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Case report

Gonadotropin secreting pituitary adenoma associated with erythrocytosis: case report and literature review

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ABSTRACT

BACKGROUND: Most pituitary adenomas with FSH- or LH-positive immunohistochemistry are endocrinologically silent, and neurological symptoms due to their large volume are the first clinical signs; they are rarely reported to be secreting gonadotropins, this usually occurring in cases with clinical endocrine findings. Gonadotropinomas are often treated surgically because they are unresponsive to conventional medical therapies. Temozolomide was recently recommended for non-responder aggressive pituitary adenoma management. CASE REPORT: A 43-year-old male with a history of 5 years of erythrocytosis presented with severe headache, orthostatic dizziness, and difficulty walking. MRI documented a giant pituitary adenoma and high uptake of ^{111}In-pentetreotide indicated somatostatin receptor (SSR) expression. Biochemical tests revealed a secreting gonadotropinoma. Therapy with somatostatin analogs and dopamine agonists improved the patient's headache, achieved partial hormone control, slightly reduced the size of the adenoma, and controlled erythrocytosis. Six months after the diagnosis, hormone escape occurred despite therapy, thus neurosurgery was performed. After the procedure the patient died of untreatable intracranial hypertension. The surgical specimen revealed SSR 2 and 3 expression, and temozolomide did not induce apoptosis in primary cell culture. REVIEW OF LITERATURE: Among gonadotropinomas, female gender (77%), macroadenoma (84%), young age at diagnosis (28 ± 12 years), delay from first symptoms to diagnosis (up to 15 years), and ovarian cysts/menstrual disorders in females or macro-orchidism in males were the foremost clinical and neuroimaging features. CONCLUSIONS: Male gonadotropin-secreting pituitary adenomas may have a variable clinical expression secondary to testosterone excess. Somatostatin analogs, dopamine agonists or temozolomide may have a role that needs to be assessed case by case.

Key words: Erythrocytosis, Giant pituitary adenoma, Gonadotroph adenoma, Somatostatin analog therapy, Temozolomide

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INTRODUCTION

Pituitary adenomas are being identified increasingly often in the general population due to a better clinical approach to patients' clinical symptoms and to the widespread diffusion of neuro-imaging techniques.[1,2] Although most clinically non-functioning pituitary adenomas reveal LH- or FSH-positive immunohistochemistry, gonadotropin secreting pituitary adenomas are still rarely diagnosed[3,4] because of clinical signs relating to their hormone over-secretion, as for example in ovarian cysts in females or macroorchidism in young male patients.[3-26]

As for their treatment, surgery is the first choice, but little is still known about the efficacy of somatostatin analogs (SSA)[3,25] or dopamine agonists.[15,24,27] Temozolomide (TMZ) has recently been recommended in pituitary macroadenomas characterized by an invasive growth and resistance to conventional therapies (i.e. neurosurgery, radiotherapy or other medical treatments), particularly those secreting ACTH or prolactin.[28,29] The outcome of TMZ treatment may depend at least to some degree on the expression of O-6 methylguanine DNA methyltransferase (MGMT), a DNA repair enzyme that has the potential to interfere with TMZ;[30,31] a recent study revealed that TMZ reduced cell viability in gonadotroph pituitary adenoma cell lines.[32]

CASE REPORT

Clinical features

A 43-year-old Caucasian male had been referred to our Department of Medicine 5 years earlier with facial plethora, arterial hypertension (160/105 mmHg), a high red blood cell (RBC) count, i.e. 6.5 x 10^9/L (normal value [n.v.] 4.3-5.1 x 10^{12}/L), high hematocrit 61.1% (n.v. 36-46), high hemoglobin 200 g/L (n.v. 123-153), and a normal platelet count (160 x 10^9/L n.v. 150-450). A full work-up for erythrocytosis had been completed in accordance with the WHO criteria 2001[33]: red cell volume was found increased (46 ml/kg) and no cause of secondary erythrocytosis was detected (no evidence of familial erythrocytosis or elevated erythropoietin: 8 U/L, n.v. 11-20). Bone marrow biopsy revealed prominent erythroid proliferation and a mild increase in reticulin; a normal male karyotype was documented, with no evidence of bcr/abl rearrangement. No mutations of the JAK2 gene (both V617F and exon 12), the erythropoietin receptor gene (EPO-R) or the genes on the oxygen-sensing pathway (HIF-1 alpha, PHD2, VHL) came to light. A diagnosis of polycythemia vera was ruled out: the patient underwent regular phlebotomies and started antihypertensive and antiaggregant therapy.

CT of the brain was performed when he complained of mood swings, acute and severe headache, diplopia, orthostatic dizziness, and difficulty walking, revealing a giant mass in the skull base. The patient was referred to the Endocrinology Unit and brain MRI confirmed the presence of a giant cystic and solid pituitary adenoma in the skull base, 68x64x60 mm in size, with peritumoral edema. The pituitary adenoma invaded the posterior cranial fossa through the clivus; the anterior cerebral arteries were encased in the lesion, without stenosis (Figure 1). Whole-body single photon emission tomography/computed tomography (SPET/CT) was performed after the intravenous administration of ^{111}In-pentetreotide (Octreoscan), showing a very high uptake in the pituitary lesion consistent with the presence of somatostatin receptors (SSR).

We diagnosed a gonadotropinoma on the basis of the patient's hormone secretion profile: FSH 106.6 U/L (n.v. 1-14, LH 19.3 U/L (n.v. 1.5-9.2), α-subunit 6.2 U/L (n.v. 1-14), prolactin 17.3 μg/L (n.v. 5-15), inhibin-B 13 ng/L (n.v. 42-213), total testosterone 52.05 nmol/L (n.v. 10-29), SHBG 25 nmol/L (n.v. 13-71); the other pituitary hormones were all normal and any ACTH deficiency was ruled out by the results for cortisol using the 1 μg corticotropin test. Scrotal ultrasound documented testicles of normal size and structure, with a left varicocele. An automatic visual field evaluation revealed left temporal hemianopsia.

We documented a drop in FSH and LH levels after a short (8-hour) test with 0.1 mg octreotide injection, therefore therapy with octreotide 0.1 mg sc. twice daily was started. Two weeks later, FSH, LH, and total testosterone levels were still high, so we increased the dose of SSA to 0.2 mg three times a day, combined with cabergoline, up to a maximum dose of octreotide 0.5 mg three times a day and cabergoline 4 mg/week, depending on the patient's FSH, LH and testosterone levels (Figure 2). We opted to

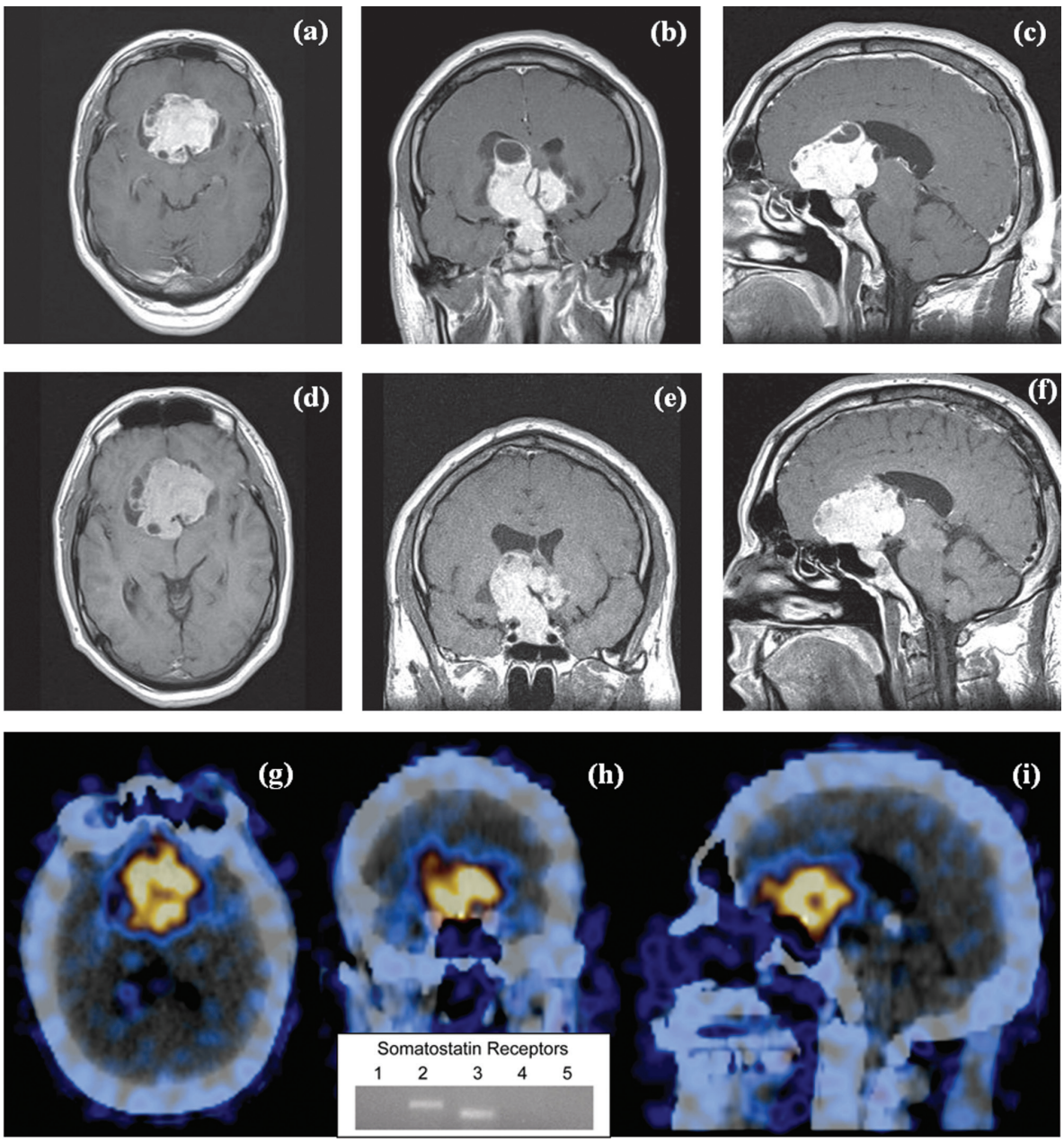

Figure 1. Gadolinium-enhanced T1-weighted MRI images: axial (a), coronal (b) and sagittal (c) views obtained at diagnosis; axial (d), coronal (e) and sagittal (f) MRI scan performed 4 months after medical therapy. 111In-pentetreotide (Octreoscan) SPET/CT: fused transaxial (g), coronal (h) and sagittal (i) images. In the box: PCR expression of somatostatin receptors 2 and 3.

try medical treatment first because of the high surgical risk and intercurrent retinal thrombosis (treated with low-molecular-weight heparin).

After 4 months of therapy, another MRI scan showed a slight shrinkage of the pituitary lesion (59x46x60 mm) and a significant reduction in the peritumoral edema (Figure 1). The SSA+cabergoline therapy resolved the headaches and restored normal testosterone (24.42 nmol/L) and LH (5.3 U/L) levels, while FSH remained high (FSH 50.9 U/L), but lower than at the baseline. The patient's RBC count also improved to 5×10^{12}/L and the phlebotomies were discontinued.

Six months after diagnosis, we documented a worsening of headache and diplopia with hormone

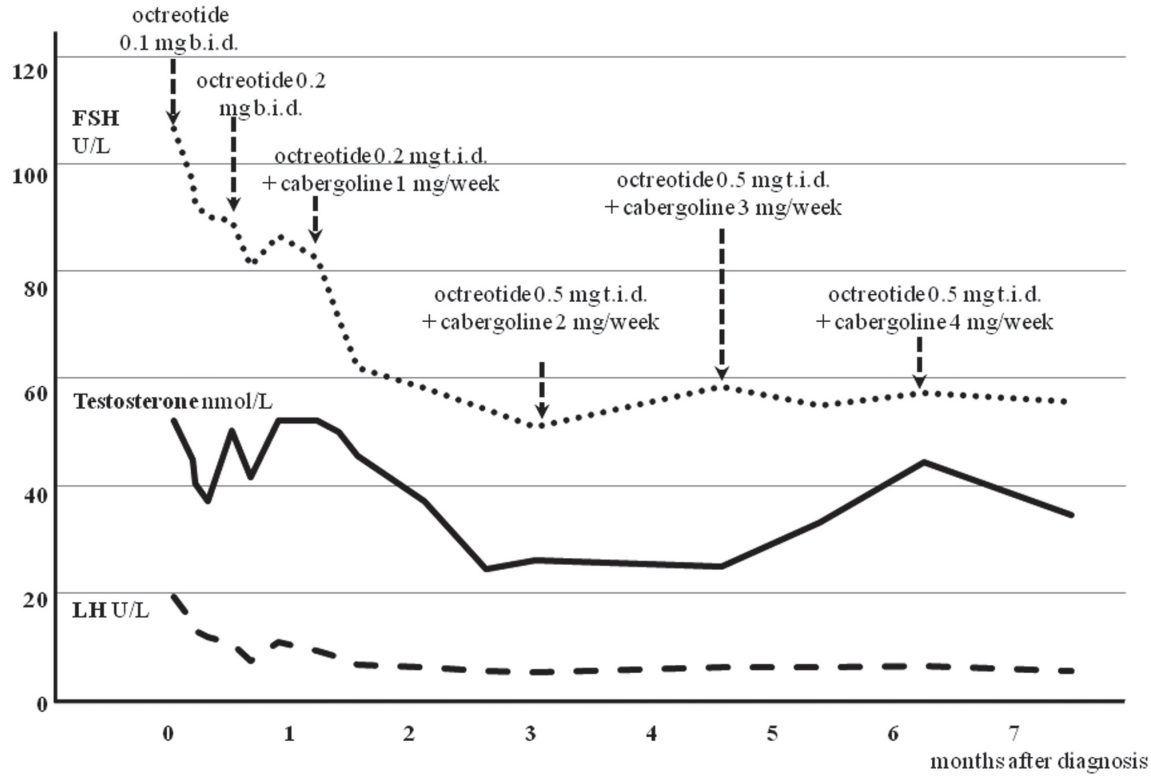

Figure 2. LH, FSH and testosterone levels in response to therapy.

escape, thus the patient underwent neurosurgery. He died 3 days after the surgical procedure (which was first trans-sphenoidal, then trans-cranial) due to severe intracranial hypertension with intralesional and intraventricular bleeding.

Histology

Histological examination was performed using light microscopy and standard hematoxylin and eosin staining. Antisera were directed against GH, prolactin, ACTH, FSH, LH, TSH, and p53; the MIB1 labeling index was evaluated. Histology revealed a cytologically uniform PAS (periodic acid-Schiff)-negative pituitary adenoma comprising sheets of monotonous cells interrupted only by a delicate capillary network. The adenoma cell nuclei were uniform, round-to-oval, and showed a delicate "salt and pepper" chromatin pattern; the nucleoli were sometimes enlarged. The cytoplasm was predominantly chromophobic or slightly acidophilic. Nuclear pleomorphism or multi-nucleation were absent. The proliferative index was low (MIB1 <3%) and only rare mitoses were reported. Immunohistochemistry was positive for FSH and LH, negative for ACTH, GH, PRL, TSH and p53 (Figure 3).

In-vitro study

The SSR profile was qualitatively assessed, collecting fragments from the surgical specimen of the tumor and extracting RNA as described elsewhere.[34] All primer sequences and polymerase chain reaction (PCR) conditions are available on request. SSTR2 expression was seen as well as SSTR3 (as expected, given the SSA uptake during the Octreoscan), while there was no sign of SSTR subtypes 1, 4 and 5 (Figure 1).

To analyze MGMT methylation status, DNA obtained from 10 μm paraffin-embedded sections of the lesion was modified with sodium bisulfite, which converts only unmethylated cytosine into uracil. Analysis of this modified DNA by methylation-specific PCR revealed unmethylated MGMT in the tumor specimens.

Tumor biopsy material was used to set up a primary culture to test the possible effects of TMZ on apoptosis. The tumoral specimen was dispersed after

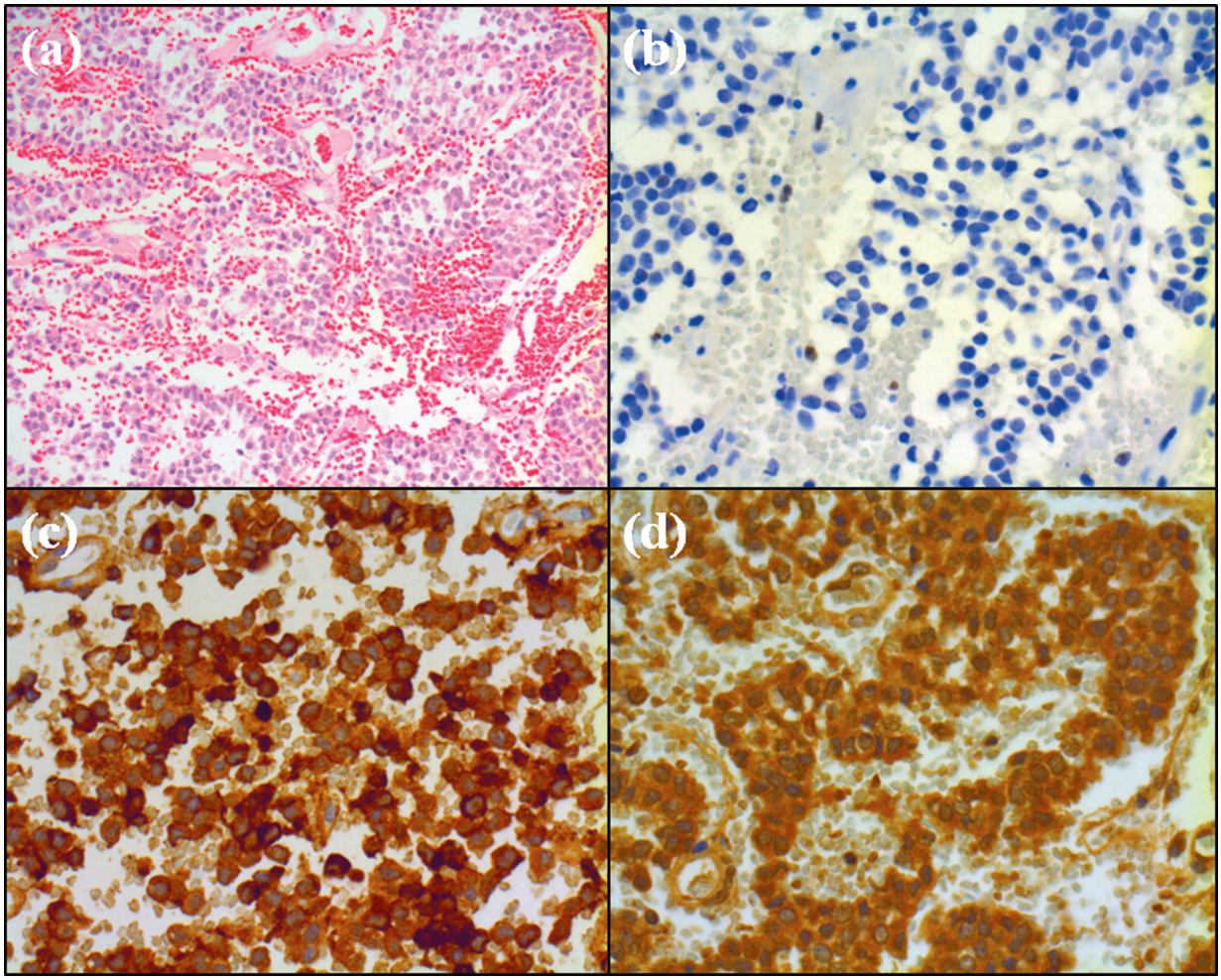

Figure 3. Biopsy specimen with hematoxylin and eosin staining (a), proliferative index with MIB-1 labeling under 3% (b), positive immunohistochemistry for FSH (c) and LH (d).

enzymatic and mechanical treatment, incubated in DMEM supplemented with collagenase 10,000 units/ml, 1 mg/ml hyaluronidase, 0.1 mg/ml trypsin inhibitor, and 40 mg/ml BSA for 1 hour at 37°C under gentle shaking. The cells were washed once in supplemented culture medium and their number and viability (always higher than 90%) were estimated using the trypan blue exclusion test. Then 10^5 cells/well were seeded in a polylysine-coated 48-well plate. After 24 hours, the medium was removed and the cells were treated with TMZ 100 μM for 24 hours. The primary cell cultures were then tested for apoptosis with the ApopNexinAnnexin V FITC Apoptosis Kit (Merck-Millipore, Germany). The cell cycle distribution was assessed using propidium iodide staining followed by cytofluorimetric analysis. Apoptosis rate in the TMZ-treated tumor cell culture was no higher than for the control cells.

LITERATURE REVIEW

The literature published in the PubMed database from 1982 to May 2012 on gonadotroph secreting pituitary adenoma was searched systematically, using the "related articles" function to identify any relevant publications. We looked for case reports with a full dataset as concerns sex, age, size of lesion, and the most important signs or symptoms prompting the suspicion of LH- or FSH-secreting pituitary adenoma. We did not consider gonadotroph pituitary adenomas diagnosed as a result of the presence of a pituitary mass and causing symptoms such as headache, deterioration of

visual field, or hypopituitarism. Including the patient described here, we identified 31 case reports, most of them involving females (24/31, 77%) with macroadenomas (4 micro- and 21 macro-pituitary adenomas); the mean age at diagnosis was similar for the two genders (28 ± 12 years) and there was a considerable delay from the onset of the first symptoms to diagnosis (ranging from 6 months to 15 years). The most important signs were ovarian cysts and menstrual disorders in females and macro-orchidism in males (Table 1).

DISCUSSION

Pituitary adenomas account for nearly 15% of all intracranial neoplasms, the majority being prolactinomas;[1,2] gonadotroph adenomas are difficult to diagnose because they are usually non-secreting, or they secrete biologically inactive peptides with no clinical effects, and they classically grow silently until neurological symptoms develop. Clinical signs or symptoms of gonadotropin hypersecretion are very rarely reported, involving a few premenopausal women with ovarian hyperstimulation syndrome and men with macro-orchidism.[3-26] In recent series, a large proportion of the adult patients undergoing surgery for non-functioning pituitary adenoma had a silent gonadotroph adenoma: the definitive diagnosis can only be established from a positive FSH/LH immunoreactivity.[35]

Here we present the unusual case, not previously reported in the literature, in which a pituitary adenoma was diagnosed due to its mass effect, though

Table 1. Gonadotroph cell adenoma diagnosed due to signs/symptoms of sex hormone hypersecretion in the literature

n, sex	Age (yr)	Duration (yr)	Size (mm)	Symptoms	Reference
2, F	8,10	NA	macro	Precocious puberty	DiRocco, 1982[5]
4, M	NA	NA	macro	Macro-orchidism	Heseltine, 1989[6]
1, F	13	NA	30	Metrorrhagia, ovarian cysts	Etzrodt, 1990[7]
1, F	31	1	14	Ovarian cysts	Djerassi, 1995[8]
1, F	34	6	40	Ovarian cysts	Christin-Maitre, 1998[9]
1, F	28	1	14	Ovarian cysts	Valimaki MJ, 1999[10]
1, F	10	1	macro	Ovarian cysts	Tashiro, 1999[11]
1, F	23	12	18	Oligomenorrhea, ovarian cysts	Pentz-Vidovic, 2000[12]
1, F	30	3	21	Galactorrhea, amenorrhea	Saveanu, 2001[3]
1, F	28	NA	30	Ovarian cysts	Shimon, 2001[13]
1, F	35	2	13	Oligomenorrhea, ovarian cysts	Castelbaum, 2002[14]
1, F	29	NA	7	Infertility, ovarian cysts	Murata, 2003[15]
1, F	21	NA	NA	Ovarian cysts	Murakami, 2004[16]
3, F	31, 30, 43	4/2/NA	9/17/61	Ovarian cysts	Mor, 2005[17]
1, F	40	NA	micro	Ovarian cysts	Maruyama, 2005[18]
1, F	27	NA	macro	Ovarian cysts	Kihara, 2006[19]
1, F	30	NA	NA	Ovarian cysts	Ghayuri, 2007[20]
1, F	40	15	27	Galactorrhea, ovarian cysts	Cooper, 2008[21]
1, F	31	NA	20	Galactorrhea, ovarian cysts	Castelo-Branco, 2009[22]
1, M	56	3	33	Macro-orchidism	Dahlqvist, 2010[23]
1, F	13	0.5	20	Ovarian cysts	Gryngarten, 2010[4]
1, M	12	1	9	Macro-orchidism	Clemente, 2011[24]
1, F	37	0.5	28	Metrorrhagia, ovarian cysts	Karapanou, 2012[25]
1, F	26	3	25	Oligomenorrhea, ovarian cysts	Garmes, 2012[26]
1, M	43	5	68	Polycythemia	This case

NA: not available.

the diagnosis could have been reached 5 years earlier, considering that erythrocytosis may be secondary to testosterone excess. In fact, when appropriate medical therapy was effective in reducing the patient's LH and FSH levels, the consequent drop in testosterone levels led to a normal erythropoiesis and bloodletting therapy was no longer necessary. Erythropoiesis is a process induced hormonally by erythropoietin and testosterone, which takes effect directly on bone marrow at polychromatophilic erythroblast level and enhances the synthesis of ribosomal RNA.[36] Some recent publications have reported that administration of testosterone is associated with serum hepcidin suppression:[37] hepcidin is a liver-derived peptide that binds to and degrades the iron channel ferroportin, and low hepcidin is associated with increased iron absorption and systemic transport, stimulating erythropoiesis. In this paper, Bachman et al reported that high testosterone levels resulted in a 60% suppression of serum hepcidin levels in a dose- and age-dependent manner within 1 week, though the mechanisms by which testosterone suppresses hepcidin remain as yet unknown. It is common knowledge that hypogonadism leads to anemia in men, that excessive erythrocytosis is the most common serious adverse event associated with testosterone replacement therapy and that the anabolic use of androgens induces an excessively high RBC count in athletes, but little is known about endogenous testosterone excess.[37,38]

In our case we found subnormal serum levels of inhibin-B, as already in reported in three out of five adults with macro-orchidism by Heseltine and Dahlqvist,[4,23] while Clemente described high inhibin-B in one male adolescent with macro-orchidism.[24] Moreover, all of six previous males described presented with macro-orchidism,[4,23,24] whereas our patients showed testicles of normal size and structure (leading probably to diagnostic delay). Testicular volume and inhibin-B secretion both depend on FSH levels, which stimulates seminiferous tubules.[6,24] In our cases the biological effects of FSH were not clinically evident, suggesting a secretion of less biologically active FSH or a reduced sensitivity to FSH, whereas LH was effective in increasing testosterone levels, leading to erythrocytosis.

For large pituitary adenoma one of the first treatment options is surgery. It was not the first choice for our patient because of the high surgical risk, given that the mass invaded the surrounding structures and there was an intercurrent retinal complication (for these same reasons we did not consider radiosurgery). Medical therapy was therefore attempted first, although only a few authors have reported on SSA[3,25] or dopamine agonist[15,24,27] treatments improving the signs or symptoms of hormone hypersecretion in gonadotropinomas. SSA uptake during the Octreoscan and the LH/FSH response to the acute octreotide test led us to suspect a finding of SSR in our patient (subsequently confirmed by the SSR 2 and 3 found in the tumor tissue by PCR), so we started SSA therapy; we then needed to add cabergoline to attain a better control. We did not consider androgen receptor antagonist in order to avoid a positive feedback on LH/FSH secretion. Moreover, we chose not to use gonadotropin-releasing hormone (GnRH) agonist or antagonist, because there is lack of expertise in male subjects: there is only one report describing the fact that GnRH agonist could induce a paradoxical increase in serum estradiol levels and may exacerbate ovarian follicular cysts,[14] and there are few experiences in woman with ovarian hyperstimulation[8,26,39-41] treated with GnRH antagonist with contradictory results. The patient's retinal thrombosis was believed to be secondary to the brain mass and erythrocytosis in combination, and it disappeared completely in 3 months.

Pituitary carcinomas are usually identified by the presence of pituitary metastases rather than by their malignant histological features.[42] Similarly, aggressive pituitary adenomas may exhibit a relatively benign histological appearance despite their local invasion, malignant growth patterns, encasement of vascular structures, and rapid enlargement. In addition, there is a subset of tumors classified as "atypical adenomas" accounting for 3-15% of cases in surgical series[35,43] that have been identified as potentially at risk of a more aggressive growth or malignant deterioration: these tumors are characterized by a MIB-1 above 3%, p53 immunoreactivity and a high mitotic index.[42] In our biopsy specimen, the proliferative index was low (MIB-1 <3%), immunohistochemistry was negative for p53, and we found only rare mitoses, meaning that the mass grew slowly year by year, leading first to hormonal conditions (erythrocytosis, arterial hypertension, mood swings).

Recent studies have shown that TMZ is effective in patients with pituitary carcinoma and aggressive pituitary adenoma failing to respond to conventional treatments.[29] The cytotoxic effect of TMZ relies on methylation of the guanine in the O-6 position in the DNA, which damages the DNA. MGMT is a DNA repair enzyme that removes the alkyl group adducts from the O-6 position, inducing TMZ resistance as a result.[30,31] MGMT expression in pituitary adenoma should not to be taken as a reason to deny treatment, and, according to a recent review, the best hormone and tumor response is seen in ACTH- and prolactin-secreting pituitary adenomas despite any MGMT expression.[29] In our in-vitro study, the tumor cell culture treated with TMZ revealed no higher rate of apoptosis than in control cells, correlating with unmethylated MGMT in the tumor specimens.

To sum up, gonadotropin-secreting pituitary adenoma in adult males may present with symptoms such as plethora due to erythrocytosis secondary to testosterone excess, as in the case described here. Combined therapy with SSA and dopamine agonists proved effective in terms of our patient's clinical picture and, to some degree, in reducing the volume of the mass, whereas using TMZ in this case would have been clinically ineffectual. A multi-disciplinary approach is needed for cases of aggressive pituitary macroadenoma with a view to ensuring a prompt diagnosis and effective treatment.

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DISCLOSURE STATEMENT

The authors have nothing to disclose.

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