Two cases of ovarian cysts in postmenopausal patients under antiestrogen treatment

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Summary: In 20% of premenopausal breast cancer women on Tamoxifen (TAM) treatment there is an ovarian enlargement: in literature one case of acutely cystic ovaries is described.

We observed 2 cases of acutely cystic ovaries in postmenopausal women surgically treated during a long-term adjuvant therapy with TAM.

Key words: Ovarian cysts; Tamoxifen; Menopause; Breast neoplasms.

INTRODUCTION

Breast cancer remains the most common malignancy among women accounting for 90 cases × 100,000 per year in all Central-North Registries in Italy and representing approximately 22% of tumor deaths ([1]).

TAM is the endocrine therapy most frequently used for the treatment of this tumor: about 2/3 of breast cancers with positive estrogen-receptors (ER) in postmenopausal women respond to tamoxifen when this drug is given as a first line endocrine treatment for metastatic disease ([2]).

The drug is one of several triphenylethylene derivatives, all of which are non steroidal partial estrogen agonist-antagonist and show many structural similarities to one another ([3]).

Tamoxifen is structurally similar to clomiphene and equivalent to this for induction of ovulation ([4]).

A long term use of tamoxifen, as commonly employed as adjuvant therapy to primary breast cancer in both pre and postmenopausal patients ([5]) either negative or positive nodes, may increase the risk of ovarian diseases.

The Authors report two cases of ovarian cysts developed in postmenopausal patients with breast cancer during long-term adjuvant therapy with tamoxifen.

CASE REPORT

Case 1

A 62-year-old woman, gravida 4, para 3, spontaneous abortion 1, underwent a right modified radical mastectomy with axillary node dissection in November 1988, to remove an infiltrating ductal breast carcinoma (G2) with negative lymphnodes and positive estrogen receptors.

She was treated with TAM (30 mg daily) as adjuvant therapy. The patient was regular follo-

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wed with scintigraphy of bones and liver, upper and lower abdominal sonography, a chest X-Ray, and blood tests. All the tests were always negative. After 3 years, during a follow-up, bimanual examination showed bilateral adnexal masses, confirmed by vaginal sonography. At laparotomy we found the right ovary completely occupied by a cyst: we performed a total abdominal hysterectomy and bilateral salpingo-oophorectomy. The pathologic findings showed a 6 cm right cyst that had, in the thickness of its wall, cavities in which were found stratification of the epithelium, papillae, cellular pleiomorphism, mitotic activity without stromal invasion. The left ovary was policystic (Fig. 1, 2).

The patient after a normal postoperative course took TAM again at the same dosage, and is currently disease free.

Case 2

A 50-year-old woman, gravida 2, para 1, underwent a left modified radical mastectomy with axillary lymphnodes dissection for removal of infiltrating ductal carcinoma in January 1988. The lymphnodes were metastatic and estrogen receptors were positive. After 11 months she had an axillary lymphnodal relapse which was removed. She was treated with 6 cycles of chemotherapy (cyclophosphamide, methotrexate and 5-fuorouracil) then she started TAM (10 mg td) as adjuvant therapy. During her regular follow-ups her gynecologic history was unremarkable and all the diagnostic procedures (blood tests, scintigraphy, abdominal sonography, chest X-Ray) were negative. Suddenly in June 1992 she developed a severe abdominal pain. She underwent a laparotomy that revealed a 5 cm ovarian left cyst with signs of torsion, and 100 cc serous-hemorragic free fluid without neoplastic cells; the right ovary appeared microcystic. She underwent a total abdominal hysterectomy and bilateral salpingo-oophorectomy.

The patient had a normal postoperative course and retook the previous dosage of TAM and she is still disease free.

DISCUSSION

It is well known that TAM is an excellent adjuvant endocrine therapy in breast cancer because of an improvement in patient survival and also the availability of this drug. In fact there are few and usually mild side effects and acute toxicity with reversible mielosuppression: thromboembolism is uncommon. However a long-term TAM administration may produce changes in the reproductive tract with development of uterine ovarian abnormalities. Besides the well known reports on uterine cancer and myomas, other Authors have described ovarian cysts: Le Boudec *et al.* [6] found 2 cases, one of which in a postmenopausal woman, among 22 patients on TAM with metrorrhagia, Terada *et al.* [7] reported one follicular cyst in a premenopausal patient; and two cases of immediate ovariectomy due to torsion of ovarian cysts in premenopausal women on TAM, have been described in literature [8]. The direct activity of TAM on the ovary is supposed, in premenopause. Following an increase of ovarian steroidogenesis, a rise in estradiol production should appear; in fact there is a constant increased secretion of the hormon with serum concentration up to 2500 pg/ml, as evidenced by Wolf *et al.* [9]. After a slight increase at the beginning of TAM administration, FSH and LH levels remain constant because of the estrogenic negative feed-back [10, 11] on the hypothalamus-hypophisis axis. In postmenopausal patients there are neither signs of a direct ovarian stimulation (i.e. E2 concentration is not increased) nor decreased gonadotropin levels, which are usually high in menopause [7]. The only sign of a metabolic activity is represented by ovarian cell trasnudation and follicular liquid formation. An explanation of this phenomenon could be connected with an increased availability of the growth-factor TGF-β, induced by TAM, as it has been evidenced in breast cells cultures [12].

In ovarian cells TGF-β might strengthen FSH action on aromatase of granulosa cells without interfering on cells multiplication [13, 14] so that an increase of TGF-β should always lead to a metabolic impulse.

However, it is not clear why only a few patients on TAM develop ovarian cysts.

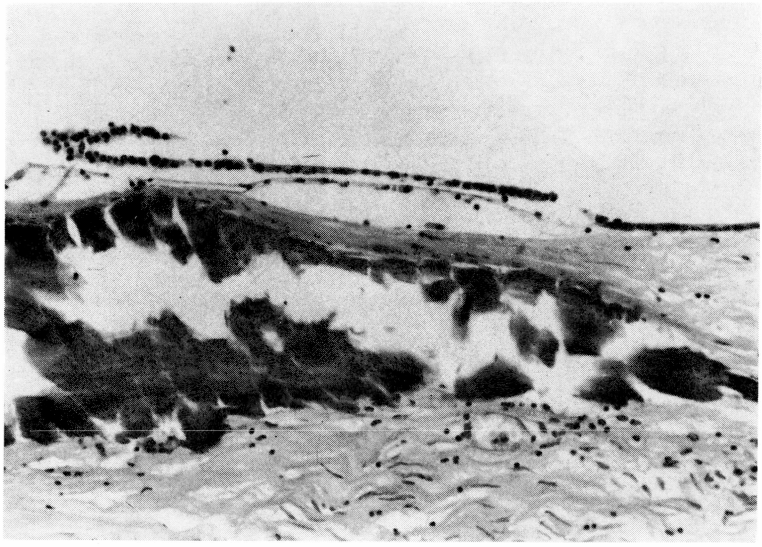

Fig. 1. — Microscopic appearance of a cyst with thick, partly calcified, content.

Fig. 2. — Microscopic appearance of inclusion cyst of celomic epithelium. A psammoma body is present in the lower right side.

The management of both breast cancer patients and high-risk women at for breast cancer, with a long-term TAM treatment will lead to an increasing number of side effects that will probably affect the reproductive tract. Therefore, a more careful check on these patients is needed in order to avoid unpleasant and possibly dangerous effects.

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