



Gynecological follow up of women with long term tamoxifen therapy for carcinoma breast

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OBJECTIVE(S) : To study the various gynecological pathologies of women who were under tamoxifen therapy for the management of carcinoma breast.

METHODS : Six women who were under tamoxifen therapy for a period of 2 to 4 ½ years were reviewed. One of them had prior hysterectomy. Five of them presented with abnormal vaginal bleeding.

RESULTS : Wide spectrum of gynecological pathologies like endometrial hyperplasia, atypia, endometrial carcinoma, myohyperplasia, uterine fibroids, and cervical cell abnormalities were observed.

CONCLUSION(S) : Tamoxifen therapy is beneficial but its adverse effects on long term use require effective surveillance jointly by the surgeon and the gynecologists.

Key words : tamoxifen, breast cancer, gynecological follow up

Introduction

Tamoxifen is a recognised adjuvant chemoprophylactic therapy in the management of breast cancer worldwide. Antiestrogenic effect of tamoxifen improves the survival of women when there is no active disease following primary therapy¹. Beneficial effects are observed when treatment is continued at least for a period of 5 years or more. Oophorectomy is also found beneficial in women with estrogen receptor positive tumor.

Currently there is a growing concern regarding the significant side effects and health risks of women using tamoxifen for a long time. Wide spectrum of side effects in the field of gynecology have been observed. Moreover other systematic side effects have also been noted.

Methods

Six women had been reviewed for their gynecologic

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problems. They were referred from different centers in our country. All of them had been under tamoxifen therapy following primary treatment of carcinoma breast. One of them (Case No. 6) had hysterectomy before the diagnosis of breast carcinoma. The cases were seen in the outpatient clinic wherefrom they were admitted for their subsequent management. The details of the individual cases were studied. Table 1 gives the history, clinical presentation, physical findings, treatment details of breast carcinoma, dose and duration of tamoxifen therapy, gynecological problems, investigations, surgical procedures, and histological diagnosis of individual cases.

Results

Two of the women (Case No. 1 and 4) were postmenopausal. Repeated episodes of irregular vaginal bleeding was the presenting symptom in four of them. One woman (Case No. 2) came for gynecological cancer screening as advised by her surgeon. Her cervical smear showed high grade squamous intraepithelial lesion (HSIL). Sonohysterography confirmed enlarged uterus with > 10 mm thick endometrium. One woman (Case No. 3) had history of breast cancer in mother. None of them were obese or diabetic. All were parous women without any other risk factor for endometrial hyperplasia or carcinoma. All underwent modified radical mastectomy with axillary clearance. Tamoxifen was used

Table 1. Details of cases.

Case No.	Age (years)	Parity	Family history	Past history	Dose/duration of tamoxifen	Presenting features	Clinical observations	Investigations	Operation done	Findings at laparotomy	Histology report
1.	61	P ₁ +0 LCB - 40 years	Nothing relevant	Underwent right sided modified radical mastectomy with axillary clearance 3 ½ years back. Stage III B infiltrating duct cancer with reactive hyperplasia of lymph nodes. Receptor positive.	10 mg twice a day for 3 ½ years	Repeated episodes of postmenopausal bleeding for last 6 months	Uterus 12-14 weeks size	USG-bulky uterus with endometrial thickness > 10 mm. Diagnostic D and C showing proliferative endometrium.	Laparotomy followed by TAH with BSO	Uterus enlarged with normal sized ovaries. Cut section of uterus showed a huge fleshy mass arising from endometrial surface (Figure 1).	Endometrial polyp, proliferative changes in endometrium with cystic dilated glands without cellular atypia.
2.	42	P ₂ +0 LCB - 15 years	Nothing relevant	Underwent right sided modified radical mastectomy with axillary clearance 3 years back. Infiltrating lobular cancer with no involvement of skin / nipple. Reactive hyperplasia of lymphnodes.	10 mg twice a day for 2 1/2 years	For gynecologic malignancy screening	Uterus bulky, irregular around 14 weeks size	USG - bulky with endometrial thickness > 10mm with polypoid endometrial changes. PAP smear high grade squamous intraepithelial lesion. Cervical biopsy - focal hyperplastic and dysplastic changes in endocervical glands. Endometrium in proliferative phase.	Laparotomy followed by TAH with BSO	Bulky uterus with normal sized ovaries with hypertrophied cervix (Figure 2).	Proliferative endometrium with adenomatous changes. Cervix - CIN II
3.	JR	P ₁ +0 LCB - 13 years	Mother with breast cancer	Underwent left sides modified radical mastectomy with axillary clearance 3 years back.	20 mg. twice a day for 3 years	Perimenopausal bleeding for 3-4 months	Uterus bulky	USG bulky uterus with multiple small fibroids in anterior wall with thickened endometrium > 10 mm. Hysteroscopy - polypoid endometrium with enlarged uterine cavity. Endometrial biopsy - adenomatous hyperplasia with atypical changes.	Laparotomy followed by TAH with BSO	Enlarged uterus around 14 weeks size, irregular in shape due to multiple fibroids.	Adenomatous hyperplasia with atypical cellular changes.
4.	LS	P 2+0 LCB - 16 years	Nothing relevant	Underwent left sided modified radical mastectomy with axillary clearance 5 years back.	20 mg. twice a day for 4 1/2 years	Post-menopausal bleeding	Uterus bulky	USG - bulky uterus, endometrial thickness > 10 mm. Endometrial biopsy - endometrial carcinoma.	Laparotomy followed by TAH with BSO	Bulky uterus with normal sized ovaries.	Endometrial carcinoma Stage Ia.
5.	CL	P 2+1 LCB - 17 years	Nothing relevant	Underwent left sided modified radical mastectomy with axillary clearance 3 years back.	10 mg twice a day for 4 1/2 years	Peri menopausal bleeding	Uterus bulky	USG - bulky uterus endometrial thickness > 8 mm. Endometrial biopsy - proliferative endometrium.	Laparotomy followed by TAH with BSO	Bulky uterus with normal sized ovaries.	Proliferative endometrium with adenomatous changes.
6.	GD	P 3+0 LCB - 15 years	Nothing relevant	Underwent right sided modified radical mastectomy with axillary clearance 2 years back. TAH with BSO for dysfunction uterine bleeding was done 6 months before mastectomy.	10 mg twice a day for 2 years	Routine check	Hot flushes	Uterus and ovaries absent.	Nil	--	--

LCB - Last child birth

TAH with BSO - Total abdominal hysterectomy with bilateral salpingo-oophorectomy

USG - Ultrasonography

by all of them in a dose of 20-40 mg a day. Duration of use varied from 2 to 4 ½ years. All the women underwent endometrial sampling by pipelle or curettage (D and C) when they presented with abnormal bleeding. Clinical examination, sonography and laparotomy revealed enlarged uterus in all of them. One woman (Case No. 3) had multiple fibroids in the uterus. All had myohyperplasia. The first case on cut section showed a huge fleshy polypoid mass (Figure 1). Case Nos. 2 and 5 had proliferative endometrium with adenomatous changes. Case No. 2 (Figure 2) had cervical

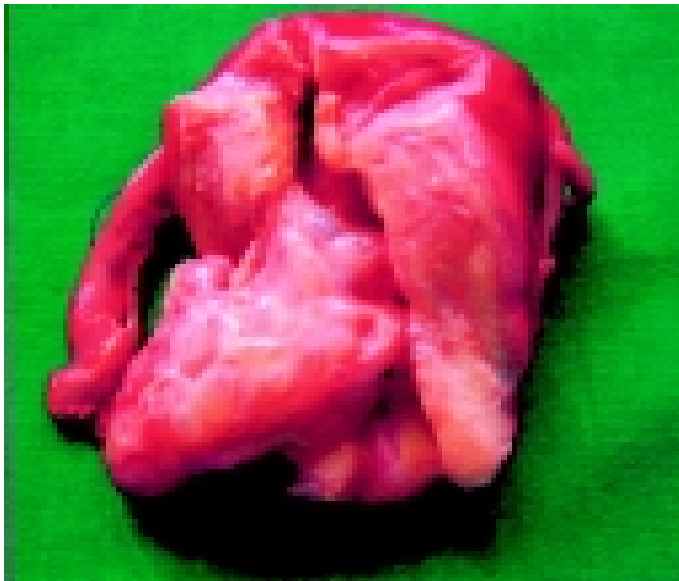


Figure 1. Hysterectomy specimen cut open to show huge fleshy mass arising from the endometrial cavity. There is myohyperplasia also.



Figure 2. Hysterectomy specimen showing thickened polypoid endometrium with hypertrophied cervix.

pathology (CIN-II) in addition to endometrial pathology. Case No. 3 showed endometrium with adenomatous hyperplasia with atypical cellular changes. Case No. 4 suffered from Stage Ia endometrial cancer as seen on histopathology.

Discussion

Gynecologic follow up of women with long term tamoxifen therapy for carcinoma breast is essential. Wide spectrum of endometrial and myometrial pathology has been observed in such women. Besides, other systemic side effects have also been noted.

Endometrial carcinoma, endometrial hyperplasia, cysts, polyps, mixed mesodermal tumors, myohyperplasia, fibroids, and exacerbation of pelvic endometriosis have been reported ^{2,3}. In our series, all the women, excluding the one (Case No. 6) who had a hysterectomy previously presented with significant gynecological pathology. Risk of endometrial cancer is increased with longer duration of tamoxifen therapy with relative risks of 2.0 for 2-5 years and 6.9 for 5 or more years use, compared to nonusers ⁴. In our study, the duration of tamoxifen use ranged between 2 and 4 ½ years. Tamoxifen competitively binds to estrogen receptor (antiestrogenic effect). This beneficial effect of tamoxifen is evident irrespective of a woman's age, estrogen receptor status and lymph node positivity. But the estrogenic activity of tamoxifen is important reason for the progression of proliferative endometrium to hyperplasia and to cancer. All our cases were evaluated with pap smear, sonography and endometrial biopsy.

Tamoxifen related side effects warn the clinician to balance the risks and benefits to an individual woman. Appearance of gynecological symptoms suggests that the physician initiate screening for gynecologic malignancy. Benefits of tamoxifen on breast cancer survival currently seem to outweigh the risks of endometrial cancer ². There remains a controversy regarding the stage of endometrial cancer developed following tamoxifen therapy. Reports with advanced stage (FIGO stage III and IV) are coming up ³. In our study two cases of proliferative endometrium with adenomatous hyperplasia, two cases of endometrial hyperplasia with atypia and one case of endometrial carcinoma Stage I have been observed amongst the five women with intact uterus. Current trend is not to use tamoxifen for longer than 2 years.

Tamoxifen therapy significantly reduces the incidence of recurrent disease following primary treatment of carcinoma breast ². There is improved survival rate and quality of life ⁴. It gives the benefits of hormone replacement in postmenopausal women. Despite the benefits, this drug has got potential side effects on the

female genital tract. Uterine malignancy is a major concern with tamoxifen therapy. Annual gynecological follow up for all women is mandatory. Pap smear screening should be done annually. Screening for gynecologic malignancy (endometrial sampling, sonohysterography, hysteroscopy) should be initiated early whenever there is any symptom. Use of selective estrogen receptor modulators that are more site specific (breast tissue) may be an ideal alternative to tamoxifen. Till then effective surveillance organised jointly by the surgeon and the gynecologist is essential.

Conclusion

Tamoxifen has sinister effects on endometrium and cervix. Regular screening for uterine and cervical malignancy is mandatory for patients taking tamoxifen.

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