Boswellia, inositol and betaine in the treatment of fibroadenoma: a case study

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ABSTRACT — OBJECTIVE: Nowadays, no completely side effect-free therapeutic approach for mammary fibroadenomas exists, considering that the election therapy is based on antiestrogens, as well as on surgery for more severe cases. Our aim was to identify an efficient and side effects free treatment, based on the association of myo-Inositol, boswellia and betaine.

PATIENTS AND METHODS: A 43-yearold woman, with a positive familiarity for mammary carcinoma, presented a benign fibroadenoma, with intra-lesional vascularization. The patient was enrolled for a previous study to receive two oral capsules twice a day of an association of myo-Inositol, boswellia, betaine, group B vitamins and N-acetylcysteine for four months.

RESULTS: After four months of supplementation with myo-Inositol, boswellia, betaine, group B vitamins and N-acetylcysteine, the injury appeared highly modified at ultrasound examination, assuming the appearance of a cystic conglomerate and branched, a sign that the lesion is regressing and about to be reabsorbed. Interestingly, the injury also became free from intra-lesional vascularization. Although these benign modifications, the patient decided for surgery since she was afraid and anxious due to her familiarity for mammary carcinoma. An excisional biopsy was performed. Histological analysis reported benign histopathological contexts of the mammary gland affected by fibroadenoma.

CONCLUSIONS: Even though the patient requested surgery in any case, considering her familiarity with breast cancer, she underwent encouraging improvement only after some months of therapy with the association of myo-Inositol, boswellia, betaine, group B vitamins and N-acetylcysteine. Hence, in patients with fibroadenomas without a history of familiarity with breast tumors, the intake of this association is reasonable, as it could avoid resorting to surgery, causing the lesion to regress until it is largely reabsorbed.

KEYWORDS

Fibroadenoma, Inositol, Boswellia, Betaine.

INTRODUCTION

The term "fibroadenoma" means a benign nodular breast pathology that occurs most often in women between 15 and 35 years of age. Under clinical observation, it appears as a relatively mobile nodular mass, frequently unique, with a well-defined shape, and a variable consistence, from rubbery to hard.

Histologically, this tumor shows stromal and epithelial elements, net margins and reduced adhesion to the surrounding tissues, features that distinguish it from the malignant form through radiological

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examination. Calcifications, when present, look like solid, rounded lumps, and never powdery. At ultrasound examination, a hypoechoic mass with structural homogeneity and net margins can be observed. Usually, fibroadenomas occur as isolated lesions, but sometimes they can be multiple, relapsing and bilateral.

Epidemiologically, a review reports that in women undergoing clinical controls the incidence rate of fibroadenomas is between 7% and 13%, whereas according to other Authors this rate was about 9% in a study carried out on 225 autopsies^{1,2}. Fifty % of all the mammary biopsies proves to be compatible with the diagnosis of fibroadenoma, with an increase of 75% of the biopsies performed in women less than 20 years old^{3,4}. Furthermore, such pathology affects more frequently women belonging to the wealthier classes⁵⁻⁷ and young black women⁸.

Although fibroadenoma is a typical pathology of reproductive age, it can be diagnosed even after menopause with the presence of multiple calcifications.

From the histological and clinical point of view, no difference can be detected between fibroadenomas found in patients less than 30 years old and those ones called "at slow growth" observed in women in menopause, although sometimes the firsts can more easily reduce their diameter spontaneously⁹.

Histopathologically, as the name points out, fibroadenomas are constituted by a double component, both glandular and stromal. Some fibroadenomas have a hyperplastic origin and are polyclonal¹⁰.

Additional studies prove that in some cancers the fibrous component shows a clonal type and it can have cytogenetic alterations, though the epithelial component is polyclonal^{11,12}. When cut a white-greyish fibrous tissue is found, sometimes with thin cracks. At light microscopy, a cellular fibroblastic stroma, containing glandular structures and small cystic spaces covered by epithelium can be observed. The stroma can surround also the epithelium, compressing and deforming it¹³.

About 5% of all the fibroadenomas have the same clinical and histopathological features of the so-called giant fibroadenomas, defined as a mass with 10-15 cm maximum diameter and weight higher than 500 gr^{14} .

Some authors affirm that patients having first-degree relatives affected by breast cancer show greater possibilities of developing single fibroadenomas^{15,16}. The surgery treatment of fibroadenoma is usually recommended for the following cases: doubtful diagnosis, presence of lesions with slow and progressive volumetric increment, wounds which seem symptomatic for any reason. Last, but not least, women experience worries and anxiety from the presence of mammary nodules usually leading to choose the surgical approach. Therefore, we tried to identify an efficient and safe therapy, considering that currently the only therapy is with antiestrogens drugs, not entirely free of serious side effects and not always ensuring positives results¹⁷⁻²⁰.

The negative effects on the endometrium can be significant, and for this reason is mandatory to continuously monitor the patients in therapy with tamoxifen, through regular pelvic sonographic controls and focusing the attention on symptoms such as pelvic pains and/or vaginal discharge.

So far, no therapeutic alternative for mammary fibroadenoma exists that is completely side effect-free. However, in our previous studies, we had already documented the efficacy exerted by the association of three natural substances: Myo-Inositol, Boswellia and Betaine in the treatment of various female mammary disorders²¹⁻²³. The rationale for such therapy is supported by the following findings:

- Inositol, and precisely myo-Inositol, induces the reversion of neoplastic phenotype through a complex pleiotropic activity on the epithelial cells and the microenvironment. At cellular level, it modifies the cytoskeleton and inhibits several pathways (PI3K/Akt, Presenilin, ERK) involved in cell proliferation and in the acquisition of features of invasiveness and migration^{24,25}. In the microenvironment myo-Inositol counters the activation of inflammatory processes (by inhibiting both PGE2 release and COX-2 activation). Such processes allow collagen remodeling, thus counteracting fibrosis and mammary density increase²⁶.
- 2) Boswellia shows a distinct anti-inflammatory and anti-fibrotic activity^{27,28}.
- Betaine (trimethylglycine) is involved in the modulation of transmethylation processes, therefore contributing to influence chromatin structure and epigenesis. It reduces not only inflammation, but also the activation of downstream proliferative signaling pathways, such as NF-kB-dependent processes²⁹.

CASE STUDY

This case report was selected from our previous study on mammary fibroadenomas²¹. Herein, we highlight the case of one woman belonging to the group treated with a composition of myo-Inositol, boswellia, betaine, in association with group B vitamins and N-acetylcysteine that required the surgical removal of the lesion, despite its evident encouraging modification, detected sonographically, after some months of therapy.

The patient gave her oral informed consent form and the study was conducted in accordance with the principles of the Declaration of Helsinki. The patient was a 43-year-old woman with a widespread bilateral fibro-nodular mastopathy. She had breast-fed both her children for six months. No relevant pathologies were found in her personal anamnesis; however, a positive familiarity for mammary carcinoma (mother and first-degree aunt) was recorded.

In the first control, before her enrollment in the study²¹ (January 2016), it was identified in the upper outer quadrant (UOQ) and axillary extension of the right breast the presence of a new tissue formation with an elongated and polylobed morphology, already known in the anamnesis, with net and well-defined margins (maximum diameter of 19 mm), separated from the neighboring glandular tissue. In such formation, sonographically definable as benign fibroadenoma, was detected an intra-lesional vascularization by means of the color Doppler control.

The patient underwent a therapy with two oral capsules twice a day of the association of 200 mg myo-Inositol, 50 mg boswellia, 175 mg betaine, 4,5 mg group B vitamins and 100 mg N-acetylcysteine (Eumastós[®], Farmares S.r.l., Rome, Italy).

After four months (May 2016) a breast ultrasound was made using a linear probe of 7.5 MHz. From the ultrasound emerged that the injury appeared to be considerably modified, assuming the morphology of a cystic conglomerate, branched and increased in size, now having a maximum diameter of 26 mm. Interestingly, after these four months of the therapy, we observed that the injury was free from intra-lesional vascularization, thus showing characteristics of a tumor, which, although modified in its appearance, was still benign. No side effects were recorded.

At this stage, considering the remarkable although benign modifications of the injury and the state of anxiety of the patient due to her familiarity for mammary neoplasm, an excisional biopsy of the signaled area was decided.

The mammary parenchyma from the biopsy, once fixed, showed on its surface a visible a 0.7 cm nodule and multi lobed margins (Figure 1a).

Thus, on the tissue samples from the biopsy the histological analysis was performed, showing how the treatment with a composition of myo-Inositol, boswellia, betaine, in association with group B vitamins and N-acetylcysteine had improved the characteristics of the injury, with evident myxoid degeneration of the connective component, epitheliosis and adenosis, indicating that the lesion was in regression (Figure 1b).

DISCUSSION

Fibroadenomas are benign breast tumors showing both stromal and epithelial components and occurring mainly in women below the age of 35 years old. It was observed that patients having first-degree relatives affected by breast cancer are more likely to develop fibroadenomas^{15,16}, so that their clinical condition needs to be monitored carefully.

This is exactly the issue discussed in the present case report, where a 43-year-old woman presented with a vascularized fibroadenoma.

After a four-month treatment with an association of myo-Inositol, boswellia, betaine, group B vitamins and N-acetylcysteine, the breast ultrasound reveled the injury changed its morphology and dimension, going through a vacuolization and taking on the appearance of a semi-liquid cyst.

These modifications are a signal that the lesion is regressing and that in time it will end up being reabsorbed. If the patient had continued a few more months the treatment, it is likely that the lesion would have reabsorbed without requiring surgery.

Anyway, considering her familiarity for mammary carcinoma and the anxiety caused by this condition, the patient started pressing for the lesion to be removed. So, an excisional biopsy was performed, followed by histological analysis. The biopsy and the histological analysis allowed us to understand the evolution that fibroadenoma had undergone during treatment, before it was reabsorbed and completely disappeared.

Indeed, what emerged from the histological analysis was that treatment highly improved fibroadenoma's benign features, considering the reduction of inflammation and since no longer vascularization was evidenced, confirming the positive effect of the association of myo-inositol, boswellia and betaine on breast lesions.

CONCLUSIONS

Overall, even if the patient underwent surgery as well, this case study confirmed the efficacy and the safety of myo-Inositol, boswellia, and betaine association in improving injury's benign characteristics.

On these bases, this supplement could represent a valid therapeutic option for women with fibroadenomas, who have not familiarity with breast tumors. This association with myo-Inositol, boswellia, and betaine could preserve those patients from surgery, directing their lesions towards vacuolization and reabsorption. Of course, other studies will have to be conducted to better understand also the mechanism underlying the effectiveness of this association.

CONFLICTS OF INTEREST:

The Authors declare that they have no conflict of interests.







Fig. 1. *A*, Macroscopic description of the fixed tissue. Portion of mammary parenchyma, with dimensions $4,5 \ge 2,5 \ge 3$ cm. On the cut surface, a 0.7 cm nodule is visible, with multi lobed margins whitish colored, soft-elastic consistency and translucent consistency. *B*, Microscopic histopathology report. The histopathology exam of the serial sections shows benign histopathological contexts of the mammary gland affected by fibroadenoma, with evident myxoid degeneration of the connective component. The last one appears to be hypocellular, associated with phenomena of epitheliosis and adenosis. Epitheliosis shows ductal ectasia, site of marked hyperplasia often in apocrine metaplasia. On the other hand, adenosis displays microglandular and sclerosant features.

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