропинома; ЛГ; ФСГ; гиперандрогения; эритроцитоз.

BACKGROUND

Functioning gonadotroph adenomas are rare pituitary tumors secreting one or two gonadotropins (follicle-stimulating hormone (FSH) and/or luteinizing hormone (LH)), which are hormonally active [1]. It is noteworthy that in the majority of cases gonadotroph tumors are endocrinologically "silent", i.e. they have FSH and/or LH positively stained during immunohistochemical (IHC) staining while they do not secrete these hormones or secrete them in a biologically inactive form (alpha-subunit, beta-subunit of FSH or LH) and therefore are not accompanied by hormonal hypersecretion signs [1-4]. Overall «silent» gonadotroph tumors occur quite often and make up to 64% of all non-functioning pituitary adenomas [5], while functioning gonadotroph tumors are described in individual cases or small case series.

Clinical signs of functioning gonadotroph tumors depend on sex and age. In children these tumors cause precocious puberty [6-8]. In women of reproductive age the prolonged exposure of ovaries to FSH leads to menstrual irregularity, causes infertility, cystic lesions in ovaries, ovarian hyperstimulation syndrome, chronic pain in pelvis or abdomen [9-15]. In the postmenopausal period signs caused by the tumor mass-effect (chiasmal syndrome, headaches, hypopituitarism) become more presented. The high level of gonadotropins in postmenopausal women does not impact the ovarian function and estrogen production that is why the secretion of functioning hormones by the pituitary

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tumor does not cause the ovarian hyperstimulation syndrome [1]. In men testicular enlargement, decrease in libido and erectile dysfunction can be observed; isolated visual function impairment without signs of hypogonadism is less common [2, 3, 9, 16]. When the tumor hypersecretes LH, there can be testosterone blood level increase [3, 17].

The main treatment modality for gonadotroph tumors is transsphenoidal adenomectomy which allows achieving remission at early stages [1]. If total tumor resection is impossible (invasive growth, cavernous sinuses invasion) or the tumor is recurrent, radiotherapy may be an option [1]. The phamacological therapy (somatostatin analogues, dopamine agonists, temozolomide) is not a method of choice to treat gonadotroph tumors due to the limited data of its efficiency [1].

In this article we describe a rare clinical case of a LH/FSH-secreting pituitary macroadenoma with bitemporal hemianopsia and secondary erythrocytosis in a 62-year-old man, the diagnostic process and treatment results.

CASE DESCRIPTION

Patient G., 62 y.o., was admitted to the Neuroendocrinology and Bone Diseases Department of the Federal State Budgetary Institution «Endocrinology National Medical Research Center» under the Russian Ministry of Health in September 2020 with complaints of significant visual impairment, blurry vision, narrowing of the visual field, and intermittent headache.

The patient started experiencing these symptoms in December 2019. In February 2020 the patient went to a local ophthalmologist who detected partial optic atrophy and early cataract of both eyes. The ophthalmologist suspected a pituitary disorder and recommended magnetic resonance imaging (MRI) of the brain. Earlier, according to the patient, during annual checkups (the last one in 2019) no significant visual function abnormalities were found. Brain MRI showed a mass lesion in the sellar region, 44x34x43 mm in size. For further examination and surgical treatment the patient was admitted to the Federal State Budgetary Institution «Endocrinology National Medical Research Center» under the Russian Ministry of Health with the referral diagnosis «Non-functioning pituitary adenoma».

During the initial medical examination ocular injections, plethora of the face, neck, trunk and palms were noticed; no clinical signs of acromegaly and hypercortisolism were found. The patient was hypersthenic, with height 174.4 cm, weight 102 kg (BMI = 33.5 kg/m2). Subcutaneous adipose tissue was evenly distributed with no swelling. Male pattern of hair distribution, secondary sex characteristics were properly developed. The liver on palpation was +1 cm from the costal margin, the liver edge was round, firm, non-tender. The rest of the organs and systems were unremarkable. There were no significant past medical and family history; no smoking or alcohol consumption according to the patient.

According to the brain MRI of September 17, 2020 the series of sagittal, frontal and axial T1- and T2-weighted images (WI) clearly showed a mass with clear and smooth margins in the sella turcica of the following size: width 40 mm, height 41 mm, A-P dimension 33 mm. The structure was heterogeneous due to fluid inclusions. The mass had suprasellar extension with the compression of the optic chiasm and the third ventricle; it was adjacent to anterior communicating arteries, extended laterally into cavernous sinuses with complete encasement of intracavernous internal carotid arteries (Knosp IV); it was adjacent to medial basal parts of temporal lobes and straight gyri. The anterior part of the mass bulged into the basilar sinus, the posterior part destroyed the clinoid plate and extended into the prepontine cistern with its moderate narrowing (fig. 1). The normal pituitary and its stalk were not differentiated. Findings: pituitary macrodenoma with supra-, infra-, retro- parasellar (D, S) extension (Knosp IV).

Ophthalmological examination findings: visual acuity OD=0.2 incorrigible, OS=up to 0.8 left of field; bilateral partial optic nerve atrophy. Perimetry discovered the narrowing of the visual field (fig. 2A). Hormonal tests excluded endogenous hypercortisolism and acromegaly (late-night salivary cortisol was 5.11 nmol/L (0.5-9.65), IGF-1 was 104.6 ng/ml (16-245)) and confirmed secondary hypothyroidism and secondary hyperprolactinemia (table 1, before surgery). The study of gonadotroph function determined the increase of FSH level while LH and testosterone were at the upper limit of the reference range (table 1, before surgery). The blood tests also showed high red blood cell count, increase of hemoglobin, hematocrit (table 1 before surgery), i.e. significant erythrocytosis in the setting of relatively normal values of other blood count results. Biochemical blood tests showed the creatinine level of 117.2 μmol/L (eGFR-EPI 58 ml/min/1.73 m2), signs of hyperuricemia, dyslipidemia; other tests demonstrated no significant clinical findings. It is noteworthy that during the previous 5-6 years the patient noticed plethora of his face, neck, trunk, but despite annual checkups the patient was not aware of erythrocytosis.

Ultrasound (US) of scrotal organs was performed on September 16, 2020: right testis volume was 22 ml, left testis volume was 20.7 ml. The ultrasound of abdomen on September 21, 2020 detected signs of hepatomegaly (the thickness of the right lobe was 13.4 cm, the left lobe was 6.2 cm), fatty liver disease, chronic calculous cholecystitis, normal spleen size of 10.1x5.2 cm.

Thus, based on the laboratory tests (high levels of LH, FSH, testosterone, secondary erythrocytosis), pituitary mass lesion verified by MRI, LH/FSH-secreting pituitary macroadenoma was suspected in the patient.

Taking into account the gonadotropin-secreting pituitary macroadenoma with chiasm compression, neurosurgery was chosen as the optimal treatment option. To prepare the patient for surgery in order to reduce the risk of thrombosis, whole blood exfusions were performed with saline replacements (3 procedures were made) to achieve peripheral blood target values (Hb up to 150-160 g/L, Ht under 51%). In September 2020 the patient underwent transnasal transsphenoidal adenomectomy in the Federal State Budgetary Institution «Endocrinology National Medical Research Center» under the Russian Ministry of Health. Intraoperatively neurosurgeons detected a yellow-brown tumor of moderately dense consistency which was fully removed. Histological findings showed a solid alveolar pituitary basophilic adenoma (fig. 3). The IHC study revealed the expression of LH in 80% of tumor cells (fig. 4) and of FSH (fig. 5) in 30% of tumor cells; weak reaction to somatostatin receptors type 2A (fig. 6) and type 5 (fig. 7) (IRS score 3) was found. The Ki-67 index was 3% (fig. 8). Thus, the diagnosis of LH/FSH-secreting pituitary adenoma was verified.

The development of adrenal insufficiency in the early postoperative period was noted (blood cortisol in the morning was 175.6 nmol/L; table 1, after surgery), and thus hydrocortisone replacement therapy was initiated. To correct the secondary hypothyroidism (table 1, after surgery) the consecutive treatment with levothyroxine was started with the initial dose of 50 μg. It was recommended to start pharmacological therapy for secondary hypogonadism (table 1, after surgery) with testosterone gel after performing prostate US. During the first week after surgery a tendency to hyponatremia was noted (up to 134 mmol/L), but water restriction (up to 1 L/day with gradual extension to 1.5-2 L/day) allowed the sodium level to normalize. Blood pressure and heart rate stayed within the normal range. The patient was discharged on the 13th day after surgery in satisfactory condition. Six months after surgery the patient was in remission: a laboratory study showed that hypogonadotropic hypogonadism persisted as well as secondary adrenal insufficiency and secondary hypothyroidism (table 1, 6 months after surgery). The patient was prescribed hydrocortisone, levothyroxine and testosterone. Ophthalmological examination findings: visual acuity OD=0.4, OS=0.8; bilateral partial optic atrophy (OS>OD), positive changes in visual field on perimetry (fig. 2B). The brain MRI on March 22, 2021 showed in the sella turcica, cavernous sinuses and in basilar bone sinuses a cystic solid mass lesion of heterogeneous structure (contained a cyst of 11x16x13 mm size) which incoherently accumulated the contrast media; the size of the lesion: vertical — 20 mm, transversal — 27 mm,

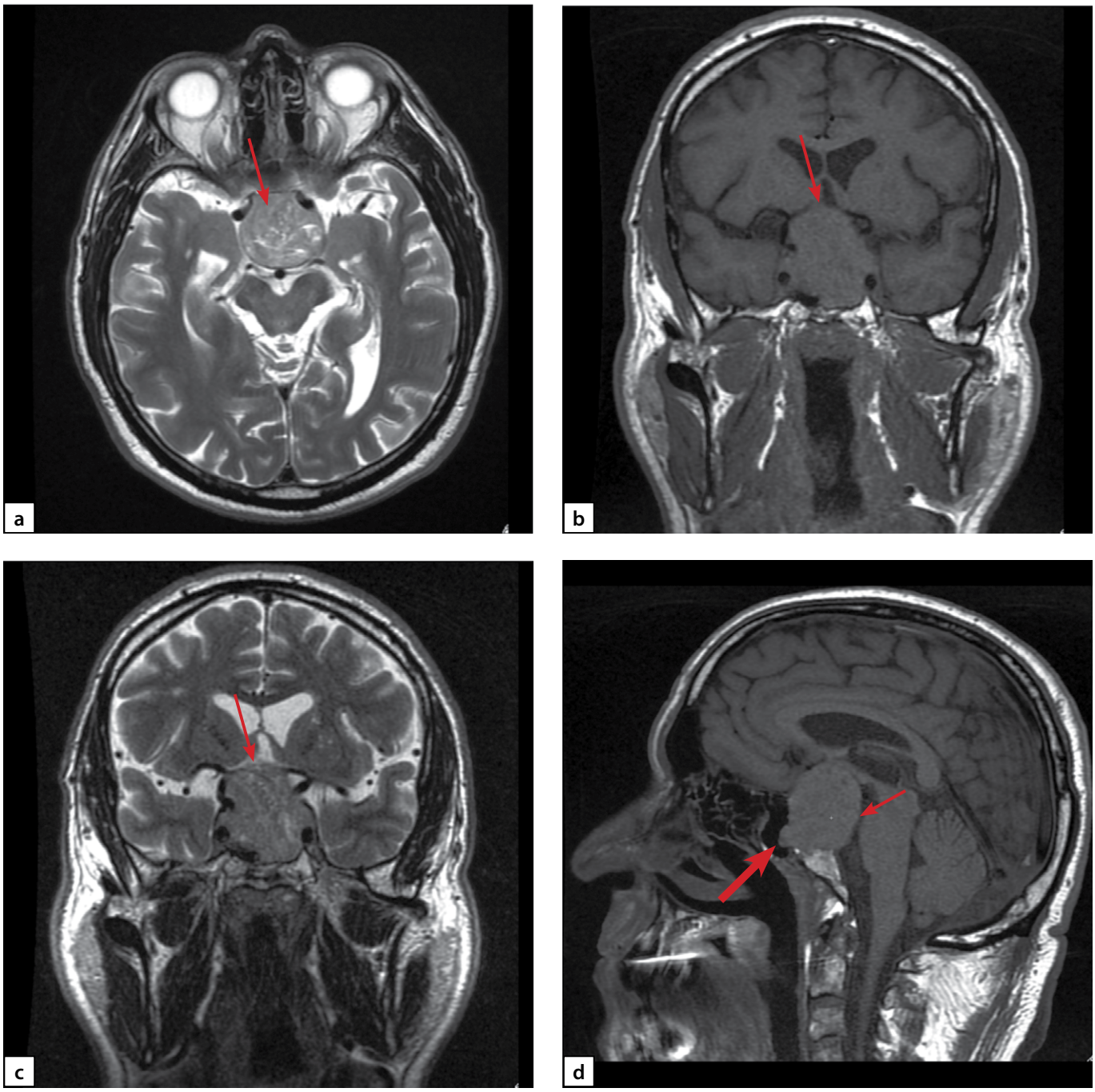

Figure 1. Brain MRI of patient G. Pituitary macroadenoma with supra-, infra- and retro- parasellar (D, S,) extension (Knosp IV):
a) T2WI (weighted image), axial projection. Pituitary adenoma (arrow); b) T1WI, coronal projection; c) T2WI, coronal projection. Optic chiasm compression (arrow); d) T1WI, sagittal projection. The adenoma infrasellar extension into the basilar sinus (thick arrow) and retrosellar extension into the prepontine cistern (thin arrow).

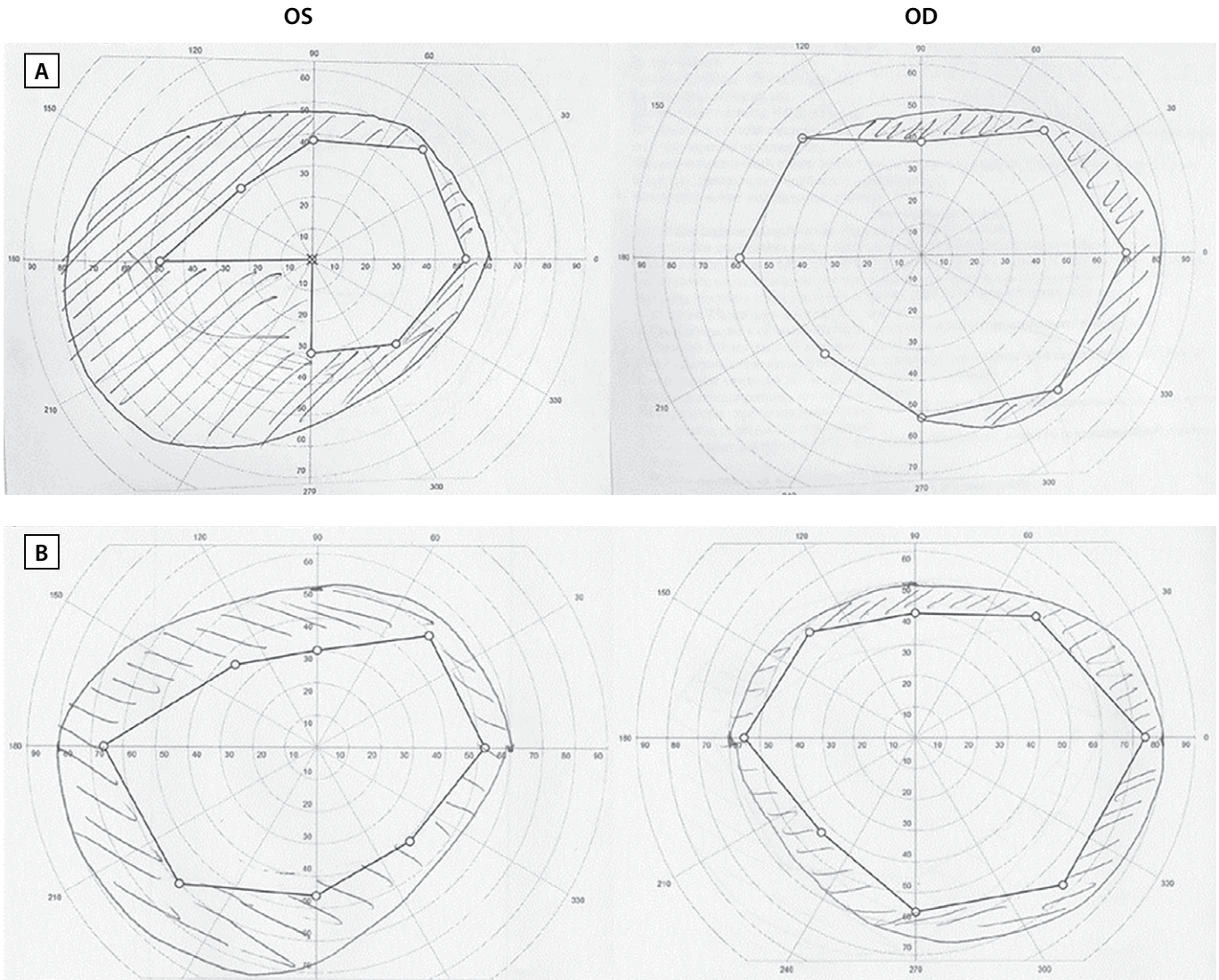

Figure 2. Perimetry findings before surgery (A, upper row) and 6 months after surgery (B, lower row). OS — left eye, OD — right eye.

Table 1. Laboratory parameters before and after surgery

Studied parameter, measurement units	Before surgery	After surgery	6 months after surgery	Reference range
Complete blood count				
Red blood cells, c/L	**6.66**x10^{12}	5.15x10^{12}	4.71x10^{12}	4.3-5.8x10^{12}
Mean corpuscular volume, MCV, fL	85.1	87.2	83.9	82-98
Hemoglobin, g/L	**196**	152	137	132-172
Hematocrit, %	**56.7**	44.9	39.5	40-51
Leukocytes, c/L	7.38x10^{9}	8.52x10^{9}	4.54x10^{9}	3.9-10x10^{9}
Platelets, c/L	20710^{9}	24910^{9}	20710^{9}	148-339x10^{9}
ESR, mm/h	9	19	18	2-20
Hormonal blood and urine tests				
LH, IU/L	10.3	**0.513**	**0.216**	2.5-11
FSH, IU/L	**22.5**	4.19	**0.87**	1.6-9.7
Testosterone, nmol/L	28	**0.62**	**0.271**	11-28.2
TSH, mIU/L	0.795	**0.088**	1.071	0.25-3.5
Free T4, pmol/L	**6.95**	**5.78**	**7.09**	9-19
IGF-1, ng/ml	104.6	-	52.36	16-245
Prolactin, mU/L	**562.1**	-	178.1	78-380
Cortisol blood in the morning, nmol/L	293.7	175.6	237.3	171-536
Daily urinary free cortisol, nmol/day	-	-	**52.7**	100-379

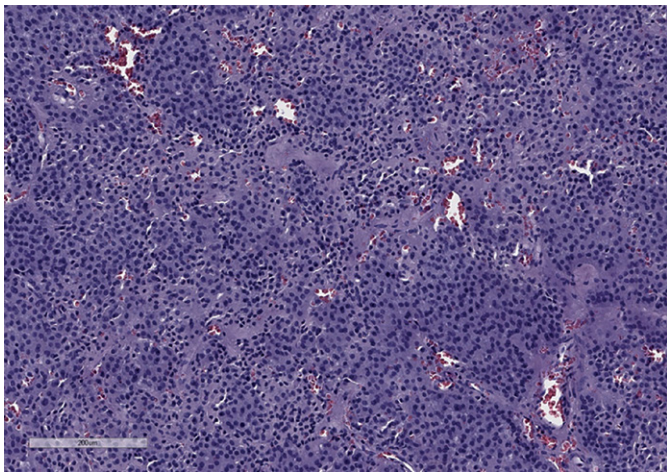

Figure 3. Tumor microstructure.
Stained with hematoxylin and eosin. Magnification x100.

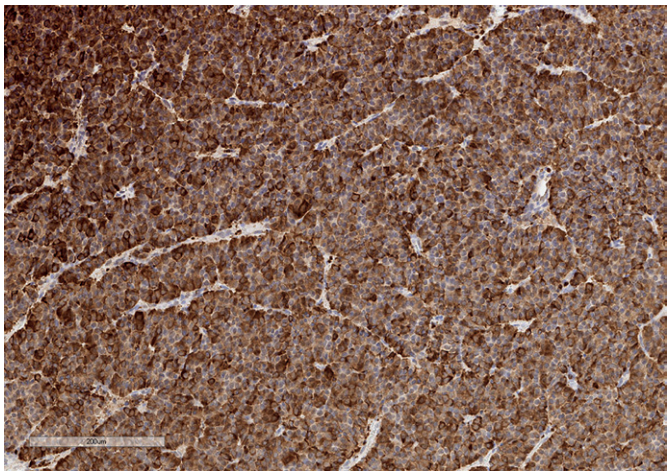

Figure 4. Luteinizing hormone expression by tumor cells.
Magnification x100.

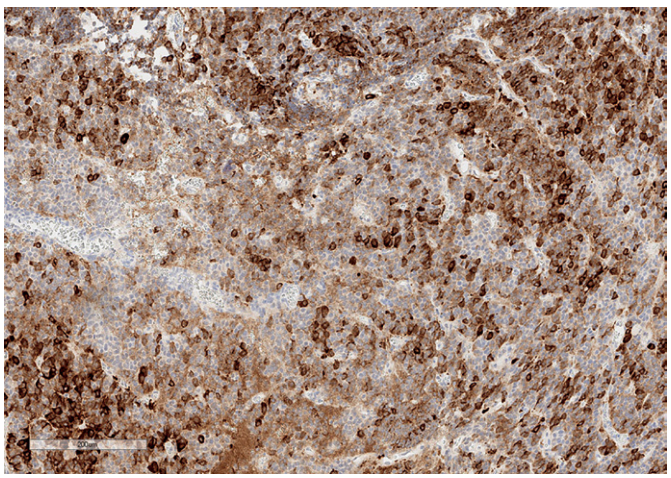

Figure 5. Follicle stimulating hormone expression by tumor cells.
Magnification x100.

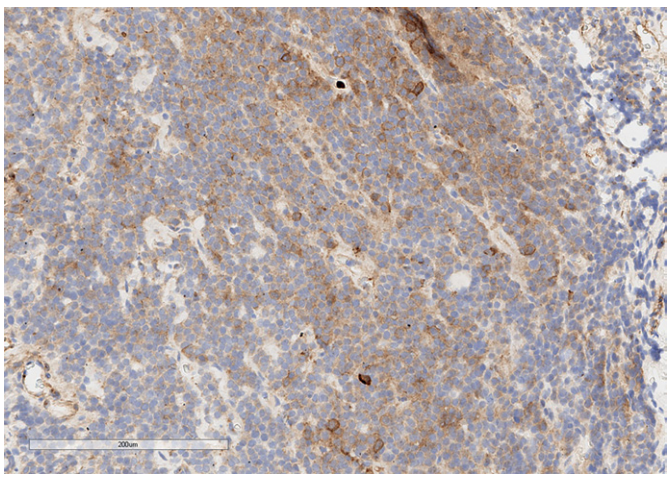

Figure 6. SSTR2A expression by tumor cells. Magnification x100.

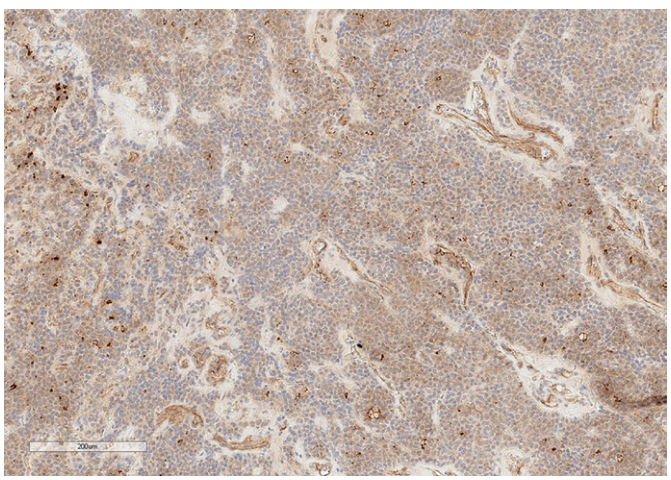

Figure 7. SSTR5 expression by tumor cells. Magnification x100.

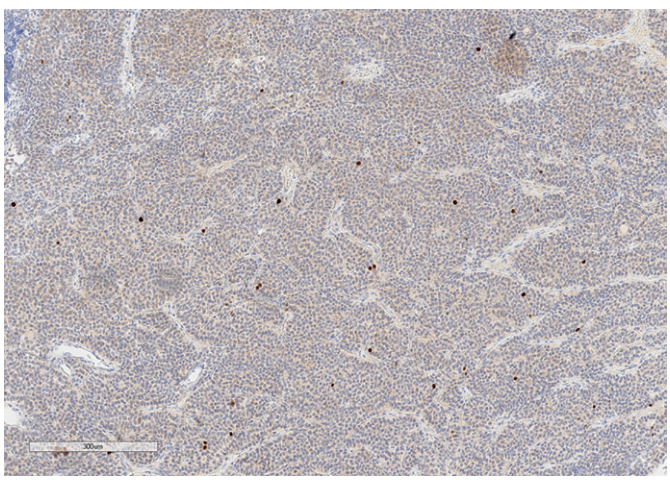

Figure 8. Tumor proliferative index (via Ki-67 expression).

A-P dimension — 25 mm; pituitary tissue was not clearly differentiated at the right edge of the lesion, stalk deviated to the right. Findings: the condition after the removal of a giant pituitary adenoma, mass lesion in the sellar region with infra- and parasellar (D, S, Knosp III) extension. Given that the laboratory study demonstrated remission, MRI data were considered as postoperative changes, and MRI dynamic follow-up was recommended.

DISCUSSION

The clinical case demonstrates difficulties in the early diagnosis of functioning gonadotroph adenomas. The peculiarity of this case is combined hypersecretion of FSH and LH with predominance of LH secretion by the tumor which led to the development of hyperandrogenism. Cases of functioning gonadotroph tumors in men described

in the literature (individual cases or small case series) mostly had FSH-hypersecretion by the tumor which led to testicular enlargement (while LH and testosterone levels were low or normal); a vast majority of tumors were macroadenomas causing visual impairment [2, 4, 8, 9, 18-20]. Some cases described had combined FSH and LH hypersecretion [3, 16, 17, 21-24]. In some singular presented cases a tumor secreted only LH [25, 26]. It is noteworthy that in most cases of combined FSH and LH hypersecretion causing testosterone level increase there were no clinical signs of hyperandrogenism [3, 16, 21, 23]. In other cases, clinical signs of hyperandrogenism included: spermatogenesis increase [22], libido enhancement [24], erythrocytosis [17]. It is also noteworthy that in some cases of FSH/LH-secreting adenomas with confirmed increase of LH and testosterone levels by the laboratory study, the IHC study of the removed tumor showed no LH expression [3, 24].

The main clinical manifestation of hyperandrogenism in the described case was the development of secondary erythrocytosis which had originated several years prior to the visual impairment development according to the medical history data. The main causes of secondary erythrocytosis development are presented in table 2. The existing recommendations for differential diagnosis of erythrocytosis consider excessive testosterone only when there was testosterone overdose and do not consider the probability of endogenous hyperandrogenism development [27, 28]. Moreover, in our case testosterone level was at the upper limit of the reference range and only «unsuppressed» levels of LH and FSH in the patient with pituitary macroadenoma indicated its excessive levels while with exogenous hyperandrogenism these levels would have been decreased. Taking into account the variety of causes of secondary erythrocytosis, it is possible to assume that the probability to detect a gonadotroph tumor at the moment of erythrocytosis onset in this case would have been low.

Surgical treatment is a method of choice to treat functioning gonadotroph adenomas as it allows eliminating tumor mass-effects (first of all eliminate its impact on chiasm) and achieve quick improvement of hormone levels [1]. There is no convincing evidence of pharmacological therapy or radiotherapy efficiency in the literature [1]. In our case there was remission after the surgical removal of the tumor, but hypopituitarism persisted and visual function was not fully restored.

Thus, in our clinical case as well as in most cases described in the literature, a functioning gonadotroph adenoma was diagnosed only at the stage of visual impairment when tumor mass-effects appeared. Currently there is no solution for possible earlier diagnosis of such tumors.

CONCLUSION

Unlike other functioning pituitary adenomas that have typical clinical presentation, the symptoms of gonadotropin-secreting tumors often escape detection till they become macroadenomas causing headache, visual field impairment and hypopituitarism. It is also important to remember that secondary erythrocytosis in men can be a sign of hyperandrogenism, and LH-secreting gonadotroph adenomas may be one of its causes.

ADDITIONAL INFORMATION

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Conflict of interest. The authors declare no obvious and potential conflicts of interest related to the content of this article.

Contribution of the authors. Elizaveta O. Mamedova — patient's attending doctor, literature data analysis, writing; Liliya S. Selivanova — histology and IHC studies; Kristina A. Potapova — writing; Svetlana A. Buryakina — MRI examination and interpretation; Vilen N. Azizyan — surgical treatment, editing; Andrey Yu. Grigoriev — surgical treatment, editing; Zhanna E. Belaya — final editing. All of the authors approved the final version of the article before publication, agreed to be responsible for all aspects of the work, implying proper examination and resolution of issues relating to the accuracy or integrity of any part of the work.

Patient consent. The patient signed the informed consent to the publication of personal medical information in an anonymized form.

Table 2. Erythrocytosis causes (adapted from [27] and [28])

Primary erythrocytosis
• Polycythemia vera
Secondary erythrocytosis
• **Generalized hypoxia**
• Smoking
• Carbon monoxide poisoning
• Pulmonary diseases
• Obstructive sleep apnoea
• Congenital heart disorder (right-to-left shunt)
• Living at high altitude
• **Local kidney hypoxia**
• Renal artery stenosis
• Hydronephrosis
• Polycystic kidney disease
• **Drug-associated**
• Testosterone
• Erythropoietin
• **Erythropoietin abnormal production by tumors**
• Hepatocellular carcinoma
• Renal cell carcinoma
• Cerebellar hemangioblastoma
• Parathyroid cancer
• Uterine leiomyoma
• Pheochromocytoma
• Meningioma

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