Tamoxifen-induced endometrial carcinoma after a lag of 14 years

Sir,

A 50-year-old gravida 4, para 4, postmenopausal female presented with a lump in her right breast of 6-month duration. She had a 5.5-cm mobile lump in her right breast with no axillary lymphadenopathy. All the routine investigations were normal. Biopsy revealed infiltrating ductal carcinoma and the patient underwent modified radical mastectomy. The final diagnosis based on histopathology report was carcinoma right breast $pT_3N_0M_0$. Her estrogen and progesterone receptor (ER/PR) status was positive. All the resected axillary lymph nodes were free from tumor infiltration, and the patient received adjuvant radiotherapy to chest wall and drainage area (45 Gy/20 fractions/4 weeks) and 6 courses of CMF regimen. The patient was started on adjuvant tamoxifen therapy, 20 mg daily, which she received regularly for 5 years without interruption. On patient's request no further hormonal treatment was given after 5 years of tamoxifen therapy. The patient was on regular follow-up till 2008 and this period was event free. Endometrial thickness was measured regularly on follow-up and the maximum thickness observed was 7 mm.

The patient did not come for follow-up for 1 year and she presented with bleeding per vaginam in January 2010. There was no evidence of recurrence of breast cancer. Gynecological examination revealed blood oozing out of cervix and a bulky uterus. Pelvic ultrasound revealed multiple small anechoic areas of size 4.0 × 2.3 cm in uterus. Cervical brush Papanicolaou (Pap) smear cytology revealed adenocarcinoma. Subsequently, endometrial biopsy was taken which confirmed the diagnosis as serous papillary adenocarcinoma.

The patient underwent radical hysterectomy with bilateral pelvic lymphadenectomy. Panhysterectomy specimen revealed moderately differentiated endometrioid adenocarcinoma infiltrating more than half the thickness of uterine wall and extending to the uterocervical junction. One out of 6 resected right iliac lymph nodes showed metastatic tumor deposits. Patient was treated with postoperative radical external beam radiotherapy 50 Gy/25 fractions/5 weeks to whole pelvis followed by vaginal cuff brachytherapy (VCB) 6 Gy per session per week for three sessions. At present the patient is disease free, 1 year after completion of treatment.

The exact etiology of endometrial carcinoma is unknown; however, tamoxifen is known to cause an increased incidence of adenocarcinoma of the endometrium.[1] The most widely used oral anticancer drug, tamoxifen is a nonsteroidal drug that has a therapeutic anti-estrogen effect on the breast and an estrogenic effect on the endometrium of postmenopausal women.[2] It has become standard adjuvant therapy in estrogen and progesterone-receptor positive premenopausal patients with breast cancer because it reduces the overall recurrence and risk of contralateral primary breast cancer by 40-50%. More recently, tamoxifen has been approved as a chemopreventive agent in women who are at high risk for breast cancer.[2] The major growth stimulators of endometrial tumors are estrogens, but paradoxically, tamoxifen acts as an estrogen antagonist in the breast and as an estrogen agonist in other tissues, increasing the thickness of the vaginal epithelium, reducing serum cholesterol levels and preserving bone density. Estrogen-like effects have been found on steroid hormone receptors in the endometrium, and growth-promoting effects have been found on endometrial carcinoma cells. Experiments suggest that tamoxifen, like estradiol, directly sensitizes endometrial cancer cells to the effects of insulin-like growth factor (IGFs) that act through the type I receptor. Furthermore, it causes a decrease in IGF-binding proteins and the increase in tyrosine phosphorylation, providing a molecular mechanism that accounts for the uterotropic effects that are seen with tamoxifen therapy.[3]

Women taking tamoxifen have thicker endometrial linings than women not taking the drug. This observation should come as no surprise, considering that tamoxifen is known to be a mixed agonist/antagonist of the effects of estrogen.[2]

Pap smears can help detect endometrial cancer when atypical glandular cells are present. Transvaginal sonography/TVS can evaluate the thickness of the endometrial lining and is useful in high-risk patients. TVS showing an endometrial thickness of less than 8 mm is a strong indication of the absence of tamoxifen-associated endometrial cancer.[4] Endometrial biopsy is recommended in patients with specific abnormalities, as in present case abnormal bleeding, presence of endometrial cells on Pap smear and atypical glandular cells of undetermined origin and for screening high-risk syndromes.

Thirty-six percent of endometrial cancers develop within 3 years of tamoxifen therapy. Results have shown a 7.5-fold increase in the risk of developing endometrial cancer in estrogen-receptor positive group treated with tamoxifen therapy. According to Barakat, the relative risk of an endometrial cancer occurring in the randomized, tamoxifen-treated group was 7.5:1000.[1] The mean lag period between initiation of tamoxifen therapy and occurrence of endometrial carcinoma is 0.7-8.1 years. In the present case, the endometrial carcinoma occurred after a lag period of 14 years.

Therefore, the patients of breast cancer on tamoxifen therapy should be followed-up for a longer period. Endometrial thickness is the main indicator to monitor the progress of carcinoma endometrium, hence regular TVS is indicated during follow up and if the thickness observed more than 8.0 mm than all the diagnostic measures should be considered. In summary, the risk of endometrial cancer increases following tamoxifen therapy for invasive breast cancer; however, the net benefit of adjuvant tamoxifen therapy greatly outweighs the risk of developing endometrial cancer.[2]

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