Case Report and Literature Review: Endometrial Carcinoma in a Postmenopausal Patient Treated with Tamoxifen for Breast Cancer

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Introduction: Tamoxifen is a selective estrogen receptor modulator. It is commonly used in the treatment of patients with hormone receptor positive breast cancer.The early breast cancer trialist group ,EBCTCG meta-analysis reported that 5 years of adjuvant Tamoxifen treatment resulted in reduction in recurrence and mortality by 47% and 26% respectively, and reduced the incidence of contralateral breast cancer by 47% [(1)]. Tamoxifen is also used for chemoprevention in women at high risk for developing breast cancer,and those with 5-year breast cancer risk > 1.7%. The benefit was found to be 49% in women > 35 years old[(2)].

A number of studies have confirmed the relation between Tamoxifen and development of endometrial cancer that has a very low, yet a serious incidence. The cumulative risk of endometrial cancer with Tamoxifen use is 1.6% at five years and 3.1% if used for 5-10 yrs[(3)].Tamoxifen has antagonistic and agonistic effects. When it exerts its agonistic effect on the endometrium in postmenopausal women it may lead to a number of effects ranging from hyperplasia to endometrial cancer[(3)].

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Case Report:

A 62 years old Sudanese lady with no significant past medical history or family history, was diagnosed as a case of breast cancer Luminal A, stage T2N0M0, in 2002.She had a mastectomy and axillary clearance. The pathology was positive for (5 x 4 cm) mass, invasive, ductal carcinoma grade II, no lympho-vascular invasion, negative margins, all more than 4 mm. 12 out of 12 negative lymph nodes. Estrogen receptor positive(7/8),progesterone receptor positive(6/8), Her 2 negative, Ki67 <13%. That was followed by external radiotherapy to the chest wall and supraclavicular area,40Gy in 15 fractions by cobalt 60. Then Tamoxifen 20 mg/day was given for 5 years.

She was then followed up regularly, and remained well till she presented one month after completing five years of Tamoxifen therapy with a history of vaginal bleeding for four weeks.

Clinical examination and PV were normal. CT scan of the abdomen and pelvis showed a bulky uterine mass,6x5cm, endometrium thickness = 13 mm, and a left ovarian cyst 2 x 2.4 cm.

Dilatation and curettage was done. The histopathology confirmed endometrial moderately-differentiated adenocarcinoma. She underwent a hysterectomy and bilateral salphingio-oophorectomy,and the same histopathology was confirmed, the tumor size was 5x5cm invading more than two thirds of the inner myometrium, and reaching the cervical stroma with positive distal margin, FIGO stage I[(4)].

She received adjuvant pelvic radiotherapy, 50 Gy in 25 fractions, 4 fields anterior, posterior, and two laterals, using linear accelerator 6 Mv. She was regularly followed, by clinical examination, PV and CT scans. She was disease free when last seen.

Discussion:

Tamoxifen,a non-steroidal selective Estrogen Receptor Modulator (SERM), has been used widely since the 1970s in the treatment of hormone receptor positive breast cancer in both premenopausal and postmenopausal patients.

In the 1980s, several preclinical studies showed that Tamoxifen exerts an estrogenic effect on the endometrium, as it blocks activation function 2 (AF2)domain of the ER, leaving the activation function 1 (AF1) domain functioning, resulting in the estrogenic effects on the endometrium[5].

The risk of developing endometrial cancer in patients on tamoxifen prophylaxis is observed in post-menopausal women ,relative risk = 4.01, (2). The cumulative risk of endometrial cancer with tamoxifen use is 1.6% at five years and 3.1% if used for 5-10 yrs (3). Population-based data suggest an apparent small increase in the risk of uterine sarcoma with tamoxifen use[6,7].

Fornander et al in 1989, reviewed the frequency of new primary cancers as recorded in the Swedish Cancer Registry for a group of 1,846 postmenopausal women with early breast cancer who were included in a randomized trial of adjuvant Tamoxifen; they noted a 6.4 fold increase in the relative risk of endometrial cancer in 931 Tamoxifen treated patients, compared with 915 patients in the control group[8], and the highest cumulative risk of developing endometrial cancer occurred after five years of Tamoxifen use[8].

Results from NSABP B-14 trial confirmed the association between Tamoxifen use and the development of endometrial cancer in a study of 2843 patients with node-negative, oestrogen receptor-positive, invasive breast cancer randomly assigned to placebo or Tamoxifen ,20 mg/d. Two of the 1,424 patients assigned to receive placebo developed endometrial cancer compared to fifteen patients randomized to Tamoxifen treatment[3]. Seventy six percent of the endometrial cancers occurred in women 60 years of age or older. The mean duration of Tamoxifen therapy was 35months. The average annual hazard rate for endometrial cancer in the placebo group was 0.2:1000, compared with 1.6:1000 for the Tamoxifen group[3].

Although some authors have suggested that uterine cancers occurring in breast cancer patients taking Tamoxifen may behave more aggressively and carry a poorer prognosis[9] several studies have documented that the type and prognosis of endometrial cancers that develop during or after Tamoxifen therapy are not different from endometrial cancers occurring in the general population[10-12].

Clinicians must counsel their post-menopausal patients on Tamoxifen that their annual risk of developing endometrial carcinoma is approximately 1:1000 (0.2%). However, the risks of Tamoxifen-induced endometrial cancer must be weighed against the benefits of Tamoxifen in reducing breast cancer recurrence and development of new contralateral breast cancers[3].

Pre-menopausal women are less likely to develop endometrial lesions and routine screening is not recommended. Post-menopausal women are at higher risk of developing significant endometrial lesions specially if they had a pre-treatment endometrial lesion. It is recommended that US abdomen and trans-vaginal US should be performed for assessment in symptomatic patients[6].

Conclusion:

Tamoxifen is used widely in the treatment of hormone receptor positive breast cancer and in chemoprevention in those at high risk of developing breast cancer. It exerts oestrogenic effect on the endometrium which has been linked with the development of endometrial hyperplasia and endometrial cancer, the risk of the latter is about 0.2%. Endometrial cancer associated with Tamoxifen use is usually diagnosed at an early stage, with favourable features, and there is no strong association with the duration of treatment.

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