Apoplexy of clinically silent pituitary adenoma during prostate cancer treatment with LHRH analog

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Abstract

LHRH analogs have become a promising modality in prostate cancer therapy as an alternative to surgical castration, and the use of these agents is generally considered to be safe. Since now, only few cases of an apoplexy of previously undiagnosed pituitary adenoma (usually gonadotropinoma) at the beginning of therapy have been described in the medical literature.

We present a case of a 74 year old patient who was diagnosed of prostate cancer at the age of 68. There was no evidence of metastatic disease. Radical prostatectomy was performed and LHRH analog gosereline (Zoladex 3,6 mg s.c.) was administered. During the first day after gosereline injection the patient developed headaches that became more severe over the next 3 days. Then the patient experienced nausea and vomiting, double vision and eyelid ptosis. On the 5th day the patient temporarily lost consciousness and was admitted to hospital.

Imaging (computerized tomography, magnetic resonance imaging) revealed the presence of a pituitary tumor and hemorrhage within the gland. There was no evidence of pituitary dysfunction in hormonal studies. Neurosurgical intervention was postponed for 5 days after admission. Pathological mass with signs of recent hemorrhage was removed via transsphenoidal route. The tumor had negative immunohistochemical GH, ACTH and PRL staining. Neurological impairment resolved within 9 months after the operation. As a result the patient required adrenal and thyroid replacement. During 6 years of follow-up there was no evidence of prostate cancer recurrence.

INTRODUCTION

The term "apoplexy" refers to sudden neurological impairment of vascular origin. Apoplexy of the pituitary gland (pituitary apoplexy – PA) is infrequent, however due to pituitary crucial role in maintaining hormonal homeostasis and close anatomical relation to important brain structures, PA is a medical emergency and requires prompt diagnosis and appropriate management.

PA is associated with distinctive clinical syndrome that consists of sudden headache, conscious-

CASE REPORT

ness impairment, nausea, vomiting, vision field defects and oculomotor palsy [1]. The course of PA can also be atypical or asymptomatic.

The majority of PA occurs spontaneously [17] however some cases can be precipitated by specific conditions. These conditions include head trauma, pituitary irradiation, arteriography, pregnancy and several pharmacologic agents i.e. anticoagulants [14], izosorbide dinitrate [3], chlorpromazine [21], bromocriptine [22] and others. PA is also thought to be facilitated by pharmaceuticals that stimulate anterior pituitary hormones secretion i.e. LHRH, TRH, insulin and CRH during pituitary reserve assessment [10,11,19].

Since the implementation of LHRH agonists into therapy, the number of indications for the use of those drugs is still increasing. The indications include uterine leiomyomas, endometriosis, gonadotropin-dependent precocious puberty, perimenopausal syndrome, ovarian androgenic hyperfunction and stimulation of ovulation. LHRH agonists are also used in therapy of several hormone-dependent neoplasm i.e. prostate and breast cancers.

CASE REPORT

68 years old man without previous medical history underwent prostate cancer annual screening. He had no complaints about his health condition. Digital rectal examination revealed mild prostate swelling. His serum prostatic specific antigen (PSA) 18,8 ng/mL (norm < 4), free PSA 0,98 ng/mL (norm < 0,72). Cystoscopy and prostate fine-needle biopsy were performed. Biopsy specimen microscopic examination revealed prostate cancer cells. There was no evidence of distant metastases in radiological imaging including bone scintigraphy. In October 1997 the patient underwent radical prostatectomy. Histopathological examination confirmed the diagnosis of prostate cancer (G1/G2). There were no metastases in regional lymph nodes. After the surgery serum PSA concentration decreased to 1,3 ng/mL. During the next 6 months a constant rise in PSA level was observed. Consequently, the decision of starting LHRH therapy (gosereline, Zoladex 3,6 mg sc monthly) was made.

4–6 hours after administration of the first dose of Zoladex mild headache occurred. The patient treated himself with acetaminophen with quite good effect. Headaches were remitting and relapsing over the next 3 days. On the 5th day (during ferry travel to Sweden) the patient experienced severe headache accompanied with nausea, vomiting and transient loss of consciousness. Two days later he developed double vision and ptosis of the right upper eyelid and was transported to hospital.

Anisocoria and ptosis of right upper eyelid were observed. Computerized tomography and magnetic resonance imaging of the sella turcica and its surroundings revealed the presence of pathological mass corresponding to pituitary adenoma with internal hemorrhage and subsequent compression of the right cavernous sinus (Fig. 1). Hormone concentrations was measured – FSH was 13 IU/L (norm < 20), LH 0,76 IU/L (norm 1,5–9,2), testosterone 1,2 nmol/L, free T_4 11,5 pmol/L, α subunit 0,26 IU/L (norm < 0,9), cortisol < 28 nmol/L. It must be emphasized that due to signs of cerebral edema the patient was receiving full dose of dexamethasone.

Transsphenoidal tumor removal was carried out. The tumor appeared yellow-white and grainy in macroscopic examination. Inside the tumor, near its right margin, a hematoma was found corresponding to a recent hemorrhage. During the operation pituitary gland appeared flattened with stalk displaced under the diaphragm of the sella turcica. Histopathological examination revealed pituitary adenoma with signs of recently accomplished apoplexy. Immunohistochemical examination did not confirm the presence of GH, ACTH and PRL in tumor cells.

Postoperative complications did not occur. Complete recovery of the right oculomotor nerve function was observed during the next 3 months. He was treated with gosereline for 1 year. The patient requires substitution with hydrocortisone and L-thyroxine. There is no evidence of pituitary tumor recurrence in radiological examinations. Hormonal follow-up: FSH 0,46 mIU/ml (norm 1,6–11,0); LH < 0,1 mIU/ml (norm 0,8–6,1); testosterone < 0,02 ng/ml (norm 2,62–15,9).

Currently there are no signs of local prostate cancer recurrence neither metastatic disease. Total PSA concentration remains normal and free PSA is below or equal to the assay sensitivity level.

DISCUSSION

Described patient might be the next example of PA during prostate cancer treatment with LHRH analogs. We found seven similar cases in medical literature including descriptions of PA complicating therapy with goserelin [2,6], leuprolide [7,8,13,18] and triptorelin [4]. Symptoms developed from several minutes to nine days after drug administration. Macroadenoma was present in each case. Six of seven described patients underwent surgical pituitary decompression – histopathological examination always revealed gonadotropinoma. One conservative treated patient had serum hormones levels characteristic for gonadotropinoma. In our case we could not confirm the gonadotroph origin of the pituitary adenoma but we could not exclude it either.

PA affects mostly male, but LHRH receive mainly women – this fact remains as open question. We found only one case of PA in female population with 22 years old woman receiving leuprolide as a preparation to ovum donation [7]. Symptoms occurred five days after the procedure had begun. Besides typical neurological symptoms unexplained high fever with negative microbiological investigation and deep hyponatremia was noted. Surgery was carried out and postoperative microscopic examination revealed gonadotropinoma.

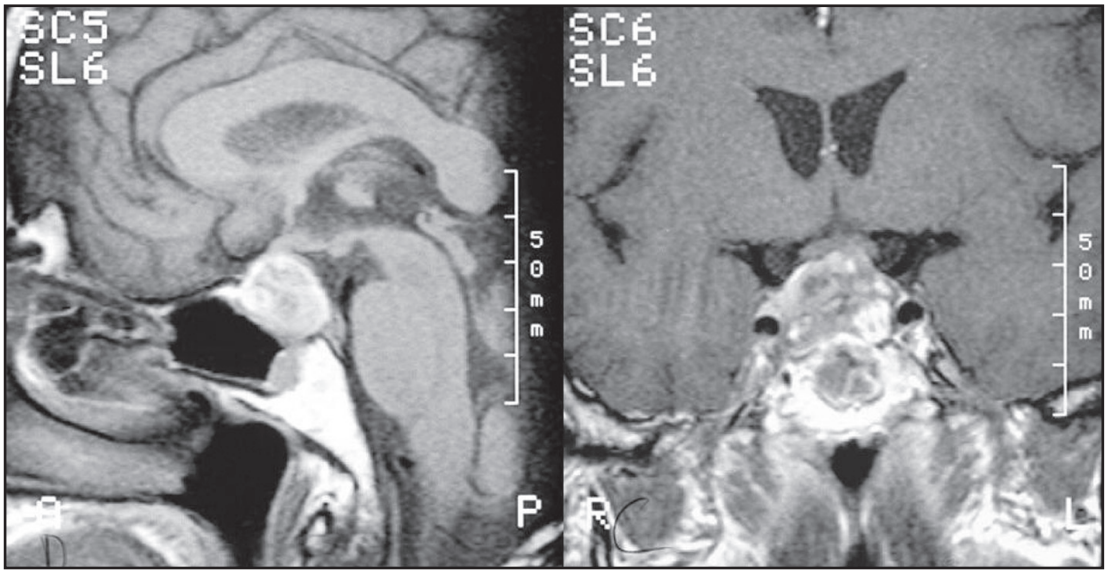

Figure 1. MRI of the sella turcica region - pathological mass corresponding to pituitary adenoma with internal hemorrhage and compression of the right cavernous sinus.

Patophysiology of PA has not been clarified yet. Vascular theory is commonly mentioned, according to this tumor compresses arteries and it leads to impairment of pituitary nutritive microcirculation. Branches of superior hypothalamic arteries running in cavernous sinus are thought to be compressed first [20], but occlusion of inferior hypothalamic arteries branches arteries results in ischemia and subsequent infarction [16]. Other hypothesis emphasized role of pharmacologic agents (including LHRH agonists), they may act directly on tumor's microvasculature leading to vasoconstriction and thus to oxygen and nutritional impairment [12,15]. Another hypothesis assume that liberins administration cause metabolic hyperstimulation triggering sudden tumor mass increase, vasculature compression and finally oxygen lack [5,9].

Symptoms of clinically overt PA depend on the extent and direction of tumor spread, and on the extent of necrotic and hemorrhagic mass. Sudden onset severe headache is the main complaint. Meningismus accompanied sometimes by fever speaks for the blood and necrotic debris penetration to the subarachnoid space. Vision field deficit and seldom visual sharpness loss are signs of the suprastellar expansion, however compression of cavernous sinus vasculo-nervous bundle causes ophtalmoplegy. Consciousness disturbances may also appear.

Acute multihormonal pituitary failure develops due to anterior lobe destruction. The failure is often permanent. The somatotroph function is most often impaired (app. 88% of cases). Gonadotropin deficiency occurs in 43–64%, secondary adrenal failure in 58–82%, secondary hypothyroidism in 45–89% of cases [17]. Because of independent anterior pituitary lobe blood supply diabetes insipidus develops exceptionally.

PA may be accompanied by ischemic stroke related to reflex vasoconstriction. This mechanism is well documented in several cases. Another hypothesis suggest that the enlarging intrasellar mass can compress carotid artery in its cavernous portion [15].

Significant hyponatremia of unknown origin can develop during the course of PA. It has been suggested that secondary hypothyroidism, secondary adrenal insufficiency or inadequate ADH secretion are responsible for that phenomenon, but it has not been well documented yet [17].

Management of PA is a matter of controversy. Only progressive visual field deficit or progressive mental state deterioration are the indications for emergency surgery. Meningismus and ophtalmoplegy are not indications for instant surgical procedure as they often resolve spontaneously. In cases similar to our delayed surgery (7–10 days) after stabilization of patient health state and correction of hormonal disturbances is recommended. This strategy significantly improves the prognosis. Mortality in clinically overt PA has decreased from 100 to 6,7% over the last three decades. This fact is assigned to improvement of neurosurgical technique and better preoperative hormonal deficit management. Normalization of eye movement range is almost a rule but visual field deficits usually persist. Also anterior pituitary insufficiency is often permanent.

Many information about potential risk of LHRH agonists administration has been gathered so far and these drugs are usually concerned safe. Nevertheless physician should be aware of serious complications resulting in life-threatening condition. This issue will be more intensively discussed if drug indications and availability still increase.

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