Int J Clin Exp Pathol 2021;14(3):355-362
www.ijcep.com /ISSN:1936-2625/IJCEP0117440

Original Article

Metaplastic breast carcinoma: a retrospective study of 26 cases

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Received July 2, 2020; Accepted December 31, 2020; Epub March 1, 2021; Published March 15, 2021

Abstract: Metaplastic breast carcinoma is a rare invasive breast cancer. Metaplastic breast carcinoma is mainly characterized by an epithelial or mesenchymal cell population mixed with adenocarcinoma. We collected 26 cases of metaplastic breast carcinoma in the First Affiliated Hospital of Bengbu Medical College from 2008 to 2014. Tumor size, tumor grade, vascular invasion, ER/PR status, histologic classification, and HER2/neu status were assessed for all cases and the literature was reviewed. Clinicopathologic characteristics of patients diagnosed with metaplastic breast carcinomas and its key points of differential diagnosis were discussed. All patients were female, with the median age of 50 years. The mean tumor size was 3.2 cm. 4 subtypes of metaplastic breast carcinomas were documented. Fibromatosis-like metaplastic carcinomas are typically characterized by wavy, intertwined, gentle spindle cells. When the tumor components are almost squamous cell carcinoma components and the primary squamous cell carcinoma of other organs and tissues are excluded, we can diagnose breast squamous cell carcinoma. In spindle cell carcinoma, atypical spindle cells are arranged in many ways and are usually accompanied by inflammatory cell infiltrate. Cancer with interstitial differentiation has mixed malignant epithelial and mesenchymal differentiation, and the mesenchymal components are diverse. Most tumors are triple negative. At present, surgical resection combined with chemotherapy or radiation therapy is the most effective and acceptable method for treating metaplastic breast carcinoma.

Keywords: Metaplastic breast carcinoma, pathology, immunohistochemistry

Introduction

Metaplastic breast carcinomas (MBC) is a rare invasive breast cancer [1]. The etiology and pathogenesis of MBC are still unclear [2]. Metaplastic breast carcinomas were first discovered in 1973 [3], accounting for 0.2% to 1% of all breast cancer [4]. Metaplastic breast carcinoma is mainly characterized by an epithelial or mesenchymal cell population mixed with adenocarcinoma. In 2000, the World Health Organization (WHO) recognized metaplastic breast carcinoma as a unique pathologic entity [5]. There is still controversy about the origin of MBC. Some scholars believe that MBC originates from a single cell line, and some scholars [6] believe that it originates from myoepithelial cells. The evidence for that is that most MBC tissues have high expression of P63 [7], especially in epithelial cell components and spindle cells [8]. According to the WHO (2012) Breast Tumor Histological Classification Standard, metaplastic breast carcinomas are divided into: low-grade adenosquamous carcinoma, fibromatosis-like metaplastic carcinoma, squamous cell carcinoma, spindle cell carcinoma, carcinoma associated with mesenchymal differentiation (Chondroid differentiation, osseous differentiation, and other mesenchymal differentiation), mixed metaplastic carcinoma, and myoepithelial carcinoma [9].

In this paper, the clinicopathologic characteristics of 26 patients with MBC were studied, and the relevant literature was reviewed to discuss the clinicopathologic features, differential diagnosis, treatment and prognosis of MBC.

Materials and methods

Case selection

26 cases of metaplastic breast carcinomas were retrieved from the First Affiliated Hospital of Bengbu Medical College from 2008 to 2014. 18 patients were admitted to the hospital and 8 were consultation cases. All patients were female, with a mean age of 52 years (median 50 years; range 31-76 years). All patients were followed from the date of diagnosis to the most recent follow-up or death. The follow-up rate was 100%.

Histopathologic analysis

Tumor size, tumor grade, vascular incasion, ER/PR status, histologic classification, HER2/neu status were assessed for all cases. All specimens were fixed with 4% formaldehyde, embedded in paraffin, and stained with H&E, and were re-read by two experienced pathologists.

Immunohistochemistry (IHC)

IHC was performed by streptavidin-peroxidase linkage method (SP method). All tissues were fixed in 4% buffered formalin and paraffin-embedded. Tissue sections were cut at 2-5 μm thickness for immunohistochemical staining. Sections were dewaxed and underwent antigen retrieval process in citrate buffer for 15 min. These pretreated slides were incubated at 4°C overnight with antibody for cytokeratin (AE1/AE3), CKH (34βE12), p53, p63, SMA, ER, PR, HER-2, Vimentin, Ki-67. Antibodies and related reagents were purchased from Fuzhou Maixin Biotechnology Development Co., Ltd.

Evaluation of immunostaining

The positive expression of antibodies was brown granules. CK (AE1/AE3), CKH (34βE12), SMA and Vimentin were localized in the cytoplasm. p53, p63, ER, PR and Ki-67 were localized in the cell nucleus. HER-2 was localized in the cell membrane. The results of immunohistochemical staining were determined by two senior pathologists through independent double-blind method. Each section was observed under high-power microscope (400×) for at least 10 non-repetitive visual fields.

Results

Clinical features

The clinical features of the patients are presented in **Table 1**. 20 cases (76.9%) showed painless or dull breast masses before diagnosis. 4 MBC subtypes were documented, including fibromatosis-like metaplastic carcinoma 5 cases, squamous cell carcinoma 10 cases, spindle cell carcinoma 5 cases, and carcinoma associated with mesenchymal differentiation 6 cases (chondroid differentiation 1 case, osseous differentiation 1 case, and other mesenchymal differentiation 4 cases). 20 cases (76.9%) were pre-menopausal. 18 cases lesions were in the left breast and 8 were in the right breast. The mean tumor size was 3.2 cm (median 3.1 cm; range 1.5-4.2 cm). Lymph node metastasis (LNM) occurred in 7 cases (26.9%). Up to the cut-off date, 17 patients were still alive. 10 patients experienced locoregional recurrence, or distant metastasis, in which 9 patients died due to disease progression. Among dead patients, carcinoma with mesenchymal differentiation was in 4 cases (15.4%), squamous cell carcinoma 3 cases (11.5%), and spindle cell carcinoma 2 cases (7.7%).

Iconography

The molybdenum targets in the mammary glands were mostly dense images with clear borders and irregular edges, which are lobulated (**Figure 1A** and **1C**) or burr-shaped (**Figure 1B** and **1C**), accompanied by different types of calcification (**Figure 1C** and **1D**). Ultrasound examination of the breast was mostly irregular solid mass or cystic solid mass. The internal echo of the mass was uneven and the boundary was unclear. Most of the cystic solid masses were breast squamous cell carcinoma.

Pathology

Fibromatosis-like metaplastic carcinoma was characterized by wavy, bundle-shaped staggered spindle cells. Collagen components are produced between the cells, chromatin is delicate, and the nucleus was slightly atypical (**Figure 2A**). In squamous cell carcinoma of the breast, tumor cells were distributed in nests with keratinized beads forming inside. The

Table 1. Clinicopathologic features of patients with MBC

Clinicopathologic feature	Number (%)
Age, years	
<50	12 (46.2%)
≥50	14 (53.8%)
Tumor size, cm	
<2	2 (7.7%)
2-4	20 (76.9%)
>4	4 (15.4%)
Tumor location	
Left breast	18 (69.2%)
Right breast	8 (30.8%)
Menopause	
Pre-menopause	20 (76.9%)
Post-menopause	6 (23.1%)
Nodal status	
Negative	23 (88.5%)
Positive	3 (11.5%)
Histologic subtype	
Low-grade adenosquamous carcinoma	0 (0.0%)
Fibromatosis-like metaplastic carcinoma	5 (19.2%)
Squamous cell carcinoma	10 (38.5%)
Spindle cell carcinoma	5 (19.2%)
Carcinoma with mesenchymal differentiation	6 (23.1%)
Myoepithelial carcinoma	0 (0.0%)
ER status	
Negative	24 (92.3%)
Positive	2 (7.7%)
PR status	
Negative	25 (96.2%)
Positive	1 (3.8%)
HER-2 status	
Negative	22 (84.6%)
Positive	4 (15.4%)
Cytokeratin status	
Negative	0 (0.0%)
Positive	26 (100%)
CKH status	
Negative	17 (65.4%)
Positive	9 (34.6%)
Vimentin status	
Negative	6 (23.1%)
Positive	20 (76.9%)
Smooth muscle actin status	
Negative	8 (30.8%)
Positive	18 (69.2%)
P53 status	
Negative	6 (23.1%)
Positive	20 (76.9%)

nucleus is large and deeply stained, and a nucleolus can be seen in some tumor cells (**Figure 2B** and **2C**). In cases with spindle cell carcinoma, tumor cells are spindle-shaped, and disorderly arranged and distributed, with marked atypia (**Figure 2D**). The spindle-shaped cells were arranged in a storiform pattern (**Figure 2E**). Tumorous bone-like tissue was found among heterotypic tumor cells in the cancer with interstitial differentiation (**Figure 2F**).

Immunohistochemistry

Estrogen receptor (ER) was negative in 24 (92.3%) patients and progesterone receptor (PR) was negative in 25 (96.2%) patients. Epidermal growth factor receptor HER-2 was negative in 22 (84.6%) patients. Most tumors were triple negative. Broad-spectrum CK was positive in all cases (100.0%) (**Figure 3A**), and nuclear positivity rate of P63 was 84.6% (**Figure 3C**). Vimentin was positive in 20 cases (76.9%) (**Figure 3B**), and 34βE12 was positively expressed in fibromatosis-like metaplastic carcinoma (100%).

Discussion

Metaplastic breast carcinoma is an uncommon histologic variant of breast cancer, that is a mixture of two or more homologous or heterologous components. Due to the lack of typical breast imaging patterns, and because the difference between MBC lesions and a wide range of uncommon benign and malignant entities is difficult to discern, the diagnosis of MBC is very difficult. At present, the diagnosis of metaplastic breast carcinoma is mainly based on postoperative pathology and immunohistochemical examination. If histological examination reveals obvious spindle cells, squamous cells, and mesenchymal metaplasia in adenocarcinoma, combined with immunohistologic examinations such as cytokeratin, 34βE12, and Ki-67 proteins, the diagnosis of MBC can be confirmed. We analyzed the pathology, immunohistochemistry, and clinical characteristics of 26 cases of MBC and found 5 cases of fibromatous metaplastic carcinoma, 10 cases of squamous cell carcinoma, 5 cases of spindle cell carcinoma and 6

p63 status	
Negative	4 (15.4%)
Positive	22 (84.6%)
Ki-67	
<15%	6 (23.1%)
15-30%	4 (15.4%)
>30%	16 (61.5%)

cases of interstitial differentiated carcinoma in metaplastic breast carcinomas. Fibromatosis-like metaplastic carcinoma tumors have unclear boundaries and are typically characterized by wavy, bundle-shaped staggered spindle cells. The cell morphology of fibromatosis-like metaplastic carcinoma tumors is bland and may form a cell nest structure. Interstitial fibrous tissue sometimes around blood vessels,can be formed by varying degrees of proliferation and collagen [10]. In highly differentiated squamous cell carcinoma, tumor components infiltrate into the surrounding space, causing a significant gap response, and keratinized beads are visible under a microscope. When the tumor components are almost squamous cell carcinoma components and primary squamous cell carcinomas of other organs and tissues are excluded, we can diagnose breast squamous cell carcinoma. In spindle cell carcinoma, atypical spindle cells are arranged in a variety of ways, and are usually accompanied by inflammatory cell infiltrate or mixed with non-specific invasive or squamous cell carcinoma. Ductal carcinoma in situ sometimes can be seen in spindle cell carcinoma [11]. Cancer with interstitial differentiation of breast usually consists of a mixture of mesenchymal components and cancer. The mesenchymal components mainly include cartilage, bone, striated muscle, or glia. When the differentiation is benign, only mild atypia is observed. When the differentiation is malignant, the atypia is significant, and it is usually sarcomatous degeneration. The ductal area may be a duct formation, solid cancer nest, or squamous differentiation. Among them, ossification is very rare, accounting for only 0.2% of all kinds of breast cancer [12].

The imaging features of metaplastic breast cancer are controversial. Some studies suggest that its ultrasound mainly manifests as large-sized irregular-shaped clumps, and the inside is mostly an uneven cystic echo, and small lobes are often seen at the edges. There is mostly horizontal growth, accompanied by bone or cartilage metaplasia with calcification. Color Doppler often manifests as a blood-rich mass. Another school of the research suggests that most metaplastic breast cancers are characterized by benign tumors, and common malignant features such as irregular morphology, glitches, internal calcification and posterior acoustic shadows are not common [13]. In this study, tumors were usually low echogenic. Regular solid mass or cystic solid mass, occasionally with leaflets, uneven internal echo, unclear boundary, glitches and crab-like changes may be seen at the boundary, and cystic or cystic solid masses are mostly found in breast Squamous cell carcinoma. In this study, MBC molybdenum targets are mostly dense images with clear boundaries and irregular edges, which are lobulated or burr-shaped, and are accompanied by different types of calcification. Although the above imaging features are not specific, they are still useful for the clinical diagnosis of MBC.

Metaplastic breast carcinoma was more likely to occur in pre-menopausal women than post-menopausal women in our study, which is not consistent with other findings. Pezzi et al. believed that MBC was more likely to occur in postmenopausal women. The inconsistent results may be due to the small samples. Confirmation of tumor epithelial components is very important for the diagnosis of metaplastic carcinoma. In addition to morphology, high molecular weight cytokeratin and broad-spectrum keratin immunohistochemical staining are often used to assist diagnosis. Commonly used markers are CK5/6, CK14, CK, 34βE12 and CK (AE1/AE3). p63 belongs to the p53 family and is an important marker. It participates in cell differentiation and is expressed in myoepithelial cells around normal breast ducts. In our current research, broad-spectrum CK and p63 expression were found in most MBC cases, which helps to distinguish MBC from fibromatosis. Recently, some reports have shown that p63 and other myoepithelial markers were positive in both myoepithelial carcinoma subtypes [14] and other types of mammary carcinomas [15], which was confirmed by our study. The positive expression of 34βE12 contributes to

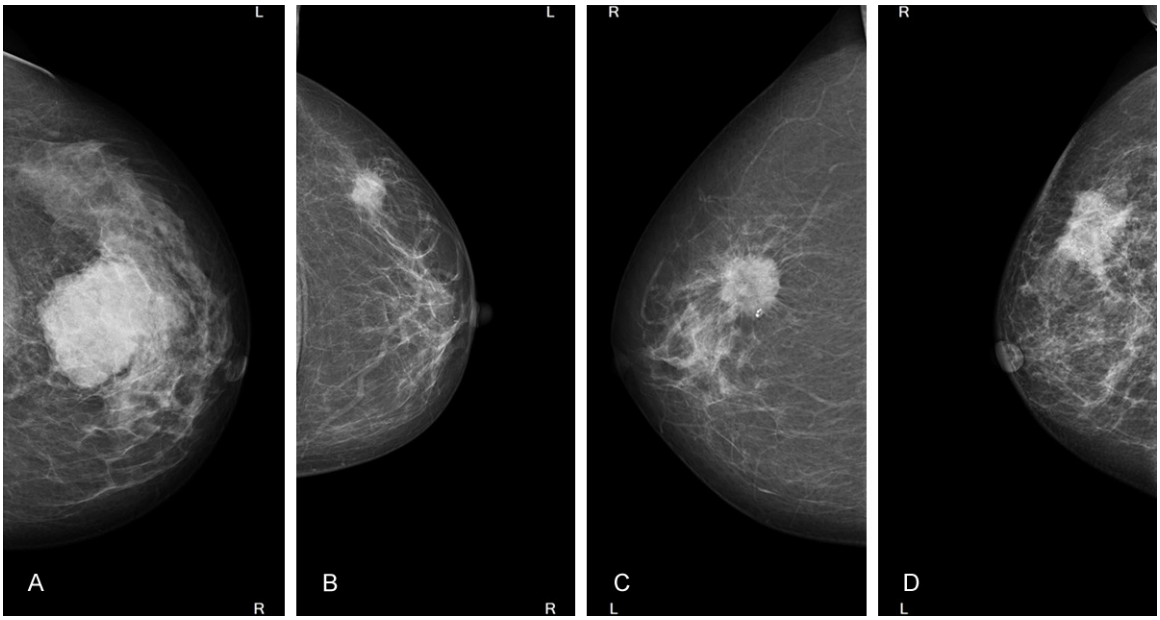

Figure 1. Molybdenum target results of metaplastic breast cancer. A. Molybdenum target displays the mass is located in the outer posterior quadrant of the left breast, with irregular shape and lobulated shape. B. Molybdenum target displays the mass is located in the outer upper quadrant of the left breast, with irregular shape and burr shape, and tortuous blood vessels can be seen around. C. Molybdenum target displays the mass is located in the right upper quadrant of the breast, irregular shape, lobulated, burr-like, with rough and uneven calcification. D. Molybdenum target displays the mass is located in the right upper quadrant of the breast, and irregular in shape, with multiple small line-like and branch-like calcifications.

fibromatosis-like metaplastic carcinoma. Negative expression of estrogen receptor ER and progesterone receptor PR suggest that endocrine therapy may be ineffective, and surgical resection is the main method of treatment.

Differential diagnosis

Fibromatosis

Fibromatosis is rare in breast diseases. Most of them occur in isolation, and often appear as painless hard tissues in the clinic. Without epithelial cell clusters and squamous differentiation, fibroblasts and myofibroblasts have a fascicular or storiform arrangement, and it is difficult to find mitosis. The immunohistochemical characteristics of fibromatosis are: vimentin-positive, SMA is focally positive, β-catenin positive expression is higher than 80%, and high molecular weight CK and p63 are negative [8, 16].

Nodular fasciitis

Nodular fasciitis is a benign lesion that occurs in the deep fascia. It often occurs in the limbs and occasionally occurs in the deep fascia of the breast [17]. The lump is mostly nodular, has no capsule, and may subside spontaneously. It has a reddish or brown section. It is visible in jelly or mucus-like areas. The nodules are mostly connected with superficial fascia or deep fascia. Microscopically, spindle cells can be arranged in a striate, spiral or nodular shape. The surrounding tumors are characterized by a crab-like infiltration of surrounding tissues, and easily visible mitosis [16]. The immunohistochemical characteristics of nodular fasciitis are: vimentin and SMA are positive and they generally do not express epithelial markers.

Malignant lobular tumors

Malignant lobular tumors are characterized by epithelial and mesenchymal hyperplasia, and the epithelial components are mostly benign. The two components of a lobular tumor are usually independent of each other, and the mesenchymal component usually infiltrates into the duct [18]. Epithelial markers are not expressed in the stroma of lobular tumors, but are positively expressed in the stroma of metaplastic tumors.

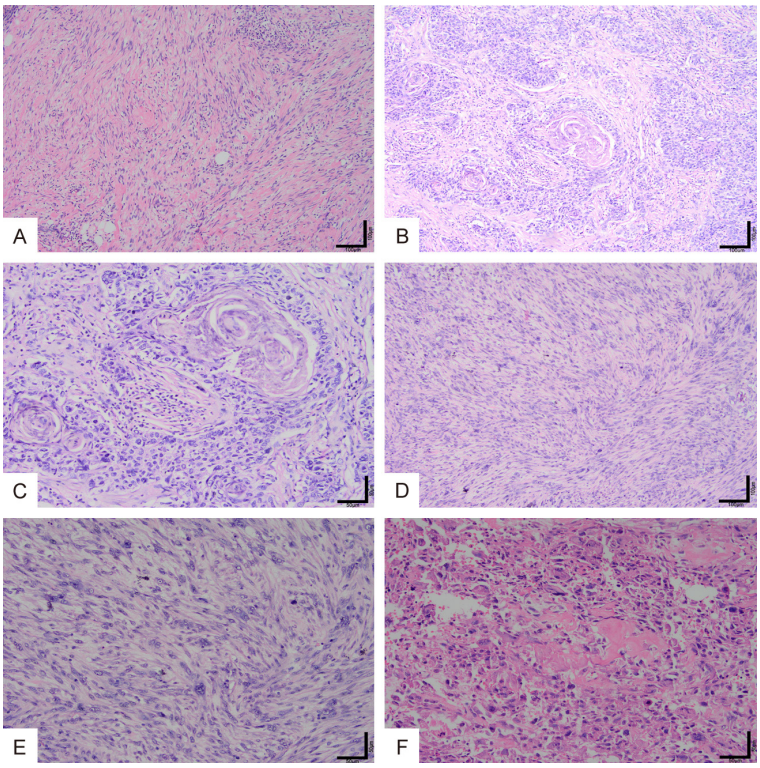

Figure 2. Microscopic manifestations of various metaplastic breast cancers. A. Fibromatosis-like metaplastic carcinoma (magnification, ×100). B. Squamous cell carcinoma (magnification, ×100). C. Squamous cell carcinoma (magnification, ×200). D. Spindle cell carcinoma (magnification, ×100). E. Spindle cell carcinoma (magnification, ×200). F. Cancer with osseous differentiation (magnification, ×200).

Carcinosarcoma

This is a type of tumor that has both malignant epithelial components and mesenchymal components. The mesenchymal component of metaplastic breast carcinomas originates from epithelial formation, resulting in an unclear boundary between the two components and possible migration. The margin of carcinosarcoma is clear, and epithelial and interstitial components do not transform into each other.

Pleomorphic adenoma

Breast pleomorphic adenoma is a rare breast disease formed by mesenchymal cells and epithelial cells. The cells of pleomorphic adenoma are relatively bland in morphology and small in shape. Pleomorphic adenoma has no infiltrating margins and the epithelial components are benign lesions [1]. In addition, the presence of keratin in pleomorphic adenoma is visible under the microscope. In terms of atypia, compared to pleomorphic adenoma, the cell atypia of MBC is more obvious, and a large amount of necrosis, apoptosis, and pathologic mitotic figures can be seen.

Treatment and prognosis

At present, there is no optimal treatment plan for metaplastic breast cancer. Mastectomy and axillary lymph node dissection are basic treatments for metaplastic breast carcinomas. In some cases, breast-conserving surgery is used [19]. Even if it is treated in accordance with the treatment of invasive ductal carcinoma, there is still widespread controversy because of drug resistance and poor efficacy [20]. Traditional adjuvant chemotherapy does not have much effect on breast metaplastic carcinoma. Although neoadjuvant chemotherapy can reduce the mass of some patients, there is still a great risk of treatment, and it may even lead to the further deterioration of the disease of breast metaplastic carcinoma. According to relevant foreign data, for patients with metastatic breast cancer who have a lumpectomy or mastectomy, especially patients with a tumor diameter of not less than 5 cm, adjuvant radiotherapy can reduce the recurrence rate of the focus and can also effectively improve the overall survival rate of the patient and disease-free survival rate [21]. With the deepening of research on metaplastic breast carcinoma, new molecular targeted therapies have also made great progress, including PARP inhibitors, angiogenesis inhibitors, protein kinase inhibitors and mTOR inhibitors [22].

From the number of cases with dead patients, it can be seen that the prognosis of carcinoma with mesenchymal differentiation is poor, and the prognosis of fibromatosis-like metaplastic carcinoma is better. Most researchers believe that the clinical prognosis of metaplastic breast cancer is not as good as that of non-specific invasive ductal carcinoma, it often recurs early, and the disease-free survival rate and overall

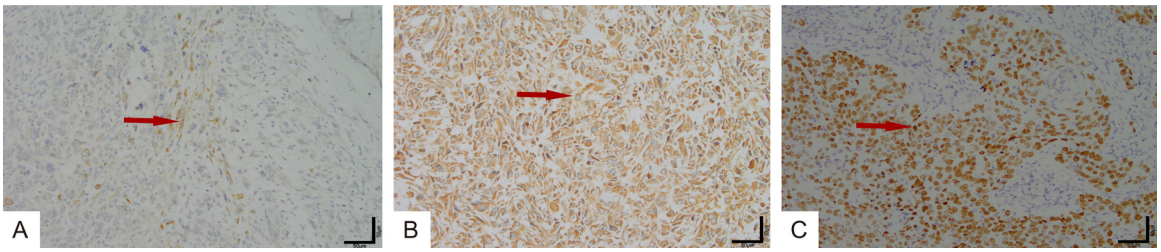

Figure 3. Immunohistochemical markers of metaplastic breast cancer. A. Immunohistochemical staining shows that broad-spectrum cytokeratin was positive in the neoplastic cells (magnification, ×200). B. Immunohistochemical staining shows that vimentin was positive in the neoplastic cells (magnification, ×200). C. Immunohistochemical staining shows that p63 was positive in the neoplastic cells (magnification, ×200). The brown-yellow staining indicated by the arrow is positive.

survival rate are lower than those of invasive ductal carcinoma [23]. However, there are a few data showing that the 5-year disease-free survival rate and 5-year overall survival rate are 76% and 80%, respectively, and the prognosis was good [24, 25]. There may be many reasons for this difference, such as insufficient sample size. This issue is still open for discussion.

Conclusion

Metaplastic breast carcinomas are a rare invasive breast cancer, more common in non-menopausal women. Most metaplastic breast cancers are triple negative breast cancers. Their clinical characteristics are atypical, making the diagnosis more challenging. Most of the molybdenum targets are dense images with clear borders and irregular edges, which are lobulated or burr-shaped, and are accompanied by different types of calcifications. Ultrasound usually shows irregular solid or cystic masses, of which squamous cell carcinoma is mostly a cystic mass. Different types of MBC have different pathologic characteristics. With the development of pathology and immunohistochemistry, the diagnosis rate of MBC has improved. In this study, the prognosis of fibromatosis-like metaplastic carcinoma was good, and the prognosis of carcinoma with mesenchymal differentiation was poor. Currently, surgical resection combined with chemotherapy or radiation therapy is the most effective and acceptable method for treating metaplastic breast carcinomas.

Acknowledgements

This work was supported by the Nature Science Key Program of College and University of Anhui Province (No. KJ2018A0213) and Nature Science Key Program of College and University of Anhui Province (No. KJ2019A0386) the Science and Technology Funds of Bengbu Medical College (No. BYKY2019102ZD). We would like to thank the patient for agreeing to our report and for providing a detailed medical history. This case has been reviewed by the Ethics Committee of the First Affiliated Hospital of Bengbu Medical College. Approval No (2020-KY217).

Disclosure of conflict of interest

None.

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