

## CASE REPORT

# Partial androgen suppression consequent to increased secretion of adrenal androgens in a patient with prostate cancer treated with long-acting GnRH agonists

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**We present a case report of a patient with prostate cancer who failed to demonstrate consistent testosterone suppression to castration levels and incomplete suppression of serum prostate-specific antigen, although treated with gonadotropin releasing hormone agonists for 48 months. Serum dehydroepiandrosterone, dehydroepiandrosterone sulphate, as well as the androgen metabolite, androsterone glucuronide, were elevated compared to the other patients. The present data suggest that those prostate cancer patients who have even marginally elevated adrenal androgens may especially benefit from combined androgen blockade.**

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## Introduction

Prostate cancer has been known to be androgen sensitive since the pioneering studies of Huggins and Hodges<sup>1</sup> conducted over 60 years ago. Over 90% of circulating testosterone (T) arises from the testis under stimulation by luteinizing hormone (LH) secreted by the gonadotrophs of the anterior pituitary.<sup>2</sup> LH secretion in turn is controlled by gonadotropin releasing hormone (GnRH) secreted by the hypothalamus. There is, however, an important component of androgens, which arises from the adrenals. These include the inactive steroids androstenedione ( $\Delta 4$ ), dehydroepiandrosterone (DHEA) and DHEA sulphate (DHEAS), which are metabolized to testosterone and dihydrotestosterone both in the prostate itself and other tissues.<sup>2,3</sup>

Suppression of testicular androgens is a recognized form of treatment of metastatic prostate cancer.<sup>1,2,4</sup> This can be achieved by surgical castration, orchiectomy or more recently, with GnRH agonists or antagonists.<sup>2,5</sup> These treatment modalities, however, do not inhibit adrenal androgen production. Labrie *et al.*<sup>2,5</sup> have pioneered combined androgen blockade, where a pure antiandrogen is given together with a GnRH analog. The antiandrogen

blocks T and dihydrotestosterone action at the tissue level. Combined androgen blockade gives results superior to administration of GnRH analogs alone.<sup>2,4-6</sup>

In this report, we describe a patient with prostate cancer who failed to demonstrate complete serum testosterone suppression on GnRH agonists and demonstrated increased adrenal androgen production.

## Case presentation and management

This patient has been previously reported together with 14 other patients who were all treated with a prototype histrelin implant with different polymer dimensions and release rates than that of the recently marketed Vantas Histrelin Implant.<sup>7,8</sup> LH, T and prostate-specific antigen (PSA) levels during treatment in the index patient were also compared to the 14 other patients in the original study.<sup>8</sup> Serum levels of  $\Delta 4$ , DHEA, DHEAS and androsterone glucuronide were measured on five occasions during the course of histrelin implant exposure in this patient and another 24 samples were also measured from other men. It was, thus, possible to compare LH, T, PSA and adrenal androgen levels in the index patient with the other patients in the same study. Androsterone glucuronide is the main metabolite of androgens.<sup>2,9</sup> LH, T, PSA,  $\Delta 4$ , DHEA, DHEAS and androsterone glucuronide were measured by previously described methods.<sup>9,10</sup> The lower limits of sensitivity of the LH and T assays were 0.1 mIU ml<sup>-1</sup> and 0.1 ng ml<sup>-1</sup>, respectively.<sup>8,10</sup>

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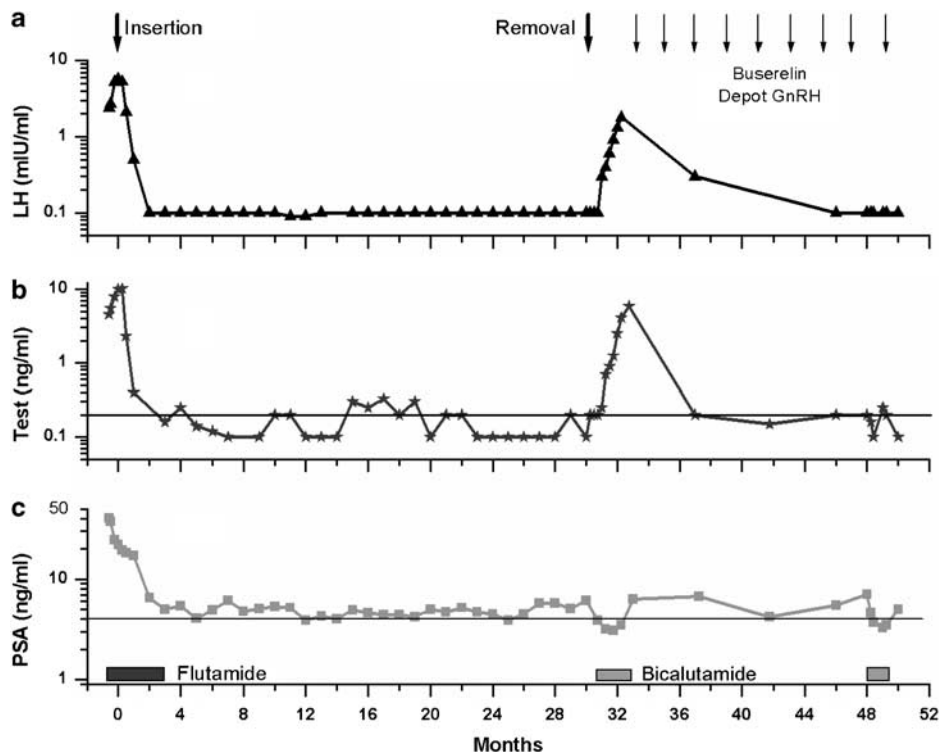
A 75-year-old male was referred to the urological outpatient clinic with an elevated PSA ( $31.7 \text{ ng ml}^{-1}$ ). His medical history was unremarkable except for glaucoma, a hiatus hernia and a partial gastrectomy for peptic disease 20 years earlier. Prostate needle biopsies were positive for adenocarcinoma (Gleason grading 4 + 4). No evidence of macroscopic metastatic disease was found on CT and bone scan. Therefore, the patient was diagnosed as prostate cancer stage T3bN0M0 and hormonal treatment was initiated with the nonsteroidal antiandrogen flutamide. Two weeks later, two histrelin implants were inserted subcutaneously into his right upper arm. Three weeks after implant insertion, flutamide was stopped due to the development of persistent diarrhea. After the GnRH agonist implants were removed (Figure 1), the patient was given bicalutamide for 1 week and bimonthly GnRH agonist injections with buserelin 6.6 mg (Superfact depot, Sanofi-Aventis, Paris, France) were started. A further 7-day course of bicalutamide was then given at 48 months and the study monitoring ceased; the patient continued on buserelin injections. Despite repeated requests, the patient refused any further investigations.

Luteinizing hormone and testosterone increased transiently and then fell following the first GnRH agonist injection and removal of the implant. LH levels decreased below  $0.2 \text{ mIU ml}^{-1}$  in all 38 samples from the index patient as well as in all 302 samples taken from the 14 other patients who had the same histrelin implant (Table 1). A total of 33 T levels in the index patient were also below castration levels ( $0.2 \text{ ng ml}^{-1}$ ). However, on seven occasions, serum T levels ranged from 0.25 to

$0.33 \text{ ng ml}^{-1}$  values, which slightly exceeded castration levels. It should be noted that only two measurements of T were above castration levels in 297 blood samples taken in the other 14 patients (Table 1). PSA levels decreased in the index patient but never below the normal upper range ( $4 \text{ ng ml}^{-1}$ ) except for a total of nine determinations when levels ranged between 3.1 and  $3.9 \text{ ng ml}^{-1}$ . On seven of these occasions, the patient was also receiving bicalutamide. In contrast in the 280 samples of the other 14 patients, following suppression and until escape in 4 patients, 272 samples were below  $3 \text{ ng ml}^{-1}$  and 8 ranged from 3.1 to  $3.9 \text{ ng ml}^{-1}$  (Table 1). In the index patient, all samples of DHEA, DHEAS and ADT-G were more than 2 s.e.m. higher than the mean in the six control subjects. Moreover, three of the five  $\Delta 4$  levels in the index patient also exceeded those of the controls (Figure 2).

## Discussion

Failure of complete serum T suppression may be related to lack of compliance, inadequate dose of GnRH agonist, increased testicular sensitivity to LH, a tumor secreting an hCG-like material or increased adrenal androgen secretion resulting in leakage into the blood stream of excess androgen production in peripheral tissues.<sup>11,12</sup> The cause in this patient appears to be related to an increased adrenal androgen production. The adrenal androgens, notably DHEA and DHEAS and to some extent  $\Delta 4$ , were higher in the index patient than the group of patients receiving the same treatment. Similarly,



**Figure 1** Clinical course of index patient (endocrine parameters). (a) Serum luteinizing hormone (LH), (b) Serum testosterone (Test) and (c) Serum-specific prostate antigen (PSA) levels. The insertion and removal of the two histrelin implants are marked by arrows. Time of administration of flutamide and bicalutamide is also indicated. Values are depicted on a log scale.

the serum levels of the androgen metabolite (ADT-G) were also higher in the index patient. Although these levels were increased, they were still in the normal range for a male of this age group.

Of interest is that compared to other patients given the same treatment, the serum PSA levels although suppressed, never decreased below 3 ng ml<sup>-1</sup> whereas 32 of the 41 samples analyzed were above 4.0 ng ml<sup>-1</sup>. This is in contrast to all the other treated patients. Serum

PSA levels transiently decreased below 4 ng ml<sup>-1</sup> in the patient when bicalutamide was added to the therapeutic regimen, thus, indicating that the addition of bicalutamide induced a greater degree of androgen blockade as well demonstrated in a series of clinical studies.<sup>2,4,6</sup> This might be a fortuitous finding but since the histrelin serum levels were constantly within the therapeutic range throughout the study period (data not shown) it is likely that the addition of bicalutamide had a positive effect on the decrease of the PSA levels.

It should be mentioned that serum T levels in this patient were markedly suppressed and were only intermittently above castration levels. This could only be discovered in a research setting where multiple blood sampling was performed. This would not be expected to be detected in the average clinic, where serum T is generally not even measured and patients are monitored only by PSA.

The present results suggest that combined androgen blockade may offer even greater benefits in those patients who have even marginally elevated serum adrenal androgens. Our best estimate from measurements of circulating and intraprostatic androgens in intact and castrated men indicate that only 10% of androgens made in peripheral tissues diffuse into the general circulation and can be measured in the blood. It is now recognized that the true total androgenic activity can only be estimated by measurement of the serum levels of the androgen metabolites and not by serum T.<sup>10</sup> Furthermore, recent studies clearly showed that standard androgen deprivation does not consistently suppress intraprostatic androgen-dependent gene expression.<sup>13,14</sup> Suboptimal suppression of androgen activity may lead to adaptive cellular changes allowing for prostate cancer cell survival in a low-androgen environment.

**Table 1** Number of measurements of luteinizing hormone (LH), testosterone (T) and prostate-specific antigen (PSA) in the index patient and the other 14 patients following testicular androgen suppression with histrelin

Levels	Index patient <sup>a</sup>	14 other patients
	LH (mIU ml <sup>-1</sup> )	
0.2 mIU ml <sup>-1</sup> and below	38	302 <sup>b</sup>
>0.2 mIU ml <sup>-1</sup>	0	0
	T (ng ml <sup>-1</sup> )	
0.2 ng ml <sup>-1</sup> and below	33	295 <sup>c</sup>
>0.2 ng ml <sup>-1</sup>	0.25, 0.3, 0.25, 0.33, 0.3, 0.25, 0.25 <sup>d</sup>	0.3, 0.23 <sup>d</sup>
	PSA (ng ml <sup>-1</sup> )	
4.0 ng ml <sup>-1</sup> and above	32	0
3.1–3.9 ng ml <sup>-1</sup>	9	8 <sup>e</sup>
3.0 ng ml <sup>-1</sup> and below	0	272 <sup>e</sup>

Only those determinations were included that were documented after suppression, usually at 2, 3 and 4 months following implant insertion for LH, T and PSA, respectively.

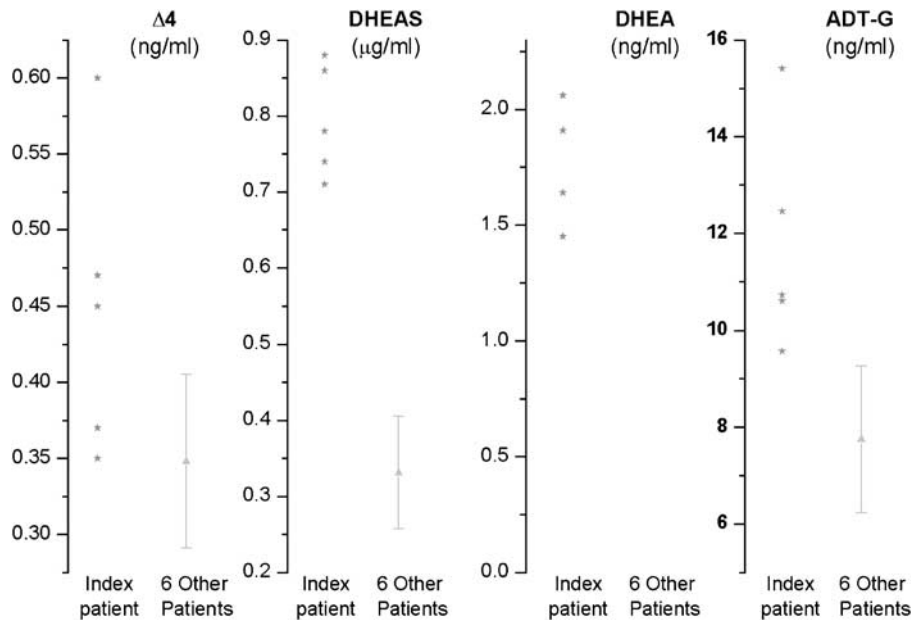
<sup>a</sup>A total of 38 LH, 40 T and 41 PSA determinations were conducted in the index patient.

<sup>b</sup>A total of 302 determinations.

<sup>c</sup>A total of 297 determinations.

<sup>d</sup>Actual T measurements.

<sup>e</sup>A total of 280 determinations including 4 patients who demonstrated escape.



**Figure 2** Serum levels of androstenedione (Δ4), dehydroepiandrosterone sulphate (DHEAS), dehydroepiandrosterone (DHEA) and the androgen metabolite androsterone glucuronide (ADT-G) are shown in the index patient and six other patients. In the latter, mean ± 2 s.e.m. are indicated.

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