Cohort Study

Unique clinicopathological characteristic and survival rate of metaplastic breast cancer;a special subtype of breast cancer a 5 year cohort study in single referral centre in North Borneo

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ARTICLE INFO	ABSTRACT
	Introduction: Metaplastic Breast Cancer (MBC) of the breast is a rare entity of breast cancer, with a very poor prognosis, and whose pathophysiology is still unwell established. Therapeutic management is very heterogeneous due to its incomplete understanding. The aim of this study is to describe the demographic, clinical, and therapeutic characteristics of our MBC patient. *Material and methods:* A cross-sectional study was conducted to evaluate the demographic and clinicopathological features of these patients. Data of patients diagnosed with metaplastic breast cancer were retrieved from our breast cancer database in Queen Elizabeth Hospital II from January 2015 in May 2021. *Results:* 14 patients were diagnosed with metaplastic breast cancer during this period of study. All of them were female, with the average age of 52 years old. The patients were predominantly Bajau and Kadazan Dusun, each comprising of 35%(n = 5). 57% (n = 8) of patients were postmenopausal. 85% (n = 12) of patients were presented with breast lump of an average largest diameter of 69.23 mm. BIRADS staging of the affected breast revealed that most of the patients were BIRADS 5.57% (n = 8) patients underwent mastectomy, 4 went for either breast conserving surgery of the breast. The most common histopathological type is squamous cell carcinoma, which accounts for 42% (n = 6) of the patients. 71% (n = 10) were pathologically triple negative. 7 patients were pathologically node positive. 35% (n = 5) had lung metastasis, and one of the patients had concurrent lung and liver metastasis. *Conclusion:* The prognosis of patients with Metaplastic carcinoma of breast remains poor because most of it detected late and histologically triple negative type. Till date, there is no specific management guideline which warrant a multi institutional studies evaluating role of new therapies such as Anti-PD-1 Therapy in combination with chemotherapy to improve patient outcome.

1. Introduction

Metaplastic breast carcinoma (MBC) is a rare type of breast carcinoma and is well recognised for its heterogeneity and worse prognosis compared to the other types of breast carcinoma [1–3]. Previous studies reported incidence of MBC of less than 1% of all types of breast carcinoma. A United States (US) population based study documented incidence of metaplastic breast carcinoma of 0.68% of the total cases of breast carcinoma, and a study in China reported incidence of 0.3% [3,4].

The number of patients being diagnosed with MBC is increasing due to an increasing recognition of the condition. We had done a study to evaluate the clinical-pathological characteristic of our MBC cases from January 2015 until May 2021 and we discuss the unique biological characteristic of our MBC cases, the prognostic outcome and the current recommendation on the management of MBC (see Tables 1–3).

Table 1
Demographic characteristics of patients.

		No. of patients, n=14, n(%)
Age (years) Mean age: 52 years old Range: 33-71	*<40*	2 (14.3%)
	41–50	3 (21.4%)
	51–60	6 (42.9%)
	61–70	2 (14.3%)
	>71	1 (7.1)%
Ethnicity	*Bajau*	5 (35.7%)
	Brunei	1 (7.1%)
	Chinese	1 (7.1%)
	Ilocano (Filipino)	1 (7.1%)
	KadazanDusun	5 (35.7%)
	Malay	1 (7.1%)
Parity	*Nulliparous*	1 (7.1%)
	1	1 (7.1%)
	2	3 (21.4%)
	3	3 (21.4%)
	4	2 (14.3%)
	Grandmultipara	4 (28.6%)
Menopausal Status	*Premenopausal*	6 (42.9%)
	Postmenopausal	8 (57.1%)

Table 2
TNM Staging of patients diagnosed with metaplastic breast carcinoma.

		No. of patients, n = 14, n(%)
T Staging	*T1*	0
	T2	6 (42.9%)
	T3	2 (14.3%)
	T4	6 (42.9%)
N Staging	*N0*	7 (50%)
	N1	7 (50%)
M Staging	*M0*	9 (64.3%)
	M1	5 (35.7%)
Stage	*1*	0
	2	8 (57.1%)
	3	1 (7.1%)
	4	5 (35.7%)

Table 3
Histopathological result and molecular status of metaplastic breast carcinoma.

		No. of patients, n = 14, n(%)
Histological subtype	*Squamous cell carcinoma*	6 (42.9%)
	Spindle cell carcinoma	2 (14.3%)
	Metaplastic carcinoma with mesenchymal differentiation	1 (7.1%)
	Metaplastic carcinoma of no specific type	5 (35.7%)
Molecular Status	*ER (+) PR/HER2 (−)*	2 (14.3%)
	ER/PR (+) HER2 (−)	1 (7.1%)
	ER/PR (−) HER2 (+)	1 (7.1%)
	Triple negative	10 (71.4%)

2. Method

2.1. Patient selection

A cross-sectional study was conducted to evaluate the demographic and clinicopathological features of these patients. Data of patients diagnosed with metaplastic breast cancer were retrieved from our breast cancer database in Queen Elizabeth Hospital II from January 2015 to May 2021 and were analysed retrospectively. We collected data concerning the age of the patient, the clinical, histological and radiological lesion characteristics, the extension assessment, the therapeutic management, and the recurrences. Male patients and unconfirmed diagnosis were excluded.

2.2. Initial investigation

All the radiological assessment including mammography with or without breast and axillary ultrasound, and a histological examination by tissue biopsy. The extension assessment included either CT scan of thorax abdomen and pelvis, or a combination of chest X-ray, abdominal ultrasound, according to the recommendations and guidelines.

2.3. Pathological examination

Cytology or surgical specimens were analysed in the hospital's pathology department. The diagnosis of MBC was confirmed when 2 pathologists of the service agreed on the histological nature. Histological features included: tumour size, presence of hormone receptors, HER2 profile, grade of differentiation, and the presence of cytokeratin.

2.4. Treatment

Surgical management was then explained to the patient: either lumpectomy or mastectomy, and either sentinel lymph node procedure or axillary dissection. Information on neoadjuvant and adjuvant chemotherapy and/or radiotherapy treatments details was also collected.

2.5. Follow-up

Patients were followed every 4–6 months in the first 5 years after surgical management, then once a year.

3. Result

3.1. Demographic characteristics

All 14 patients included in this study were female, with age ranging from 33 to 71 years old (Mean: 52 years old). Most of the patients were above 50 years old (n: 9, 64.3%) during initial presentation. The patients were predominantly Bajau and KadazanDusun, each consisting of 5 patients (35.7%). The remaining patients include 1 Brunei, 1 Chinese, 1 Malay and 1 Ilocano (Filipino). Only 1 (7.1%) of the patients was nulliparous, and 4 was grand multiparous (28.6%). Most of the patients were postmenopausal (n: 8, 57.1%) upon initial presentation.

3.2. Clinical diagnosis

All of the patients presented with breasts lump of duration ranging from 2 weeks to 3 years. The average largest diameter of the tumor is 69.23 mm, ranging from 15 mm to 200 mm. Most of the patients were staged T2 and T4 upon diagnosis, each comprising of 6 patients (42.9%). The remaining 2 patients were staged T3 upon diagnosis (n: 2, 14.3%). 50% of the patients had no lymph nodes enlargement, the remaining half were of N1 status during initial presentation. 5 (35.7%) out of 14 of the patients were found to have developed distant metastasis, all 5 cases

involving the lungs, and one patient had a concurrent liver metastasis. Based on the TNM staging, most of the patients were categorised as Stage 2 breast carcinoma (n: 8, 57.1%), and 5 patients were Stage 4 disease (35.7%).

3.3. Imaging tests

Mammogram was done for the patients to assess BIRADS score of the breast lesions. Majority of the patients were categorised as BIRADS 5, which accounts for 5 out of 14 patients, followed by 3 patients who were categorised as BIRADS 4.2 patients were BIRADS 6 and 1 was BIRADS 3. The BIRADS scores for 3 patients from the cases series were not available due to several reasons, including unable to perform mammogram at the affected breast due to presence of open wound.

3.4. Histopathological result

Specimens from trucut biopsies and surgical operations were evaluated. The most common subtype of metaplastic breast carcinoma in this case series was squamous cell carcinoma, accounting for 6 (42.9%) out of 14 patients, followed by metaplastic carcinoma of no specific type, which is 5 (35.7%) patients. Other types include 2 cases of spindle cell carcinoma and 1 case of metaplastic carcinoma with mesenchymal differentiation. Bloom and Richardson grading system was applied, majority of the cases was Grade 3 (n: 9), followed by 3 cases which was Grade 2.

Majority of the patients were triple negative, accounting for 71.4% (n: 10) of the total cases. 2 (14.3%) patients were ER/PR positive and HER2 negative, 1 (7.1%) was ER positive but PR and HER2 negative, and 1 (7.1%) ER/PR negative but HER2 positive.

3.5. Treatment

One patient, who was stage 2 upon diagnosis, refused all forms of treatment options and was loss to follow up. All remaining 12 patients received surgical treatment, 8 (66.7%) of them underwent mastectomy with axillary clearance, 2 (16.7%) patients underwent breast conserving surgery. The remaining 2 (16.7%) initially underwent wide local excision, however, subsequently went through mastectomy with axillary clearance in view of local recurrence. The duration of development of recurrence ranged from 7 months to 2 years.

Most of the patients received adjuvant chemotherapy (n: 8, 66.7%), with 5 receiving radiotherapy concurrently. 2 stage 4 patients received palliative chemotherapy. Majority of the patients (n: 7, 70%) who were treated with chemotherapy was administered with the FEC regimen (5-fluorouracil, epirubicin and cyclophosphamide), with 4 of them additionally treated with docetaxel. One stage 4 patient who received FEC/Docetaxel chemotherapy regimen showed no improvement, hence was subsequently treated with second line chemotherapy drug, paclitaxel (C1D15). Other chemotherapy regimen administered include cisplatin/5 FU, AC (Adriamycin, Cyclophosphamide) and Carboplastin/Docetaxel. The number of cycles of chemotherapy administered ranging between 3 and 6 cycles.

In light of majority of the cases were triple negative, targeted therapy was not suitable for the patients. Only 3 patients received hormonal therapy, tamoxifen, on account of their molecular status of breast tumour revealing ER positive.

3.6. Treatment outcome

Median follow up duration is 36.5 month with the range of 3 months–6 years. One stage 4 patient passed away before receiving treatment.Two patients who underwent wide local excision developed local recurrence, one within 7 months and another within 2 years duration. They were later surgically treated with mastectomy and axillary clearance, during follow up, no recurrence noted. The other patients who underwent mastectomy did not develop any local or axillary recurrence upon follow up.

4. Discussion

Metaplastic breast carcinoma (MBC) is a rare type of breast carcinoma and is well recognised for its heterogeneity and worse prognosis compared to the other types of breast carcinoma [1–3]. Previous studies reported incidence of MBC of less than 1% of all types of breast carcinoma. A United States (US) population based study documented incidence of metaplastic breast carcinoma of 0.68% of the total cases of breast carcinoma, and a study in China reported incidence of 0.3% [3,4].

However, a case series of 7 reported a predilection towards younger age, documenting an average age of 36 years old. Most studies agreed that a higher proportion of patients are postmenopausal (65–84%) during initial presentation [5,7,8], our study reported a lower proportion (57.1%), however is still higher compared to the premenopausal group in our case series.

Histological diagnosis of MBC has been a challenging task, due to the wide range of diversity in its histological appearance [9]. The World Health Organisation (WHO) Classification of Breast Tumors categorised MBC into (1)metaplastic carcinoma of no special type, (2)low-grade adenosquamous carcinoma, (3)fibromatosis-like metaplastic carcinoma, (4)squamous cell carcinoma, (5)spindle cell carcinoma, (6)metaplastic carcinoma with mesenchymal differentiation, (7)mixed metaplastic carcinoma and (8)myoepithelial carcinoma [10]. This classification has been widely adopted in multiple studies in the past, including our current study. Our case series reported that squamous cell carcinoma is the most common histological subtype (42.9%), which corresponds to the findings of several studies, with documented incidence ranging between 26 and 48% [5–8]. Schroeder et al. which included a total of 1516 cases of MBC in the United States, documented the most common histological type was metaplastic carcinoma of no specific type (81.9%) [4]. Zhang et al. reported spindle cell carcinoma (34.4%) was the most prevalent in their cohort [3]. Rakha et al. compares case series of MBC taken from different population, and revealed that there is higher incidence of squamous cell carcinoma among the Asian population and is associated with higher histological grading [2]. Several studies agrees that there is no significant association between the histological subtype of MBC and the prognosis of patients [3,4]. However, some demonstrated that mixed type of metaplastic carcinoma has an inferior outcome with poorer overall survival compared to non-mixed type [5,8]. Microscopic examination of MBC usually reveals poorly differentiated tumor cells. The current study reported 64.3% of the patients were high grade. This corresponds to the findings of previous studies, which documented significantly higher histological grading of MBC (75–100%) [2,5,6,8,11]. When compared with invasive ductal carcinoma, MBC also showed preponderance towards high histological grading (68.4% vs 34.5%, p=<0.001) [4].

MBC is commonly presented with large sized breast lesions, previously reported an average largest tumor diameter of 30–57.5 mm [3,6–8,12]. Our study revealed a slightly higher average largest tumor diameter, 69.23 mm. Our finding is similar to that of reported by Altaf et al., which documented a median tumor size of 70 mm [13]. This variation might be due to the rarity of cases hence involving only a small sample size. Our case series revealed equal numbers of patients diagnosed as T2 and T4, each constitute of 6 patients. T status of MBC from previous studies documented higher proportion of T2 status (44–54.6%), along with lower incidence of T4 status [2,5,6,8,11]. Fayaz et al. reported high incidence of T4 status among their case series of 31 (42%) [7]. Lymph node involvement were rarely reported, incidence of N0 status documented previously was 70.6–79.2%, and presence of lymph node metastasis were associated with poorer prognosis and reduced overall survival [2,3,5]. The current study revealed that half of the patients were N0 (50%). Distant metastasis upon initial presentation of MBC is not very common (3–26.1%), and the most common site of

metastasis is the lungs [5–8]. This corresponds with the findings of our study. 5 cases of distant metastasis were noted in our case series, all of which involving the lungs, and one patient developed a concurrent liver metastasis. Other less common site of distant metastasis reported include brain and bone metastasis [6,12]. According to the TNM staging, our study showed higher proportion of Stage 2 patients (57.1%) during initial presentation. This finding is consistent with that of Schroeder et al. (59%) [4]. However, this study did not include Stage 4 patients, hence might not reflect the actual proportion of patients in its cohort.

There are no standardized guidelines in managing MBC, management plan is usually adopted from that of classical breast carcinoma, which involves a wide array of treatment strategies including surgical treatments, chemotherapies, radiotherapies and targeted therapies [14]. Surgical treatment is usually offered on account of the typical presentation of large-sized solid tumor of MBC, and the common choice of surgery is mastectomy [3,5,6]. In the current study, there was no difference in the outcome between patients who received mastectomy and patients who underwent breast conserving surgery, no local recurrence was noted. This corresponds to the findings of that by Corso et al., which demonstrated that mastectomy did not provide added therapeutic benefit in MBC when breast conserving surgery is attainable [5]. Several studies showed that patients who were surgically treated with mastectomy had an inferior outcome compared to the group of patients who underwent breast-conserving surgery or lumpectomy [4,11,15]. Interestingly, our series revealed 2 patients who underwent wide local excision who later developed local recurrence over a duration of 7 months and 2 years respectively, needing a second operation where mastectomy is opted in both cases. None of the other patients who undergone mastectomy or breast conserving surgery in our series developed local recurrence. This shows that wide local excision showed inferior therapeutic benefit compared to mastectomy and breast conserving surgery.

Metaplastic breast carcinoma typically demonstrates significantly higher incidence of triple negative molecular status(71.1–88.7%) [3,5,8, 11]. This finding is consistent to that of our current study, in which 71.4% of the patients were identified as triple negative subtype. This finding are consistent with NCCN (National Comprehensive Cancer Network 2020 guideline) where it mention that MBC are highly unusual to have ER positive biology. Triple negative subtype of MBC revealed inferior outcome and poorer prognosis when compared to their invasive ductal carcinoma counterparts [1]. This brings about limited potential of targeted therapies for patients diagnosed with MBC. HER2 overexpression in patients with MBC is rare(5.4%), but demonstrated better prognosis due to availability of HER2 directed therapies [4]. MBC patients with HER2 positivity showed better prognosis compared to invasive ductal carcinoma with HER2 positivity. The therapeutic potential of hormonal therapy in managing MBC is also limited due to the low incidence of ER or PR positivity [3,4,8].

Rakha et al. demonstrated that chemotherapies are associated with improved survival outcome in early stages of MBC, however not in advanced stage of MBC [2]. Han et al. showed that administration of chemotherapy and radiotherapy is associated with improved overall survival. This study also noted that 59% of those receiving neoadjuvant chemotherapy showed reduction in tumor size and 17% attained pathological complete response [11]. In a recent study, it was found that patients who received combined chemotherapy and radiotherapy demonstrated better cumulative breast cancer specific death incidence compared to patients who received chemotherapy alone and those who did not receive any systemic treatment [15]. A study found that MBC patients with distant metastasis showed poor response towards palliative systemic therapy, revealing only 6% of them attaining partial response and 18% who achieved stable disease [8]. One patient from our case series who presented with lung metastasis was received palliative chemotherapy (4 cycles of FEC regimen, and 2 cycles of docetaxel) and also received second line chemotherapy paclitaxel, experienced no reduction in tumor size along with worsening lung metastasis. Although

evidence shown little benefit of systemic therapy in metastatic disease of MBC, it was also demonstrated that those who did not received chemotherapy or undergo any surgical treatment over the site of primary tumor, was associated with decreased survival outcome [16]. Corso et al. found that patients who received CMF/CMF like regimen showed better prognosis and improved overall survival [5]. In the current study, 10 patients from the case series received chemotherapy, and the most common regimen administered was FEC regimen.

The average follow up duration in our case series was 1 year and 9 months (median follow up duration was 12 months). 1 stage, 4 patient passed away 4 months after first presentation due to lung complication.

One patient refused treatment and was loss to follow up. The overall survival for the current study was 92.3%. The overall survival rate from the literature was much lower compared to that of our study, this could be due to the difference in sample size of patients involved in the study. Zhang et al. revealed that the 5 year overall survival rate of MBC patients was shorter compared to that of invasive ductal carcinoma patient group and triple negative subtype of invasive ductal carcinoma patients (78.7% vs 93% vs 90.6%) [3]. Elimimian et al. demonstrated inferior prognosis of MBC patient group compared to 2 other special type of breast carcinoma, which is adenoid cystic carcinoma and medullary carcinoma (5 year overall survival rate: 63.1% cs 88.4% vs 91.7%) [16].

Other novel therapies that has been gaining attention include the potential therapeutic benefit of EGFR tyrosine kinase inhibitor and EGFR monoclonal antibody therapies. Studies shown that EGFR overexpression was seen in metaplastic breast carcinoma, especially the squamous cell carcinoma histological subtype [3,13].

5. Conclusion

The prognosis of patients with Metaplastic carcinoma of breast remains poor because most of it detected late and histologically triple negative type. Till date, there is no specific management guideline which warrant a multi institutional studies evaluating role of new therapies such as Anti-PD-1 Therapy in combination with chemotherapy to improve patient outcome.

Ethical approval

Ethical approval was obtained . We also would like to thank the Director General of Health Malaysia for his permission to publish this article.

Author contribution

Nik Amin Sahid initiated, planned the study. Nik Amin and Gracyvinea Nold Imon did the writing of the manuscript. Others help in the data collection and statistical analysis. Nik Amin Sahid supervised, reviewed and edited the manuscript. Siti Zubaidah Sharif supervised the project

Provenance and peer review

Not commissioned, externally peer-reviewed.
This article compliant with the STROCSS 2021 criteria [17].

Declaration of competing interest

All authors declare that they have no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amsu.2022.103822.

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