Flutamide Withdrawal plus Hydrocortisone Resulted in Clinical Complete Response in a Patient with Prostate Carcinoma

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BACKGROUND. Combined androgen blockade (CAB) (medical or surgical castration plus antiandrogen therapy) is considered by many to be the optimal endocrine maneuver for patients with metastatic prostate carcinoma. When progression occurs after CAB, the discontinuation of the antiandrogen is recommended. The authors present a patient that had a clinical complete response to flutamide withdrawal plus hydrocortisone that, at last follow-up, had been maintained for more than 46 months.

METHODS. A 71-year-old man with a positive family history of prostate carcinoma presented in 1989 with urinary frequency and a suspicious digital rectal examination. He was found to have a poorly differentiated adenocarcinoma (Gleason 4+4). He was started on CAB and his prostate specific antigen (PSA) concentration declined from 96 ng/mL to the normal range and was maintained for the next 24 months. In 1991 his PSA began to rise, and reached 64 ng/mL by 1993. The patient was enrolled on a clinical trial that discontinued the flutamide administration and hydrocortisone was initiated.

RESULTS. Physical examination at the time of enrollment was unremarkable. His PSA declined to below the limits of detection after this maneuver and at last follow-up had been maintained there for more than 46 months. In 1995, the patient underwent a repeat biopsy of the prostate and all six tissue cores were negative for carcinoma. At last follow-up in December 1996, the patient had no evidence of disease and was being followed routinely; however, the authors were continuing treatment with testicular suppression (leuprolide) plus hydrocortisone.

CONCLUSIONS. The authors believe the residual androgens and steroids produced by the adrenal cortex play a meaningful role in prostate carcinoma cell proliferation. Based on this case and data from trials supporting the activity of flutamide withdrawal plus adrenal suppression, it appears reasonable to evaluate prospectively the discontinuation of antiandrogen versus antiandrogen withdrawal plus adrenal suppression in individuals failing CAB. ***Cancer* 1997;79:1964–8.**

KEYWORDS: prostate carcinoma, metastatic, hormone refractory, androgen independent.

Metastatic prostate adenocarcinoma is now the leading cause of cancer in the U.S. and the second leading cause of cancer-related deaths (estimate: 41,400 per year).[1] Total androgen deprivation is considered by many to be the optimal endocrine maneuver for patients with metastatic prostate carcinoma.[2] This can be accomplished by orchiectomy or luteinizing hormone-releasing hormone analogues, plus antiandrogen therapy (i.e., flutamide or bicalutamide). Unfortunately, hormonal manipulation in patients with Stage D

prostate carcinoma is considered noncurative in nature. When progression occurs after combined androgen blockade the antiandrogen should be subsequently withdrawn.[3] There are four studies documenting the effect of withdrawing the antiandrogen, flutamide, in patients with advanced prostate carcinoma.[4–7] Furthermore, there are four more reports suggesting that withdrawal activity can be enhanced with the addition of an inhibitor of adrenal synthesis (i.e., aminoglutethimide, ketoconazole, or hydrocortisone).[8–11] In this article, the authors present the first patient, to their knowledge, who had a clinical complete response to flutamide withdrawal plus hydrocortisone treatment. At last follow-up, this clinical response was approaching 4 years ($>$ 46 months).

Case Report

A 71-year-male with a positive family history of prostate carcinoma (grandfather on maternal side) presented in 1989 with urinary frequency and a suspicious digital rectal exam. He subsequently underwent a prostate biopsy that revealed poorly differentiated adenocarcinoma (Gleason 4+4) and an iliac lymph node biopsy that was consistent with metastatic adenocarcinoma of prostatic origin. Antigen retrieval immunohistochemical assay showed reactivity for prostatic specific antigen (PSA) in that tissue (Fig. 1). At the time of diagnosis, the patient had a negative bone scan and bilateral iliac adenopathy on computed tomography (CT) scan (Fig. 2a). His PSA was 96 ng/mL (Fig. 3). The patient began treatment with a combined androgen blockade (leuprolide plus flutamide) and his PSA declined to the normal range over the next 6 months, and remained there for 24 months. His iliac adenopathy also regressed over that period of time. In October 1991, the patient's PSA began to rise, and reached a level of 64 ng/mL by February 1993. The bone scan was negative at that time. The patient was enrolled on an approved experimental treatment trial that discontinued the flutamide and initiated hydrocortisone treatment (20 mg orally every morning and 10 mg every evening). Leuprolide was continued indefinitely (7.5 mg intramuscularly every 28 days).

Physical examination at the time of flutamide withdrawal and the initiation of hydrocortisone was unremarkable and laboratory values were notable only for mild anemia and thrombocytopenia. A digit rectal examination revealed a small firm prostate without nodules. The patient continued to receive tolazamide for control of diabetes and lovastatin for hypercholesterolemia. Since being diagnosed with prostate carcinoma he has undergone a repeat coronary artery bypass (initial surgery in 1982 and follow-up surgery in 1996). After the discontinuation of flutamide and the initiation of hydrocortisone, the patient's PSA declined to the normal range within 2 months and then gradually became undetectable by February 1995. Since enrollment on the trial, his testosterone has consistently been $<$ 10 ng/mL and his androgens have been suppressed after the addition of hydrocortisone (androstenedione $\leq$ 61 ng/mL, dehydroepiandrosterone $\leq$ 140 ng/mL, and dehydroepiandrosterone sulfate $\leq$ 0.1 ng/mL; multiple measurements since enrolling on the study). In March of 1995 he underwent a repeat sextant biopsy of the prostate (transrectal). All six tissue cores were negative for carcinoma cells. This was 35 months after protocol therapy began. At that time, the patient's CT showed no adenopathy (Fig. 2b). Furthermore, the size of his prostate decreased over the 3-year period (5 cm $\times$ 3 cm to 4 cm $\times$ 1 cm). Symptomatically,

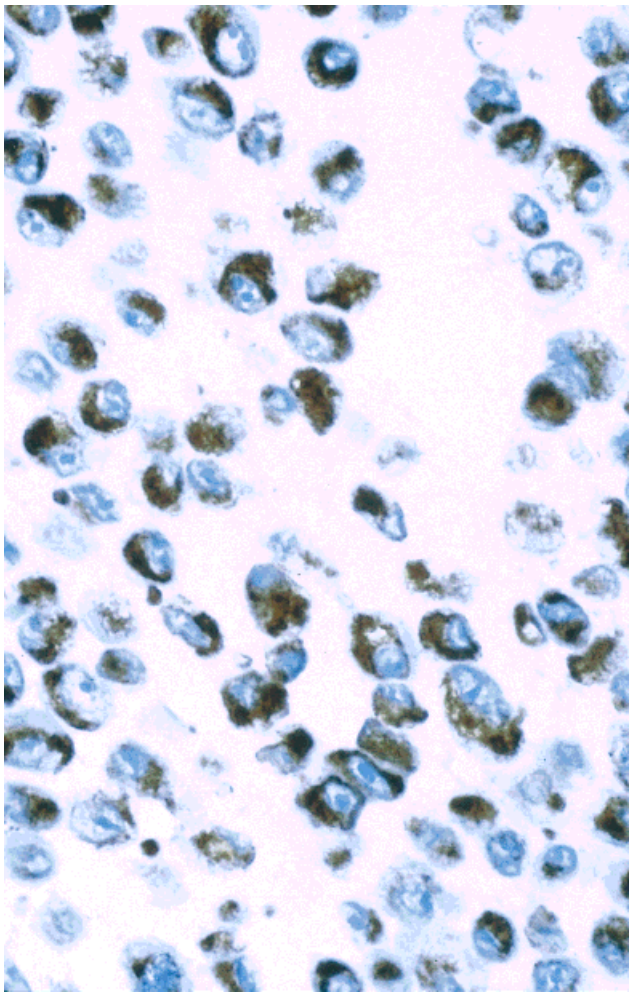

FIGURE 1. Biopsy of the iliac lymph node at the time of diagnosis that was found to be metastatic poorly differentiated adenocarcinoma. The microwaved tissue sample was reactive for prostate specific antigen. The chromogen used was deaminobenzidine (original magnification $\times$400).

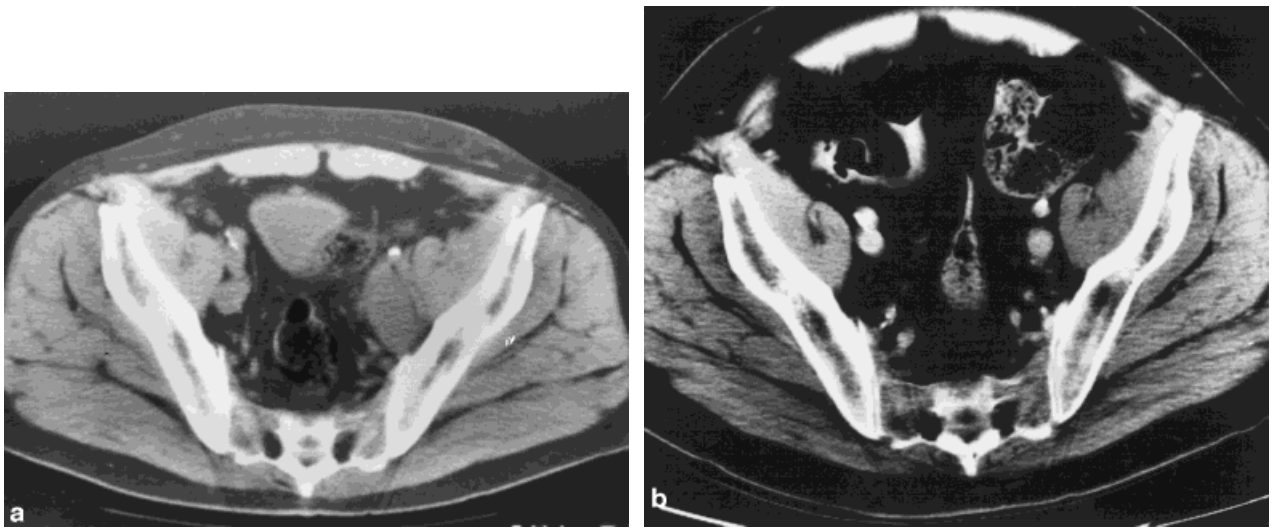

FIGURE 2. (a) A computed tomography (CT) scan of the patient's abdomen at the time of initial diagnosis showing lymphadenopathy in an iliac lymph node. This lymph node was biopsied and found to be prostate specific antigen positive and histologically consistent with prostate carcinoma. (b) A CT scan after the discontinuation of flutamide and the initiation of hydrocortisone showing no lymphadenopathy in the region previously noted to be positive for soft tissue involvement.

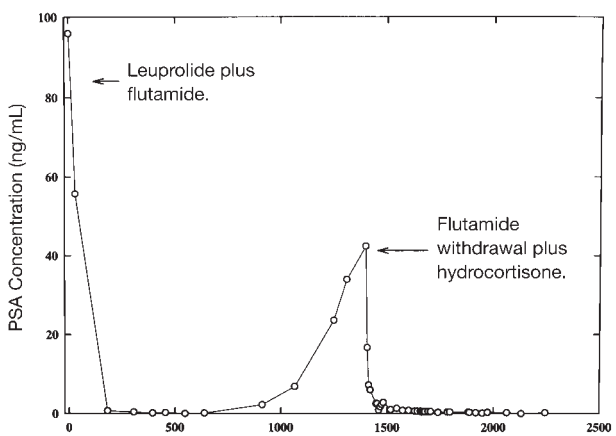

FIGURE 3. A graph of prostate specific antigen (PSA) (ng/mL) versus time (days) for this patient. Initial therapy with combined androgen blockade (leuprolide plus flutamide) resulted in a PSA decline from 96 ng/mL to below the limits of quantitation. Subsequently, the patient's PSA started to rise, reaching a peak of 64 ng/mL. At that time, flutamide was discontinued and hydrocortisone was initiated. This resulted in a PSA decline to below the limits of quantitation that at last follow-up (December 1996) had been maintained for more than 1000 days.

his performance status has continued to be Eastern Cooperative Oncology Group 0, with marked improvement in urinary frequency and hesitation. At last follow-up (December 1996; Month 46) the patient was being routinely followed with no evidence of disease; however, the authors were continuing treatment with testicular suppression with leuprolide and adrenal suppression with hydrocortisone.

DISCUSSION

In 1992, Kelly and Scher first reported the antiandrogen withdrawal phenomenon.[12] They described 3 cases in which patients who had undergone complete androgen blockade experienced declines in PSA (mean, 61.3%) after discontinuing flutamide.[12] Subsequently, they reported the effects of flutamide withdrawal in a larger cohort of 35 evaluable patients with progressive prostate carcinoma receiving hormonal treatment with flutamide.[4] Approximately 29% (n = 10) were noted to have a decline in PSA of $\geq$ 50% after discontinuation of the antiandrogen.[4]

The authors confirmed that observation in their report on 21 androgen-independent patients treated with leuprolide plus flutamide.[5] Seven patients (33.3%) were noted to experience PSA declines of >50% from baseline after the withdrawal of flutamide. Subsequently, Srinivas and Small have evaluated flutamide withdrawal in 82 patients who progressed while undergoing complete androgen deprivation.[6] Twelve of the 82 patients (14.6%; 95% confidence interval, 7.8–24.2%) were reported to have > 50% decline in PSA with a median response duration of 3.5 months (range, 1–12+ months). Finally, Herrada et al. noted a 28.2% response rate (> 50% decline in PSA) in 39 patients after the discontinuation of flutamide (95% confidence

interval, 14–45%).[7] The median duration of response was 13 weeks (range, 7–52+ weeks).

Recent efforts have focused on suppressing adrenal steroid synthesis concomitantly with flutamide withdrawal.[8–10] Sartor et al. evaluated flutamide withdrawal when accompanied by the concomitant initiation of aminoglutethimide (plus hydrocortisone).[8] Of the 29 patients evaluated, 14 (48%) experienced PSA declines of $>$ 80%, with normalization in 7 patients. Dupont et al. evaluated the efficacy of flutamide withdrawal in 40 patients with progressive metastatic prostate carcinoma.[9] A majority of this cohort received aminoglutethimide and/or hydrocortisone during this maneuver. PSA declines of $\geq$ 50% were experienced by 29 patients (72.5%). The therapeutic efficacy of flutamide withdrawal with the concomitant initiation of aminoglutethimide (plus hydrocortisone) has recently been re-evaluated by the authors in 17 patients.[10] Eleven patients (65%) exhibited a reduction of PSA of $>$ 50%. The authors have also reported a 29% response rate associated with flutamide withdrawal plus hydrocortisone in 34 patients (95% confidence interval, 15.1–47.1%). Of the 34 patients treated, 50% (n = 17) received flutamide as part of initial hormonal therapy, whereas the remaining 50% (n = 17) received it as a secondary hormonal maneuver. All the patients who responded to flutamide withdrawal plus hydrocortisone received the flutamide as part of initial combined androgen blockade.[11]

Glucocorticoids have long been known to have activity against androgen-independent prostate carcinoma; in fact, many observers consider these agents to be the standard of care for the palliative treatment of patients with advanced disease.[13] The mechanism of glucocorticoids has traditionally been related to suppression of adrenal synthesis; however, the possibility remains that these agents may have additional mechanisms of action (inhibition of neovascularization, etc.). Activity of glucocorticoids is present at relatively low doses and a number of trials indicate that these agents can be administered with a minimum of side effects. In reviewing the literature, it appears between 9–34% of patients with androgen independent prostate carcinoma will have a PSA decline of $>$ 50% with the initiation of glucocorticoids (hydrocortisone dose between 30 and 80 mg/day).[14,15] These response rates appear to be dose related; however, the median progression free survival at these doses is modest (2 months).

The hypothesized mechanism for the flutamide withdrawal phenomenon is a mutation in the androgen receptor of prostate carcinoma tumor cells.[16] A hormone responsive cell line, LNCaP, has been found to exhibit accelerated growth in vitro when grown in the presence of hydroxyflutamide, the active metabolite of flutamide.[17–19] Sequencing of the LNCaP androgen receptor revealed a point mutation located at codon 877 (ACT→GCT; threonine→alanine) in the ligand binding domain of the protein.[20] This single point mutation significantly alters the receptor's steroid binding specificity. Apparently, the mutation does not affect the receptor's binding affinity for steroid hormones such as DHT. Veldscholte et al.[19] cloned the LNCaP receptor into an expression vector to compare the ability of certain compounds to stimulate the androgen receptor and alter transcription of an androgen responsive reporter gene. Hydroxyflutamide inhibits the stimulation of the wild type androgen receptor, but activates the mutant androgen receptor; however, bicalutamide inhibits the stimulation of both the wild type and mutant androgen receptors.[17,20,21] The mutant androgen receptor loses binding specificity and binds DHT as well as progestins, estrogens, and hydroxyflutamide. These compounds are now capable of stimulating the androgen receptor, resulting in aberrant control of relevant gene transcription. Recently, a number of investigators have successfully isolated similar and identical androgen receptor gene mutations from patients with prostate carcinoma.[22–26]

Based on these data and the response of the patient reported in this study, the authors hypothesize that residual androgens and steroids produced by the adrenal cortex may play a meaningful role in some patients with prostate carcinoma. Furthermore, the authors speculate that patients who respond to withdrawal of antiandrogen may have carcinoma cells that express a mutant androgen receptor similar in function to the LNCaP cell line.[20,26,27] Although glucocorticoids have activity as single agents in this disease, the duration of response for this patient, combined with the published data supporting the activity of flutamide withdrawal plus adrenal suppression, leads the authors to speculate that antiandrogen withdrawal plus adrenal suppression may be more active than either alone. Thus, they believe it is reasonable to prospectively evaluate flutamide withdrawal versus flutamide withdrawal plus adrenal suppression in individuals failing combined androgen blockade.

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