Bladder Cancer: The Hormonal Dependence Enigma and a New Hormonal Player

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Dear Editor,

Bladder cancer is considered to be a hormonal-independent malignancy. However, an increasing number of studies show that sex hormones might have an important role in the etiology or progression of specific urothelial carcinoma subtypes. The most important indication that bladder cancer might be influenced by sex hormone is that the incidence and risk of developing bladder cancer in men is notably greater comparing to women, even when established risk factors such as smoking, occupational exposure, and urinary tract infection are counterbalanced between the sexes.

The effect of sex hormones in bladder tissues is documented during pregnancy and menopause where the bladder undergoes dramatic changes in structure, function, histology, and gene expression. Bladder tissues are shown to express androgen, estrogen, and progesterone receptors. Additionally, in animal models, estrogens are shown to inhibit and androgens to promote bladder cancer development even when carcinogenetic substances are used such as N-butyl-N-(4-hydroxybutyl)nitrosamine [1]. Another indication of the hormonal contribution in bladder cancer development is the relatively lower risk of parous women to develop this malignancy compared to the nulliparous females. A human bladder tumor cell line, R198, was shown to develop under the effect of androgens while it regressed under the presence of estrogen [2]. Finally, there is also the report of a man who developed

endometriosis of urinary bladder, after 5 years treatment with estrogen therapy for prostate cancer [3]. The lesion regressed after estrogen withdrawal, indicating a metaplasia potential of the urothelium under extreme changes of hormonal environment.

Under these circumstances, we would like to report our experience of a 65-year-old woman treated for breast cancer who developed urothelial carcinoma at the trigone of the urinary bladder, 1 year after the onset of adjuvant hormonal therapy with third-generation non-steroidal aromatase inhibitor. The patient underwent modified radical mastectomy with ipsilateral axillary lymphadenectomy 4 years ago and subsequently chemotherapy (FEC and docetaxel) and radiotherapy. Three months after the onset of aromatase inhibitor treatment, the patient claimed to have aggravated hirsutism of both arms and no hair growth on the parietal skull following a pattern of androgenetic alopecia. A year since the onset of adjuvant hormonal therapy, a papillary protrusion was detected at the trigone of the urinary bladder. The histological report showed a non-muscle invasive low-grade papillary urothelial carcinoma, grade 1 by WHO-ISUP. One and a half year later, the patient was found to have bladder cancer relapse with the same histological urothelial tumor and the same androgenetic effects of the adjuvant hormonal therapy.

The current hypothesis we propose is that the excessive androgen environment produced by the aromatase inhibitor in a postmenopausal woman with lack of the counterbalancing hormones (estrogen and progesterone) could contribute to the development of bladder cancer.

There are some hypotheses which try to explain the hormonal dependence of bladder cancer and especially of the trigone of the urinary bladder. The trigone and the prostate have the same embryologic endodermic origin. This hypothesis is supported by the finding that the tumor cells of R198 cell line have some similar characteristics with human prostatic carcinomas [2]. Additionally, one of the ways that

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cigarette smoking could contribute to bladder cancer development might be its antiestrogenic effect on circulating estrogens. There is also the hypothesis that lack of estrogen in postmenopausal women alters the functionality of urinary bladder, increasing the risk of infection and inflammation which in turn increases the risk of bladder cancer. Finally, there is a report of a case where the treatment with SERM (tamoxifen) led to resolution of metastatic transitional cell carcinoma which is not considered as a hormone-sensitive subtype [4]. Although it is not certain whether the SERM exhibits antiestrogenic or estrogenic effect, since it has different effects on different tissues, it is another indication that certain subtypes of urothelial carcinoma could be hormonal responsive.

Bladder cancer is a candidate for entering the hormone-dependent malignancies' list. More sophisticated studies are required in order to conclude whether it is or it is not a hormone-dependent cancer. The current trend shows that sex hormones can influence somehow the bladder cancer progression. The genetic, epigenetic, and environmental background in addition to sex hormone contribution should be investigated, in order to elucidate the exact role of estrogen and androgen in bladder cancer development and progression. Our contribution to this effort is to draw attention to another hormonal player, the aromatase inhibitors. In postmenopausal

women, who lack estrogen and progesterone, aromatase inhibitors could be a crucial androgenic, estrogen-depleting factor contributing to the development of bladder cancer.

Consent Written informed consent was obtained from the patient for publication of this letter to the editor. A copy of the written consent is available for review by the Editor of this journal.

Conflict of Interest The authors declare that they have no conflict of interest.

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