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Case Report

Metastatic Prostate Cancer After Orchiectomy, Radiotherapy, and Testosterone Replacement in a Patient With Bilateral Seminoma

FRANCESCA MANASSERO*, PAOLA ERBA†, GIULIANO MARIANI†, ANDREA MOGOROVICH*, GIANLUCA GIANNARINI* AND CESARE SELLI*

*From the * Department of Urology and the † Regional Center of Nuclear Medicine, University of Pisa, Italy.*

Correspondence to: Francesca Manassero, Department of Urology, University of Pisa, Ospedale "Santa Chiara," via Roma 67, 56126 Pisa, Italy (e-mail: francy_manassero{at}hotmail.com).

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Although its clinical benefits remain unproven and its indications controversial, the popularity of testosterone replacement therapy has grown substantially in recent years, in order to maintain vigor and health into a more mature age. A potential risk of this therapy is an increased incidence of prostate cancer. However, whereas exogenous testosterone may stimulate the growth of metastatic prostate cancer, it is unclear whether lower levels of serum testosterone are associated with a reduced risk, and the published data regarding the relationship between testosterone levels and prostate cancer are, so far, conflicting (Loughlin et al, 2004). Moreover, it is widely accepted that radiation exposure increases the risk of secondary malignancies in proportion to the time and the dose. Pelvic radiation increases the risk of rectal and bladder cancer, and recently some cases of prostate cancer have also been reported.

To the best of our knowledge, this is the first report of metastatic prostate cancer in a patient who underwent long-term testosterone replacement after bilateral orchiectomy plus double extended radiotherapy for metachronous seminoma.

Case Report

A 67-year-old man presented to our Institution for a second opinion at the end of his long clinical history. At 27 years of age he had been treated with left orchiectomy and adjuvant radiotherapy for

an early-stage seminoma. At 41 years of age he had been treated with right orchiectomy and adjuvant radiotherapy for contralateral seminoma. Both radiotherapies with telecobalt were given to pelvis and para-aortic lymph nodes, including the whole pelvic area, each time with total dose of 30 Gy. At that moment, 2 months after the last operation, the total testosterone level was 0.1 ng/mL and free testosterone 1.5 pg/mL. Early in the following months, the patient developed a denial syndrome, refusing any kind of clinical and instrumental follow-up. Seven years later, in 1986, the patient underwent a new urological evaluation because of worsening sexual function. After clinical, laboratory and instrumental examinations, reduced testosterone levels were the only abnormal test results. Therefore, he began a long-term replacement therapy with intramuscular injections of testosterone enanthate (250 mg every 4 weeks). Once again, probably due to the improvement of his sexual life, he did not undergo follow-up investigations. In 1999, by a chance finding, the PSA was found to be 404 ng/mL, and a rectal examination revealed a firm, hard prostate gland. At that moment the total testosterone level was 14.3 ng/mL and free testosterone 63 pg/mL. The testosterone injections were immediately discontinued. Subsequent prostatic biopsy demonstrated adenocarcinoma of the prostate Gleason 3+4, involving 90% of bilateral cores. A ^{99}Technetium bone scan was positive for widespread metastatic disease. The patient was asymptomatic for bone pain.

An oral therapy with daily bicalutamide 50 mg was begun, thus obtaining a complete androgen blockade, with a progressive drop in the PSA (nadir at 1.28 ng/mL) and the almost complete disappearance of the bone lesions within two years.

In July of 2004, the PSA rose again to 40.83 ng/mL. The antiandrogen therapy was discontinued, and the PSA declined (13.51 ng/mL in January 2005). In December 2005, the patient was symptomatic for lumbar pain, and the imaging evaluation revealed several bone metastases and lymph node adenopathy. After 6 months of therapy with estramustine, the patient died of disease.

Discussion

The present case proposes the three following issues: the role of the baseline sex hormonal status, the effect of testosterone replacement therapy, and the impact of radiotherapy for other malignancies in the development of prostate cancer.

It is now commonplace for men with metastatic prostate cancer to undergo treatment designed to lower testosterone levels. If reducing testosterone levels causes prostate cancer to regress, does elevating testosterone cause prostate cancer to appear? It is well known that testosterone affects prostatic cell differentiation, but it does not have a direct influence on cell proliferation.

There is no evidence that androgens could trigger prostate carcinogenesis in aging men without prostate cancer. While the majority of epidemiological studies have failed to demonstrate a consistent, dose-related correlation between prostate cancer and testosterone levels, others have suggested a link between low testosterone levels and prostate cancer (Morgentaler et al, 1996; Mohr et al, 2001). Recently others have reported an increased risk of prostate cancer with higher free testosterone levels. In fact, free testosterone, unbound, may diffuse into the prostate and reflects the amount of androgens to which prostate cells are exposed: since prostate androgens seem to play a more prominent role in the development of prostate cancer than serum androgens, free testosterone could be a more relevant measure of prostate cancer risk (Parsons et al, 2004).

Regarding anorchid patients, either native or post-orchiectomies as in our case, it remains to be elucidated which role the hypodysgonadal status can have in the development of prostate cancer.

Some clinical studies have suggested that an androgen pathway disruption in prostate is responsible

for cell deregulations that may be associated not only with the apoptosis of differentiated prostatic cells but also with potential cell transformation. In particular, persistent low levels of testosterone might induce changes in the molecular balance of epithelial prostate cells, and the accumulation of changes over the years may induce deregulations that lead to tumorigenesis (Algarté-Gènin et al, 2004).

In recent years the topic of androgen deficiency in aging males and testosterone replacement has attracted increasing attention in the scientific community and lay press. Common indications for testosterone replacement include erectile dysfunction, decreased libido, depression, osteoporosis, anemia, and sarcopenia, as well as all the signs and symptoms described in the clinical condition of hypogonadism. This substitutive therapy encompasses several potential risks, the most alarming and controversial being prostate cancer.

Whereas it is the general opinion that patients diagnosed with prostate cancer should not receive androgen supplementation, since additional androgens are likely to increase cancer progression, disagreement exists regarding the causative role of testosterone therapy in prostate cancer. In fact, prospective studies have demonstrated a low frequency of prostate cancer in association with testosterone replacement therapy, but they were performed in a heterogeneous population of hypogonadal men, with no more than 36 months of follow-up (Rhoden and Morgentaler, 2004). On the other hand, testosterone administration might cause latent or occult prostate cancers to grow and become clinically significant, since we do not know what the long-term effects of testosterone replacement on occult prostate cancer could be (Bhasin et al, 2003).

It is generally accepted that exposure to radiation places patients at risk of developing secondary malignant neoplasms, the incidence increasing as time increases, after treatment and with increasing doses (Dorr and Herrmann, 2002). In a recent report by Birgisson et al, prostate cancer was the most frequent secondary malignancy among patients treated with radiotherapy for rectal cancer followed up to 20 years, accounting for 18% of cases (Birgisson et al, 2005).

In experimental studies, Takizawa et al observed a high incidence of prostate cancer in radiated rats and subsequently the role of testosterone influencing the occurrence of prostate cancer in the radiated rat model (Hirose et al, 1976; Takizawa and Hirose, 1978).

It has been described that radiation-induced malignancies tend to occur within or adjacent to the radiated volume, and it often takes years for the radiotherapy to become evident (Dorr and Herrmann, 2002).

Hughes et al reported a case of prostate and renal cell cancer in a patient who underwent orchiectomy and radiotherapy for seminoma, with extended fields including the pelvic area as well as the renal fossa (Hughes et al, 2003).

In our report, the patient was twice radiated, after each orchiectomy, with both higher doses and larger fields than those currently used, doubling the risk of exposition.

To our knowledge this is the first case of widespread metastatic prostate cancer after bilateral orchiectomy for seminoma, radiotherapy, and uncontrolled long-term testosterone replacement. We acknowledge that at present it is impossible to discover whether this case of prostate cancer represents the natural evolution of the prostate gland in patients with prolonged hypogonadal status, the effect of high-dose radiotherapy, or a response to exogenous testosterone stimulation.

Thus, given the beginning of hormone replacement therapy, many years after radiotherapy and hypogonadal status, and its extended duration without any control, we only can postulate that radiotherapy and low testosterone levels could have had a role in carcinogenesis, which was further sustained by uncontrolled androgen substitution.

Autopsy studies found increasing percentage of occult prostate cancers with each decade of life and screening trials reported quite high cancer detection rate (Sakr et al, 1993). In particular, in the PCPT trial, Thompson et al reported 24.4% of patients in the placebo arm developing prostate cancer, although serious concerns have been raised about the clinical significance of the cancers that were detected (Scardino, 2003; Thompson et al, 2003). Prostate cancer almost certainly includes a wide spectrum of biological potentials ranging from clinically insignificant histological carcinomas to slowly growing cancers, to highly malignant neoplasms resulting in death in a few years. Unlike the probably clinically insignificant cases, our report regards a life-threatening metastatic prostate cancer.

The time period between diagnosis of metastatic prostate cancer and earlier potentially carcinogenetic treatments is quite long to be suggestive of a causal relation, but it is recognized that metastatic spreading occurs several years after the onset of the primary cancer. Therefore it is likely that the patient developed the cancer not only because of his age.

However, our report suggests the importance of a still more careful monitoring of those patients with androgen substitution when they also underwent radiotherapy, which by itself increases the rate of development of secondary malignancies.

Bhasin et al have proposed a standardized, albeit not yet validated, monitoring algorithm for the follow-up of patients receiving testosterone replacement. Recommendations include digital rectal examination, serum PSA, and AUA or IPSS symptom scores for BPH as a baseline evaluation, as well as follow-up at 3, 6, and 12 months and annually thereafter. A prostate biopsy is suggested when the serum PSA is more than 4.0 ng/mL or increases more than 1.0 ng/mL during the first 3 or 6 months of therapy or more than 0.4 ng/mL per year thereafter, or in the presence of doubtful digital rectal examination (Bhasin et al, 2003).

In conclusion, the literature is still unclear as to what role, if any, testosterone plays in the development of prostate cancer and this remains an area of concern and investigation. Further studies are required to provide better care for patients requiring testosterone replacement.

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