



Case Report

Case Report: A Metaplastic Like Triple Negative Breast Cancer with Good Prognosis Histological Subtype

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Abstract

Background: We report here the clinical case of a patient with low-grade metaplastic carcinoma, which represents a very rare subtype of breast cancer characterized by its triple-negative molecular profile but associated with a favourable prognosis. In this report, we present the diagnostic complexity of this subtype and review the literature to extract the principles of current management.

Case presentation: A 77-year-old woman presented with a lesion of the left breast classified as ACR 4 during a screening examination. Microbiopsy revealed a grade 3 non-specific metaplastic carcinoma, finally requalified after lumpectomy as a grade 2 fibromatosis-like metaplastic carcinoma.

Treatment by lumpectomy associated with adjuvant radiotherapy was finally retained after analysis of the literature and iterative discussion in multidisciplinary consultation meetings.

Conclusion: This clinical case underlines the importance of the analysis of the whole lesion with a better immunohistochemical and molecular description that can conduct to a therapeutic de-escalation for the subtypes with good prognosis. Thus, the management of local triple negative metaplastic breast carcinoma is based on surgery with large margin alone. Nether less due to the few number of case around the world the level of evidence is still low and it is essential to continue a long-term survey after the treatment for improving the disease management.

Keywords: Low-Grade Metaplastic Carcinoma Fibromatosis-Like; Metaplastic Carcinoma

Introduction

Since 1988, the incidence of breast cancer in France has been increasing except until 2004 where the incidence still stable, while conversely, breast cancer mortality has been decreasing [1]. In 2020, the incidence of breast cancer worldwide was estimated to be around 2.3 million cases with an estimated incidence of breast cancer cases around 3,2 million cases per year in 2040. Mortality from breast cancer is also expected to increase, particularly due to the increase in the incidence of breast cancer from 0.7 million deaths per year to 1 million deaths per year [2]. Among breast cancers, the triple-negative molecular subtype represents a subtype with a poor prognosis characterized by the absence of the estrogen and progesterone receptor, as well as the absence of the HER 2 receptor. Estimated 5-year survival rates for patients with triple-negative breast tumors between 2011 and 2017 were 91% for localized disease, 65% for locally advanced disease, 12% for metastatic disease, and 77% for all stage [3]. However, among this unfavourable molecular subtype, several histological forms would have a good prognosis: cystic adenoid carcinomas, low-grade adenosquamous carcinomas, secretory carcinomas, low-grade fibromatosis-like metaplastic carcinomas, low-grade mucoepidermoid carcinomas, acinar cell carcinomas, and finally, large-cell carcinomas with reversed polarity defined according to the new 2019 International Classification of Breast Cancers [4,5]. All favourable subtype have mainly a local presentation without nodal involvement and metastasis and their prognosis are also better than other subtype of triple negative breast cancer with prolonged survival and low rate recurrence. But attention should be paid to avoid misdiagnoses specially for early grade, and the combination of cells morphology on histology and immunochemistry is essential [5,6]. Metaplastic carcinomas represent less than 5% of all invasive breast cancers. They are often triple-negative molecular subtype and represent a rather heterogeneous group with a mesenchymal epithelial transition notably composed of squamous, glandular and fibroblastic cells. We distinguish the high-grade forms composed by squamous cell carcinomas, spindle cell carcinomas and heterogeneous mesenchymal differentiation carcinomas. Low grades forms were composed with low-

grade adenosquamous carcinomas and fibromatosis-like carcinomas [7]. This distinction between low and high grade forms is important because the prognosis differs radically and the management is not really consensual due to the few case around the world described in the literature. Thus, the addition of radiotherapy or chemotherapy is still debated, and the place of immunotherapy is not clearly define. We present here the case of a patient with a low-grade fibromatosis-like metaplastic carcinoma first described in 1999 and which represents less than 1% of all invasive breast cancers with 67 cases reported up to now in the literature [5,8,9].

Clinical case

A 77-year-old patient with a history of arterial hypertension on dual anti-hypertensive therapy with amlodipine and valsartan, dyslipidemia on rosuvastatin, and a cardiac arrhythmia that justified the introduction of anticoagulant treatment with rivaroxaban and class 2 antiarrhythmic treatment with sotalol. The patient was also allergic to aspirin. During the biennial breast examination performed on November 2021, the patient presented a suspicious abnormality of a non-fluid opacity with lobulated contours in the left breast classified as ACR 4. A breast micro biopsy was performed on November 2021 in the upper left quadrant and revealed a grade III NST metaplastic carcinoma with no associated carcinoma in situ, no vascular embolism and no tumor necrosis. The expression of progesterone and estrogen receptors was negative as well as the absence of HER 2 overexpression (0+) thus classifying the tumor according to the Triple Negative molecular phenotype. The CK5/6 and EGFR markers were positive pointing to a triple negative basal-like carcinoma and the tumor proliferation index (KI 67) was evaluated at 25%. The patient underwent a left partial mastectomy on January 2022 at the upper-external quadrant with sentinel node procedure confirming a 32mm fibromatosis-like metaplastic carcinoma (according to WHO 2012 classification) with on the immunochemistry AE1/AE3+, Ecadherine+ and P63+ that excluded a differential diagnosis of benign form of fibromatosis, grade II (Architecture 3, Atypia 2, mitosis 1), with absence of carcinoma in situ, absence of vascular embolus and absence of tumor necrosis. The amount of lymphocyte infiltrating the tumor stroma was less than 10% (Grade A). The resection limits were healthy with a minimum margin of 1 mm deep, 3 mm inferior and 7 mm superior.

Confirmation of triple-negative status was obtained on the operative specimen with a KI 67 of 15%. A single sentinel node was analyzed, finding no macro or micro metastasis. The lesion was finally classified as pT2N0MXsR0 according to the 2017 UICC classification, thus corresponding to a low-grade triple-negative fibromatosis-like metaplastic carcinoma with a favourable prognosis not warranting an initial distant extension workup. The TEP scan showed only moderate fixation with SUV = 6,4 in the left upper external quadrant with 3cm meseread lesion without adenopathy or metastasis identified. In the context of a triple-negative tumor with a rare and specific histology with a good prognosis, the patient's case was discussed during successive multidisciplinary consultation meetings before an indication for adjuvant radiotherapy of 50 gray given the low level of evidence of surgery alone as local treatment and the risk of local recurrence mainly. Accordingly a normo-fractional scheme of 25 sessions of 2 gray with an integrated boost at the level of the lumpectomy zone by 16 gray in 8 fractions of 2 gray, given the histological form of the tumor with a good prognosis. During the radiotherapy, the patient presented only grade 1 dermatitis with no other adverse event. At 6 month after the end of the radiotherapy, mammography and echography were normal with bilateral ACR 2 classification justifying only an another clinical control by the physician every 6 month and an another echomamography each year. The analysis of the literature making it possible to avoid the use of chemotherapy in this form of relatively good prognosis with a limit of healthy exegesis and in the absence of adenopathy or distant metastasis.

Discussion

Metaplastic fibromatosis-like carcinomas are composed of more than 95% fibroblast-like spindle cells and myofibroblast-like stellate cells. Squamous or glandular contingents should not exceed 5% and high-grade cytonuclear atypia is never demonstrated to distinguish them from high-grade metaplastic carcinomas [5]. The use of immunohistochemistry is essential to distinguish the different forms of metaplastic carcinoma, but also to eliminate strictly benign forms such as simple fibrosis, phyllodes tumors, solitary fibrous tumors, pseudoangiomatous stromal hyperplasia, or nodular fasciitis [10] or other malignant forms such as melanoma, dermatofibrosarcoma or myoepithelial carcinoma [11]. Many immunohistochemical markers are used to characterize carcinomas and fibromatous. Low-grade

fibromatosis-like tumors are most commonly AE1/AE3, CAM5.2, P63, CK, vimentin, S100, and α -SMA positive, whereas ER, PgR, HER2, ALK, beta-catenin, and CD34 are negative [11-14]. Many other immunohistochemical markers can be used to make the differential diagnosis with benign tumors given the complexity of the diagnosis but it's possible to make the diagnosis thanks to the combinaison of morphotype on histology, a few number of immunochemistry markers and the proliferation index [10] (Figure 1).

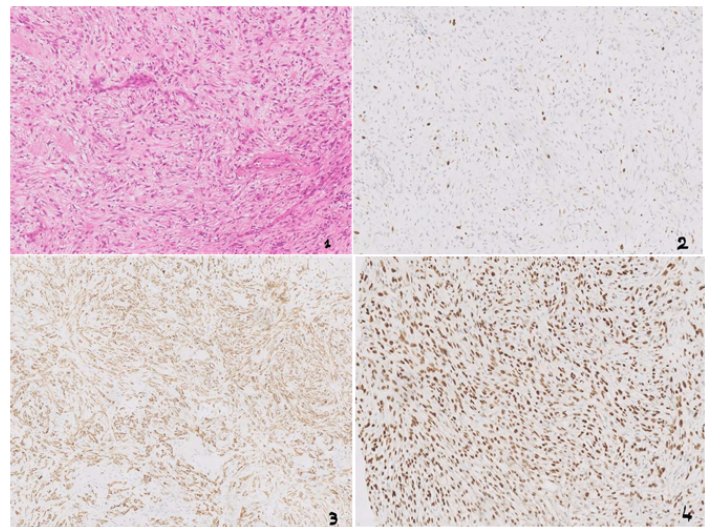


Figure 1: 1. Hematin Eosin Saffron (HES) stain: proliferation of spindle cells with unclear cytoplasmic boundaries, medium density, slightly to moderately atypical nuclei and rarely mitotic. 2. Weak marking (a minority of elements) with anti-Ki67 antibody (marker of cells engaged in the cycle, giving an idea of the little active character of the proliferation). 3. Membrane (and to a lesser degree cytoplasmic) marking of proliferation with the anti-cytokeratin antibody AE1/AE3 (testifying to the epithelial - carcinomatous - nature of the lesion). 4. Nuclear labeling of proliferation with anti-P63 antibody.

Clinically, fibromatosis-like metaplastic carcinomas are most often found in women between 40 and 85 years of age with an average age of about 65 years. The size of the tumor can vary from one to several centimetres and presents as a mass that can be palpable and growing rapidly. The lesion is most often unilateral with no specific location found within the breast. Lymph node metastases are extremely rare justifying the use of the sentinel node technique before any courage and distant metastases are also uncommon and are

mainly located in the lungs and bones [8,10,12,15]. The risk of recurrence is mainly local and depends on the resection margin [8,12]. The appearance of the lesion on mammography resembles that of a benign lesion, most often round, ovoid, or irregular with well-circumscribed or lobular contours and generally without micro calcifications. On ultrasound, the lesion is most often hypoechoic and heterogeneous, whereas on MRI, there is T2 hyper signal and Iso or hypo signal T2. These imaging specificities can distinguish invasive intraductal and lobular carcinomas from fibromatosis-like metaplastic carcinomas but are insufficient to differentiate between the different subtypes of metaplastic carcinomas, which require a thorough immunohistochemical analysis [15-19] (Figure 2).

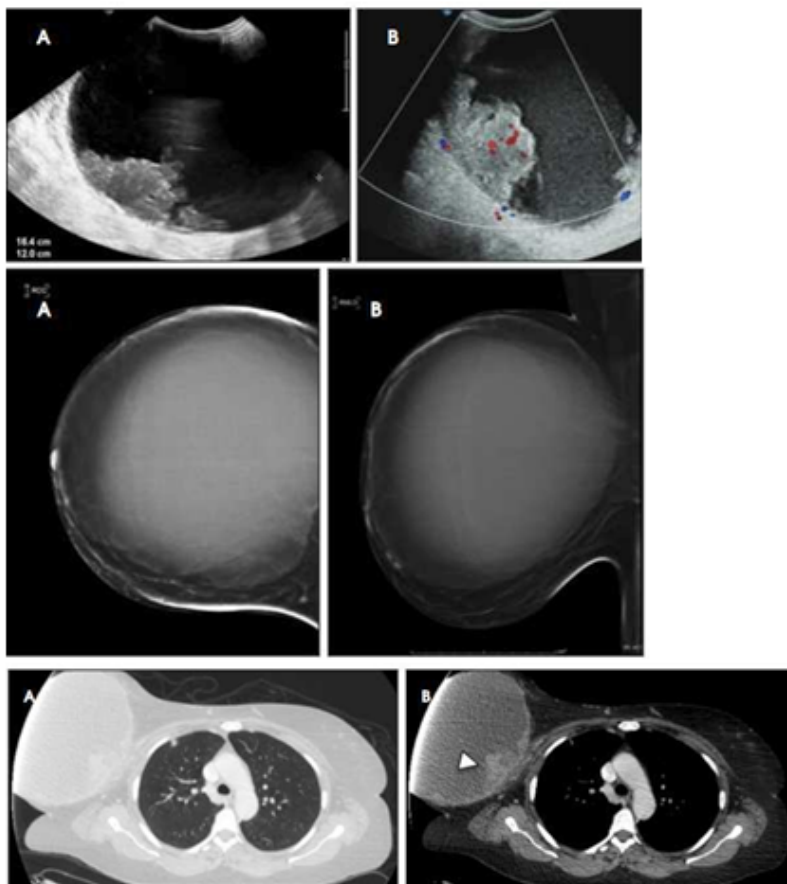


Figure 2: Ultra sonographic, radiographic, and CT appearance of a fibromatosis like metaplastic carcinoma from the literature in a 48-year-old woman with an 18.3 cm tumor of the right breast [15].

According to all the studies concerning this favourable histological subtype, the NCCN (National Comprehensive Cancer Network) in its updated recommendations of 2022 recommends the use of a single local treatment in the absence of adenopathy or distant metastases. A R0 resection with wide margins is the basic principle to limit the risk of local recurrence by associating sentinel lymph node analysis. The use of radiotherapy in the area of excision should be discussed, particularly for large tumors [20]. No clear evidence of the positive impact of immunotherapy was found in the literature. The use of systemic treatment should be considered in cases of N+ or M+ status. However, because of the small number of cases in the literature, the level of recommendation remains low for the moment (Table 1).

Authors (Names, years)	Number of cases (n)	Médian age (years or interval)	Average tumor size (mm or interval)	Number of lymph nodes involved (n)	Number of metastasis(n)	Initial treatment	Adjuvant treatment	Number of recurrence (n)	Interval without relapse (month)	Follow up (Month)
Gobbi et al. 1999 [8]	30	63.4	27	0	0	TM/TME: 12 T+ Curage: 5 MT + curage : 5 NC : 8	RT : 3 HT : 1 CT : 1	8	5 à 72	6 à 72
Sneige et al. 2001 [12]	24	66.8	28	0	2	TM/TME: 7 MT : 13 NC : 4	RT : 5 HT : 0 CT : 1	4 (2 LR et 2 MR)	5 à 32	5 à 70
Kinkor et al. 2002	4	54-72	20-35	NC	2	NC	NC	NC	NC	NC
Schafernak et al. 2006 [11]	1	59	30	NC	NC	NC	NC	NC	NC	NC
Rekhi et al. 2007 [21]	1	77	20	0	0	TM/TME	RT	0	NC	16
Podetta et al. 2009 [22]	2	78.5	*57 *30	0	0	*TM/TME + Curage *MT + Curage	*RT *0	0	NC	*27 *21
Nonnis et al. 2012 [20]	1	73	20	NC	NC	TM X2 puis TME	0	1	9 & 11	62 (Après deux récidives)
Pagnon et al. 2017 [23]	1	66	NC	NC	NC	TM/TME	NC	NC	NC	NC
Victoor et al. 2020 [10]	1	65	19	0	0	TM/TME	0	0	NC	24
Pham et al. 2022 [24]	1	52	35	0	0	MT	0	0	NC	3

0: None, CT: Chemotherapy, HT: Hormone therapy, NC: Not communicated, LR: Local recurrence, MR: Metastatic recurrence, MT : Mastectomy, RT : Radiotherapy, TM : Lumpectomy, TME : Extended lumpectomy

Table 1: Cases and management of fibromatosis-like metaplastic tumors from the literature.

Conclusion

Metaplastic fibromatosis-like carcinoma is a subtype of triple-negative metaplastic breast cancer with a good prognosis. It is characterized by its risk of local recurrence but with a low risk of lymph node dissemination or distant dissemination, justifying, according to current recommendations, a simple surgical removal with wide margins. For the majority of triple negative metaplastic breast carcinoma there is no indication of radiotherapy or chemotherapy as adjuvant treatment. Radiotherapy should be discussed usually for very large tumor but we have to keep in mind that the growing of triple negative metaplastic breast carcinoma is often quick. Chemotherapy is indicated when there are lymph node involved or when there is a metastatic disease. Recently pembrolizumab have obtain an authorisation for the treatment of triple negative breast cancer in neoadjuvant than adjuvant for localised breast cancer and in metastatic condition when the CPS score is above 10. For now, the place of pembrolizumab and more widely immunotherapy as not been evaluated for favourable prognosis triple negative breast cancer due to the low prevalence of locally advance and metastatic disease in these specific subtype.

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