Uterine Sarcoma after Tamoxifen Therapy for Breast Cancer

Abstract:
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Tamoxifen has been shown to significantly reduce the risk of tumour recurrence in women with receptor positive breast cancer and has been used for chemoprevention in women with both non-invasive cancer and those with a high risk of developing breast cancer. An established and accepted risk with this treatment is the increased incidence of adenocarcinoma of the endometrium. Less well recognised is uterine sarcoma, a rare and aggressive tumour accounting for under five percent of uterine malignancies, with five year survival rates in the order of 50%.

Introduction
All cases of uterine sarcoma encountered in our gynaecology service since 2007 were reviewed. Those who had been previously treated with tamoxifen underwent a comprehensive chart review. In addition a literature search was performed using Medline.

Case Report
The first patient is a fifty-three year old para 0 who was diagnosed with Grade 3 estrogen (ER) and progesterone (PR) positive, invasive ductal carcinoma of the right breast. After treatment with surgery, chemotherapy, radiotherapy tamoxifen was prescribed for five years. Several weeks after completing treatment post-menopausal bleeding developed and an MRI demonstrated a large pelvic mass. Histology proved to be high grade endometrial stromal sarcoma. The second patient was a seventy six year old para 6 who was diagnosed with a Grade 1 low grade cribriform ductal carcinoma with minimal lobular carcinoma in-situ (LCIS) of the left breast and was treated by left breast wide local excision. Adjuvant radiotherapy this lady was commenced on tamoxifen which she received for 5 years.

She presented with post-menopausal bleeding and examination revealed a large pelvic mass. Histology proved this to be carcinosarcoma (Malignant Mixed Mesodermal Tumors), which had metastasized to the lungs. The third patient is a forty-seven year old para 3 who was diagnosed during pregnancy with Grade 2 ER/PR positive invasive ductal carcinoma of the right breast. At the time of diagnosis she had a co-existent LCIS. She was treated with right mastectomy followed by chemotherapy, radiotherapy and adjuvant hormonal therapy tamoxifen was initiated. This lady subsequently complained of irregular vaginal bleeding and a dry cough. Histology of a large pelvic mass identified a leiomysarcoma, which was also proven histological to have metastasized to the lungs.

Discussion
Tamoxifen binds to oestrogen receptors and elicits oestrogen agonist or antagonist depending on the target tissues. The efficacy of Tamoxifen in breast cancer is due to its anti-oestrogen properties but it exhibits weak oestrogenic effects. Tamoxifen binds to oestrogen receptors and elicits oestrogen agonist or antagonist depending on the target tissues. A lot of reports published in recent years have demonstrated a significant association between longer duration of tamoxifen treatment and the appearance of uterine sarcoma. Most of the Tamoxifen associated sarcomas were MMMT (Malignant Mixed Mesodermal Tumours).

Other studies suggest that Tamoxifen enhances the risk of developing more aggressive form of uterine malignancies. In a review of all national Surgical Adjuvant Breast and Bowel Project (NSABP) trials, the rate of sarcoma in women treated with tamoxifen was 17 per 100,000 patient years versus none in the placebo group. Similarly in a separate trial of high risk women without breast cancer taking tamoxifen as part of breast cancer prevention trial with median follow up of 6.9 years, there were 4 sarcomas in the Tamoxifen group versus none in placebo group 5. This is compared with the incidence of 1 to 2 per 100,000 patient years in the general population. Pelvic radiation was a risk factor for developing uterine sarcoma. Duration of Tamoxifen administration is crucial for its effectiveness, but this also effects related to the partial oestrogenic activity of the drug. A lot of reports published in recent years have demonstrated a significant association between longer duration of tamoxifen treatment and the appearance of uterine sarcoma. Most of the Tamoxifen associated sarcomas were MMMT (Malignant Mixed Mesodermal Tumours)

The purpose of this report is to highlight the association of tamoxifen and uterine sarcoma, and to emphasize the need for formulating a standardized follow-up protocol by multidisciplinary team including breast surgeons, oncologists (Radiation and Medical) and GPs for women receiving tamoxifen. Any women on Tamoxifen who developed gynaecological symptoms should be referred to Gynaecologist for review.

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References

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