MALIGNANT MIXED MULLERIAN TUMOR OF THE UTERUS— A COMPLICATION OF TAMOXIFEN THERAPY FOR BREAST CARCINOMA

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Abstract

Patients with breast cancer exhibit an increased risk in developing neoplasms of other organs. In case of endometrium, the increased risk might be due to tamoxifen adjuvant therapy and prior radiotherapy. Carcinosarcomas are rare uterine cancers and carry poor prognosis. We present a case of Malignant Mixed Mullerian Tumor (MMMT) of the uterus in a 46-year-old woman, after tamoxifen treatment and radiotherapy for breast cancer. We emphasise that postmenopausal women taking tamoxifen should be monitored closely for symptoms of endometrial lesions.

Keywords: Breast cancer; Uterine cancer; Tamoxifen; Radiotherapy

1. Introduction:

Malignant Mixed Mullerian Tumors (MMMT) or carcinosarcomas of the uterus are rare, high-grade neoplasms comprising only 1-2% of uterine cancers1 and 3-5% of all uterine malignancies2. They are the most common variety of mixed epithelial and non-epithelial endometrial tumors, with a clinically aggressive course. They occur in postmenopausal women and usually present in an advanced stage with abdominal pain, distension, and atypical spotting/bleeding per vaginum. While it is presumed that MMMTs arise from pre-existing carcinomas, little is known about its etiopathogenesis. Exposure to radiation and excessive estrogen, obesity and nulliparity3, 4 are believed to be associated with their development. Use of tamoxifen in the treatment of breast carcinoma has also been associated with uterine sarcoma. Subsequently, positive association has also been noted when tamoxifen was given to prevent breast cancer in women at increased risk—a possible result of the estrogenic effect of tamoxifen on the uterus5, 6. Here, we report a case of a woman who developed Malignant Mixed Mullerian Tumor of uterus after radiotherapy and tamoxifen therapy for treatment of breast carcinoma.

2. Case Report:

A 46 year old woman, para 3 with 3 living children was admitted in department of Obstetrics and Gynaecology of a rural medical college of central India with complaints of postmenopausal bleeding and pain in abdomen since two months. Her past medical history revealed standard radical mastectomy of right breast for carcinoma breast four years back. She had received radiotherapy post operatively and was put on oral tamoxifen 20 mg daily. However after one and half years she developed a lump of 3x4 cm in upper outer quadrant of left breast. FNAC was done which showed carcinomatous changes and radical mastectomy was performed on left side. Tamoxifen 20 mg daily was continued post operatively for 2 and half years. During this treatment she presented with abnormal bleeding per vaginum. On physical examination her general condition was fair and systemic examination was within normal limits. On per-speculum examination cervix was hypertrophied and on per-vaginum examination uterus was anteverted, enlarged approximately 16 weeks in size, mobile with bilateral fornices free. Abdominal ultrasound was done which showed bulky uterus of size 14x10.3x8 cm with endometrial collection of 155 ml. Examination under anaesthesia was done and endometrial biopsy was obtained by fractional curettage which showed a mixture of carcinomatous and sarcomatous elements. In sarcomatous component, pleomorphic cells with atypical mitoses and bizarre tumoral giant cells were observed and in the carcinomatous part, malignant epithelial cells were arranged in tubular structures or cords. The preliminary pathological diagnosis was carcinosarcoma.
Laparotomy was performed with a pre-operative diagnosis of malignant uterine mass. A total abdominal hysterectomy and bilateral salpingo-oophorectomy and pelvic lymph node sampling were performed. On gross examination, there was a polypoid tumoral mass measuring 6 x 4 cm in diameter which occupied the endometrial cavity. The tumor invaded inner one third thickness of the myometrium. On microscopic examination, tumor consisted of tumoral epithelial cells with foci of pleomorphic atypical spindle cells. The diagnosis of malignant mixed mullerian tumor was confirmed on histopathology. Postoperative period was uneventful and the woman was put on adjuvant chemotherapy in the form of Cisplatin and Ifosfamide for six cycles and radiotherapy. The patient is under regular follow up and in good condition.

3. Discussion:
Malignant Mixed Mullerian tumors (MMMT) of the uterus are rare entities and are composed of malignant epithelial (carcinomatous) and mesodermal (sarcomatous) cells. They can occur in any of the female reproductive organs but most commonly in the uterine corpus due to the embryological development of the uterus. They have an aggressive course with extremely poor prognosis. Three theories have been proposed to ascertain its histogenesis and state that MMMTs may be 1) collision tumors, 2) combination tumors or 3) composition tumors. Immunophenotypical and ultrastructural studies that favor the third theory explain MMMTs as being monoclonal in origin, with diverse carcinomatous and sarcomatous elements. MMMTs are sub-divided into homologous and heterologous tumours. In homologous tumours, both the carcinomatous and sarcomatous elements present are normal components of the Mullerian system. In heterologous tumours, sarcomatous elements that have no benign counterpart in the uterus, such as skeletal muscle, bone and cartilage, are present. Homologous and heterologous MMMTs occur with approximately equal frequency. MMMTs of the uterus arise in the endometrium and the epithelial component usually predominates. Endometroid adenocarcinoma is the most common epithelial component but other variations such as clear cell, mucinous and papillary-serous also occur. The mesodermal component is most commonly undifferentiated sarcoma in homologous tumours and rhabdomyosarcoma in heterologous tumours.

FIGO staging of MMMTs of the uterus is the same as for endometrial carcinoma. Tumour spread occurs by direct extension to the cervix and vagina followed by other pelvic organs including the bladder and rectum. Lymphatic spread to local and regional lymph nodes appears to occur at an early stage of the disease. Haematogenous spread is also common usually to lung, liver and bone. Stage of the disease and the depth of myometrial invasion are recognized as important prognostic factors. Two-year survival rates have been reported as 53% in stage I (confined to uterine corpus) and 8.5% in stages II (cervical metastases) and III (pelvic metastases), with none reported in Stage IV.

Number of researchers have worked to elucidate the etiopathogenesis of MMMT’s and have found that exposure to radiation, excessive estrogen, obesity, and nulliparity are believed to be associated with its development. Use of tamoxifen in the treatment of breast carcinoma has also been associated with an increased incidence of uterine sarcoma. In the present case tamoxifen exposure was present for a period of approximately 3 years. Tamoxifen is a non-steroidal anti estrogen that was synthesized in the United Kingdom in the 1960s as a contraceptive and was approved in 1977 by the US Food and Drug Administration (FDA) for the treatment of metastatic breast cancer in postmenopausal patients. Now it has been approved by FDA for adjuvant treatment of breast cancer, metastatic breast cancer and reduction in breast cancer incidence in high risk women. It is in fact a selective estrogen receptor modulator (SERM) with anti estrogenic properties in the breast and estrogenic effect in tissues such as bone, endometrium and the cardiovascular system. The most common pathologic change encountered in uteri from patients treated with tamoxifen is the endometrial polyp. Most studies have found that the relative risk of developing endometrial cancer for women taking tamoxifen is two to three fold that of age-matched populations. The estrogen-agonist myometrial response to tamoxifen therapy may include diffuse smooth muscle hyperplasia (myohyperplasia), leiomyomata, and adenomyosis, with or without hyperplastic glandular changes. The estrogenic effects of tamoxifen on uterus consist of endometrial polyps, glandular hyperplasia, and epithelial metaplasias, most often mucinous and squamoid. High-grade
endometrial tumors in patients receiving tamoxifen therapy have been reported in the literature. Carcinosarcomas (malignant mixed mullerian tumors) of the uterus have been reported as well, representing the second most common malignancy to be associated with tamoxifen therapy, as have adenosarcomas. The mechanisms underlying tamoxifen-related MMMTs are unclear. Immunohistochemical and molecular analyses have suggested that MMMTs may originate as an adenocarcinoma that acquires sarcomatous differentiation over time. Despite limited epidemiologic evidence that MMMTs and endometrial carcinomas may share reproductive and hormonal risk factors, the delayed time to diagnosis and more aggressive behavior associated with tamoxifen-related MMMTs relative to endometrial adenocarcinomas suggest differences in pathogenic mechanisms.

The low incidence of uterine sarcomas makes it difficult to establish a relationship with tamoxifen. Nevertheless, looking at the literature, 20 mg/day of tamoxifen over 1 year could be enough to develop uterine sarcoma; the sarcoma appears mainly during the first 8 years and seems to behave more aggressively. Postmenopausal women taking tamoxifen should be closely monitored for symptoms of endometrial lesions as there is a very strong association between tamoxifen treatment and occurrence of MMMTs of the uterine corpus. The distinct possibility of such an association should be kept in mind at the follow-up of breast cancer patients, or in those suffering from abnormal uterine bleeding. However, the overall, benefits of tamoxifen in the treatment and prevention of breast cancer is much higher than its risk for uterine malignancies. It should be kept in mind that high-risk patient for endometrial cancer should be identified before tamoxifen therapy. Also, in patients receiving tamoxifen, regular uterine sonography in con-junction with endometrial biopsies would be appropriate for early diagnosis of endometrial malignancies. Women taking tamoxifen should be informed about the risks of endometrial proliferation, endometrial hyperplasia, endometrial cancer, and uterine sarcomas. If atypical endometrial hyperplasia develops, appropriate gynecologic management should be instituted, and the use of tamoxifen should be reassessed. If tamoxifen therapy must be continued, hysterectomy should be considered in women with atypical endometrial hyperplasia. Tamoxifen use may be re instituted following hysterectomy for endometrial carcinoma in consultation with the physician responsible for the woman’s breast care.

Another important risk factor for MMMT is radiotherapy. Twenty years ago, it was reported that pelvic irradiation may be implicated in the development of extremely aggressive uterine cancers, particularly sarcomas. At this point, it was noted that in one study, five of the eight patients with uterine malignancies had a previous pelvic malignancy treated by radiation. It is now estimated that 5%–30% of patients with carcinosarcoma have a history of pelvic irradiation. These neoplasms will often be diagnosed after a latent period of 14 years after irradiation. In the present case radiotherapy and tamoxifen were the associated factors. Due to the aggressive nature of MMMTs and its poor prognosis, various therapeutic modalities have been employed in its treatment. Surgery in the form of abdominal hysterectomy and bilateral salpingo-oophorectomy remains the principal treatment. Adjuvant chemotherapy has been shown to be beneficial. Adjuvant radiotherapy was noted to improve disease controllability in the pelvis. The role of combined adjuvant radiotherapy and chemotherapy has also been proposed.

**Conclusion:**
Uterine carcinosarcoma is a rare, highly aggressive, rapidly progressing neoplasm associated with a poor prognosis that has not significantly improved in the past thirty years despite advances in imaging and adjuvant therapies. Breast cancer patients who use tamoxifen are at increased risk of having endometrial cancers especially MMMT. Abnormal uterine bleeding or vaginal discharge is the most important symptoms indicative of lesion development. So any patient put on tamoxifen therapy should undergo regular gynaecological follow up for detection of any malignant changes in uterus.

**References:**
1. Nguyen CP, Levi AW, Montz FJ, Bristow RE: Coexistent Choriocarcinoma and Malignant Mixed Mesodermal Tumor of the Uterus. *Gynecol Oncol* 2000, 79(3):499-503
2. Robinson-Bennett B, Belch RZ, Han AC: Loss of p16 in Recurrent Malignant Mixed Mullerian Tumors of the Uterus. *Int J Gynecol Cancer* 2006, 16(3):1354-7.
3. Moe MM, El-Sharkawi S: Is There Any Association Between Uterine Malignant Mixed Mullerian Tumor Breast Cancer and Prolonged Tamoxifen Treatment? J Obstet Gynaecol, 2003,23(3):301-3.

4. Wang X, Tangjitgamol S, Liu J, Kavanagh JJ: Response of Recurrent Uterine High-Grade Malignant Mixed Mullerian Tumor to Letrozole. Int J Gynaecol Cancer, 2005, 15(5):1243-8.

5. Bergman L, Beelen ML, Gallee MP, Hollema H, Benraadt J, van Leeuwen FE. Risk and prognosis of endometrial cancer after tamoxifen for breast cancer. Comprehensive Cancer Centre’s ALERT Group. Assessment of Liver and Endometrial cancer Risk following Tamoxifen. Lancet, 2000; Sep. 356 (9233): 881-7.

6. Cohen I. Endometrial pathologies associated with postmenopausal tamoxifen treatment. Gynecol Oncol, 2004; Aug. 94(2): 256-66.

7. Yoshida Y, Kurokawa T, Fukuno N, Nishikawa Y, Kamitani N, Kotsuji F: Markers of Apoptosis and Angiogenesis Indicate That Carcinomatous Components Play an Important Role in the Malignant Behavior of Uterine Carcinosarcoma. Hum Pathol, 2000, 31(12): 1448-1454.

8. Bissett D, Davis JA, George WD (1994). Gynaecological monitoring during tamoxifen therapy. Lancet, 344, 1244.

9. Sismondi P, Biglia N, Volpi E, et al (1994). Tamoxifen and endometrial cancer. Ann N Y Acad Sci, 734, 310-21.

10. Clement PB, Oliva E, Young RH. Mullerian adenosarcoma of the uterine corpus associated with tamoxifen therapy: a report of six cases and a review of tamoxifen-associated lesions. Int J Gynecol Pathol 1996; 15:222–9.

11. Arenas M, Rovirosa A, Hernández V, Orti J, Jorcano S, Mellado B et al. Uterine sarcomas in breast cancer patients treated with tamoxifen. Int J Gynecol Cancer. 2006 Mar-Apr; 16(2): 861-5.

12. Meredith R F, Eisert D R, Kaka Z, Hodgson, Johnston Jr G A, Boutselis J G: An excess of uterine sarcomas after pelvic irradiation. Cancer, 1986, 58(9): 2003-7

13. Doss L L, Llorens A S, Henriquez E M: Carcinosarcoma of the uterus: a 40-year experience from the state of Missouri. Gynecol Oncol, 1984, 18(1): 43–53

Figure 1: Microphotograph showing Malignant Mixed Mullerian Tumour of the uterus (40X)

Figure 2 Showing Malignant Mixed Mullerian Tumour of the uterus (100X)