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CASE REPORT

Pituitary apoplexy in an adrenocorticotropin-producing pituitary macroadenoma

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Abstract Adrenocorticotropin (ACTH) producing macroadenomas and pituitary apoplexy are unusual in Cushing' s disease. A 20-year-old man who had been diagnosed Cushing' s disease 2 months ago, presented with sudden headache, nausea, and vomiting. His serum cortisol level was 0.4 μg/dl and ACTH level was 23.9 pg/ml. Magnetic resonance imaging of the pituitary gland disclosed a hemorrhage in the pituitary macroadenoma (22 × 19 mm). He was treated with IV methylprednisolone immediately and then the symptoms were relieved within the first day of the treatment. The hemorrhagic lesion was resected by transsphenoidal surgery successfully. Impaired secretion of pituitary hormones may be seen after the pituitary apoplexy. We communicate a case with pituitary apoplexy of an ACTH secreting pituitary macroadenoma, causing acute glucocorticoid insufficiency.

Keywords Pituitary apoplexy · Pituitary macroadenoma · Cushing's disease · Glucocorticoid insufficiency

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Introduction

Pituitary tumor apoplexy is a rare but potentially life-threatening clinical syndrome, occurring often spontaneously as a result of hemorrhage and/or infarction in a pituitary adenoma. It is reported in 0.6–10%, usually <5% of all surgically resected pituitary adenomas [1–6]. Even though apoplexy can occur in all types of pituitary adenomas, it was shown in the studies that 45–70% of all adenomas developing apoplexy are non-secreting [1, 2, 6–8]. In addition, it occurs primarily in macroadenomas [1, 6, 9]. Cushing's disease resulting from an adrenocorticotropin (ACTH)-producing pituitary macroadenoma is mostly unusual [10]. Here, we describe a patient who developed pituitary apoplexy leading to acute glucocorticoid insufficiency with an adrenocorticotropin-producing pituitary macroadenoma.

Case report

A 20-year-old male was admitted to our outpatient clinic with complaints of erectile dysfunction and weight gain (20 kg in the last year). There was no history of drug use. Physical examination revealed moon facies, a buffalo hump, centripetal obesity (weight: 142 kg, height: 184 cm) and 1-cm-wide purple abdominal striae. His blood pressure was 130/80 mmHg. He had no muscle weakness, no facial plethora or visual disturbance.

Laboratory analysis produced the following data: fsh: 0.5 mIU/ml (normal 1.5–12.4), lh: 0.5 mIU/ml (normal 1.7–8.6), free testosterone: 4.2 pg/ml (normal 15–40), total testosterone: 2.06 ng/ml (normal 2.8–8). Due to symptoms of hypogonadotrophic hypogonadism and clinical signs of hypercortisolism, all pituitary hormones and hypothalamo-

pituitary-adrenal axis were examined. Serum ACTH level was 96.1 pg/ml and cortisol level was 40.09 μg/dl. All the results are shown in Table 1. Further biochemical tests were carried out in order to check hypercortisolism. Urinary free cortisol excretion was 556 μg/day (normal <60 μg/day). His serum cortisol failed to suppress during a 2 mg dexamethasone test (3.56 μg/dl). Thus, Cushing's syndrome was confirmed biochemically. Then, to determine the cause of Cushing's syndrome, 8 mg dexamethasone was given for 2 days and serum cortisol suppressed to 0.7 μg/dl. Magnetic resonance imaging (MRI) of the pituitary gland showed a pituitary macroadenoma (22 × 19 mm) (Fig. 1). Then, he applied to hospital with the complaints of severe headache, nausea, vomiting and fatigue. He did not have any visual complaint such as diplopia, restricted visual fields or decreased visual acuity.

Physical examination revealed a heart rate of 92 beats/minute, blood pressure of 130/70 mmHg, temperature of 37°C. He had no additional clinical signs other than described above. His morning serum cortisol level was 0.4 μg/dl and ACTH level was 23.9 pg/ml. The other pituitary hormone levels are also shown in Table 1. Magnetic resonance imaging (MRI) of the pituitary gland showed a hemorrhage in the pituitary macroadenoma (Figs. 2, 3). These findings led to the diagnosis of pituitary apoplexy in the macroadenoma. He was treated with methylprednisolone (20 mg IV 3 × 1 for 3 days, and then peroral methylprednisolone 7.5 mg/gün for 4 days). His response to the steroid administration was immediate: the headache, nausea and vomiting were relieved within the first day of the treatment. After the seventh day of the steroid treatment, he underwent the transsphenoidal surgery (40 mg methylprednisolone was given IV bolus before the operation). The hemorrhagic lesion was successfully removed by trans-sphenoidal surgery. Histological examination confirmed that the adenoma was entirely necrotic. All the pituitary hormones were measured on the

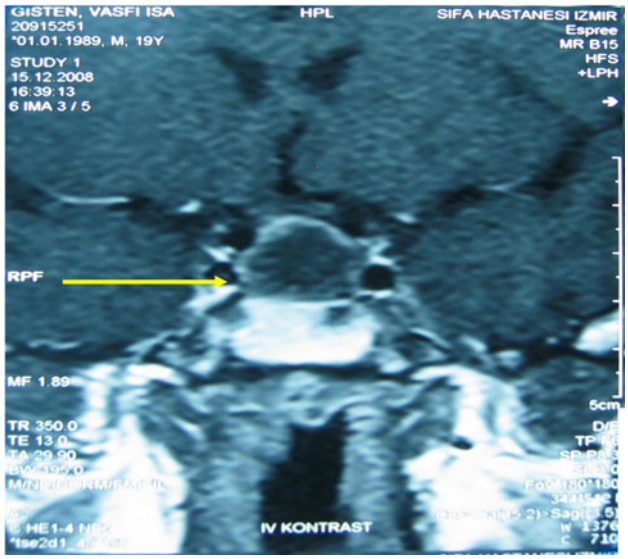

Fig. 1 Coronal contrast-enhanced magnetic resonance imaging (MRI) disclosing the cystic macroadenoma (22 × 19 mm)

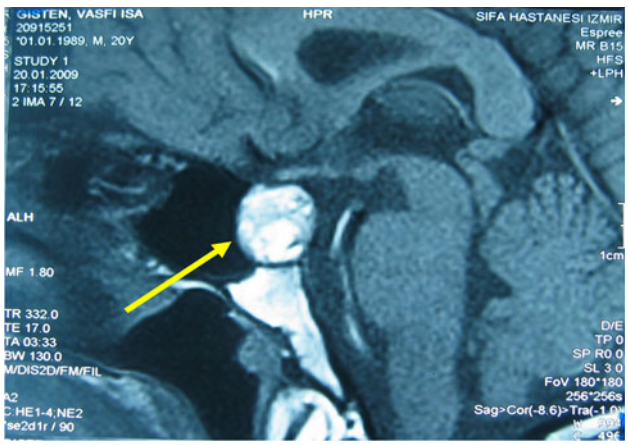

Fig. 2 Enhanced sagittal T1-weighted magnetic resonance images showing the hemorragic transformation in the cystic macroadenoma (subacute hemorrhage)

Table 1 Pituitary hormone levels of the patient

Pituitary hormone values (normal values)	Before the pituitary apoplexy	After the pituitary apoplexy	After the surgery (postoperative day 4 at 0800 h)
ACTH (10–46 pg/ml)	96.1	23.9	31.6
Cortisol (5–25 μg/dl)	40.09	0.4	0.2
Free T3 (2–4.4 pg/ml)	2.32	2.83	4.25
Free T4 (0.93–1.7 ng/dl)	1.29	1.26	1.35
TSH (0.27–4.2 μIU/ml)	1.86	1.42	3.72
Prolactin (4.04–15.2 ng/ml)	34.03	6.72	5.4
GH (0.06–5 mIU/ml)	0.15	<0.05	4.9
FSH (1.5–12.4 mIU/ml)	0.5	2.51	4.39
LH (1.7–8.6 mIU/ml)	0.5	2.87	4.03
Free testosterone (15–40 pg/ml)	4.2	–	6.9
Total testosterone (2.8–8 ng/ml)	2.06	–	1.73

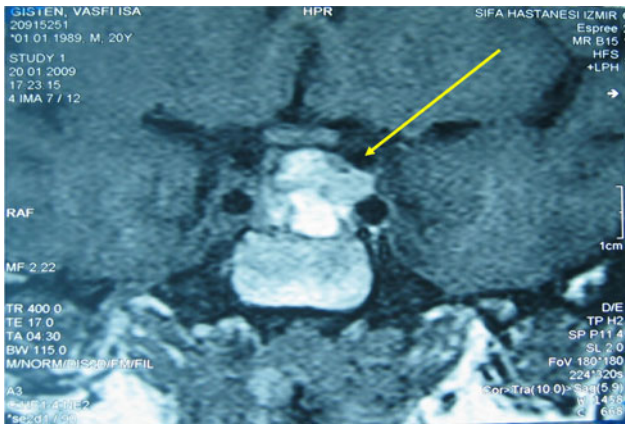

Fig. 3 Coronal contrast-enhanced MRI showing the pituitary tumor hemorrhage

postoperative day 4 at 0800 h (glucocorticoid supplementation was withdrawn 24 h ago) and these laboratory data are shown in Table 1. According to these results, he did not need thyroid hormone replacement and was recommended to continue the peroral steroid replacement treatment (7.5 mg/day methylprednisolone) and to follow up closely [11, 12]. He did not have symptoms such as erectile dysfunction or reduced libido after the operation, so testosterone replacement was not initiated postoperatively. It was planned to assess the pituitary hormones at 6 week postoperatively [13].

Discussion

Cushing's disease is the most common cause of Cushing's syndrome, apart from iatrogenic causes. It is caused by a pituitary adrenocorticotropin secreting adenoma and leads to cortisol hypersecretion. This patient presented with symptoms and signs suggestive of Cushing's syndrome. Biochemical evaluation indicated that he migt be suffering from Cushing's disease. MRI of the pituitary gland demonstrated a macroadenoma (22 × 19 mm). The majority of adrenocorticotropin secreting tumors are small microadenomas (<1 cm), but larger macroadenomas might develop in the 4–10% of the patients [14, 15].

Even though histological confirmation of the diagnosis of a corticotroph tumor is not available in our patient, the clinical and biochemical presentation, coupled with the spontaneous remission after apoplexy, strongly supports the diagnosis of Cushing's disease.

Pituitary apoplexy is rare in adrenocorticotropin secreting adenomas [16]. A possible explanation is that corticotrophinomas are usually microadenomas. In fact, the incidence of apoplexy in corticotroph macroadenomas can be fairly high [17]. Pituitary apoplexy is the result of spontaneous hemorrhage and/or infarction into the pituitary adenoma, frequently large macroadenoma. It is reported in 2–14% of patients operated on for pituitary macroadenomas [1–6].

The clinical picture of pituitary apoplexy is variable, however it usually presents with acute headache, nausea, vomiting and visual symptoms such as photophobia, ocular palsy, decreased visual acuity or visual field defects. Lethargy, reduced level of consciousness and fever may also occur. The earliest and the most frequent symptom of pituitary tumor apoplexy is sudden, severe, retro-orbital, frontal or diffuse headache. Our patient was admitted to our clinic with headache, nausea and vomiting. He had no visual defect or neurological defect.

Impaired secretion of pituitary hormones may be seen after the pituitary apoplexy [1–3, 18–21]. The extent and the severity of hypopituitarism vary among published reports. ACTH deficiency which can develop in 40–100% of the cases is clinically the most important one, because it leads to acute glucocorticoid insufficiency [18]. TSH deficiency can be seen in 25–80%, and gonadotropin deficiency in 60–100% of the cases [18]. Most patients with pituitary apoplexy have macroadenomas, therefore partial hypopituitarism can be seen in many patients even before apoplexy [21–24]. This patient had an ACTH secreting macroadenoma and hypogonadotrophic hypogonadism at the time of diagnosis. Two months after the diagnosis of Cushing's disease, he presented to the hospital with complaints of severe headache, nausea and vomiting. He was diagnosed with pituitary apoplexy and cortisol deficiency was detected secondary to the apoplexy. Serum cortisol level was measured as 0.4 μg/dl and ACTH level was 23.9 pg/ml. After the steroid replacement, he recovered immediately. While the patient did not have TSH, prolactin, or ADH deficiency, he did remain hypogonadal.

Hypopituitarism may develop because of the large macroadenoma's mechanical compression of the pituitary stalk and/or the portal vessels [21, 23]. In this situation, elevated serum prolactin levels may be seen, like in this case. Arafah et al. [24] clarified that the growth of adenoma causes increased intrasellar pressure, decreased blood flow through the portal vessels, and decreased delivery of the hypothalamic hormones to the anterior pituitary gland. If the intrasellar pressure increases suddenly and severely, ischemic necrosis of the gland becomes more extensive and so the recovery of the pituitary functions may be difficult after the decompression surgery [19, 24]. In a retrospective study including 37 patients, it was shown that long term steroid replacement therapy was necessary in 82%, thyroid hormone in 89%, vasopressin therapy in 11% of the cases and 64% of the male patients required testosterone replacement therapy[1]. Another study reported by Vidal et al. [25] showed similar findings; in 12 cases of pituitary apoplexy, eight cases had permanent panhypopituitarism,

two cases had pluritropic anterior pituitary dysfunction, and three cases had persistent hyperprolactinemia.

As a result, patients with symptoms of pituitary apoplexy must be evaluated clinically and provided hemodynamic stability immediately. All the pituitary hormone levels must be measured. Urgent imaging studies, such as CT or MRI should be obtained to confirm the diagnosis. As glucocorticoid deficiency is observed in the majority of the patients, the patients must be evaluated in this respect. If the deficiency is detected, glucocorticoid replacement should be supported rapidly. In most cases transsphenoidal decompression surgery is recommended urgently. After the surgery, pituitary hormone functions should be monitored carefully and the patients should be followed closely by imaging studies against probability of any residual tumor.

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