

# Leiomyomas in patients receiving Tamoxifen

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*Summary:* In literature there have been only 8 cases of unavoidable laparotomy due to uterine leiomyomas performed in patients with breast cancer on Tamoxifen (TAM). Our article describes two cases of rapidly growing leiomyomas in patients treated with TAM: one of these underwent abdominal hysterectomy while the second stopped taking TAM and began therapy with Triptorelin. This therapeutical alternative could be a useful choice.

*Key words:* Leiomyoma; Tamoxifen; Breast neoplasms.

## INTRODUCTION

At the present time, Tamoxifen (TAM) seems to be an extremely useful substance as adjuvant treatment of breast cancer: in fact, an overview of 61 randomized trials among 28.896 women on TAM in early breast cancer indicates a significant improvement of both recurrence - free survival and overall survival in postmenopausal patients <sup>(1)</sup>.

The acute side effects of TAM are few, and the most frequent adverse reactions are hot flushes, nausea, and vomiting; less frequent reactions are vaginal bleeding, visual disturbances, and skin rashes. However, patients who should stop taking TAM because of its side effects are only 2-4%.

Due to the mild estrogenic-effect within estrogen-sensitive tissues, unexpected da-

ta regarding a longterm use of TAM are emerging.

Among stimulatory effects upon the uterus, myomas, even quickly growing, have been described <sup>(2)</sup>. The purpose of our observation is to report 2 cases of myomas arising in 2 breast cancer patients, one in premenopause and the other in postmenopause, treated with TAM.

## CASE REPORT

### Case 1

A 36-years old woman, gravida 2, para 1, spontaneous abortion 1, underwent a left modified radical mastectomy with axillary node dissection in July 1988 for removal of an infiltrating ductal breast carcinoma (G2) with 2 out of 17 micrometastatic nodes. Estrogen receptors were positive.

Therefore she was treated with 6 cycles of chemotherapy (cyclophosphamide, methotrexate, 5-fluorouracil) and TAM (10 mg td), as adjuvant therapy. The patient was regularly checked (blood tests, bone and liver scintigraphy, abdominal and pelvic sonography, chest X-ray), and no abnormal test nor any pelvic mass was found.

After 4 years, during a follow-up, sonography showed a sudden increase of uterine volume

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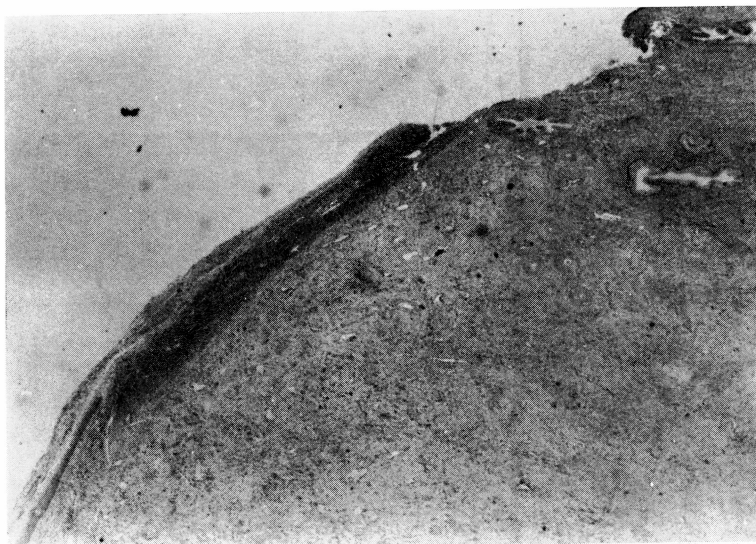


Fig. 1. — Microscopic appearance of submucous myomatous nodule with thin hemorrhagic mucosa. In the left lower side endocervical glands are evidenced.

(9.4×4.3×5.4 cm) and a leiomyoma (4.6 cm) of the corpus uteri.

The patient stopped taking TAM and began therapy with Triptorelin (Decapeptyl - Ipsen 3.75 mg every 4 weeks i.m.). After a 12-month treatment there was a decrease of the uterine volume and no further evidence of the fibroid. The patient is currently disease-free and continue the therapy with Triptorelin at the same dosage.

#### *Case 2*

A 50-year old woman, gravida 2, para 1, spontaneous abortion 1, underwent left modified radical mastectomy with axillary nodes dissection for removal of infiltrating ductal carcinoma (G3) in 1988.

Because of axillary node involvement and of an omolateral axillary relapse, removed in November 1988, she was treated with adjuvant chemotherapy (cyclophosphamide, methotrexate, and 5-fluorouracil).

At the end of the 6 cycles of chemotherapy, she was started on TAM (10 mg td) because both tumors were estrogen-receptor (ER) positive. The regular interval checks were unremarkable and pelvic examination and sonography were negative up to January 1992. In June 1992 the patient developed a sudden severe abdominal pain; vaginal sonography showed an uterine fibroid of the corpus uteri and an in-

creased irregular endometrial thickness. Therefore she underwent a total abdominal hysterectomy and bilateral salpingo-oophorectomy. The pathologic findings showed a firm elastic subserous isthmic leiomyoma (dimensions 7×6×4 cm) (Fig. 1), a peduncolated polyp of the fundus (dimension 2×1.5×0.5 cm) and a proliferative polypoid endometrium.

The patient had a normal post operative course and began again the therapy with TAM at the previous dosage. She is currently disease free.

#### DISCUSSION

In 1971 Tamoxifen was used in clinical trials as adjuvant therapy for breast cancer<sup>(4)</sup> and is now the endocrine treatment most frequently used for breast cancer.

This drug is one of the several triphenylethylene derivatives and is classified as partial estrogen agonist/antagonist.

The antiestrogenic effect of TAM is explained by its binding to the ER and occupying the ER sites in DNA; this action inhibits the replenishment of ER to cytoplasm, so that the estrogen effects, such

as cell growth and reproduction of autocrine growth-factors, are inhibited <sup>(5)</sup>.

However Clark *et al.* have shown that the complex between TAM and its receptor exhibited longterm nuclear retention, resulting in an early estrogen-like responses, and then in antiestrogen action <sup>(6)</sup>.

In animal experiments the balance between the antiestrogenic and estrogenic effects of TAM has been shown to be both organ and species specific <sup>(7)</sup>.

Gottardis *et al.* have demonstrated that TAM inhibited breast cancer cell growth and stimulated endometrial tumor growth in athymic mice <sup>(8)</sup>.

It is now clear that the endometrium represents one of the most important secondary targets of TAM action.

De Muylder *et al.* <sup>(9)</sup>, have shown that 50% of 46 non-hysterectomized women treated with TAM as adjuvant therapy for breast cancer, in 3-6 months, presented at hysteroscopy some endometrial lesion, ranging from endometrial and endocervical polyps to endometrial hyperplasia of adenocarcinoma. The same Authors underlined that endometrial response to TAM seemed to vary according to the menopausal status of the patient. Endometrial cancers reported in literature were 92 among breast cancer patients on TAM. Even though the majority of these neoplasms are a chance observation, nevertheless the problem cannot be ignored. With the three sarcomas reported in the Scottish Adjuvant Trial <sup>(10)</sup>, one carcinosarcoma following an adenomyoma reported by Bocklage *et al.* <sup>(11)</sup>, two mixed mullerian tumors reported by Magriples *et al.* <sup>(12)</sup>, two sarcomas reported by Champion *et al.* <sup>(13)</sup>, and two sarcomas reported by Mignotte *et al.* <sup>(14)</sup>, a total of twelve sarcomas appears in recent literature among postmenopausal breast cancer patients receiving tamoxifen therapy. Eleven cases of uterine myomas have been observed by Amoroso *et al.* among premenopausal wo-

men in the GROCTA study on TAM and breast cancer, in the study no myoma was found in the group of patients treated with TAM and chemotherapy <sup>(15)</sup>.

Among the side effects there are adenomas, pelvic endometrioses, and uterine myomas whose quick growth may mimic a metastasis and should have an exploratory. Boudouri *et al.* <sup>(16)</sup> described 7 patients with myomas who needed laparotomy; Dilts *et al.* <sup>(17)</sup> one case; Le Boudec *et al.* <sup>(2)</sup> had, among 22 breast cancer patients on TAM with metrorrhagia, 7 cases who underwent laparotomy and had uterine fibroids.

In our first case the premenopausal patient stopped taking TAM and started a therapy with Triptorelin.

The rationale of our treatment is that it is possible that TAM might bind to receptor sites on the leiomyoma, providing a direct stimulatory effect.

However, TAM may have, besides the blocking of the estrogen receptors, an indirect stimulatory effect, on the hypothalamus, leading to an intense output of gonadotropins with subsequent ovarian stimulation, as shown by Dilts *et al.* <sup>(17)</sup>. The GnRh analogue is able to induce a hypoestrogenic ambient useful to both the primary tumor and the leiomyoma.

Surgical exploration was necessary in the second case because of the rapid growth of a new pelvic mass.

This observation and experimental data are in accordance with the mainly estrogenic effect of the drug on the endometrium.

Until research finds another triphenylethylene agent with less prominent estrogenic effects, we must intensify the clinical and instrumental surveillance not only on the corpus uteri but also the genital tract of patients taking TAM for adjuvant therapy and for chemo-prevention of breast cancer <sup>(18)</sup>.

In conclusion the relationship between TAM and the appearance of myomas, often quickly growing is evident, as can be assumed from international literature data and our. However, if one considers that TAM provides a yearly reduction of relapses in 20% of premenopausal ER positive women, in 30% of menopausal patients in general and in 36% of the ER positive, as well as a reduction in the mortality risk in 20% and 23% respectively of the last 2 groups of women<sup>(19)</sup>; the possibility of having a myoma should not imply a reduction either of the dosage or the length of treatment with TAM. It is only advisable to make a careful sonographic follow-up.

It will be the size of the myomas and/or the appearance of symptoms which will determine, at the end of the therapy, the avoidance of surgical treatment for weakened patients. The association of GnRh analogues and TAM represents an open question regarding cancer control. In fact the analogues oppose the advantages of a chemical castration, with a worsening of side effect, while there is not, any difference in disease free survival among patients with or without TAM-induced amenorrhea<sup>(20)</sup>. However, the association could represent a good non-surgical option in the treatment of fibroids, allowing the continuation of the hormonal therapy.

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