Stimulation of a non-functioning pituitary macroadenoma after administration of goserelin acetate for locally advanced prostate cancer causing a sustained elevation in PSA and testosterone

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Abstract

Long-acting luteinizing hormone-releasing hormone (LHRH) agonists, such as goserelin, have been used for locally advanced and metastatic prostate cancer for many years and are the main forms of androgen deprivation therapy (ADT). Acting on pituitary LHRH receptors, they initially stimulate a transient rise in serum follicle-stimulating hormone (FSH) and LH. Long-term administration of an LHRH analogue will eventually lead to down regulation of LHRH receptors, thus suppressing FSH and LH secretion. This in turn suppresses testosterone production hence achieving and maintaining androgen deprivation. This case highlights the potential anomaly of a sustained elevated serum testosterone in the context of newly diagnosed locally advanced prostate cancer with a co-existing pituitary macroadenoma after administration of LHRH analogues. Alternative methods of androgen deprivation must be considered in such patients.

Introduction

Long-acting luteinizing hormone-releasing hormone (LHRH) agonists, such as goserelin, have been used for locally advanced and metastatic prostate cancer for many years and are the main forms of androgen deprivation therapy (ADT). Acting on pituitary LHRH receptors, they initially stimulate a transient rise in serum follicle-stimulating hormone (FSH) and LH. Long-term administration of an LHRH analogue will eventually lead to down regulation of LHRH receptors, thus suppressing FSH and LH secretion. This in turn suppresses testosterone production hence achieving and maintaining androgen deprivation.

Case report

A 75-year-old man was admitted to hospital with a one and a half week history of dizziness and weight loss. He

had significant postural hypotension, with serum sodium of 115 mmol/L (range: 135-145) with normal renal function. A short synacthen test was suboptimal, and he was started on replacement therapy with hydrocortisone. Serum testosterone was at the low end of normal at 7.3 nmol/L (range: 7-18) and prolactin slightly elevated at 476 mU/L (range: 0-456). Thyroid function, insulin-like growth factor (IGF)-1 and gonadotrophins were normal. Subsequent pituitary magnetic resonance imaging demonstrated a 34 × 27 × 24 mm pituitary macroadenoma. The tumour partially encased the carotids, and compressed the optic chiasm. There was no significant visual disturbance. Neurosurgical opinion was to opt for a conservative approach with visual field monitoring.

The patient was kept under regular review, and described feeling marvellous on hydrocortisone. His other pituitary function remained stable, with testosterone levels at the lower end of normal. Two years after initial presentation, he complained of erectile difficulties. A repeat 9 am testosterone at this time was low at 5.6 nmol/L and testosterone replacement was discussed. Prostate-specific antigen (PSA) level was 3.9 ng/mL (<6.5), and digital rectal examination (DRE) revealed a benign-feeling prostate. He started topical testosterone gel supplementation at a dose of 50 mg daily. Three months later, he was reviewed in clinic, and admitted having stopped the testosterone after one month because he felt it had made little difference to his well-being. One year later, his serum testosterone had dropped further to 2.6 nmol/L and he complained of tiredness. Thyroid function continued to be normal. A further trial of testosterone was discussed and the patient consented. He started on 60 mg of testosterone gel daily.

Three months later he came to clinic, and felt he had more energy since starting testosterone. His PSA, though, had risen significantly to 12.2 ng/mL. Testosterone was stopped and he was referred urgently to a urologist.

Repeat DRE revealed locally advanced prostate cancer, clinically T3. Transrectal prostate biopsies confirmed a moderately differentiated adenocarcinoma of the prostate (Gleason score 4+3 = 7). Following cessation of testos-

one therapy, his PSA and random serum testosterone were 7.3 ng/L and 4.6 nmol/mL, respectively. He started medical ADT in the form of the anti-androgen cyproterone acetate initially, with subsequent monthly preparations of the gonadorelin analogue goserelin acetate 3.6 mg injections.

Three months later, repeat PSA was 12.2 ng/mL, and random serum testosterone was 15.8 nmol/L. These had both risen significantly since the diagnosis of prostate cancer and the start of treatment. This suggested the goserelin acetate was stimulating FSH and LH secretion from his previously non-functioning pituitary macroadenoma. His FSH levels were elevated at 22.3 U/L (<9 U/L) and LH levels were also elevated at 10.9 U/L (<9 U/L). Prior to treatment with goserelin acetate, his gonadotrophins had been consistently in the normal range. Serum testosterone at this point had also continued to rise to 17.8 nmol/L.

The goserelin acetate was stopped and a bilateral subcapsular orchidectomy was performed. One month following this, serum testosterone was <0.4 nmol/L confirming that androgen deprivation had been achieved.

Discussion

Long-acting LHRH agonists, such as goserelin, have been used for locally advanced and metastatic prostate cancer for many years and are the main forms of ADT.^{1,2} They are synthetic analogues of LHRH and are given as depot injections on a 1, 3 or 6 monthly basis. Acting on pituitary LHRH receptors, they initially stimulate a transient rise in serum FSH and LH. This leads to a temporary rise in serum testosterone or "testosterone surge." This begins in the first 2 to 3 days and lasts for about 1 week following the first injection.³ To avoid clinical flares associated with this testosterone surge (i.e., namely bone pain, acute bladder outlet obstruction, obstructive renal failure and spinal cord compression), concomitant anti-androgen therapy is administered. The most common anti-androgen used is cyproterone acetate 100 mg three times daily, which is usually started 1 week prior to the first LHRH injection and continued for 2 weeks thereafter.

Long-term administration of an LHRH analogue will eventually lead to down regulation of LHRH receptors, thus suppressing FSH and LH secretion. This in turn suppresses testosterone production hence achieving and maintaining androgen deprivation. Hormone castrate levels are usually achieved within 2 to 4 weeks.^{4,5} Seidenfeld and colleagues stated in a meta-analysis that single therapy ADT in the form of LHRH analogues for advanced prostate cancer had similar efficacy to orchidectomy in achieving androgen deprivation levels.⁶ In rare cases (10%), some individuals fail to achieve serum testosterone values within the castration range during treatment with LHRH analogues.⁷ Specific causes have been reported, such as reactions at the depot injection site,

thought to represent granulomatous reactions to leupoprotein acetate induced by the biodegradable nature of the microcapsules.^{8,9}

This case describes a patient with a non-functioning pituitary macroadenoma, who had secondary hypogonadism and hypoadrenalism. Locally advanced prostate cancer was detected 18 to 24 months after the start of testosterone supplementation. Controversy exists regarding testosterone supplementation and whether increasing serum testosterone above a threshold has a causative effect in prostate cancer. Recent evidence has suggested this does not have a negative impact on prostate cancer progression.^{10,11} The initial treatment plan was to use the LHRH analogue, goserelin acetate. However, with this treatment serum testosterone rose unexpectedly to 15.8 nmol/L and continued to rise to 17.8 nmol/L after 3 months. At this time, we would expect treatment with an LHRH analogue to have achieved androgen deprived levels of serum testosterone. This was associated with a rise in FSH and LH levels suggesting the LHRH analogues had stimulated further production of gonadotrophins and thus the normal process of down-regulation had not occurred. Consequently, there was a sustained rise in the serum testosterone levels. Bilateral scrotal orchidectomy was then successful in achieving castrate levels of serum testosterone.

Conclusion

This interesting case highlights the potential anomaly of a sustained elevated serum testosterone in the context of newly diagnosed locally advanced prostate cancer with a co-existing pituitary macroadenoma after administration of LHRH analogues. Alternative methods of hormone castration must be considered in such patients.

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