



Challenges in Managing Metaplastic Breast Cancer-Referencing an Indexed Case and a Ten-Year Experience in a Developing Country



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Abstract

Metaplastic breast cancer is rare and aggressive, accounting for only 0.2% of all breast cancers with a survival ranging from 40-65%. A recent case from our institution posed many diagnostic and management challenges prompting a review of our local ten-year experience with this cancer and a review of the literature to compare the behaviour of this cancer in a developing country and considering guidelines for management.

The incidence is higher with what appears to be a better prognosis in our patient population. Early diagnosis and treatment may be responsible for the apparent better outcome in our patient population. Successful treatment consists of surgery, radiotherapy and with comparable results from both breast conservation and modified radical mastectomy. Preoperative biopsy does not usually yield the correct diagnosis so most patients undergo axillary node dissection even though the mode of spread is supposed to be primarily hematogenous.

Keywords: Metaplastic; Breast; Cancer; Management; Outcome; Surgical

Abbreviations: CT CAP: Computed Tomography Scan of the Chest, Abdomen and Pelvis; WHO: World Health Organisation; MRI: Magnetic Resonance Imaging; SEER: Surveillance, Epidemiology and End Results Program; IDC: Invasive Ductal Carcinoma; DFS: Disease Free Survival

Introduction

Breast cancer is the leading cause of cancer related deaths in Caribbean women [1]. Metaplastic breast cancer is a rare subtype. The tumours consist of both epithelial and mesenchymal components and are fast growing with advanced disease at presentation [2]. Diagnosis via traditional means can be difficult due to mixed tumour makeup and most cases are recognised postoperatively. Axillary nodal involvement is uncommon and most spread is hematogenous. Most tumours are triple negative and show poor response to systemic therapy. Surgery and radiotherapy have been shown to be of benefit, however this disease still carries a high risk of locoregional recurrence and poor prognosis.

Our institution in the developing country of Trinidad and Tobago with a population of 3.3 million is the main referral centre for breast cancer with 1120 new cases over the ten year period from January 1st 2005 to December 31st 2014 during which time we treated 7 new cases of Metaplastic breast cancer (incidence of 0.63% compared to the 0.2% incidence reported in the literature).

Although the disease is still rare among our breast cancers, it appears to be more frequent in our population based on our small sample.

We present our recent indexed case, a review of our ten-year experience, and compare this to the literature reports of this cancer, highlighting the diagnostic and management challenges.

Case Description

A 64-year-old Afro-Trinidadian female was referred to us, from a private institution, for a diagnosis of right breast cancer with a palpable axillary node. She initially presented with a five-month history of a right sided breast mass, progressively increasing in size, accompanied by the appearance of an axillary mass. She has no other significant past medical, family, gynaecological or surgical history, apart from a diagnosis of hypertension, controlled with the use of Nifedipine, and a total abdominal hysterectomy which was performed for a fibroid uterus.

On examination, a 2x2cm hard, irregular lesion was palpated at the nine-ten o'clock region of the right breast. It was mobile, and there were no overlying skin or nipple changes noted. A 0.5cm, well circumscribed mass was palpated in the right axilla, which was also mobile.

Investigations

CT CAP (22/07/17) demonstrated a 1.8 x 1.9cm irregular, right, lateral breast mass, with a dominant level I right auxiliary lymph node, with no evidence of distant metastases (initially staged as T1N1M0). TruCut Biopsy of the right sided breast lesion (16/6/17) reported Grade 2 invasive ductal carcinoma and TruCut Biopsy of the right axillary mass reported invasive ductal breast adenocarcinoma in the lymph node, with tumour emboli seen in the lymphatic channels.

Management course

The patient was booked for a right wide local excision of the breast mass with axillary lymph node clearance. Her only postoperative complication was a right axillary seroma which was aspirated.

Histological analysis of the surgical specimen demonstrated a 1.7x1.7x1.5cm tumour, high grade metaplastic carcinoma of the breast, with poorly differentiated squamous carcinoma pattern. Extensive necrosis noted. Cancerisation of the lobules was seen. There was lymphatic invasion. The skin was free of tumour and all surgical margins were clear. It was staged as T1cN1MX, Stage IIA.

One out of ten axillary lymph nodes demonstrated metastasis of metaplastic carcinoma of the breast. No extracapsular extension was noted. Immunohistochemistry was triple negative. The patient was referred to medical oncology, where she underwent four cycles of adjuvant doxorubicin/cyclophosphamide which was completed on 05/04/18 and she is now scheduled to receive external beam radiation therapy.

Discussion

Metaplastic breast cancer is a rare and aggressive condition, accounting for a reported 0.2% of breast cancer cases. The term metaplastic refers to a heterogenous group, which has both malignant epithelial and mesenchymal components. It was only recognised as a unique pathological entity in 2000. The WHO describes five subtypes, spindle cell, squamous cell, matrix producing, carcinosarcoma and metaplastic breast carcinoma with osteoclastic giant cells [2].

It commonly affects women in the age 49-59 group, with most patients presenting with larger size and more advanced tumours, compared to those with invasive ductal carcinoma, which is the most common type of breast cancer [3]. In an epidemiological study by the National Cancer Database by Campbell et al. [4] women of African descent and low socioeconomic status were found to be at increased risk for diagnosis.

Most metaplastic breast tumours are triple negative, as compared to those which are of the invasive ductal carcinoma type.

Triple negative hormone receptor status, however, is also more likely to be associated with the aforementioned sociodemographic factors [4].

Diagnosis of this condition is made via traditional modalities such as mammogram, ultrasound, MRI and biopsy, but the associated findings do differ based on the tumour makeup, which is variable and makes diagnosis difficult [3]. It has been shown that metaplastic breast cancer is less likely to be diagnosed correctly prior to surgical intervention, due to its mixed histological makeup [4]. The diagnosis is made via morphology for the carcinomas with a squamous component or a pure squamous carcinoma, and via immunohistochemistry for those with sarcomatoid or spindle cell carcinoma, which coexpress cytokeratin and vimentin [5].

Many differential diagnoses exist for this condition, for example, myofibroblastic tumours, pleiomorphic adenomas and adenomyoepithelioma [2].

Notably, as compared to other breast cancer subtypes, axillary nodal involvement are only found in 8- 40% of cases and haematogenous spread to the bone and lungs is more common, as compared to the lymphatic route [4].

Regarding management of metaplastic breast cancer, no standard regimens exist due to its rare and aggressive nature. Surgical management more commonly involves mastectomy as opposed to breast conservation, but this may be due to increased tumour size at presentation and poor response to neoadjuvant chemotherapy and not necessarily increased overall survival or disease-free survival [3]. Conceivably, early diagnosis and treatment could lead to avoidance of mastectomy in some of these patients [6]. In a retrospective review by Dave et al. [7], breast conservation surgery for metaplastic cancer was found to be a reasonable treatment option, achieving equal local recurrence free survival and overall survival as compared to mastectomy.

The use of both adjuvant and neoadjuvant chemotherapy in these patients is controversial. It has been shown that chemotherapy is used more often for patients with metaplastic breast cancer, as compared to those with invasive ductal carcinoma, but this is due to more advanced stage at presentation [8]. However, a single centre retrospective study at the Mayo Clinic for the period 1976-1997 demonstrated that systemic therapy is less effective in the metaplastic subtype as compared to invasive ductal carcinomas [9]. This is further reinforced by Chen et al. [10], who also reported that tumour response to chemotherapy is poor in those with metaplastic breast cancer, but, in those patients, who did receive systemic therapy, taxane based regimens were more effective than those that were anthracycline based [10]. It is common for larger tumours to be treated with neoadjuvant chemotherapy prior to surgical intervention. However, given the poor response of metaplastic tumours to chemotherapy, neoadjuvant chemotherapy could lead to unnecessary delay of definitive surgical intervention.

The use of adjuvant hormonal therapy is also debatable. Most metaplastic breast cancer cases are triple negative. However, in a retrospective study of 2338 patients, positive hormone receptor

status did not necessarily confer a better prognosis [11]. Also, the use of tamoxifen as a form of systemic therapy in the metaplastic subtype was found to be less effective than in those with invasive ductal carcinoma [10]. In a recent study by Schroeder et al. [12], using the SEER database, HER2 positive receptor status was associated with improved survival, which was comparable to that of HER2 positive IDC disease. This suggests that HER2 positive disease may be responsive to targeted therapy which can then be considered as one of the therapeutic modalities used for this disease.

Radiotherapy has been shown to be of substantial benefit in the management of metaplastic breast cancer. In the largest study to date evaluating metaplastic breast cancer, using the National Cancer Database, radiotherapy was associated with a higher overall survival in patients undergoing breast conservation surgery, and in those who had mastectomy for T3-T4 nodal positive disease [13]. Surprisingly, even though metaplastic breast cancer is known to be more aggressive, a study by Mills et al demonstrated that there were no major clinical differences in the regional dose, boost dose, or duration of treatment [14].

Metaplastic breast cancer carries a poor prognosis. In a population-based analysis of 250 patients, it was demonstrated that overall survival (OS) was worse than with invasive ductal, and that the outcome is not influenced by hormone receptor status [4]. Additionally, a study using the SEER Database, reported that patients with metaplastic breast cancer have shorter disease-free survival (DFS) than those with invasive ductal carcinoma [15].

Traditionally, histology, tumour grade, stage and axillary lymph node involvement are all thought to influence prognosis [15]. A multivariate analysis Song et al. [16] suggested that a tumour size greater than five centimetres, lymph node involvement and Ki-67 of more than fourteen percent were poor prognostic indicators. Furthermore, Leyrer et al. reported that there does not appear to be a clear histological subtype of metaplastic breast cancer which has significantly different outcomes as compared to the others. There were only positive correlations with tumour stage and presence of distant metastases and a negative correlation between the use of radiotherapy and locoregional recurrence [12].

Our local experience

On analysis of our data for the ten year period from January 2005 to December 2014, the median age at diagnosis was found to be 57 with 71.4% of patients being triple negative. This is in keeping with international statistical data.

In our population, the presenting tumour size averaged 44 millimetres. Only 28.5% of cases were recognised preoperatively via core biopsy. This is a challenging factor regarding management since incorrect histological diagnosis preoperatively can result in neoadjuvant chemotherapy being used for large metaplastic tumours, which respond poorly, thereby delaying early definitive surgery, which may affect survival.

All patients received surgical intervention, except for one, who presented with metastatic disease. 57.1% of patients underwent mastectomy and axillary lymph node clearance, with 28.5% receiving breast conservation surgery. No patients received neoadjuvant chemotherapy. All patients receiving breast conservation surgery received adjuvant chemotherapy and radiation to the breast and axilla. Those who underwent mastectomy and axillary lymph node clearance received adjuvant chemotherapy and no radiotherapy. Notably, HER 2 positive patients did not receive Herceptin due to limited availability in our setting.

Histologically, 57.1% of tumours were of the mixed spindle /mesenchymal type. Only 14% of patients had axillary nodal metastases, which is known to be an uncommon finding in metaplastic breast cancer.

Our overall incidence, based on our limited sample size, is 0.63%, compared to 0.2% worldwide. Despite this higher occurrence, 71.4% of patients at our institution have a disease free five-year survival, suggesting better prognosis. This may be attributed to smaller tumour size at presentation, short time to surgical intervention, together with the use of adjuvant chemotherapy and radiotherapy.

Conclusion

Though rare, metaplastic breast cancer runs an aggressive course and has a poor prognosis. As such, focus needs to be placed on the early detection and accurate diagnosis of this condition. It is evident that early surgery and adjuvant radiotherapy are of prime importance in the management of this disease, which may account for the good survival of our patients, despite a higher than normal incidence in our population. Preoperative Trucut biopsy does not usually yield the correct diagnosis. However, due to our small series size our ability to make recommendations is limited. Large scale studies are required for the development of standardised treatment regimes for this disease.

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