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Combined Treatment with Buserelin+Cabergoline in Patient with Prostate Cancer and Pituitary Macroprolactinoma

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ABSTRACT

Twelve years following hemicolectomy for colon adenocarcinoma, a 75-year-old patient with prostate cancer was treated for 4 weeks with the antiandrogen nilutamide and then with the long-acting GnRH agonist buserelin. The serum testosterone and prostate-specific antigen levels had decreased dramatically after 3 months of treatment. After 2 years of buserelin administration, the hormonal state was examined. Serum estradiol, testosterone, DHEA, DHEAS, FSH and LH levels proved to be suppressed, but the serum PRL concentration was extremely high (3 365 mIU/l). The pituitary MRI revealed a macroadenoma. The patient was treated with the dopamine agonist cabergoline, together with buserelin. After 9 months of this combined treatment, the prostate-specific antigen and testosterone levels were very low; the serum estradiol, DHEA, DHEAS, FSH and LH concentrations remained suppressed. The serum PRL level fell dramatically to 6.95 mIU/l, and a significant reduction in tumor size was observed on MRI. In conclusion: Combined buserelin + cabergoline treatment proved a highly successful procedure to cure this patient with prostate carcinoma and subsequent pituitary macroprolactinoma.

Keywords*: *Prostate cancer, Prolactinoma, Buserelin; Cabergoline

1. Introduction

It has long been known that prostate cancer displays an androgen sensitivity [1], and the different treatments of prostate cancer are based on the blockade of androgen production. This can be achieved by surgical castration [2, 3] or by chemical or hormonal suppression of the androgens. Initially, stilbestrol was administered, with moderate success, but with significant side-effects [4]; later, treatment with the steroidal antiandrogen cyproterone acetate [4] or the nonsteroidal flutamide [5] was introduced.

In 1983, a new potent luteinizing hormone releasing hormone analog was synthetized: [D-Ser(Bu^t)^6] LHRH–(1-9) nonapeptide ethylamide (busereline, BUS) [6,7]. Treatment with BUS greatly reduced the serum testosterone and prostate-specific antigen (PSA) levels [8]. The rate of production of testosterone was lowered to values comparable to those observed after bilateral orchidectomy [10]. Chronic treatment of prostate carcinoma with BUS, generally in patients with advanced metastatic prostate cancer, was reported to be a safe, nontoxic and effective form of palliation [8,9].

The prolonged administration of BUS blocks gonadotropin release and thereby achieves the effective suppression of gonadal steroidogenesis [7]. There is no uniform opinion in the relevant literature as concerns the possible changes in prolactin (PRL) secretion following BUS treatment: unchanged or decreased [10,11] and increased [12] PRL levels have all been observed. The various changes in PRL secretion following BUS treatment may be explained by differences in individual sensitivity, in the doses of BUS applied, in the duration of treatment, etc. Grotas and Nagler described the case of an 87-year-old man with prostate adenocarcinoma who had high PRL levels and a pituitary macroadenoma [13].

The present paper reports on a case with prostate cancer treated with BUS, the development of prolactinoma

after 3 years of BUS administration, and the effects of combined BUS + cabergoline (CAB) treatment.

2. Case Report

In 1997, a 63-year-old man underwent a hemicolectomy because of colon adenocarcinoma (Grade: I. Dukes B2). Neither regional nor systemic metastases were detected. No X-ray or cytostatic treatment was given postoperatively. The patient was regularly controlled by colonoscopy, abdominal ultrasonography, whole-body isotope examinations and serum carcinogenic antigen (CEA) concentration determinations. No recurrence or metastasis of the colon carcinoma was observed during the subsequent 12-year period. Besides the serum CEA, the serum PSA level was also determined (**Figure 1**), which gradually increased from the normal range (3.00 μg/ml) in 2000 to above the critical level (10.74 μg/ml) in 2005. The pituitary, testicular and adrenal androgen levels and thyroid function were normal. In 2005, transrectal ultrasound-guided prostate needle biopsy revealed a Gleason 1 prostate adenocarcinoma **(Figure 2**). The immunohistochemical examination confirmed the presence of the carcinoma. The absence of the cytokeratin-5 positive basal cell layer and a significant increase in the levels of the p504S racemase enzyme supported the diagnosis of carcinoma (**Figure 3**). Following a 4-week course of nilutamide treatment (300 mg/d, Anandron, Sanofi-Aventis, Paris, France), a BUS injection cure was commenced (Suprefact Depot, Sanofi-Aventis, Paris, France; 6.30 mg at 2-month intervals), and this treatment was continued during the next 2 years. The PSA and testosterone levels dropped to < 0.003 μg and < 0.07 nmol/l immediately following the initiation of BUS administration, and as side-effect impotence developed. It is noteworthy that the patient earlier had essential hypertension (BP: 190/110 mmHg), which was treated with antihypertensive drugs (betaxolol 20 mg + indapamide 1.5 mg in the morning and doxazosin 4 mg + amlodipin 5 mg in the evening), and the blood pressure rapidly normalized. However, when the combined antiandrogen treatment was started, the blood pressure fell dramatically (80/45 mmHg) and severe hypotension developed. Accordingly, the antihypertensive treatment was considerably moderated (betaxolol 20 mg + amlodipin 5 mg/d), after which the general circulation became stable and the antiandrogen treatment was continued. After 2 years of BUS treatment, the hormonal state (**Table 1**) revealed that the thyroid function (TSH, FT_4, FT_3) and SHBG, ACTH, cortisol and hGH levels were normal. The serum estradiol, testosterone, DHEA, DHEAS, FSH and LH concentrations proved to be suppressed. Surprisingly, the serum PRL concentration was extremely high (3 365 mIU/l).

Table 1. Serum hormone levels after 2 years of buserelin treatment (Changes: Ø: unchanged; ↓: decreased; ↓↓: significantly decreased; ↑↑↑: highly significantly increased).

		Changes	Ref. range
TSH	3.19 mIU/l	Ø	0.27 – 4.2
FT_4	12.61 pmol/l	Ø	12 – 22
FT_3	4.47 pmol/l	Ø	3.1 – 6.8
Estradiol	< 18.4 pmol/l	↓	28 – 156
Testosterone	< 0.07 nmol/l	↓↓	9.9 – 27.8
SHBG	33.7 nmol/l	Ø	13.0 – 71.0
ACTH	3.11 pmol/l	Ø	1.1 – 10.12 (8 h)
Cortisol	348 nmol/l	Ø	171 – 536 (8 h)
DHEA	3.2 nmol/l	↓	8.5 – 36
DHEAS	0.17 μmol/l	↓	0.44 – 3.34
FSH	0.85 IU/l	↓	1.50 – 12.40
LH	0.10 IU/l	↓↓	1.70 – 8.60
PRL	3 365 mIU/l	↑↑↑	86 – 324
hGH	0.34 μg/ml	Ø	0.01 – 1.0

Radiologic assessment of the pituitary was performed in the International Diagnostic Centre, Szeged, in 2009. The MRI protocol consisted of sagittal and coronal T1–weighted images. All scans were read by one neuroradiologist (EV). The MRI demonstrated a pituitary macroadenoma measuring 0.8 cm × 1.2 cm (**Figure 4(a)**). No visual field defects or neurologic symptoms were observed. The patient was treated with CAB (2 × 0.5 mg/week) together with BUS. After 5 months of this combined treatment, the PSA and testosterone levels were very low; while the estradiol, DHEA, DHEAS and FSH levels proved to be unchangingly suppressed and the serum PRL concentration had fallen dramatically to 6.95 mIU/l, with no significant change a further 2 months later (6.51 mIU/l). Repeated MRI demonstrated a reduction in tumor size (about 50%) (**Figure 4(b)**). The dose of CAB was decreased (1 × 0.5 mg/week), and 2 months later the serum PRL level remained very low (9.95 mIU/l).

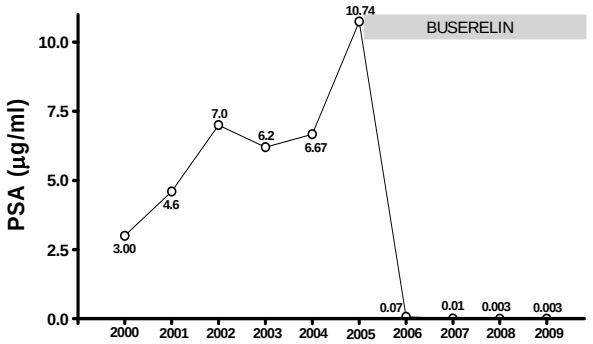


Figure 1. The serum prostate-specific antigen (PSA) level before and after treatment with buserelin.

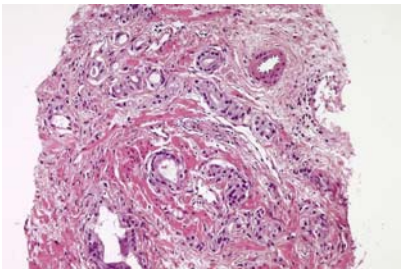


Figure 2. Histological examination of prostatic tissue cylinder (hematoxilin-eosin staining).

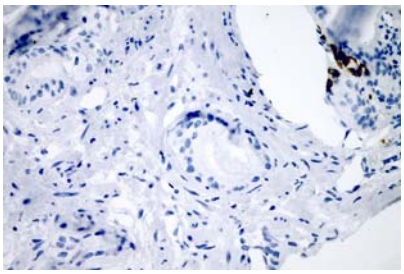
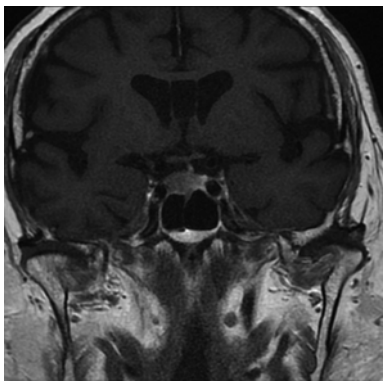
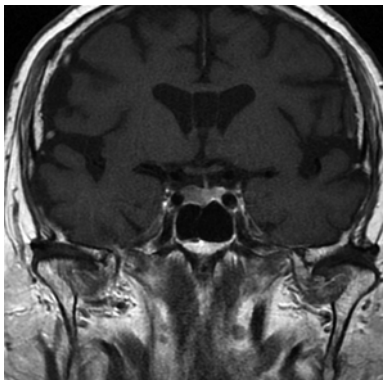


Figure 3 . The immunohistochemical examination of prostatic tissue cylinder.



(a) Before the cabergoline administration.



(b) After 9 months cabergoline treatment.

Figure 4 .Pituitary MR examination.

3. Discussion

Numerous data have been published on the relationship between PRL secretion and the prostatic function in animal experiments. PRL has been stated to play a significant role in the growth of the prostate in rodents. In contrast, Robertson *et al*. (2003) did not find any correlation between hyperprolactinemia and prostate carcinogenesis in PRL receptor knockout mice[14]. However, the whole pituitary function is important in this respect: hypophysectomy induced greater degree of atrophy in the rat prostate comparable to the effect of castration [15].

Chronic treatment with the gonadotropin-releasing analog BUS blocks gonadotropin secretion and at the same time effectively suppresses gonadal steroidogenesis [8]. It is somewhat surprising that the very low testosterone secretion during BUS treatment does not induce increased FSH or LH release because of the feedback regulation. The mode of action of this compound is not yet fully explained.

The androgens that arise from the adrenals include the inactive steroids androstenedione, dehydroepiandrosterone (DHEA) and DHEA sulphate (DHEAS), which are metabolized to testosterone and dihydrotestosterone in the prostate itself [16]. BUS suppresses the testicular androgens, but does not inhibit adrenal androgen production [17]. Combined androgen blockade involving a receptor-blocking antiandrogen with BUS led to results that were superior to those of treatment with BUS alone [16].

In our case, the most important problem was how to modify the treatment because of the severe hyperprolactinemia. The strong argument in favor of BUS treatment continuation is the persistence of prostate cancer. However, the introduction of specific hyperprolactinemia treatment cannot be avoided. Supplementation of the BUS treatment with a PRL-reducing agent was supported when the prolactinoma was discovered by MRI as the source of the high PRL level. The prolactinoma is the most common subtype of active, hormone-secreting pituitary adenoma. Dopamine agonists are highly effective in normalizing hyperprolactinemia and decreasing the tumor size in patients with prolactinoma. CAB is a new, potent, selective and long-acting dopamine agonist which blocks PRL secretion. Reports on long-term CAB treatment, indicated that it was better tolerated [18] than bromocriptine and side-effects seldom developed. Delgrange *et al*. (2009) [19] described the normalization of high PRL levels in (96% of their cases) and significant tumor shrinkage (in 82%) during CAB administration to 122 patients with macroprolactinoma. In our case, the starting dose of CAB was 0.5 mg twice weekly, and after treatment for 5 months the serum PRL concentration had

fallen to 6.95 mIU/l and significant tumor shrinkage was observed on MRI. Finally, the dose of CAB was reduced to 0.5 mg/week.

As an unpleasant side-effect, severe hypotension, developed immediately after the introduction of antiandrogen therapy. We earlier observed that androgens are able to increase the sensitivity of blood vessels to vasoconstriction induced by different vasoactive agents (e.g. vasopressin), and antiandrogen compounds (cyproterone acetate or flutamide) can prevent this effect of androgens [20]. Hypotension induced by antiandrogen administration is not a well-known side-effect, and attention should be drawn to this important aspect. At the beginning of antiandrogen therapy, we have to control the blood pressure frequently, and if necessary to reduce the doses of antihypertensive drugs.

In conclusion: The combined treatment with BUS + CAB proved to be a highly successful procedure in this patient with prostate adenocarcinoma and pituitary macroprolactinoma. The minimal length of CAB treatment recommended by The Pituitary Society is 1-3 years [21].

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