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Male Breast Adenocarcinoma in a Prostate Cancer Patient Following Prolonged Anti-androgen Monotherapy

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Abstract. *We report the case of an 82-year-old male patient with a > 8-year history of prostate cancer (PrCa), who developed breast adenocarcinoma (BrCa) (Ki-67+ and negative for ER, PR, PSA and HER2/neu) after prolonged (~7-year) anti-androgen (flutamide) monotherapy for locally advanced PrCa. Biochemical and molecular analyses showed hyperestrogenemia (serum estradiol = 266 pg/ml, with normal range < 74 pg/ml), germline BRCA-1 mutation (T to C at nucleotide 3232, in exon 11, causing Glu to Gly change at codon 1038) and chromosome 9 inversion (karyotype of 46,XY with inv(9) (p11q21)). Following bilateral mastectomy without adjuvant systemic therapy, the patient has been disease-free (from both BrCa and PrCa) for > 3 years. In contrast to LHRH-based hormonal therapies for PrCa, anti-androgen monotherapy causes hyper-estrogenemia due to the suppressed negative feedback loop of androgens on LHRH and LH production, stimulation of testicular androgen production and their intracrine transformation to estrogens in peripheral target tissues. In this case report, the hyperestrogenemia may have further increased the BrCa risk in a patient with other risk factors (BRCA-1 mutation and chromosome 9 inversion, which has been previously shown to impinge upon testicular function and intracrine balance of androgens vs. estrogens). This case report illustrates that PrCa patients receiving anti-androgen monotherapy may be at risk of BrCa, in the event of the concomitant presence of other genetically-determined predisposing factors, and indicates the importance of exercising caution against indiscriminate and prolonged use of anti-androgen monotherapy in patients with risk factors for male BrCa.*

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Case Report

Male breast cancer corresponds to <1% of all cancer cases in men and is > 100 times less common than in women (1-3). While its rarity has impeded the detailed characterization of its clinical behavior and pathophysiology, male breast cancer is generally considered more prevalent in individuals with a genetic background known to confer an increased risk of breast cancer in females (*e.g.* germline mutations in BRCA-1 / -2 genes (4)) and/or disorders in the relative balance of androgens *vs.* estrogens *e.g.* in chromosomal abnormalities impinging upon testicular function including Klinefelter's syndrome (5,6) or Kallman syndrome (7), as well as in exogenous administration of estrogens (*e.g.* in transsexual males) (8,9). Previous reports (10,11) have suggested that estrogen-based hormonal manipulations in prostate cancer patients may contribute to the development of breast cancer. However, the majority of hormonal therapy cases in prostate cancer do not involve exogenous estrogen administration, but rather abrogation of endogenous androgenic activity, *e.g.* by luteinizing hormone-releasing hormone (LHRH) analog monotherapy, anti-androgen monotherapy, or their combination (combined androgen blockade, CAB), and it has not been clearly elucidated whether such treatments confer an increased risk for development of breast cancer. This question is becoming increasingly important because of the continuous trend, in recent years, to use such androgen ablation therapies not only in metastatic disease, but also at earlier disease stages, thereby leading to the longer overall exposure of patients to such endocrine manipulations.

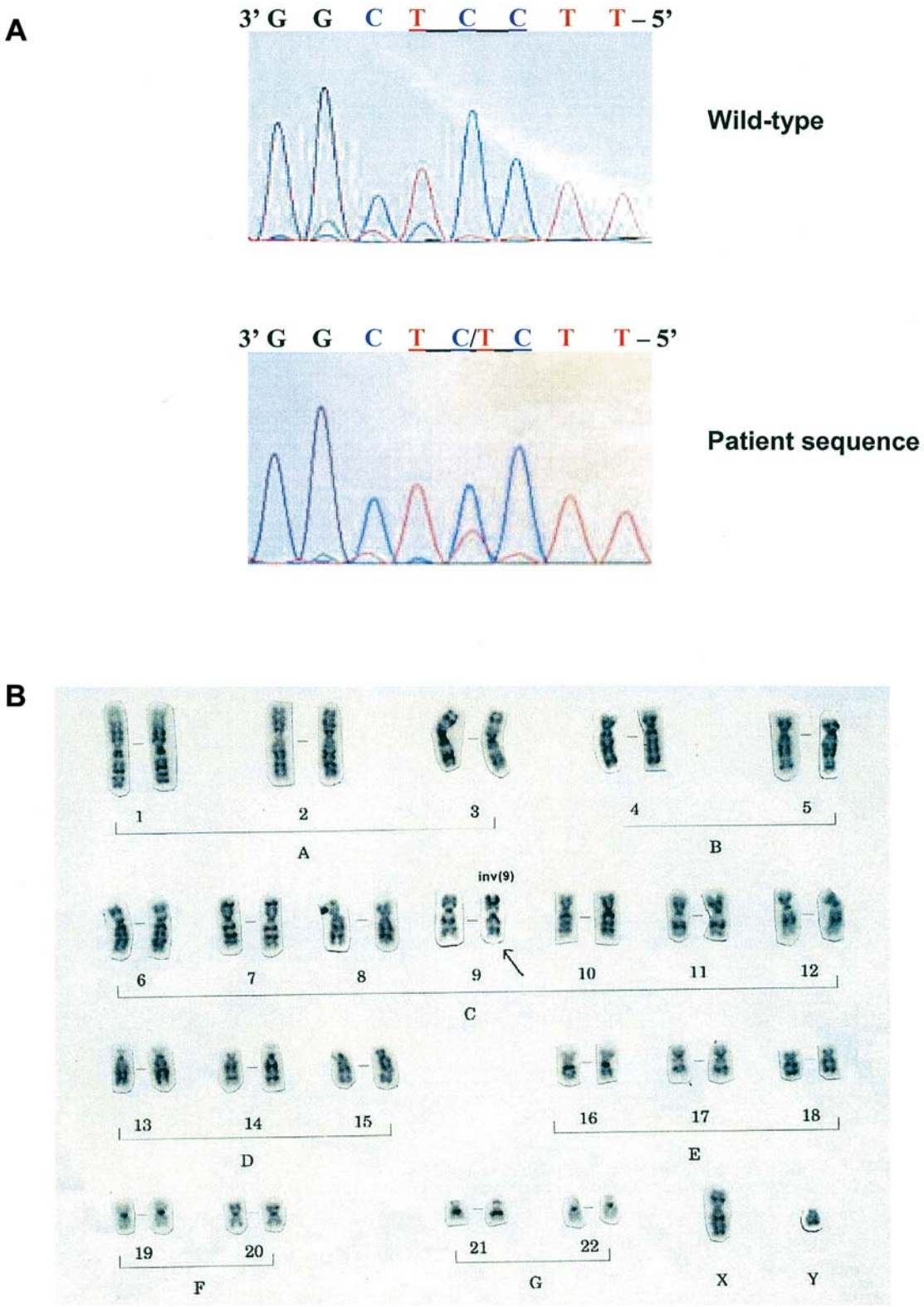

Figure 1. *A) Wild-type homozygous 3' to 5' sequence of the non-coding strand of the BRCA-1 gene (top panel) shows a C at nucleotide 3232, while the sequence of the reported patient (bottom panel) is characterised by the presence of normal and mutated (C→T) sequences. This C→T mutation corresponds to mutation from 5'-GAA-3' to 5'-GGA-3' of the coding strand, generating a replacement of Glu (E) by Gly (G), at codon 1038. B) Chromosomal analysis reveals a karyotype of 46,XY with inv(9) (p11q21) in 50/50 studied metaphases (50/50).*

Herein, we report the case of an 82-year-old male patient with a > 8-year history of prostate cancer (PrCa), who developed breast adenocarcinoma (BrCa) in the context of prolonged administration of anti-androgen (flutamide) monotherapy for locally advanced prostate cancer, plus germline BRCA-1 mutation and chromosome 9 inversion. The patient was originally diagnosed with prostate cancer 8 years prior to referral [serum PSA 22 ng/ml; Gleason score = 7 (3+4)] and underwent radical prostatectomy (RP). Pathologic analysis was consistent with stage $T_3N_0M_0$, Gleason score= 7 (3+4) and positive surgical margins. However, 3 months post-operatively, serum PSA levels were 2.2 ng/ml and the patient underwent postoperative salvage external beam irradiation for 6 months. Post-radiotherapy PSA levels remained > 2.0 ng/ml and anti-androgen monotherapy (flutamide 250 mg, tid) was initiated. Since then his PSA declined to < 0.5 ng/ml and remained at those levels, while anti-androgen monotherapy was maintained. However, he developed bilateral gynecomastia and (3 months prior to referral to our Center) he reported, during a regular follow-up visit to his physician, a painless, firm, retro-areolar lump in the left breast. The patient's informed consent for the subsequent diagnostic work-up was obtained after full explanation of its purpose and nature. All studies performed within the context of this investigation have been approved by the local ethical committee of our Institution. Fine-needle aspiration (FNA) of the lesion revealed malignant cells consistent with breast adenocarcinoma. Blood measurements revealed PSA levels < 0.5 ng/ml, alkaline phosphatase (AP) = 88 IU/L (normal range < 105 IU/L), testosterone (T) = 6.58 ng/dL (normal range = 2.8-9.0 ng/dL), free-T = 20.6 pg/dL (normal range = 8.7-55.0 ng/dL) and estradiol (E_2) = 266 pg/ml (normal range < 74 pg/ml). The pre-operative work-up for metastases (bone scan, CT-scan and metastatic X-rays survey) was negative. Other biochemical and endocrine tests included measurements for 17-OH progesterone, dehydroepiandrosterone sulfate (DHEA-S), DHEA, Δ_4-androstenedione (Δ_4-A), progesterone (PG), prolactin (PRL), luteinizing hormone (LH) and follicular stimulating hormone (FSH) levels, which were within normal limits. The patient underwent modified left radical mastectomy and axillary lymph node dissection, as well as right subcutaneous mastectomy. The histopathological analysis was consistent with bilateral gynecomastia and the presence, in the left radical mastectomy specimen, of invasive ductal carcinoma (3.0 x 1.9 cm), $T_2N_1M_0$ (1/20 dissected lymph nodes was positive), grade III tumor, with negative surgical margins. Immunohistochemistry confirmed that the tumor was positive for Ki-67 and negative for estrogen receptor (ER), progesterone receptor (PR), p53, PSA and c-erb-2. Following his bilateral mastectomy, the patient has received no additional systemic therapy and has been disease-free (with regards to both PrCa and BrCa) for > 3 years.

While the hyper-estrogenic state in this patient may have contributed to the development of breast cancer, we also addressed the putative role of genetically-determined risk factors for this disease, by performing sequencing analysis of the p53, BRCA-1 and BRCA-2 genes in genomic DNA isolated from the patient's peripheral blood mononuclear cells. We detected a mutation in the BRCA-1 gene, at nucleotide 3232 (T to C/3232, altering the sequence of the sense strand from 5'-GAA-3' to 5'-GGA-3', in exon 11; HSU 14680). This mutation caused a change in amino acid 1038 from Glu (E) to Gly (G) (Figure 1a). No mutations were detected in the other genes studied. Peripheral blood lymphocytes of the patient (cultured in McCoy's 5A medium supplemented with 10% FCS, 1% L-glutamine and antibiotics, at a cell density of 0.8-1.0 x 10^6 /ml) were stimulated with PHA for 72 hours and then treated with colcemid for 3 hours. Cytogenetic analysis of 50 metaphases was carried out on trypsin G-banded chromosome preparations (GTG-banding) (12). The karyotype analysis and description occurred according to the ISCN nomenclature (13) and revealed a karyotype of 46,XY with inv(9) (p11q21) in 50/50 studied metaphases (50/50) (Figure 1b).

Similarly to breast cancer in females, male breast carcinoma has been associated with germline mutations of the BRCA genes (more so for BRCA-2, less so for BRCA-1) (14-16). Pericentric inversions of chromosome 9 occur in the general population with an incidence of 1% to 2% and are often considered as normal variants or minor chromosomal rearrangements with normal phenotypes(17). However, the most frequent type of chromosome 9 inversion, inv(9)(p11;q13), is reported to be associated with subfertility and recurrent abortions (17-19), while inv(9) (p11q21), a less frequent type which was found in this case report, has also been associated with primary sterility, abnormal spermograms and testosterone levels at or below the lowest normal range (20). Interestingly pericentric inversions of chromosome 9, *e.g.* inv(9) (p11q21), include chromosomal regions encompassing genes potentially implicated in tumorigenesis, *e.g.* p16, p15. Taken together, these reports indicate that, in this case presented herein, the presence of a germline BRCA-1 mutation and a pericentric chromosome 9 inversion could potentially confer an increased risk for breast cancer. The precise roles of these 2 genetic events in this patient's tumors, either breast or prostate, are not clearly defined (although prior studies have suggested that BRCA gene mutations conferring high risk for breast cancer may also predispose to prostatic cancer in male carriers(21)). It is, however, conceivable, that these lesions may have provided at least some degree of breast cancer predisposition, which may have been amplified by the prolonged hyper-oestrogenic state created by long standing anti-androgen monotherapy.

Indeed, anti-androgen monotherapy not only competitively inhibits the transcriptional activity of the androgen receptor (AR), but also leads to increased levels of estrogenic compounds in blood and peripheral tissues: in contrast to LHRH analogs (either when used in monotherapy, or as part of CAB therapy), anti-androgen monotherapy does not inhibit testicular androgen production and, in fact, blocks the negative feedback loop which is exerted by androgens themselves on the hypothalamic LHRH production and pituitary LH release, by inhibiting the activity of the AR in those tissues. This leads to increased LH production and stimulation of production of testicular androgens which, in turn, undergo intracrine transformation to estrogens in peripheral target tissues (22,23). This hyper-estrogenic state may not only explain the relatively high percentage of gynecomastia in patients treated with anti-androgen monotherapy in comparison to CAB (24-26), but may also contribute to a higher risk for male breast cancer.

The hypothesis that the hyper-estrogenenic state in the blood and peripheral tissues generated by anti-androgen monotherapy in prostate cancer patients may confer increased risk for breast cancer might appear at odds with the apparent lack of a major increase in the incidence of this neoplasm in prostate cancer patients, thousands of whom have received androgen ablation therapies over the last 2 decades. However, it must be emphasized that: a) while androgen ablation therapies were traditionally reserved for patients with metastatic prostate cancer (with a median overall survival <3 years), there now is an increasing trend for their use at earlier stages of the disease, *e.g.* immediately after radical prostatectomy (27) (with a median overall survival of > 6 years); and b) this trend for earlier initiation of hormonal therapy is also associated with more frequent use of anti-androgen monotherapy, mainly because it is associated with a lower frequency of anemia and osteoporosis than LHRH-analog-based endocrine treatment (LHRH analog monotherapy or its combination with anti-androgens) (28). However, LHRH analog-based androgen ablation does not result in hyper-estrogenaemia, which may explain not only the lower frequency of gynecomastia (in comparison to anti-androgen monotherapy), but also the lack of major increases in breast cancer incidence in this group of patients. Therefore, the trend for anti-androgen monotherapy administration at early stages of prostate cancer may lead to prolonged exposure of those patients to a hyper-estrogenic state which, in turn may potentiate the risk for breast cancer, especially in patients (such as the one presented herein) who may harbor other predisposing factors, *e.g.* BRCA mutations, chromosomal abnormalities and who might otherwise not develop breast cancer, in the absence of excess estrogens.

This case report illustrates several important observations. Male prostate cancer patients are at risk not only for recurrences of prostate cancer, but also for development of breast cancer, especially in the context of genetically-determined predisposing factors, such as those relevant to female breast (and probably ovarian) cancer, *e.g.* BRCA gene mutations, or those pertinent to male breast cancer (*e.g.* chromosomal abnormalities impinging upon testicular function and intracrine balance of androgens *vs.* estrogens). It is unclear whether anti-androgen monotherapy can increase by itself the risk of breast cancer in men. However, it is still important for clinicians to exercise caution against indiscriminate and prolonged use of anti-androgen monotherapy in patients with risk factors for male breast cancer. Such patients may be identified by a detailed review of their familial history of cancer (*e.g.* breast and ovarian), as well as careful serial follow-up during anti-androgen monotherapy, including thorough physical examination, *e.g.* palpation of breasts (particularly in the setting of gynecomastia), patient education regarding breast self-examination, careful assessment of suspicious lesions and signs (*e.g.* nipple discharges), or even mammographic evaluation. These diagnostic measures, on which significant experience has been generated in the field of female breast cancer, may also be particularly important for male patients, especially because breast cancer in this population is often diagnosed at a late stage (and a less favorable overall prognosis) because of the minimal awareness of presenting symptoms by the patient and sometimes by health care providers (29).

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