Tamoxiphene Associated Changes in the Uterus

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Summary

Tamoxiphene is commonly used in the posttreatment follow up of breast cancer patients worldwide. It is a non-steroid antioestrogen derivative of diethylstilboestrol. This ambivalent drug has both antagonist and agonist effects. It blocks, the growth of breast tumours but can also have undesirable agonist effect on the genital tract such as pro-oestrogenic stimulation of the endometrium and the myometrium.
In view of the known adverse effects on the uterus, patient must be counselled well and motivated to come for regular check up. While on tamoxiphene, pretreatment assessment should include cervico-vaginal and endometrial cytology. If the transvaginal scan of the would diagnoses pathology, it may be advised to do hysterectomy prior to starting therapy. While on therapy they must be told to have a regular work out. If at anytime endometrial thickness goes to 16mm a hysteroscopy with D & C should be performed. A good co-ordination amongst the oncologist, gynaecologist, sonologist and pathalogist is important to make an early diagnosis of pre-cancerous lesions. With careful supervision all cases of invasive endometrial cancer can be prevented.

Introduction

Tamoxiphene is commonly used in the posttreatment follow up of breast cancer patients worldwide. Tamoxiphene is a non-steroid antioestrogen derivative of diethylstilboestrol. It is the main drug used for hormone therapy of hormone dependent breast cancer. This ambivalent drug has both antagonist and agonist effects. It blocks growth of breast tumours but can also have an undesirable agonist effect on the genital tract (Boucdes et al 1995). The uterus is a target organ for this paradoxical action due to pro-oestrogenic stimulation of the endometrium and the myometrium.

We report herewith 4 cases.

Case No. 1 —Mrs. R. M. age 67 years was treated for breast cancer by radical mastectomy and was disease free with tamoxiphene 20 mgs daily for 5 years. She reported with postmenopausal bleeding. Investigations revealed a 30mm endometrial thickness on sonography (Fig I) with increased vascularity on colour doppler.

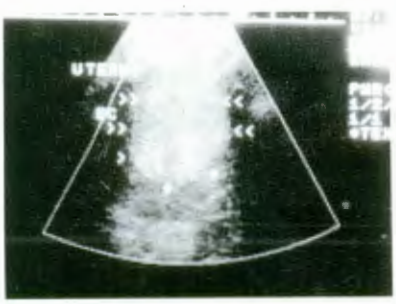

Fig 1: Endometrial thickness 30 mm Case No. 1

Hysteroscopy and fractional curettage was done. The endometrium was thick and histological pattern was simple hyperplasia. The patient was advised to discontinue tamoxiphene. She was a uncontrolled diabetic, hypertensive, obese patient and had fatty infiltration of the liver. Hence hysterectomy was considered risky and she chose to be under observation. The endometrial thickness after D & C was 8mm. It grew again to 20mm in 3 months time. A second D & C was performed. The report was again simple hyperplasia (Fig. 2). M.R.I. revealed 2 subserous fibroids (Fig. 3). Patient was keen on medical treatment. She was given injection Testosterone 50 mg. weekly for 2 months. Subsequent sonography revealed that endometrial thickness remained 8.5 cms. Patient has been now under observation for two & half years with no increase in endometrial thickness.

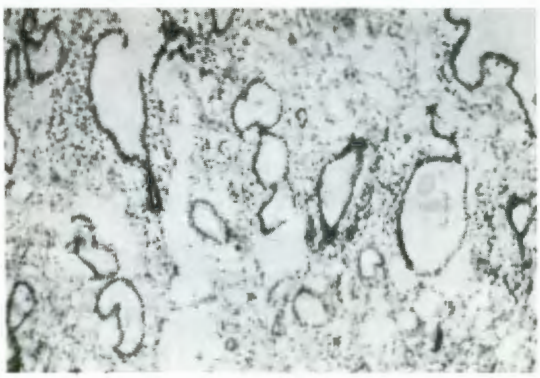

Fig. 2: Histology showing endometrial Hyperplasia

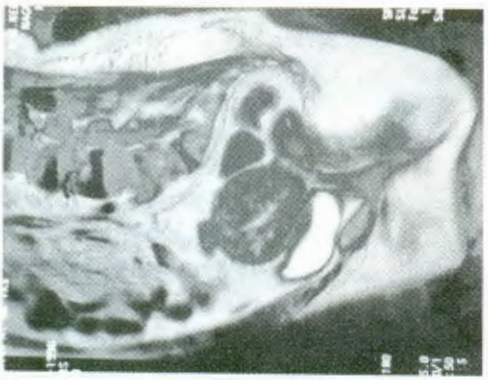

Fig. 3 MRI showing subserous fibroids

Case No. 2 - Mrs G. A. aged 68 years was treated by radical mastectomy and was under tamoxiphene for 5 years. She reported with postmenopausal bleeding. The transvaginal scan showed an endometrial thickness of 22 mm. with 2 submucus fibroids and 2 intramural fibroids (Fig. 4). She underwent hysteroscopic resection of the fibroids and curettage. The histology revealed cystic glandular hyperplasia.

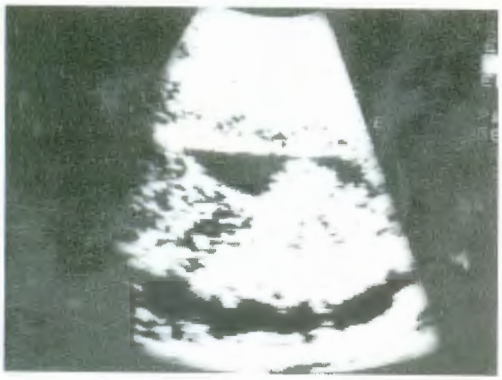

Fig. 4: Submucus Fibroid

She was advised to continue tamoxiphene by her oncologist. She underwent a total abdominal hysterectomy with bilateral salpingo-oophorectomy and is reported to be normal after 1 year.

Case No. 3 - Mrs J. G. 65 years had radical mastectomy and was advised to start tamoxiphene. She was referred for gynaecological check up before that. She was diabetic, hypertensive, obese and had fatty infiltration of the liver. She was a multiparous lady. On examination she had a bulky uterus. Sonography revealed 4 small fibroids and endometrial thickness of 4 mm. She refused hysterectomy and started tamoxiphene and agreed for regular follow-up. While under observation, she has been symptom free, the fibroids have not grown and the endometrial thickness has remained at 4-6mm. She takes 40 mg. tamoxiphene since 2 years.

Case No. 4 — Mrs. L. P. aged 50 years was treated by radical mastectomy. She had amenorrhoea for 3 months before operation and again for 3 months after operation. After starting tamoxiphene she started getting regular periods. After another 3 months she had menorrhagia. The U.S.G. scan showed bulky uterus with endometrial thickness of 20mm. She refused D & C and agreed for endometrial aspiration cytology and biopsy. It revealed hyperplastic endometrial cells. She took medroxyprogesterone acetate from day 15 to day 25 of cycle for 6 months along with tamoxiphene. Thereafter she refused further medication and stopped tamoxiphene also. Two years later on follow up she is disease free and has lapsed into menopause. Total tamoxiphene exposure in her case was one year.

Discussion

Since its introduction in the early seventies the list of indications for tamoxiphene has been continuously expanded. Initially it was used for the treatment of metastatic breast cancer. Currently it is recommended for long term and often indefinite administration as an adjuvant therapy. Recently, large clinical trials are evaluating its efficacy as a preventive agent in high risk cases (Fried and Jordan, 1994). However, its deleterious effect on the uterus is now described. Its link with the development of endometrial cancer has been well established.

Review of Literature:- Ismail (1996) has stated that prolonged tamoxiphene use leads to an increased incidence of proliferative abnormalities of the endometrium with an overlapping spectrum from simple hyperplasia to invasive malignancy with hyperplastic endometrial polyps and polyp cancers occupying intermediate ground. He felt that causes of these lessions included a combination of inherited factors and cumulative tamoxiphene dosage.

Fotiou et al (1998) studied 56 cases who were on tamoxiphene for abnormal bleeding. Cervical and endometrial polyps were found in 44%. At laparotomy hyperplasia combined with leiomyoma, adenomyosis,

ovarian tumours were frequently seen. Five primary adenocarcinomas were detected in 56 cases.

Le-Bouedec et al (1994) performed transvaginal endosonography on 300 patients out of which 150 were on adjuvant tamoxiphene therapy. Hydrometra was seen in 6.6% in controls and 49.3% in tamoxiphene group. Average endometrial thickness was 6mm in controls whereas it was 12 mm in tamoxiphene group.

Megonigle et al (1996) suggest that the effect of tamoxiphene on the endometrium may vary with menopausal status. In their study, the incidence of endocervical and endometrial polyps was 43% in post menopausal patients on tamoxiphene as compared to 24% in untreated postmenopausal patients. In contrast there was no increase in premenopausal patients treated with tamoxiphene.

MRI was found useful by Ascher et al (1996). They studied 35 postmenopausal women with breast cancer on tamoxiphene therapy. They report 2 distinct uterine patterns. In pattern I there was homogenous high signal intensity of endometrium and enhancement of endometrial-myometrial interface and a signal void in the lumen. In pattern II there was heterogenous endometrial signal intensity.

Kedar et al (1994) studied 111 postmenopausal women with a family history of breast cancer and willing to take tamoxiphene as a preventive measure. In this randomised double blind controlled study transvaginal ultrasonography with colour doppler imaging and endometrial biopsies were performed. There were significant abnormalities in tamoxiphene group as compared to controls. The results are as follows: - In the tamoxiphene group, histologically abnormal endometrium was seen in 39% of cases as compared to 10% in the control group. The tamoxiphene group had atypical hyperplasia in 16% and polyps in 8% of the cases. Further women with histological abnormality had a significantly thicker endometrium and a decreased impedance to blood flow in the uterine arteries. This study indicates that the condition of breast cancer does not necessarily play a significant role.

These changes are refuted by Katase (1998). In his study of 825 cases tamoxiphene was given to 279 patients out of which 1.4% developed uterine cancer whereas those who did not take tamoxiphene 1.6% developed it. This study further states that 6 of 15 tamoxiphene treated cancer patients had taken HRT prior to the development of breast cancer and perhaps HRT is the "culprit". These diseases therefore could all be iatrogenic! He has taken his end point as uterine cancer and does not report intermediate conditions like, simple hyperplasia, polyps or atypical hyperplasia.

Van Leeuwen et al (1994) surveyed all women diagnosed to have endometrial cancer. Out of these 24% had used tamoxiphene. Their findings support the hypothesis that tamoxiphene use increases the risk of endometrial cancer.

Rayter et al (1994) report a series of cases studied by cervical and endometrial cytology and pelvic ultrasound. Their results indicate that tamoxiphene has mild oestrogenic activity however carcinogenic potential is low. They believe that the beneficial effects outweigh the theorotical risk of uterine camcer.

Marconi & Exacoustos (1997) report on a prospective study of breast cancer patients who had been on tamoxiphene for at least one year. They believe that all such cases should be carefully monitored by TVS with colour doppler studies and selected cases should undergo hysteroscopy & endometrial biopsy.

Achiron et al, (1996) report that transvaginal sonography of these cases may show cystic changes in the sub-endometrial zone without epithelial pathology. Hence they suggest evaluation by additional methods such as saline contrast hysterosalpingography and endometrial blood studies, prior to invasive procedures.

Conclusions: -

Tamoxiphene is no doubt a useful drug for women with breast cancer. However, in view of the known adverse effects on the uterus, patients must be counselled well and motivated to come for regular check up.

Pretreatment assessment should include careful menstrual history, physical and internal examination. This should be further supported by cervico-vaginal and endometrial cytology. The transvaginal scan of the uterus would diagnose fibroids, polyps and note the endometrial thickness. Those with significant pathology may be advised hysterectomy prior to starting therapy. While on therapy they must be told to report any bleeding or pelvic pain. A regular 6 monthly or annual workout should include endometrial cytology and TVS. If at anytime endometrial thickness reaches 16 mm, hysteroscopy with D & C would have to be done. A good co-operation amongst the oncologist, gynaecologist, sonologist and pathologist is important to make an early diagnosis of precancerous lesions. With careful supervision all cases of invasive endometrial cancer can be prevented.

A gynaecologist, therefore, has to be fully involved and aware of this new modality of treatment of breast cancer and has to play an active role in the management of these cases.

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