CASE REPORT

Malignant mixed Mullerian tumour of uterus secondary to tamoxifen therapy for hormone responsive breast cancer

Mayank Gupta, Kala Gnanasekaran Kiruthiga

Department of General Pathology, Christian Medical College, Vellore, Tamil Nadu, India

Correspondence to

Dr Mayank Gupta,
gupta.mayank103@gmail.com

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SUMMARY

Tamoxifen is used in the treatment of hormone responsive breast cancer because of its antiestrogenic effect. However, it also has an estrogenic effect on the uterus, thereby increasing the risk of endometrial hyperplasia, endometrial polyp and endometrial neoplasms such as endometrial adenocarcinoma and malignant mixed Mullerian tumour (MMMT). This case describes the possible pathogenesis and risk of developing MMMT due to long-term tamoxifen intake in hormone responsive breast cancer.

BACKGROUND

Malignant mixed Mullerian tumours (MMMTs), or carcinosarcomas, account for <5% of the malignant neoplasms involving the uterine corpus.¹ Owing to low prevalence, the risk factors for MMMT have been difficult to determine. Zelmanowicz *et al*² speculated that MMMT and endometrial carcinoma may share risk factors such as nulliparity, body weight and exogenous estrogen use. Owing to its antiestrogenic properties, tamoxifen is used in the treatment of estrogen receptor (ER)-positive breast cancer. However, tamoxifen also has a weak estrogenic effect on the endometrium, thereby increasing the risk of endometrial polyp, endometrial hyperplasia, endometrial adenocarcinoma and sarcoma of the uterus.³ We report a case of uterine MMMT occurring with tamoxifen therapy in a patient with a history of breast cancer.

CASE PRESENTATION

A 52-year-old woman presented with bleeding per vaginum, generalised weakness, dysuria, decreased urine output and lower abdominal distension at an outside hospital. Imaging revealed a large polypoid mass within the endometrial cavity, and endometrial biopsy was suggestive of MMMT. The patient underwent a total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy and bilateral pelvic and para-aortic lymphadenectomy, and the specimen was sent to the Department of General Pathology at Christian Medical College, Vellore. The patient had a history of ER-positive breast cancer, diagnosed in July 2009, for which she had been on 20 mg tamoxifen daily until the presentation of the aforementioned symptoms in January 2015.

Histopathological examination confirmed the diagnosis of MMMT (figure 1) infiltrating less than

half of the myometrium. Cervix, bilateral adnexae, omentum and all lymph nodes were free of tumour.

Presently, the patient is on adjuvant radiation therapy and chemotherapy comprising of paclitaxel at 175 mg/m² followed by carboplatin dosed to an area under the serum concentration time curve (AUC)=5 on day 1, every 3 weeks for six cycles, as MMMT is a high-grade tumour and can recur.

DISCUSSION

MMMTs, although very rare, with an incidence of <2/100 000 women in a year, are aggressive tumours of the uterus resulting in >15% of deaths.⁴ These tumours are classified under mixed epithelial and mesenchymal tumours of the uterus by WHO, and are believed to be of epithelial origin, exemplifying epithelial-mesenchymal transition (EMT). Tamoxifen intake for hormone responsive breast cancer is one of the factors that has been associated with the development of MMMT apart from other factors such as long-term unrestricted estrogen intake and pelvic radiotherapy.⁵

Depending on the target organs, tamoxifen exerts both an estrogenic and an antiestrogenic effect. The variability of response to tamoxifen depends on the differences in tissue distribution of ER subtypes (ER α and ER β are two subtypes of ERs), various transcriptional activating factors and function of co-regulator proteins. Because of its antiestrogenic effect, it is used in the treatment of ER-positive breast cancer in adjuvant and metastatic settings, and for treatment of ductal carcinoma in situ (DCIS). However, tamoxifen has an estrogenic effect on the uterus, bone and liver.^{3 6} It can induce proliferation of endometrial glands and periglandular stromal condensation due to the presence of ERs in the glandular epithelium and stromal cells.^{3 7} Moreover, tamoxifen induces genes producing adrenomedullin, a growth factor for endothelial cells that upregulates bcl-2 and enhances the survival of malignant cells under hypoxic conditions.⁸ The fact that tamoxifen promotes carcinogenesis is supported by three previously published studies. In a study by Treilleux *et al*,⁹ the relative risk of developing endometrial cancer in cases of early breast cancer was significantly reduced when the dose of tamoxifen was halved. In a study by Ismail,¹⁰ irrespective of the daily dose of tamoxifen, endometrial malignancies were seen in females who had cumulative doses of more than 35 g. In our case, the patient had

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Figure 1 H&E stain: (A) malignant glandular (long arrow) and malignant stromal (short arrow) component, $\times 4$ magnification; (B) malignant glandular component, $\times 10$ magnification; (C) glandular component showing neoplastic glands lined by cells displaying nuclear enlargement and nuclear pleomorphism, $\times 40$ magnification; (D) malignant stromal component, $\times 10$ magnification; inset showing malignant stromal component with spindle cells displaying marked nuclear pleomorphism and nuclear hyperchromasia, $\times 40$ magnification.

already received about 40 g of the drug. In a study by Curtis *et al*, the relative risk for MMT was substantially higher than for endometrial adenocarcinoma. Moreover, in those females who survived for 5 years or more, the relative risk for developing MMT was significantly higher than for endometrial adenocarcinoma.¹¹ Immunohistochemical and molecular analysis have speculated that MMT may begin as adenocarcinoma and acquires sarcomatoid differentiation over a period of time, exemplifying the clonal origin of these tumours. Both high-grade endometrial carcinoma and MMT have a similar

molecular profile, with TP53 mutation being the most common molecular alteration.⁵ However, the aggressive characteristics of tamoxifen-induced MMT compared to endometrial adenocarcinoma, and delayed time to diagnosis, reflect differences in pathogenic mechanisms.¹¹ As previously described, EMT is the fundamental feature in the pathogenesis of MMT. In this process, cells of epithelial origin acquire mesenchymal phenotype and lose epithelial features and polarity. EMT, at the molecular level, is characterised by upregulation and downregulation of mesenchymal and epithelial markers, respectively, leading to

Figure 2 Normal ultrasound of the abdomen and pelvis, postsurgery and on chemotherapy: (A) liver; (B) pancreas; (C) gallbladder; (D) spleen; (E) urinary bladder; (F) right and left kidney; (G) para-aortic region; (H) para-iliac region.

cytoskeleton reorganisation, and increase in invasiveness, motility and metastatic potential.¹² Transcriptional repression of the E-cadherin gene by specific transcription factors such as Slug, Snail, Twist and SIP-1, leads to loss of E-cadherin expression, an important component of adhesion junctions that maintains epithelial integrity, promoting EMT. Moreover, the oncogenic serine/threonine kinase Akt, promotes EMT by modulating several transcriptional and signalling networks linking Wnt/ β -catenin, retinoblastoma (RB) gene product and nuclear factor (NF)- κ B/p65.¹² It is speculated that long-term intake of tamoxifen may cause alteration in the Akt/ β -catenin pathway and/or promote transcriptional repression of E-cadherin.

MMMT has a poor prognosis and most of the patients have extra-uterine spread at the time of diagnosis.⁵ Fortunately, in our case, extrauterine spread was not evident. Metastatic spread of MMMT is similar to high-grade endometrial carcinoma and most patients die due to local pelvic or abdominal recurrence. The risk of higher stage disease and metastasis is closely related to depth of myometrial invasion.⁵ In the study by Ferguson *et al*, cases of stage I uterine MMMT were more aggressive compared to stage I grade III endometrioid, serous or clear cell carcinoma. Moreover, the 3-year disease free survival was 42% for cases with MMMT compared to 87% for cases with high-grade carcinoma.¹³ Ten cases of stage I uterine MMMT, including cases of stage II, III and IV MMMT, received adjuvant chemotherapy in the study by Domenica *et al*. Three of 10 patients received cisplatin, ifosfamide and prophylactic granulocyte-colony stimulating factor, while 7 patients received carboplatin and paclitaxel. Overall, the group that received carboplatin and paclitaxel had a better progression-free survival and overall survival.¹⁴ Another study concluded that adjuvant chemotherapy with carboplatin and paclitaxel appeared to be more efficacious

than radiation-only adjuvant treatment for completely resected uterine MMMT.¹⁵

Hence, adjuvant radiotherapy and chemotherapy should be given to patients diagnosed with stage I uterine MMMT. To date, follow-up in our case has been uneventful and the patient is on chemotherapy and radiotherapy to prevent recurrence. Ultrasound of the abdomen and pelvis performed a few days back was unremarkable (figure 2).

Contributors MG was involved in defining intellectual content, the literature search, manuscript preparation and manuscript review. KGK was involved in the literature search, manuscript editing and manuscript review.

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Learning points

- ▶ Although tamoxifen is used in the treatment of hormone responsive breast cancer due to its antiestrogenic effect, it has an estrogenic effect on the uterus, thereby increasing risk of malignant mixed Mullerian tumour (MMMT) and other neoplasms.
- ▶ Variability of response to tamoxifen depends on the differences in tissue distribution of estrogen receptors, function of co-regulatory proteins and various transcriptional activating factors.
- ▶ Epithelial–mesenchymal transition is the fundamental feature of uterine MMMT and is characterised by upregulation of mesenchymal markers along with downregulation of epithelial markers at the molecular level.

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