Treatment of Stage D_2 Prostatic Carcinoma with Combined Gonadal and Adrenal Suppression in a 60-Year-Old Man

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A 60-year-old man with stage D_2 prostatic carcinoma received treatment with a new luteinizing hormone-releasing hormone superagonist. After a seven-month remission, relapse of the disease occurred and an adrenal-suppressing dose of dexamethasone was added. The resulting combined gonadal and adrenal suppression led to another remission that lasted five months. This case supports other observations of the importance of adrenal androgen production in the pathobiology of prostatic carcinoma.

Encouraging results in the treatment of metastatic prostatic carcinoma have been achieved recently with the use of superactive luteinizing hormone-releasing hormone agonists [1–5]. The efficacy of these agents in the treatment of prostatic carcinoma results from inhibition of pituitary gonadotropin secretion and the subsequent decrease in the production of gonadal androgens. The majority of prostatic carcinomas are believed to be dependent on gonadal androgens; approximately 75 percent of patients with the disease benefit from therapies directed at lowering gonadal androgen levels [6]. The role of adrenal androgens in the biology of prostatic carcinoma is less well understood. We herein describe a patient who received treatment with a new luteinizing hormone-releasing hormone agonist, 6-D(2-naphthyl)-alanine luteinizing hormone-releasing hormone (Syntex), and had a temporary dramatic response. After relapse, dexamethasone in doses sufficient to suppress adrenal androgen production was added to luteinizing hormone-releasing hormone agonist therapy. This combination suppression therapy led to a second remission.

CASE REPORT

A 60-year-old white man presented with a left neck mass that he had first noted one month previously. Examination revealed a 10 × 8 cm mass in the left supraclavicular fossa. Biopsy demonstrated adenocarcinoma, and immunohistochemical staining yielded positive results for prostate-specific antigen. Urologic evaluation demonstrated a hard mass in the right lobe of the prostate, and results of biopsy were positive for poorly differentiated prostatic carcinoma. Abdominal computed axial tomography showed extensive retroperitoneal adenopathy and a normal liver. Results of bone scanning were negative. Prostatic acid phosphatase level was 48 ng/ml (normal range, 0 to 4.0 ng/ml). Two weeks later, the neck mass measured 16 × 12 cm, and the patient began receiving luteinizing hormone-releasing hormone agonist, 400 μg daily, as a single subcutaneous injection. During the next five months, the neck mass progressively diminished in size to 2.5 by 2.5 cm. Repeat abdominal computed axial tomography three to five months later showed marked regression of the retroperitoneal adenopathy with minimal residual enlargement present in a few nodes. Prostatic acid

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TABLE I Laboratory Data

Treatment	Luteinizing Hormone		Testosterone (ng/ml)	DHEA-S (μg/dl)	Cortisol (μg/dl)	Prostatic Acid Phosphatase (ng/ml)
	Radioimmunoassay (ng/ml)	Bioassay (μg/ml)				
Control	22	0.38	2.9	229	20	47.9
LHRH-A remission	11	<0.08	0.3	179	20	3.9
LHRH-A recurrence	13	<0.08	0.4	187	19	8.5
LHRH-A plus dexamethasone	8	<0.08	0.04	6	2	3.1
Normal range	8–50	0.08–0.50	2.7–8.8	80–400	7–18	0–4

DHEA-S = dehydroepiandrosterone sulfate; LHRH-A = luteinizing hormone-releasing hormone agonist.

phosphatase level was 3.9 ng/ml at six months. At seven months, examination of the neck revealed four distinct enlarged nodes, the largest measuring 3.5 by 5 cm. Computed axial tomographic scanning demonstrated an increase in the retroperitoneal adenopathy. The prostatic acid phosphatase level was 8.5 ng/ml. Because of the disease progression despite continued suppression of testosterone (**Table I**), an attempt was made to suppress adrenal androgen production. Therapy with aminoglutethimide, 250 mg twice daily, with hydrocortisone replacement, was begun; however, an extensive rash developed three weeks later, necessitating discontinuation of aminoglutethimide. Therapy with dexamethasone, 5 mg daily, was begun. One month later, the prostatic acid phosphatase level was 3.1 ng/ml. The neck nodes diminished in size and were not palpable within three months of the institution of dexamethasone. The prostate was small and soft, without nodules. Computed axial tomography once again demonstrated regression of the retroperitoneal adenopathy. Because of the development of cushingoid features, the dose of dexamethasone was decreased slowly to 2 mg per day. Five months after dexamethasone therapy was begun, a mass was again palpable in the left supraclavicular fossa. Gonadotropin, testosterone, dehydroepiandrosterone-sulfate, and cortisol levels throughout the patient's course are shown in Table I.

COMMENTS

This 60-year-old man had stage D_2 prostatic carcinoma with widespread lymph node metastases. The lymphadenopathy profoundly regressed during suppression of testicular function due to treatment with 400 μg per day of 6-D(2-naphthyl)-alanine luteinizing hormone-releasing hormone (Syntex). Other parameters of his disease such as acid phosphatase level also improved during treatment. The remission lasted for seven months. When recurrence was noted, he was treated with a regimen designed to further inhibit androgen production. During treatment with dexamethasone, adrenal steroid production was greatly diminished (Table I). In addition, the testosterone level decreased further from already castrate levels. During the combined treatment, the prostate cancer again regressed. This strongly suggests that the continued production of adrenal androgens was capable of maintaining tumor growth.

Although prostatic carcinoma is known to be dependent on androgens in the majority of cases, the contribution of the adrenal gland to androgen levels has received little attention. The adrenal gland directly secretes 16 to 217 μg per day of testosterone in men with prior orchiectomy who have prostatic carcinoma. In addition, approximately 250 μg per day of testosterone is produced by conversion from androstenedione [7]. Treatment with luteinizing hormone-releasing hormone agonist in our patient resulted in testosterone levels found in men with prior orchiectomy. The addition of dexamethasone resulted in a 10-fold decrease in his already suppressed testosterone level. The dehydroepiandrosterone sulfate level, unaffected by the luteinizing hormone-releasing hormone agonist, was markedly reduced by dexamethasone treatment.

That adrenal androgens may play a role in the growth of prostatic carcinoma is suggested by favorable responses of the disease to therapies directed at diminishing adrenal androgen production. Adrenalectomy or hypophysectomy results in a response in 35 to 70 percent of men with prior orchiectomy [6]. Forty-eight percent of men with prior orchiectomy experienced improvement in the disease during treatment with aminoglutethimide, a potent inhibitor of adrenal steroid production [8]. Ketoconazole, an antifungal agent that inhibits steroid synthesis, results in decreased disease activity when given alone [9] or in combination with a luteinizing hormone-releasing hormone agonist [10]. Treatment directed at decreasing androgen action also is effective, either alone, or in combination with luteinizing hormone-releasing hormone agonists. Flutamide administration results in an 88 percent response rate in previously untreated patients [11]. The administration of RU-23908, a new antiandrogen, blocks the disease flare occasionally seen in patients during the first few weeks of luteinizing hormone-releasing hormone agonist therapy [12].

During agonist administration, luteinizing hormone levels as measured by radioimmunoassay were suppressed, but never decreased below the range found in normal men (Table I). However, measurement of luteinizing hormone by bioassay showed extreme suppression to levels well below the range found in normal men (Table I), consistent with the very low testosterone levels in the serum at that

time. These results are consistent with the interpretation that this luteinizing hormone-releasing hormone agonist leads to marked suppression of bioactive luteinizing hormone, but that the pituitary continues to secrete a molecular variant of luteinizing hormone that is recognized by the radioimmunoassay. Similar results have been reported for other luteinizing hormone-releasing hormone agonists [13].

The remissions of the prostate cancer in this patient, which resulted first from selective gonadal suppression and then combined gonadal and adrenal suppression, are further evidence of the importance of androgens from both sources in the pathobiology of prostate cancer. Although our patient received significant clinical benefit from adrenal suppression, he also was affected by some of the well-known adverse effects of supraphysiologic glucocorticoids, including fat redistribution and thinning of the skin. The combination of antiandrogens together with luteinizing hormone-releasing hormone analogs [12] shows promise for near-total elimination of androgen effect without the unwanted effects of glucocorticoid excess. Carefully controlled clinical studies of this combination are required to assess the eventual usefulness of this regimen in the hormonal therapy of prostate cancer.

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