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Complex treatment of invasive corticotropic pituitary macroadenoma - Case report

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Abstract:

Introduction: Cushing's disease is a hypercortisolemic state caused by the excess secretion of corticotropin by the pituitary adenoma. Cushing's disease is diagnosed on the basis of clinical and laboratory signs of hypercortisolemia and the presence of an MRI pituitary adenoma. Pituitary surgery represents the first-line therapy, but it is non-curative in one third of patients, requiring additional treatments. Second-line treatments include pharmacotherapy, pituitary radiotherapy and bilateral adrenalectomy.

Keywords: macroadenoma; Cushing diseases; hypercortisolemia

Case report: A 57-year-old patient with clinical symptoms of hypercortisolemia was admitted to the Endocrinology Clinic due to dizziness and headache. Laboratory tests and MRI confirmed Cushing's disease caused by invasive pituitary macroadenoma. The tumor was not completely resected through the sphenoid sinus. Disease symptoms were remitted and hormone levels were stabilized. After 2 years, the underlying disease was relapsed. A second tumor removal operation was performed. The tumor was incompletely removed. The disease has progressed.. The patient was referred for stereotaxic CyberKnife radiotherapy.

Conclusion: Cushing's disease should be diagnosed and treated in a specialized endocrinology center, and the success of treatment depends on a multidisciplinary team of physicians consisting of an endocrinologist, neurosurgeon and neuroradiologist. About 50% of untreated patients die within 5 years of the disease due to complications of hypercortisolemia. Surgical treatment is effective in the case of microadenomas, while in the case of macroadenomas, it may turn out to be ineffective when the tumor is highly invasive. If subsequent surgeries are unsuccessful, treatment with radiotherapy or pharmacotherapy should be given.

Introduction:

Cushing's disease is a rare endocrine disorder characterized by excessive adrenocorticotrophic hormone (ACTH) secretion by a corticotroph pituitary tumor, consequently driving an excessive cortisol secretion by the adrenal glands. CD represents the most frequent cause of the endogenous type of Cushing's syndrome (CS), accounting for about 70% of cases of CS[13, 10]. Over 80% of ACTH-secreting pituitary tumors are microadenomas. The prevalence in the population is estimated at 40/million and the annual incidence is 1.2-2.4 / milion[13]. This disease often is diagnosed 3 to 6 years after the onset of the illness. The peak incidence of Cushing disease is in women between the ages of 50 and 60 years[16]. It occurs 2-8 times more often in women than in men [11]. Disorders related to the presence of microadenomas are associated with the overproduction of certain hormones. Large tumors, in addition to the excessive secretion of hormones, can cause a "mass" effect in the form of visual field disturbances - in the case of pressure on the optic nerves or headaches caused by an increase in intracranial pressure[1]. Despite their benign nature, they can infiltrate adjacent cavernous sinuses and their structures. This feature is predictive of the effectiveness of complete resection[2].

The main disturbance observed in Cushing's disease is the increase in the amplitude and frequency of pulsatile ACTH secretion. The consequence of this is the abolition of the ACTH and cortisol circadian rhythms. The inadequate, autonomous secretion of ACTH leads to the hypertrophy of the fasciculata and reticularis zones of the adrenal cortex and the excessive production of cortisol and adrenal androgens. The symptoms of Cushing's disease depend on the direct effect of hypercortisolemia on the organism [15,19]. It causes weight gain and fatty tissue deposits on abdomen, in the face (moon face) and around the midsection and upper back and between the shoulders (buffalo hump), pink or purple stretch marks (striae) on the skin of the abdomen, thighs, breasts and arms, thinning, fragile skin that bruises easily, slow healing of cuts, acne, thin arms and legs. Complications can include: muscle weakness, extreme fatigue, hypertension, cardiovascular complications, impaired glucose tolerance or diabetes, dyslipidaemia, osteoporosis, infections, depression and memory loss. Decreased libido, hypogonadism in men, and menstrual irregularity in women are the most common clinical features[18].

Cushing's disease is diagnosed on the basis of clinical symptoms and laboratory indicators of hypercortisolemia, and confirmation of the presence of pituitary adenoma in imaging tests. It should be remembered that, however, failure to visualize a focal pituitary lesion on MRI does not exclude Cushing's disease. Microadenomas are diagnosed in MRI only in 60% of patients[15,19].

If a primary ACTH secreting tumor is found, first-line treatment is surgical resection of the adenoma via trans-sphenoidal surgery (TSS)[20]. Preoperative medical treatment to improve hypercortisolemia is recommended, mainly using steroidogenesis inhibitors[21]. In a situation where the tumor is not visible both in MRI and intraoperatively, and the preservation of fertility is not important for the patient, subtotal hypophysectomy or hemi-hypophysectomy should be considered, (GammaKnife, CyberKnife) or pharmacotherapy [14]. Lastly, bilateral adrenalectomy can be used to provide an immediate reduction of cortisol levels in patients with Cushing disease[16]. This method allows for the control of hypercortisolemia in 100%, but is associated with lifelong replacement therapy of glucocorticosteroids and mineralocorticosteroids and the risk of developing Nelson's syndrome[14,19]. After bilateral adrenalectomy for CD, 21% of adults developed Nelson's syndrome, whereas corticotroph tumor progression without all of the features described by Nelson was observed on MRI in 50% of cases[22].

Materials and methods:

The patient's medical documentation covering the years 2013-2022 was analyzed. The following subjects were analyzed: history and physical examination, results of laboratory and imaging tests, and treatment history.

A case report:

57-year-old patient, initially hospitalized due to sudden onset of headache and dizziness accompanied by nausea. The CT examination revealed a pituitary tumor, which was then confirmed by MRI of the hypothalamic-pituitary system. An irregularly shaped pathological mass was found in the Turkish saddle with dimensions 24x33x28mm. Isointense, encapsulated lesion undergoing homogeneous contrast enhancement. The substantial mass of the tumor penetrated and filled the sphenoid sinus, emphasized the diaphragm of the saddle, but without modeling the optic nerves. The lesion was in direct contact with the cavernous sinus structures. The tumor mass comprised the right internal carotid artery with its normal diameter and patency maintained.

The laboratory tests performed showed the correct function of the thyrotropic, somatotropic and gonadotropic axes and the correct concentration of prolactin. On the other hand, attention was drawn to the increased concentration of morning ACTH, the rhythm of cortisolemia with a relatively high concentration of cortisol at night with normal urinary cortisol excretion. The Liddle test was performed, in which inhibition was not achieved after low-dose dexamethasone suppression test (LDDST), but was obtained after High-dose dexamethasone suppression test (HDDST). Based on the research conducted, ACTH-dependent Cushing's syndrome was found. Physical examination revealed the deposition of fatty tissue on the face, a symptom of "moon face", thinning of the skin with translucent blood vessels (plethora). Moreover, the patient had arterial hypertension (properly controlled) and hypercholesterolemia. Due to the concentration of cortisol in the circadian rhythm within the reference norms and the proper excretion of free cortisol in the diurnal urine, despite the abnormalities in the Dexamethasone inhibition test, it was not decided to include a steroidogenesis inhibitor as preparation for surgery.

The tumor resection through the sphenoid sinus was performed on July 19, 2013 at the Department of Neurosurgery of the Military Institute of Medicine in Warsaw. After the procedure, hydrocortison substitution was started at a dose of 30 mg per day. The histopathological examination confirmed the diagnosis of adrenocorticotrophic adenoma with immunohistochemical reaction: GH (-), PRL (-), ACTH (+), TSH (-), FSH (-), LH (-), int. alpha (-), MIB1 <3%, Ki67> 5%, in an electron microscope ultrastructural features of a sparsely granulated corticotrophic pituitary adenoma. The tumor was incompletely removed.

After two months, the hormonal function of the pituitary gland was assessed, after discontinuation of hydrocortison replacement therapy, no abnormalities were found. Therefore, this treatment was abandoned. Further hormone control has been recommended.

Control hormonal tests evaluating the function of the hypothalamic-pituitary system (2014 and 2015) were within the reference standards. The patient felt well, he did not report any headaches or visual field disturbances. MRI scan from December 2015. revealed a progression of residual tumor mass 18x17x17mm.

During hospitalization (June 2016), recurrence of subclinical ACTH-dependent Cushing's syndrome was diagnosed. The performed tests showed an abnormal rhythm of cortisolemia and ACTH, as well as no inhibition of 2 mg and proper inhibition of 8 mg of Dexamethason. MRI shows the progression of the residual tumor size to 21 x 21 x 23 mm. The tumor was in the immediate vicinity of the right internal carotid, covering more than 50% of its circumference, while the lumen of the artery was preserved. The patient did not report any complaints. He was consulted regarding the possibility of treatment with the GammaKnife method, but due to the location of the lesion, he was disqualified from this treatment.

In January 2018, the patient was hospitalized in the Department of Endocrinology due to increasing headache. Symptoms of arterial hypertension were found. The antihypertensive therapy was modified and the lercanidipine preparation was introduced with good results. The progression of the tumor dimensions (25x23x26mm) was described in the MRI examination. Consultation at the Neurosurgical Clinic was recommended. As a result of which the patient was qualified for surgery.

Transsphenoidal adenomectomy was performed. The tumor was incompletely removed. The MRI examination performed 3 months after the procedure revealed a lesion measuring 31x29x25mm. Moreover, the patient developed pain and weakening of the muscles of the lower limbs. Increased fatigue.

Dyslipidaemia secondary to hypercortisolemia, impaired fasting glycaemia and hypertension were diagnosed. It was decided to start treatment with an inhibitor of adrenal steroidogenesis. Due to the unavailability of ketoconazole, treatment with fluconazole (100mg) in the label off protocol was applied twice a day.

After one month, the efficacy of fluconazole treatment was assessed, showing a slight decrease in cortisol concentration in the daily urine collections compared to the baseline values. At the same time, a persistent, rigid circadian rhythm of cortisol secretion with its high concentrations during the night was found. At the same time, no undesirable effects were found. Therefore, the dose was increased to 400 mg/d with good tolerance. Due to the disqualification from operation, a decision was made to refer the patient to stereotaxic radiotherapy using the CyberKnife method. The procedure was performed on May 6, 2019. at the Department of Radiotherapy at the Institute of Oncology in Gliwice, additionally fluconazole therapy was continued.

During the next hospitalization (August 2019), the secretory function of the pituitary gland was assessed, with no abnormalities in the somato- and gonadotropic axis, the concentration of PRL was normal. In the corticotropic axis, the persistence of elevated ACTH concentration was still found, but a significant decrease was noted in comparison to the results from the previous hospitalization. A stiff rhythm of cortisol secretion with low levels in the morning was observed.

After one month, the patient reported symptoms in the form of progressive weakness, dizziness and loss of appetite. Due to the lowered level of cortisol, with its low excretion, Hydrocortison was introduced at a daily dose of 10 mg, and then, the second hypothyroidism was diagnosed and started for treatment the L-thyroxine.

Discussion:

Diagnosing Cushing's disease is difficult and complex. The clinical symptoms are not always characteristic; in addition, there is no single optimal test with the appropriate sensitivity and specificity to diagnose the origin of hypercortisolemia[5]. First of all, it is necessary to exclude the exogenous origin of hypercortisolemia, which gives the same clinical symptoms as Cushing's disease[7].

Screening tests are used to diagnose hypercortisolemia, confirm the loss of the circadian rhythm of ACTH and cortisol secretion, and feedback secretion disorders in the hypothalamic-pituitary axis[3]. The accepted guidelines for the diagnosis of Cushing's disease for the detection of hypercortisolemia recommend at least two selected screening tests[11]. Cortisol secretion is variable and dependent on pulsatile ACTH secretion. The highest concentration of cortisol is observed in the morning, while the lowest value is at midnight [3]. In patients with Cushing's disease, the circadian rhythm disappears. And the concentration of cortisol exceeding 200 nmol / l in the North allows the diagnosis of the disease with great certainty. However, it does not differentiate ACTH-dependent and ACTH-independent Cushing's syndrome. The concentration of free cortisol in the daily urine collection exceeding 3-4 times the upper limit of normal is likely to indicate Cushing's syndrome[6,26]. However, in 8-15% of patients these values may be correct. Midnight serum cortisol levels after awakening greater than 7.5 µg / dL are characteristic of hypercortisolemia. On the other hand, the concentration in saliva above 0.2 ng / ml in two independent measurements is 95% specific and sensitive in the diagnosis of Cushing's syndrome[5,26]. The determination of cortisol concentration in saliva is a measurement of the free cortisol fraction, therefore it is less likely to give false-positive results. In addition, it is a non-invasive method, all of the above features make that salivary cortisol is the best screening test for Cushing's syndrome. However, in Poland, this study is not widely available[6]. A valuable screening test for the detection of hypercortisolemia is the overnight dexamethasone suppression test (ONDST) with 1 mg dexamethasone. Reduction of the cortisol level below 1.8 µg / dL (50 nmol / L) precludes the diagnosis of Cushing's syndrome. The test that differentiates the etiology of hypercortisolemia is the determination of plasma corticotropin (ACTH). Due to the circadian rhythm of ACTH secretion, its highest concentration should be in the morning (8-9). In the case of a low concentration of ACTH (<10 pg / ml), ACTH-independent Cushing's syndrome is diagnosed, while when the concentration of ACTH is above 20 pg / ml, ACTH-dependent Cushing's syndrome should be diagnosed. The next step is to perform the classic Liddle cortisol inhibition test with 2 and 8 mg of dexamethasone. This test allows the differentiation of ACTH-dependent Cushing's syndrome in the course of pituitary adenoma from ectopic tumors producing ACTH or CRH. Ectopic ACTH secretion accounts for 10-15%. A reduction in urinary cortisol excretion or serum cortisol concentration to less than 50% of the baseline value indicates Cushing's disease. A reduction in urinary cortisol excretion or serum cortisol concentration to less than 50% of the baseline value indicates Cushing's disease.

A reduction in urinary cortisol excretion or serum cortisol concentration to less than 50% of the baseline value indicates Cushing's disease[9,14,19].

If ACTH-dependent Cushing's syndrome is diagnosed, MRI should be performed using gadolinium as a contrast agent. Only 60% of patients can diagnose microadenomas smaller than 10mm in MRI, which constitute 90% of cases[15]. In our patient the symptoms of hypercortisolemia were poorly marked, but the dominant symptoms were neurological symptoms (pain, dizziness, nausea and vomiting). Therefore, the patient first had a CT scan followed by an MRI of the head, which confirmed the presence of a tumor in the hypothalamic-pituitary region. Only then was the hormonal diagnosis performed which revealed subclinical ACTH-dependent Cushing's syndrome.

The treatment of choice is transsphenoidal removal of a corticotropic tumor (adenectomy), while maintaining normal pituitary function in the remaining tropic axes[17]. While disease remission is defined by a low serum cortisol (SC) in the immediate postoperative period and in some studies normal UFC and normal LNSC, there is no clear established definition of CD recurrence[23]. On the first or second day it should be less than 1.8 $\mu\text{g} / \text{dL}$ (50nmol / l)[8]. Other authors believe that a cortisol concentration below 5 $\mu\text{g} / \text{dL}$, assessed 6-12 weeks after surgery, is responsible for biochemical remission[3]. Persistent disease is defined as when the serum cortisol concentration exceeds 300 nmol / l [8]. Remission rates for CD following transsphenoidal surgery (TSS) vary between 42 and 90% and are considerably lower in macroadenoma cases. Recurrence after initially successful TSS may occur in up to 66% of cases, with a higher rate in macroadenomas cases[23]. Relapse occurs most often in the first 2 years after surgery[8].

This was the case with our patient. After two years, recurrence of hypercortisolemia was observed, and there was a constant progression in the dimensions of the residual tumor mass on MRI. The obtained result of the histopathological examination revealed a small-grain corticotropic pituitary adenoma with the Ki67 index above 5%. Small-grained tumors have a lower secretory activity, but a higher growth rate and are usually diagnosed as macroadenomas and are less frequently associated with remission of Cushing's disease compared to rich-grained tumors[12,17]. Moreover, some authors showed a significant relationship between the increase in the volume of the corticotropic adenoma and the higher category of Ki67% antigen expression[17]. In our patient, a recurrence of subclinical Cushing's syndrome was observed after two years. Gradual build-up of hypercortisolemia and neurological symptoms. Therefore, the patient was qualified for a second operation (2018). However, no remission was achieved, and even a very rapid progression of the tumor size and the intensification of clinical and biochemical symptoms of hypercortisolemia.

Stereotactic RT (SRT), including the Gamma Knife™ (GK), Cyberknife™, and proton-beam RT, has become the mainstream rather than the conventional fractionated RT (CRT) and could be a second treatment option for aggressive Cushing's disease if residual or recurrent tumors are visible on MRI despite TSS (GammaKnife, CyberKnife)[3,21]. However, regardless of the treatment modality, RT leads to tumour control in 83–100% of patients 76-90.

In contrast, endocrine remission occurs in 28–84% of treated patients after a variable time interval, which may extend to many years. These patients require medical therapy to control hypercortisolism until the salutary effects of RT occur.[8,24]. Due to the location of the tumor, the patient was disqualified from the GammaKnife method, but it was decided to use the CyberKnife method. In preparation for the procedure, a steroidogenesis inhibitor was introduced and its administration was continued while waiting for the effects of radiotherapy. Due to the difficulties in obtaining ketoconazole, it was decided to administer fluconazole after obtaining the patient's consent to use the drug on an "off-label" basis. Ketoconazole is the drug of first choice for the treatment of hypercortisolemia in Cushing's disease, but fluconazole is an alternative option when accessibility is difficult. The available literature emphasizes that this treatment is less effective than ketoconazole[4]. In our case, we observed a slight decrease in the biochemical markers of hypercortisolemia. Other authors describe that the result of the use of radiosurgery describes the achievement of biochemical control in Cushing's disease in 42-54% of patients within 45-55 months of using this method, with the onset of remission after 13-22 months[8]. Subsequent authors believe radiotherapy is a valid therapeutic option, with median remission rates of 80% (123 patients in 7 studies), no recurrence rate and a median time to remission of 8 months[25].

In the case of a patient treated in the Department of Endocrinology, earlier effects of radiotherapy were observed, and after 5 months the adrenocorticotrophic axis hypothyroidism was diagnosed, which was related to the introduction of hydrocortison substitution. Moreover, hypothyroidism was also found in the thyrotropic axis, and therefore L-thyroxine was included in the substitution treatment. Even patients with a cured Cushing's disease require lifelong follow-up as the disease may recur even after many years. Annual check-ups are recommended[8]. The patient described above remains under the constant care of the Endocrinology Clinic.

Conclusions:

1. Cushing's disease should be diagnosed and treated in a specialized endocrinology center, and the success of treatment depends on a multidisciplinary team of physicians consisting of an endocrinologist, neurosurgeon and neuroradiologist.
2. About 50% of untreated patients die within 5 years of the disease due to complications of hypercortisolemia.
3. Surgical treatment is effective in the case of microadenomas, while in the case of macroadenomas, it may turn out to be ineffective when the tumor is highly invasive.
4. If subsequent operations are unsuccessful, treatment with radiotherapy or pharmacotherapy should be used.

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