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Metaplastic breast carcinoma: an overview of the radio-pathologic features in retrospective cohort tertiary hospital

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Abstract

Background: Metaplastic breast carcinoma (MBC) is a rare type of breast carcinoma. It accounts for 0.2–1% of all invasive breast carcinoma. The aim of this study is to investigate the radiological features of this tumor and correlate them with the pathological findings.

Results: Of the 22 patients with pathology-proven metaplastic cancers, 18 patients (81.82%) presented with a palpable mass. The majority of the mammogram findings were masses with irregular shapes ($n=12$, 63.16%) and indistinct margins ($n=11$, 57.89%). Similarly, the majority of the ultrasound studies showed masses with irregular shapes ($n=16$, 72.73%) and indistinct margins ($n=8$, 36.36%). Most of the echopatterns were complex or with heterogeneous textures, each presented in eight cases (36.36%). More than half of the cases had a posterior acoustic enhancement ($n=12$, 54.55%). Most of the cases tested negative for estrogen receptors, progesterone receptors and HER2 protein, and they were high-grade tumors with a high proliferative index (Ki-67%) of > 15%.

Conclusion: MBC is a rare and distinct aggressive breast cancer with no definite characteristic imaging compared to other breast cancer. It shows a mass with irregular shape and indistinct margins in both mammogram and ultrasound. Additionally, it reveals posterior acoustic enhancement and rarely contains microcalcifications. The correlation with the pathological findings is crucial for the diagnosis and subsequent appropriate treatment.

Keywords: Metaplastic breast carcinoma, Imaging, Pathology, Clinical, Prognosis

Background

Metaplastic breast cancer (MBC), a rare type of breast carcinoma, constitutes less than 5% of mammary carcinoma [1–5]. It includes a group of neoplasms characterized by the differentiation of the neoplastic epithelium into squamous cells and/or mesenchymal-looking elements [5–7]. MBC was first described by Huvos et al. in 1973, as a mammary carcinoma with mixed epithelial and sarcomatoid components [7]. Recently, it has been classified by the World Health Organization (WHO) as a special type of breast carcinoma, comprising a heterogeneous group of tumors including low-grade adenosquamous carcinoma, fibromatosis-like metaplastic carcinoma, squamous cell carcinoma, spindle cell carcinoma and metaplastic carcinoma with mesenchymal differentiation. It is noteworthy that a large proportion of MBCs display a mixture of different elements [8, 9].

MBC has an aggressive clinical presentation; therefore, differentiating it from other types of breast carcinoma is essential for proper management and prognosis [10]. It has been previously observed that MBC is clinically more aggressive than other types of breast carcinoma. It usually presents as a large, rapidly growing mass, usually not detected with a screening mammogram, and more likely to be managed with a mastectomy than conservative therapy [11]. The spread of the tumor is potentially hematological rather than

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the lymphatic system. It may present in later stages with distant metastases and primarily affect bone and lungs, despite the absence of nodal involvement [3, 12]. Tumors larger than 5.0 cm, with lymph node involvement, are highly correlate with a poor prognosis [11].

Although radiological studies are the initial line of diagnosis, MBC has no defined characteristic imaging features. This could be due to the variability in the pathological features, as described above, and the rarity of the disease. Some studies report that it has benign imaging manifestations causing a diagnosis dilemma and delayed management; however, other studies suggest that MBC may have an aggressive radiological appearance [3, 8, 13].

Although a core biopsy is essential to make a precise diagnosis, this can be achieved only in 40% of MBC cases, compared to 60% in ordinary breast cancers [14]. The reason may be related to the tumor heterogeneity and tumor necrosis [5, 6, 13]. For example, conventional invasive ductal carcinoma can overlap with MBC in the initial tissue sampling, if the metaplastic component is not present in the core biopsy. Metastatic and primary breast sarcoma can also mimic MBC containing a sarcomatous element, with the former requiring a different approach in management [15, 16].

In general, most MBCs are triple negative with a high-grade morphology and a high proliferative index (Ki-67%) [11, 13, 17, 18]. Although the loss of hormonal receptors is considered as an unfavorable biological pattern, MBC has a worse prognosis regardless of the hormonal status and is more aggressive than conventional triple negative infiltrating ductal carcinomas [11, 19–21].

Though some researches have been done on metaplastic carcinoma, there are very few studies describing the association between the imaging features and the pathological findings. Our aim is to enrich the literature about this rare tumor and evaluate its radio-pathological features in our population.

Methods

The study was approved by the institutional ethics review board. This was a retrospective cohort study of 22 cases with pathology-proven MBC, and therefore, the consents were not obligatory according to the institutional review board. The data were collected from the pathology database tertiary hospital in Riyadh, Saudi Arabia, from 2009 to 2019.

The clinical data and patients' demographic information, including age, gender, clinical presentation, risk factors, nationality, type of treatment as chemotherapy, radiotherapy and surgery, staging and living status, were collected from the hospital clinical information system.

Inclusion criteria

All the cases of pathologically proven MBC, regardless of gender, age, new or recurrent cases, were included. Any treated cases outside the hospital were excluded.

Tissue sampling and analysis

The pathological data, including the morphologic subtype, grade, hormonal receptor and HER-2 status, and proliferative index (using Ki-67 immunostain), were also collected. The morphologic subtypes were classified according to the WHO 2019 classification. Estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor-2 (HER2) immunostains were categorized as positive or negative, according to the American Society of Clinical Oncology/College of American Pathologists Guidelines. ER and PR were interpreted as positive when the staining was observed in $\geq 1.0\%$ of the tumor cells. The HER2 was considered positive when $> 10\%$ of the cells of the invasive carcinoma showed a complete intense, circumferential membrane staining. The proliferative index, using the percentage of the Ki-67 immunostain, was also evaluated. The pathological information after surgery was collected for the pathological TNM and morphologic subtype, if not included in the initial biopsy.

Imaging acquisition and analysis

The interpretation of the radiological data was performed by two radiologists with more than 4 years of experience in breast imaging. The mammogram, ultrasound and MRI were analyzed using the American College of Radiology Breast Imaging Reporting and Data System (ACR-BI-RADS), 5th edition (latest BI-RADS lexicon).

Mammogram examination

A mammogram examination was done for all cases, except one due to the patient's condition (unable to tolerate the exam). Patients below 30 were also included because of suspicious clinical findings, suspicious ultrasound findings or presence of risk factors. Craniocaudal (CC) and mediolateral oblique (MLO) views were evaluated. The mammogram examination analysis included the breast composition, mass shape, margin, density and location. Any mass with a lobular shape was considered as irregular, because of a limited description in the latest criteria. Suspicious microcalcifications were analyzed in terms of the morphology and distribution. Any additional findings, such as asymmetries, architectural distortion and skin changes, were noted.

Ultrasound examination

An ultrasound was done for all 22 cases. The images were reviewed from the PACS, and a bilateral complete ultrasound examination with a straight linear array probe (7–12 MHz frequency) was used. The images were analyzed in terms of the shape, margin, echogenicity orientation, posterior features, location and size of the mass. The size was classified according to the TNM staging, in which T1 is equal or < 2 cm, T2 is > 2–5 cm, and T3 is > 5 cm.

MRI technique

An MRI was done for only four cases, to evaluate the extent of the disease and to assess the other breast. It was reviewed using the same data system and using a 1.5 and 3 Tesla machine with a standard protocol for the hospital technique, including the DWI and ADC map. The masses were analyzed in terms of the shape, margins, pattern of enhancement, type of kinetic curve, with type I progressive, type II plateau and type III washout, as well as the signal intensity in T2WI. The kinetic curves were reviewed from the available images.

Statistical analysis

The data were analyzed using the statistical program SAS (version 9.4). The data are presented as frequency with a percentage for categorical variables. The Fisher's exact test was used to calculate the association between categorical variables. All statistical tests were considered significant at $P < 0.05$. The age of the patient and size of the masses are presented as a median.

Results

Presentation

All the cases with metaplastic breast carcinoma in the study cohort were female (22 cases), with median age of 48 years (ranging from 27 to 82 years). Only four cases (22.74%) had risk factors related to the family history, oral contraception or hormonal replacement therapy. Of the 22 patients, 18 cases (81.82%) presented with a palpable mass, one with a mass and nipple discharge, one came for screening and two presented with metastasis. Table 1 summarizes the clinical features.

Table 1 Clinical findings

Main presentation	Frequency (%)
Mass	18 (81.82)
Mass and nipple discharge	1 (4.55)
Metastasis	2 (9.09)
Screening	1 (4.55)
Mean age (year ± SD	(52.00 ± 15.37)

Mammography, ultrasound and MRI

A mammogram was done in all but one case (21 cases). Masses were the most frequent feature in 19/21 cases (95.24%) and two cases presented with asymmetrical findings. The most prevalent shape was irregular presented in 12/19 case (63.16%), followed by oval and a rounded shape in five and two cases (26.31% and 10.53%), respectively. The margins were mainly indistinct in 11/19 cases (57.89%), followed by circumscribed in six cases (31.58%). Architectural distortion was infrequent and only seen in four cases in the study, two of which showed squamous differentiation on the core biopsy and the other two exhibited mesenchymal differentiations. Microcalcifications were seen only in 3/21 cases (14.29%). No case showed calcification alone without a mass (Table 2).

An ultrasound was performed in all cases. All findings were masses with a median size of 5.4 cm (ranging from 0.8 to 20.4 cm). Most masses had an irregular shape (16 cases, 72.73%). Regarding the margins, most were indistinct (8 cases, 36.36%), followed by microlobulated (6 cases, 27.27%). The echopattern was, with equal frequency, complex and heterogeneous masses, both with 36.36%. 12/22 had posterior acoustic enhancement and no one had posterior acoustic shadowing and 45.45% had a desmoplastic reaction (Table 3).

Only four cases had a breast MRI, all had a mass, two had heterogeneous enhancement, one with rim enhancement and one with homogenous enhancement. The masses had an equal frequency of T2 intensity between hyperintense and heterogeneous. All the masses exhibited type III kinetic curve.

Table 2 Mammogram characteristics ($n = 21$)

Findings	Frequency (%)
Mass	19 (90.47)
Asymmetry	2 (9.5)
Mass shape	
Oval	5 (26.31)
Round	2 (10.53)
Irregular	12 (63.16)
Mass margin	
Circumscribed	6 (31.58)
Indistinct	11 (57.89)
Spiculated	2 (10.53)
Suspicious microcalcifications	
No	18 (85.71)
Yes	3 (14.29)

Table 3 Ultrasound features ($n=22$)

Findings	Frequency (%)
Shape	
Oval	5 (22.73)
Round	1 (4.55)
Irregular	16 (72.73)
Orientation	
Parallel	16 (72.73)
Vertical	6 (27.27)
Margins	
Circumscribed	3 (13.64)
Indistinct	8 (36.36)
Angular	3 (13.64)
Microlobulated	6 (27.27)
Spiculated	2 (9.09)
Echopattern	
Hypoechoic	6 (27.27)
Complex	8 (36.36)
Heterogenous	8 (36.36)
Tumor size	
Equal or < 2	2 (9.09)
> 2–5	8 (36.36)
> 5	12 (54.55)
Desmoplastic reaction	
No	12 (54.55)
Yes	10 (45.45)

Table 4 Pathological and surgical characteristics ($n=22$)

Findings	Frequency (%)
ER status	
Positive	1 (4.55)
Negative	21 (95.45)
PR status	
Positive	1 (4.55)
Negative	21 (95.45)
HER 2	
Positive	4 (18.18)
Negative	18 (81.82)
Tumor grade	
Grade 2	2 (9.09)
Grade 3	20 (90.91)
Ki 67	
< or equal 15%	1 (4.55)
> 15%	21 (95.45)
Histological subtype	
Squamous cell	10 (45.45)
Spindle cell	5 (22.73)
Metaplastic with mesenchymal differentiation	5 (22.73)
Mixed	2 (9.09)

ER estrogen receptor, *PR* progesterone receptor, *HER2* Human epidermal growth factor receptor-2

CT staging

A chest and abdominal CT scan were performed as a staging method; four patients had metastasis at the initial presentation (18.18%) mainly in the lung. Five patients developed metastasis during therapy (22.73%), four cases metastasized to the lung and two cases to the liver and bone.

Histopathology and management

A core needle biopsy was performed on all cases. The diagnosis of MBC was made on the initial biopsy in 16 cases (72.73%), and the metaplastic component was observed on the resection specimen in 6 cases (27.27%). All tumors, except one, had a high proliferative index of > 15%. The most common histopathological subtype was squamous cell carcinoma (10 cases, 45.45%) (Fig. 1d), followed by spindle cell carcinoma (Fig. 2c) and metaplastic carcinoma with mesenchymal differentiation (Fig. 3c) in 10 cases (22.73%). The majority of tumors were not associated with lympho-vascular invasion (19 cases, 90.48%). Most of the hormonal receptors who were negative with 21/22 had negative ER and PR while 18/22 had negative HER 2. With regard to the Ki67, it was ranging from 10 to 95% with a mean of 59.5. Nineteen cases (86.36%) were treated with chemotherapy, and 13 (59.09%) received radiotherapy. In addition, 16 patients underwent subsequent surgical resection, of which 13 had mastectomy (86.36%) and three lumpectomies (13.64%). Table 4 summarizes the histopathology findings.

Follow-up

Follow-up data were available for 19 patients, with a median of 19.5 months (3–72 months). In total, three patients died of disease (two were pregnant) and 16 are still alive (72.73%).

Discussion

MBC is a rare breast malignancy, constituting a small proportion (5%) of breast cancer [1–5]. It consists of pathologically heterogenous tumor formed of epithelial and/or mesenchymal elements [5–7]. Some studies reported that MBC occurs in older women (> 50 years), with a large tumor size; however, other studies report a younger age at presentation [3, 6, 13, 15]. In this study, about (45.45%) of the patients presenting with MBC were 50 years and older. The main presentation was a mass (81.82%), one tumor presented during screening and two

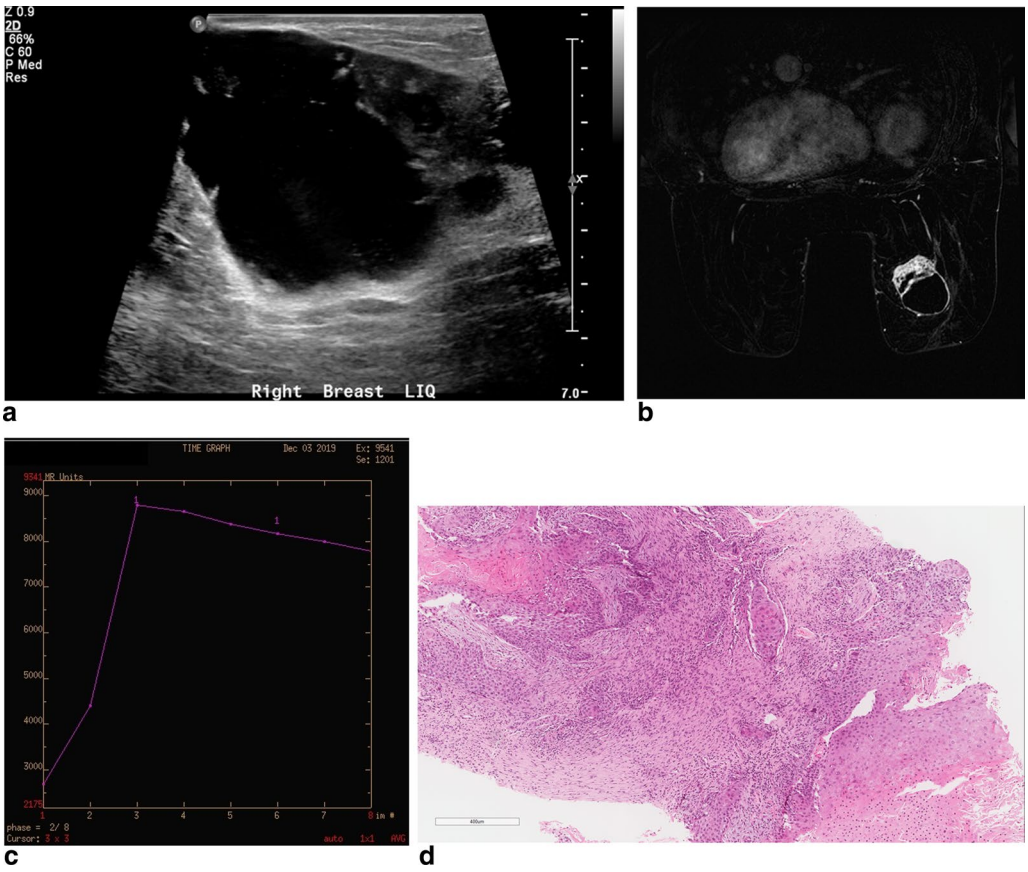

Fig. 1 A right breast mass in a 53-year-old woman with squamous cell carcinoma subtype. **a** The ultrasound shows a complex mass with cystic and solid component at lower inner quadrant. **b**, **c** Shows the MRI in dynamic phase that revealed a rim enhanced mass with washout pattern of enhancement. **d** The pathology slides shows a squamous cell carcinoma

presented with metastasis. As a result, all the patients had a diagnostic breast imaging, regardless of their age, rather than a screening as an initial investigation, excluding the two patients who presented with metastasis.

In our study, the mean size of the masses is 5.96 cm, and 12/22 of the cases (54.55%) the masses measured more than 5 cm which is higher compared to other publications [4, 8]. In view of the heterogeneous histological patterns, MBC imaging features tend to be variable. Based on the mammogram, the current study demonstrated that most masses (63.16%) were irregular in shape, with indistinct and spiculated margins in 57.89% and 10.53%, respectively. A similar observation was observed on the ultrasound with the majority (72.73%) of the masses had an irregular shape, and indistinct and microlobulated margins in 36.36% and 27.27%, respectively, with a complex echopattern in more than a third of the cases.

Apart from our own evaluation of the masses with the latest criteria or the cases referred as known cancers (BI-RADS 6), only two cases were coded as BI-RADS 3 (one presented with microcalcifications and the other with a complex echopattern) and both missed their 6-month follow-up. The overall mass description was suspicious, resulting in the ACR-BI-RADS reaching 4 and 5 in 16/18 cases (the remaining were not coded at time of reporting), similar to some previous studies where malignant features were evident, and in contrast to other studies reporting that the radiological features could be mistaken for a benign pathology [3, 5, 6, 8, 13, 15, 16, 22, 23].

Although squamous cell carcinomas are likely to be associated with irregular and spiculated margins and spindle cell with a more oval shape and circumscribed margins [22], this was not the case in our study (Figs. 1, 2). No characteristic radiological appearances in any of the subtypes were demonstrated.

Just more than half (54%) of the cases demonstrated posterior acoustic enhancement, which is within the 50–67% range reported in the literature [3, 13, 15, 22]. Yang et al. observed that MBC presents with posterior acoustic enhancement more frequently than invasive ductal carcinoma [3]. Although it was present in more

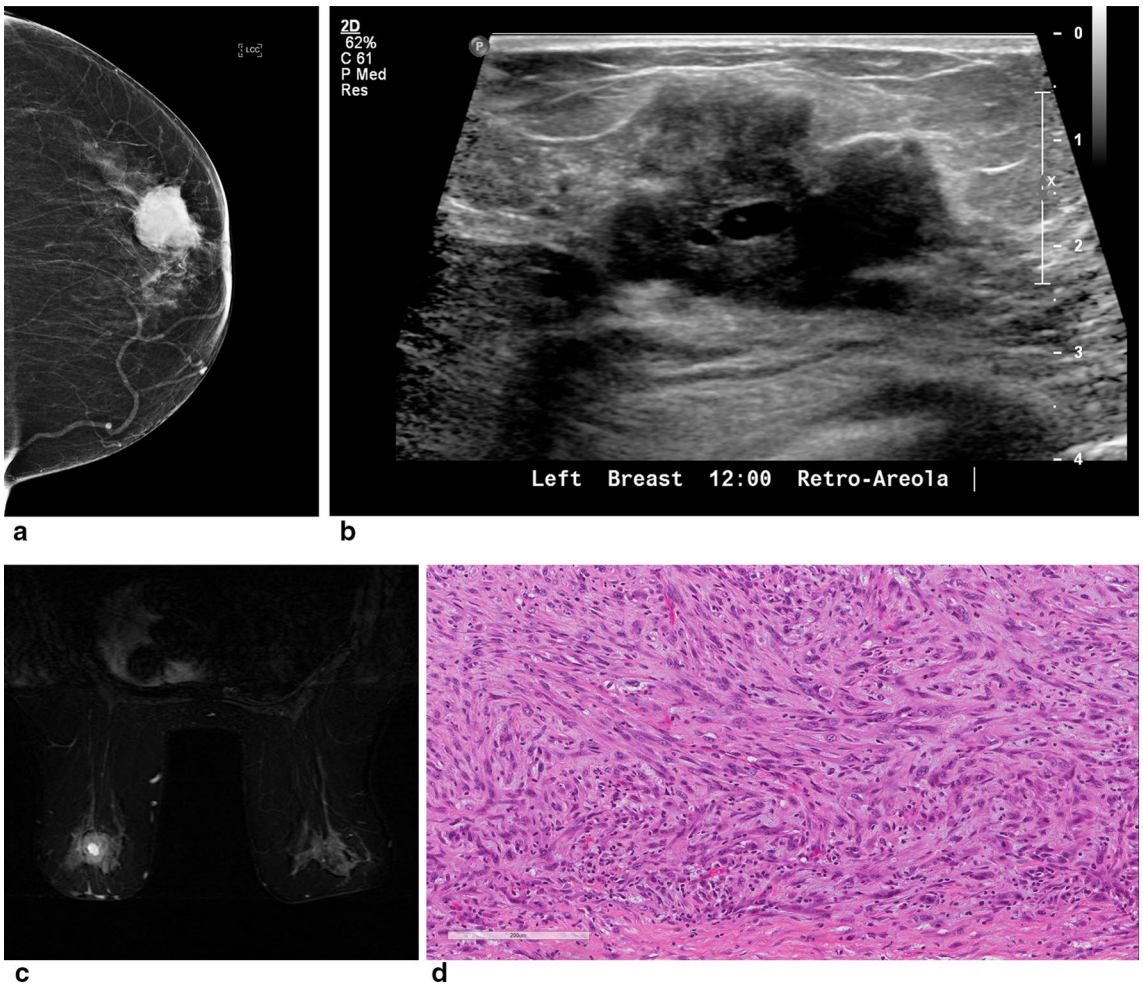

Fig. 2 A left breast mass in a 69-year-old woman with a spindle cell carcinoma subtype. **a** The craniocaudal view of mammogram shows an irregular shape, high density mass with indistinct margins located at outer aspect. **b** The ultrasound reveals a microlobulated, irregular, complex mass in the left breast with central cystic area. **c** MRI T2-weighted image reveals a central hyperintense area representing necrosis. **d** The pathology shows the tumor is entirely composed of spindle cells

than half of the cases, it cannot be considered as a differentiating sign from other breast cancer, even with the absence of hormonal receptor expression.

The increased proportion of irregularly shaped masses observed in the current study could be due to the fact that we described the lobular shaped masses as irregular, according to the latest ACR criteria. However, this description did not affect the overall results of the assessment of the masses in recent studies, using the previous ACR criteria [8, 15, 22]. In addition, microcalcifications were seen only in three cases (14.29%) with suspicious patterns of pleomorphic /coarse heterogeneous morphology and a regional/segmental distribution, in which two of these were a squamous subtype of MBC. This observation is consistent with the literature demonstrating less than 25% of calcifications in their results [3, 6, 8, 13].

Regarding the additional features in the mammogram, skin changes (thickening and ulceration) were present in 52.38% of the cases. This is considerably higher than previous reports and was significantly related to lymph node involvement (p value = 0.022) [3, 6, 9, 15, 24]. Though it was associated with an increased mass size, this observation was not statistically significant (p value = 0.853).

In our study, squamous cell subtypes had cystic and solid components (Fig. 1a) similar to other studies that have classified it in a differential diagnosis of complex breast masses [6, 16, 25]. However, this finding was not statistically significant in our study (p value = 0.568).

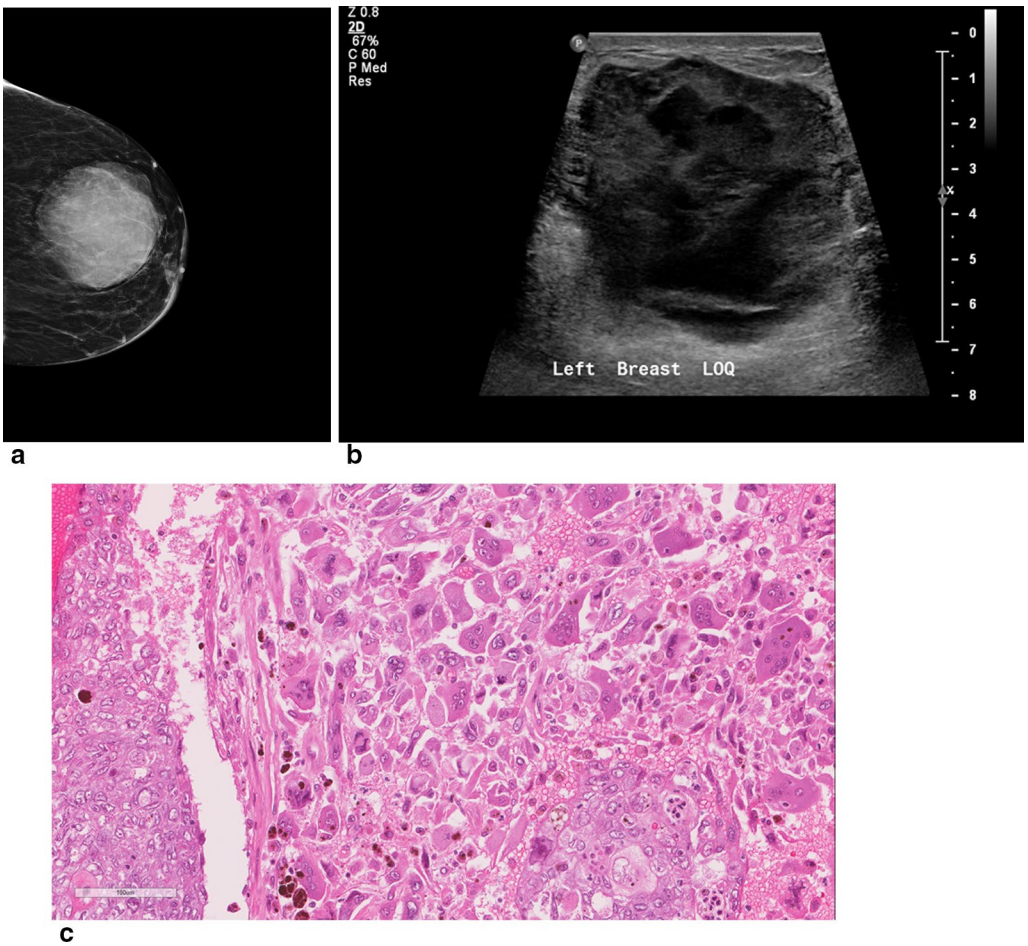

Fig. 3 A large left breast mass in an 82-year-old woman with mesenchymal differentiation subtype. **a** The craniocaudal view of mammogram shows a rounded, dense mass with circumscribed margins and mild periareolar skin thickening. **b** The ultrasound shows an irregular shaped mass with indistinct margins along with complex echotexture and posterior enhancement. **c** The pathology shows a metaplastic carcinoma with mesenchymal differentiation showing prominent multinucleated giant cells

A breast MRI was done in only four cases. The masses had different shapes and T2 signal intensity, with only one an oval-shaped mass with irregular margins, and a hyperintense signal in the T2-weighted image with rim enhancement, similar to the literature [2, 5, 8]. All four cases displayed a washout enhancement pattern in the kinetic curve (Fig. 1b, c).

Core needle biopsy is the gold standard for breast cancer diagnosis; however, in some circumstances it is difficult to differentiate MBC from other breast cancers on core needle biopsy alone. In the current study, approximately one third of the cases were initially diagnosed as a conventional infiltrating ductal carcinoma on core needle biopsy, and subsequently reclassified as MBC on the resected specimens. This is most likely related to a sampling issue [5, 6, 13].

Generally, most MBC is triple negative with high-grade morphology and high proliferation index (Ki 67%), and these findings are similar to our results [2, 8, 22]. The HER2-positive cases have a relationship with increased mammogram calcifications [26]. However, in our study, there were only four cases (18.18%) showed HER2-positive staining (3+) by immunohistochemistry and they did not show microcalcifications in their mammograms. This could be due to a limited HER2 expression in MBC and the rarity of calcifications within it [27]. It is noteworthy that our results indicated that HER2-positive masses are primarily observed in the cases with squamous differentiation; however, this observation was not statistically significant (p value of 0.846). The squamous type is the most prevalent type of MBC which is consistent with the current study, with 45% of the cases [6, 9].

MBC has a potential of hematological metastasis, more than lymphatic spread [3, 11, 12]. Consequently, it presents with few lymph nodes involvement in 25–40% of

the cases [3, 5, 6, 12, 13, 17]. In our study, 10/22 of cases (45.45%) presented with axillary lymph node involvement. This may be contributed to the frequent large mass size in our series; however, there was no statistical significance (p value = 1.000). The majority of the cases (12/19 cases) had advanced disease at presentation with either T3 or T4 clinical or pathological staging. More than one third of the cases already had metastasis at the initial diagnosis or diagnosed in the follow-up period (18.18% and 22.73%, respectively), most frequently to the lung. For the group who underwent surgery, a mastectomy was most frequently performed, and three cases had lumpectomies, as supported by recent studies [11, 23].

This study is limited by the small sample size, which is due to the rarity of the disease. Another limitation is that most of the documents from the hospital electronic system were missing and the ultrasound was evaluated from the PACS images which are operator dependent. We collected the BI-RADS classifications from the initial radiological report, and thus we avoided any bias in the study given the known diagnosis by the authors. The strong point of the study is the reassessment of the radiological appearance to obtain additional characteristics. In addition, this is one of the first studies of metaplastic carcinoma using the latest ACR criteria in association with the latest pathological WHO classification.

Conclusion

MBC is a rare aggressive breast tumor with no definite characteristic imaging from other breast cancer. It shows a mass with irregular shape and indistinct margins in both mammogram and ultrasound. Additionally, it revealed posterior acoustic enhancement and rarely containing microcalcifications. The correlation with the pathological findings may be crucial in the diagnosis and subsequent appropriate treatment.

Abbreviations

MBC: Metaplastic breast carcinoma; WHO: World Health Organization; ER: Estrogen receptor; PR: Progesterone receptor; HER2: Human epidermal growth factor receptor-2; ACR: American College of Radiology; BI-RADS: Breast Imaging Reporting and Data System; CC: Craniocaudal; MLO: Mediolateral oblique; MRI: Magnetic resonance imaging; CT: Computed tomography.

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Author contributions

All authors read and approved the final manuscript.

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Availability of data and materials

Data available upon request.

Declarations

Ethics approval and consent to participate

This study was approved by the institutional ethics review board in Saudi Arabia with reference no. IRBC/1847/19. The consent was not needed due to cohort retrospective design of the study.

Consent for publication

Not applicable since the identification of patients was removed.

Competing interests

The authors declare that they have no competing interests.

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