

First case of transformation for breast fibroadenoma to high-grade malignant phyllodes tumor in an *in vitro* fertilization patient: misdiagnosis of recurrence, treatment and review of the literature

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Abstract. – **INTRODUCTION:** Cystosarcoma phyllodes are very rare tumors and may be difficult to diagnose clinically.

BACKGROUND: Fibroadenomas have long been considered benign hyperplastic lesions rather than true neoplastic processes. However, previous clonality studies have shown differing results.

AIM: to assess diagnostic and treatment options for phyllodes tumor.

MATERIALS AND METHODS: A 41-year-old female patient undergoing assisted fertilization treatment. The patient underwent fine needle aspiration biopsy that confirmed fibroadenoma before the IVF attempt. At 17 weeks of gestation, due to an increase in volume of the fibroadenoma, an excisional biopsy was performed that showed a malignant phyllodes tumor. Then she underwent quadrantectomy and chemotherapy. After 1 year there was a recurrence of phyllodes tumors and she underwent mastectomy and chemotherapy.

RESULTS: Fibroadenoma that was transformed into high-grade malignant cystosarcoma after ovarian stimulation, relapsed after one year and it was not immediately diagnosed. The patient underwent mastectomy and chemotherapy.

DISCUSSION: it is difficult to diagnose recurrence and to determine the frequency and the right treatment for such a rare cancer, so it is important to report any case in the literature.

CONCLUSIONS: We recommend to remove a fibroadenoma before attempting IVF for the risk of malignant transformation.

Key Words:

Cystosarcoma phyllodes, Recurrence, Treatment.

Introduction

Fibroadenomas have long been considered benign hyperplastic lesions rather than true neoplastic processes¹. This view has been supported by the observation that most fibroadenomas behave in a benign clinical fashion and the majority regress with time². However, previous clonality studies have shown differing results. There has been less controversy regarding the neoplastic nature of phyllode tumors or cystosarcoma phyllodes^{3,4}. Cystosarcoma phyllodes are very rare tumors and may be difficult to diagnose clinically. The epidemiology and pathobiology are different from those of breast carcinoma. Risk factors, multicentricity, and bilaterality, commonly associated with breast carcinoma, are not observed in patients with cystosarcoma phyllodes. Although the term sarcoma indicates a malignant tumor, only 10%-30% of cystosarcomas are histologically diagnosed as malignant; clinical diagnosis of malignancy does not exceed 10%. Axillary node involvement is rare, but the hematogenous spread of the cystosarcoma occurs in the lung, pleura, bone, and liver. We previously³ described a case of fibroadenoma that was transformed into a malignant phyllode tumor after ovarian stimulation for IVF. Now, we present the evolution and treatment of cancer recurrence and, through a review of the literature, helps to establish the proper treatment of phyllodes tumor of the breast.

Materials and Methods

A 41-year-old patient underwent IVF cycle for male factor infertility. Before starting ovarian stimulation, she underwent mammography that showed a large, well-circumscribed, oval or lobulated mass with rounded borders.

Fine needle aspiration biopsy was performed, and the smears were stained with hematoxylin and eosin. A cytologic examination showed typically branching monolayered sheets of epithelial cells with myoepithelial cells within the clusters, and variable numbers of bare nuclei in the background, suggesting the presence of a fibroadenoma.

Ovarian stimulation was started with GnRH analogues (triptorelin, Decapeptyl; Ipsen) from the 1st day of the cycle and recombinant FSH (Gonal F; Serono, Italy) plus urinary FSH (Meropur; Ferrig, Italy) from the 2nd day of the cycle⁵⁻⁷. The FSH dose was adjusted when necessary according to follicular size and E2 level. Final oocyte maturation was triggered by the administration of 10,000 IU of hCG (Gonasi HP; IBSA, Italy). The retrieved oocytes were denuded immediately after retrieval and were assessed for their maturity. The oocytes were then inseminated with the use of intracytoplasmic sperm injection.

Ultrasound-guided embryo transfer took place 48 h after insemination. The luteal phase was supported with the administration of progesterone (50 mg IM), folic acid (5 mg)⁸. The patient did not become pregnant, however. After the first unsuccessful IVF attempt, therefore, she underwent a new breast tumor screening with unchanged results. After 3 months, she started a new stimulation protocol the same as the previous one. Subsequently, she became pregnant. At 17 weeks, because of an increase in the volume of the fibroadenoma, she underwent an excisional biopsy, which showed a 6.0 × 4.0 × 4.0 cm mass with pale, white, granular, and lobulated cut surfaces. Small foci suggestive of hemorrhage were noted. The histologic criteria were based on the 2003 WHO classification of the breast and female genital organs⁹. Later, she underwent quadrantectomy, and a cesarean section was performed at 36 weeks of gestation. After delivery she underwent chemotherapy (mesna, doxorubicin, ifosfamide, and dacarbazine).

Eighteen months later, the patient made an MRI which showed, in the right subareolar area, a focus of the expansion of diameter of 5 mm, attributed to benign disease, whose appearance is to be related to the resumption of normal physiological hormonal stimulation of the breast after breastfeeding.

Five months later the patient reported the reappearance of pain in the right breast and the presence of a swelling of about 1 cm in diameter.

Ultrasound highlighted an oval image of 20 x 10 mm, solid, hypoechoic, vascularized. At the next TC total body, the same image showed a positive enhancement. Patient underwent a unilateral mastectomy. Histological examination gave evidence of recurrence of high grade of malignancy (Ki67 80%) sarcoma phyllodes.

Discussion

Phyllodes tumors can be found at any age including adolescence¹⁰, even if the peak incidence in women is between 35 and 55 years. Few cases are reported in men¹¹ and during pregnancy^{3,12,13}. Phyllodes tumors are classified as benign (58%), borderline (12%), or malignant (30%) based on the presence of cellular atypia, mitotic activity, and overgrowth in the stroma^{9,14}. The malignant form accounts for 0.3-1% of all breast neoplasias¹⁵. Phyllodes tumors usually present as rapidly growing breast lumps. Other symptoms and signs are non-specific (dilated skin veins, blue discoloration of the skin, nipple retraction, fixation to the skin or the pectoralis muscle, a skin ulcer, pressure necrosis of the skin, or palpable axillary lymphadenopathy) making the clinical diagnosis difficult¹⁶. Mammography and ultrasound are notorious for their inability to distinguish the benign or malignant histologic nature of phyllodes tumors except for the irregular shape and a tumor diameter > 3 cm on sonography^{17,18}. MRI, instead, is a useful tool for the diagnosis: it can show morphological features (such as mass shape and margin) and also signal changes (on T1-weighted, T2-weighted and enhanced images), which illustrate some special component in the lesions, like fat, hemorrhage or necrosis. Some authors demonstrated that some MRI features correlate significantly with histologic grade^{17,18}. Fine-needle aspiration cytology (FNAC) may not be helpful for differentiating benign and malignant phyllodes tumors, because of the heterogeneity of these tumors (co-existence of benign, intermediate, and malignant areas within the same tumor). Moreover, FNAC is not reliable to distinguish a fibroadenoma from a phyllodes tumor^{19,20} while core needle biopsy has a strong negative (93%) and positive (83%) predictive power to differentiate them²¹. However, only histopathologic examination of the entirety of the excised specimen allows an accurate diagnosis to be made, including

an evaluation of tumor grade²¹. Estrogen receptors were found in phyllodes tumors²² and exposure to hormones, such as ovarian stimulation, may contribute to malignant transformation from a fibroadenoma³. This is a case of malignant transformation of breast fibroadenoma in a cystosarcoma phyllodes in a women undergoing ovarian stimulation and IVF, followed by misdiagnosed recurrence after quadrantectomy and adjuvant chemotherapy. The management of this type of tumor is complex first of all because the diagnosis is difficult to achieve and then because it tends to recur. The local recurrence rate of cystosarcoma phyllodes is 20%. Metastasis are rare, mostly hematogenous, and usually found in lungs or bones²³. Grading and adequate surgical excision with clear margins are the most important preventions of recurrence as well as of long term prognosis since recurrent cystosarcoma phyllodes usually has a higher grade than the primary neoplasia²⁴. Surgery is the best weapon to use against phyllodes tumors²⁴. The role of chemotherapy and radiotherapy has not been established yet in literature^{14,25,26}. There is, however, no clear consensus concerning the type of surgery to be performed (conservative or radical). Shelling out of tumors is not adequate, but frequently done because of the similitude with fibroadenomas and the difficulties of preoperative histologic diagnosis²⁷. For small lesions, wide excision of the tumor with a 10 mm clear margin seems to be appropriate, while mastectomy or wide quadrantectomy have to be chosen if breast conservation surgery is not possible¹³. Breast conservation surgery is acceptable only when the margins are safe, this guarantees a local control rate of approximately 90%; for this reason authors recommend this approach whenever cosmetically feasible¹⁴. Certain studies have demonstrated better locoregional control^{28,29} or improvement in disease free survival^{11,29} when comparing mastectomy with conservative surgery. Moreover, as the outcome of patients with malignant phyllodes tumors and a previous history of fibroadenoma was found significantly better than that of cases without history of fibroadenoma, it would be suitable to perform aggressive treatment in patients with malignant phyllodes tumors but without prior history of malignant transformation who exhibit rapid growth within 6 months³⁰. Lymphadenectomy can be considered just in case of axillary metastatic disease, which occurs in < 10% of patients. Otherwise it is not routinely performed²⁴. Patients with phyllodes tumors require careful follow-up after the surgical procedure. Recurrence of the tumor in the breast or elsewhere by

distant metastasis varies depending on the reported series, but can be as high as 27%^{31,32}. Recurrence or distant metastasis is related to poor histopathologic factors such as stromal overgrowth, infiltrative margins, and pleomorphism and tumor size³¹⁻³³. Metastases or recurrence tend to develop within the first 2 years after diagnosis and represent a hematogenous pattern of spread³⁴. Majeski et al¹⁰ proposed to follow patients with phyllodes tumor with repeat mammograms and physical examination every 6 months postoperatively for the first 3 years and then annually. In our case the first mistake was the misdiagnosis of phyllodes tumor using FNAC. We cannot exclude that the phyllodes tumor probably coexisted with the fibroadenoma, but the needle did not reach it. Eighteen months after quadrantectomy the second diagnostic mistake was done: the patient had a relapse, which was confused at MRI examination with the physiological parenchymal changes due to breastfeeding, so delaying the mastectomy of about 5 months.

Conclusions

The peak incidence of phyllodes tumors in women is between 35 and 55 years³⁵. Besides the recommendation to remove a fibroadenoma before attempting IVF for the risk of malignant transformation, it is also important to follow the patient strictly after surgery. Given the characteristic tendency of phyllodes tumors to recur, any dubious MRI images in cases of patients with a history of previous breast cystosarcoma phyllodes calls for attention to investigate the nature. Although many studies are investigating about peculiar imaging signals of these tumors, the histological examination of entire excised specimen remains the best diagnostic tool³³.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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