CASE REPORT

Inadequate testosterone suppression after medical and subsequent surgical castration in a patient with prostate cancer

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SUMMARY

Androgen deprivation is a cornerstone in prostate cancer management. We present a 69-year-old man, with a poorly differentiated prostate cancer with skeletal and lymph node metastases. After medical and subsequent surgical castration serum testosterone concentrations remained inappropriately high (4.9 and 4.5 nmol/L; castration range <0.5). For cancer staging a CT was performed which showed bilateral adrenal enlargement. Endocrine workup revealed elevated levels of adrenal androgens and adrenal precursors. Mutation analysis confirmed a non-classical 21-hydroxylase deficiency, that is, a mild form of congenital adrenal hyperplasia (CAH). To suppress adrenocorticotrophic hormone and the excess adrenal androgen secretion, treatment with hydrocortisone and prednisolone was started with success. Inadequate testosterone suppression after castration due to previously undiagnosed CAH has not previously been reported. Considering the estimated prevalence of 1% in selected populations, non-classical CAH should be considered when testosterone is not adequately suppressed after castration in men with prostate cancer.

BACKGROUND

Androgen deprivation therapy is a cornerstone in the management of advanced prostate cancer.¹ In patients with locally advanced or metastatic disease, androgen deprivation delays progression and reduces complications.² Measurement of serum testosterone concentration is recommended to ensure adequate treatment.³ However, biochemical monitoring of androgen deprivation treatment is often not performed.⁴ A recent study found that follow-up measurement of serum testosterone was omitted by one-fourth of treating physicians.⁵

CASE PRESENTATION

We present a 69-year-old man with prostate cancer and skeletal and lymph node metastases, with inadequate testosterone suppression after medical and subsequent surgical castration. The patient presented with symptoms of urinary frequency, hesitancy and nocturia. Except for treatment for hypertension his medical history was unremarkable. On digital rectal examination the right side of the prostate was enlarged with firm consistency. Biopsy showed a poorly differentiated prostate cancer (Gleason score 4+4). Prostate-specific antigen (PSA) was 1.0 µg/L (ref <3.0). For cancer staging a

CT was performed which showed skeletal and lymph nodes metastases. In addition, bilateral homogeneous adrenal gland enlargement was noted (figure 1A,C). Owing to metastatic disease androgen deprivation therapy with an antiandrogen agent (bicalutamide 50 mg once daily) and gonadotropin-releasing hormone (GnRH) agonist (leuprolide acetate, 45 mg) was started. Three months later serum testosterone concentration was not adequately suppressed (4.9 nmol/L; normal reference range 6–30; castration range <1.0). Therefore, another GnRH agonist (busereline acetate) was administered. One month later serum testosterone was still high (5.1 nmol/L). PSA was unchanged at 0.8 µg/L. Consequently, bilateral orchiectomy was performed. Two weeks postoperatively serum testosterone was essentially unchanged at 4.5 nmol/L.

INVESTIGATIONS

Further endocrine workup revealed elevated levels of adrenal androgens and adrenal precursors (table 1).

After a cosyntropin test, that is, stimulation with synthetic adrenocorticotrophic hormone (ACTH), serum levels of cortisol increased from 810 to 910 nmol/L and 17α-hydroxyprogesterone from 140 to 430 nmol/L. Owing to the markedly increased concentrations of serum 17α-hydroxyprogesterone, congenital adrenal hyperplasia (CAH) was strongly suspected. A mutation analysis confirmed a non-classical 21-hydroxylase deficiency (21-OHD), that is, a mild form of CAH with partial enzyme deficiency.

OUTCOME AND FOLLOW-UP

In order to suppress the excess adrenal androgen secretion, treatment with hydrocortisone and prednisolone was started with success, resulting in serum testosterone concentrations <1.0 nmol/L, that is, corresponding to the target castration level (table 1).

DISCUSSION

CAH, an autosomal recessive disorder, is one of the most common inherited metabolic diseases.⁶ In 90–95% of the cases, CAH is caused by mutations in the gene encoding the adrenocortical enzyme 21-hydroxylase, an enzyme essential for the synthesis of cortisol and aldosterone.⁷ 21-OHD leads to partial or complete cortisol deficiency and accumulation of cortisol precursors that are diverted to

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Figure 1 (A) CT in transaxial plane and (C) coronal plane showing bilateral homogeneous adrenal enlargement (white arrows) in a 69-year-old man diagnosed with a non-classical congenital adrenal hyperplasia. For comparison, normal adrenal glands are shown in (B) and (D).

biosynthesis of adrenal androgens, which are partly converted to testosterone in peripheral tissues (figure 2). Through loss of negative feedback in the hypothalamic–pituitary–adrenal-axis, pituitary ACTH secretion is increased, stimulating the adrenal cortex to increase synthesis of cortisol- and aldosterone precursors resulting in further increase in the secretion of adrenal androgens and ultimately adrenal hyperplasia. The phenotype of 21-OHD varies considerably, depending on the degree of enzyme inactivation. Traditionally CAH is categorised into three

different forms: two classic forms (the salt-wasting form with no enzyme activity and the simple virilising form with 1–2% residual enzyme activity) and a milder form, the non-classical 21-OHD with higher residual activity of the enzyme.⁸

The estimated prevalence of non-classical 21-OHD is 0.1%,⁹ although the prevalence may be as high as 1% in certain ethnic groups.^{10–11} The classical salt-wasting and simple-virilising forms are diagnosed in the neonatal period due to adrenal insufficiency and/or ambiguous genitalia. In contrast, patients with non-classical 21-OHD are typically diagnosed in late childhood because of premature puberty and accelerated growth, or in adolescence and young adulthood due to hirsutism. In many countries CAH is included in a neonatal screening programme by analysis of 17 α -hydroxyprogesterone at 2–5 days of age. However, since unstimulated levels of 17 α -hydroxyprogesterone are most often only marginally elevated in non-classical 21-OHD the patients are usually not identified by the neonatal screening.⁷ A substantial number of patients with non-classical 21-OHD, especially men, are asymptomatic.¹² There are, however, small series and case reports indicating that non-classical 21-OHD, in otherwise healthy men, may be associated with infertility,¹³ acne vulgaris¹¹ and adrenal incidentalomas.¹⁴

Insufficient testosterone suppression after pharmacological androgen deprivation therapy ('testosterone escape') occurs in a few per cent of patients with prostate cancer and may require additional treatment. In the present case, testosterone escape occurred also following surgical castration, which is considerably less common.¹⁵ To our knowledge, an underlying undiagnosed CAH has not been reported previously. Furthermore, in the present case, measurement of testosterone concentration was of utmost importance since PSA was normal at presentation and could therefore not be used for monitoring the treatment effect.

Table 1 Hormone concentrations in serum and urine after medical and surgical castration and after combined glucocorticoid treatment with hydrocortisone and prednisolone

	After surgical castration	After glucocorticoid treatment	Reference range
S-Testosterone (nmol/L)	4.2	0.38	6–30
S-DHEAS (μ mol/L)	8.2	0.72	0.6–6.6
S-Androstenedione (nmol/L)	>35	5.2	2.1–10.8
S-17 α -Hydroxyprogesterone (nmol/L)	140	12	0.9–7
S-17 α -Hydroxyprogesterone (nmol/L), after cosyntropin stimulation	430	—	—
S-Cortisol (nmol/L)	810	—	200–800
S-Cortisol (nmol/L), After cosyntropin stimulation	910	—	—
P-ACTH (pmol/L)	16	3.1	2–11
U-Pregnenetriol (μ mol/24 h)	28	3.4	<4.5

ACTH, adrenocorticotrophic hormone; DHEAS, Dehydroepiandrosterone sulfate.

Figure 2 Schematic illustration of adrenal steroid synthesis. In patients with partial 21-hydroxylase deficiency there is an accumulation of cortisol precursors. The precursors are diverted to biosynthesis of adrenal androgens, which are partially converted to testosterone in peripheral tissues. The accumulation of the precursors is further augmented by a compensatory increase of pituitary adrenocorticotrophic hormone secretion required for sufficient cortisol production.

The case demonstrates the importance of monitoring serum testosterone in patients with prostate cancer receiving androgen deprivation therapy. Considering that the estimated prevalence may be as high as 1% in selected populations, non-classical 21-OHD should be considered when testosterone is not adequately suppressed after castration.

Learning points

- ▶ Serum testosterone should be monitored after medical and surgical castration in men with prostate cancer.
- ▶ Non-classical congenital adrenal hyperplasia is likely to be overlooked in many patients, mainly men.
- ▶ Non-classical congenital adrenal hyperplasia should be considered in prostate cancer patients with inadequate testosterone suppression after castration therapy.

Contributors OR, GJ, PL and PD diagnosed and treated the patient. All authors wrote the report. KG analysed the radiological findings.

Competing interests None.

Patient consent Obtained.

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