Endometrial Carcinoma Can Develop in Patients on Tamoxifen Therapy

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Introduction

Breast cancer constitutes 54.8 percent of deaths from malignancies in female genital tract in Malaysia, 1995[1]. It is also the second most common death (19.4%) from malignancies in females in Malaysia. The use of adjuvant tamoxifen therapy continuously for five or more years has contributed to longer survivals in these patients. Several recent reports of possible association between tamoxifen treatment and endometrial pathologies, such as endometrial hyperplasia, endometrial polyps, adenomyosis, endometrial carcinoma and endometrial sarcoma are of concern to the clinicians. We present here 2 cases of advanced endometrial carcinoma after tamoxifen therapy.

Case History 1

HA was a 70 years old lady, para 5, seen in the gynaecology clinic with a one-year history of occasional per vaginal bleeding. She attained menarche at the age of 12 and menopause about thirty years ago. In 1991, she was diagnosed to have carcinoma of right breast. A right mastectomy and axillary nodes clearance were performed. Following surgery, she was commenced on tamoxifen 20 milligram daily for a period of five years. There was no significant medical history of hypertension, diabetes mellitus or family history of breast cancer.

On examination, there was mild pallor noted. A healed right mastectomy scar with no local recurrence was seen. The abdomen was soft with a mass just palpable in the suprapubic region. Vaginal examination revealed a ten weeks size uterus palpable bimanually. No other masses noted in the adnexal region. Histopathological examination of the endometrial tissue was reported as "adenocarcinoma of the endometrium". CT scan of the abdomen and pelvis showed the uterus to be enlarged measuring 8.5 x 7 x 6.5cm with hydrometra, there was an omental cake, ascites and enlarged paracaval and paraaortic nodes. No focal lesions were noted in the liver or spleen.

Patient and family were counselled and a total abdominal hysterectomy, bilateral salpingo-oophorectomy, supracolic omentectomy and appendicectomy were undertaken. Operative findings were that of about 700mls straw coloured ascitic fluid, omental cake adherent to the anterior abdominal wall and inferior edge of the liver. The uterus was about 10 weeks size, with tumour nodules over its surface; tumour infiltration was extensive to the parametrium, the rectal serosa and the pelvic and bladder peritoneum. Both ovaries were normal, an enlarged para-aortic node close to the renal artery was palpable. The rest of the abdominal contents were normal. The estimated intra-operative total blood loss was 300mls.

Post-operative recovery was uneventful and the histology confirmed the findings of an endometrial adenocarcinoma, the presence of an endometrial polyp and adenomyosis of the myometrium. The right ovary, omentum and appendix showed evidence of metastasis. Surgico-pathologically she had Carcinoma of the Endometrium Stage 3C Grade 3. She was then commenced on adjuvant chemotherapy, Carboplatinum 300mg/m^2. Following the third course of chemotherapy, she was noted to have recurrence of the tumour. She was managed symptomatically and succumbed soon after.

Case History 2

Miss FM was a 53 years old single nulliparous postmenopausal lady who presented with an episode of pervaginal bleeding with clots. Four years ago she had a simple right mastectomy and axillary node sampling for a Manchester stage 3 infiltrating ductal carcinoma of breast. Post-operatively she had DXT to loco-regional nodes and was prescribed tamoxifen 20 milligram daily.

On examination, a healed right mastectomy scar was seen with no local recurrence. No abnormalities were detected on abdominal palpation. Vaginal examination revealed a mobile uterus of about 8 weeks size. No adnexal masses were noted. She was then counselled for a fractional dilatation and curettage and the histopathological examination of the endometrial curetting was reported as a "well differentiated adenocarcinoma". She subsequently underwent an extrafascial hysterectomy and bilateral salpingo-oophorectomy. Postoperatively she recovered uneventfully and the histology of the specimen showed no residual endometrial malignancy but the presence of a metastatic adenocarcinoma in the left ovary. In view of the surgicopathological stage 3 grade 1, she subsequently received DXT to the pelvis and has had no evidence of tumour recurrence at eight years follow-up.

Discussion

Tamoxifen is widely used as adjuvant therapy for breast cancer patients. It has minimal side effects and is judged to be safe. Adjuvant tamoxifen treatment significantly improves both the recurrence-free interval and the overall survival rate[2]. In the uterus, tamoxifen has the capacity to occupy the oestradiol receptor in the endometrial cells. Nevertheless, in the low oestradiol (E2) environment of menopause/premenopause women, tamoxifen can also function as an oestrogen agonist on these receptors. Such an effect on the human endometrium in vivo had already been demonstrated by Gorodeski et al[3]. These findings indicate that the postmenopausal endometrium is sensitive to tamoxifen.

Recent studies have shown an increased incidence of endometrial proliferation, hyperplasia and polyposis in women taking tamoxifen[4]. Agonist actions of tamoxifen could explain these effects, but these actions are thought to be early, transient and quickly replaced by an overwhelming oestrogen antagonism. Endometriosis has been reported in several women who were treated with tamoxifen, including one who was diagnosed after 15 years of menopause[5].

Varying endometrial pathologies, including endometrial carcinoma has been reported in 18 - 35.5% of patients who have been on tamoxifen therapy. This fact is important and should not be overlooked. Majority of these patients will be asymptomatic and could have escaped detection if they were not under proper medical supervision; including vaginal scan to assess the endometrial cavity and if necessary endometrial sampling at regular intervals. Women receiving tamoxifen as treatment for breast cancer who subsequently develop uterine carcinoma are at risk for high grade endometrial carcinoma with a poor prognosis[5] as illustrated in Case 1.

It has been claimed that endometrial and breast cancers may share certain common risk factors, which predispose those with primary breast cancer to develop second primary cancer of the endometrium, irrespective of tamoxifen treatment. It has been suggested that progestogen treatment may be considered for protection from and reduction of the risk of endometrial cancer in tamoxifen-treated patients. However, various studies have also shown the negative effect of such therapy in increasing the risk of breast cancer[4].

It is thus, important to closely monitor the effects of tamoxifen therapy on the genital tract in breast cancer patients, so as to give a positive overall effect on the women's life expectancy.

References

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