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Atypical breasts cancers

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ABSTRACT

INTRODUCTION: With increasing incidence of breast cancers there are now a larger number of cases diagnosed with rare malignancies. These can be diagnostic dilemmas and management strategy can be different by various breast multi-disciplinary teams (MDT).

We aim to discuss the evidence-based approach for management of these atypical breast cancers which were identified in patients from a single breast screening unit.

METHOD: Patient with unusual breast malignancies (all types except invasive ductal and lobular) treated under the care of a single surgeon were identified during the breast multi-disciplinary discussion from 2011 to 2015. The histology and management of these cases were reviewed and literature search of electronic databases via PubMed and the search engines Google/Google Scholar was performed. Emphasis on keywords based on the histology type was used to limit search. Search was focused on the diagnosis, management and prognosis of these unusual breast cancers.

CONCLUSION: This series aims to focus on the evidence-based management of these rare breast malignancies; the diagnosis of which is crucial as it affects the overall treatment and prognosis.

1. Introduction

Breast cancer is a heterogeneous condition of which there is a high degree of variation between and within tumours [1]. Despite the small number of cases that consist of atypical breast malignancies, the rising rate of breast cancers has created a larger proportion of rare malignancies.

This is a series of some atypical breast cancers encountered during one surgeon's practice. Including a case of malignant myoepithelioma which is an extremely rare entity and diagnostic challenge for the breast multi-disciplinary team (MDT). Along with this we report interesting cases of invasive mucinous carcinoma and apocrine carcinoma which are less widely seen than the more commonly seen invasive ductal and lobular cancers but require vigilance of their variable characteristics to ensure right management [2].

The aim of these cases is to discuss the evidence based approach for these cancers following our previous review [3].

2. Malignant myoepithelioma of breast

2.1. Case report

A 58 year old lady who was known to have a ductal adenoma of her left breast for 3 years was identified on screening mammogram which suggested that the adenoma had enlarged in size and looked atypical in appearance and was graded as indeterminate on mammogram (M3). She underwent an ultrasound of the breast which suggested this to be a suspicious lesion (U4). A fine needle aspiration (FNA) biopsy was performed for the lesion this suggested a cellular aspirate with benign ductal epithelial cells, some showing apocrine changes associated with myoepithelial cells. As such, cytology was overall graded as indeterminate in nature (C3). The patient underwent a core biopsy of the lump and this revealed an atypical ductal lesion with cellular and nuclear atypica, moreover myoepithelial cells were seen throughout most of the lesion. The differentiation between an adenoma and adenoma–myoepithelial lesion could not be made and therefore a diagnostic biopsy of the lesion was performed which suggested a grade 3 metaplastic carcinoma in an existing adenomyoepithelioma. The tumour measured 19 mm with clear excision margins. Due to the complexity around histological analysis, the case was referred to experts in a tertiary centre for their views. A detailed report reads as follows: *'a tumour from an admixture of relatively scanty tubular structures with surrounding cells of variable appearance. For the most part these latter are also rather epithelioid with abundant cytoplasm and large nuclei and elsewhere more spindle in nature* (Fig. 1). *Immunohistochemistry*

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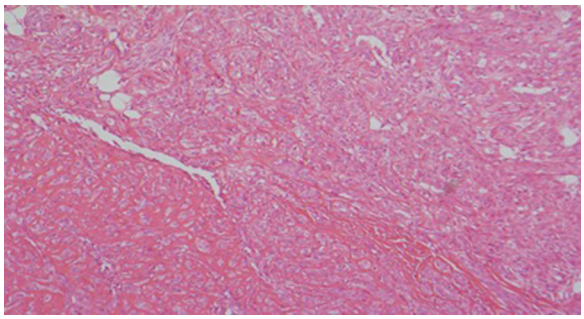

Fig. 1. Malignant adenomyoepithelioma with a central component of small well-formed tubules and spindle cells, and a more atypical epithelioid component at the periphery.

for smooth muscle myosin (SMM) appears to show myoepithelial cells. Many of the immunohistochemistry suggested dual population of cells, the tubular structure was positive with epithelial membrane antigen (EMA) and focally with oestrogen receptor (ER), although not progesterone receptors and HER 2 is negative too. The tubular portions stain up particularly strongly with CK7, although the surrounding cells also show reactivity. The latter are confirmed to be of myoepithelial phenotype with smooth muscle actin (SMA), smooth muscle myosin heavy chain (SMMHC) and p63. Staining for CK5/6 and S100 was seen throughout the lesion but more pronounced in the atypical periphery. Even within the peripheral, well-defined islands of more atypical forms, there is still immunopositivity with both epithelial and myoepithelial markers in adjacent cells within an individual cluster indicating there is an underlying dual phenotype. Therefore it is advised to best regard it as malignant adenomyoepithelioma based on the morphology and immunopattern.'

After confirming the diagnosis of malignant myoepithelioma, the patient subsequently underwent radiotherapy to the affected breast for 3 weeks with 15 Gy given in 15 fractions over 21 day period. Due to ER positivity adjuvant endocrine treatment in the form of Letrozole 2.5 mg once a day was commenced. She has remained well and has been disease free for 22 months.

2.2. Literature review

Myoepithelial cells are located around sweat, lacrimal, and salivary glands, and also seen around the secretory alveoli of mammary glands [4]. Myoepithelium has both epithelial and smooth muscle cells and tumours arising from this site are called myoepitheliomas. Although breast glands like the salivary glands are tubulo-acinar exocrine glands, myoepitheliomas are very rare in breast tissue compared to the salivary glands [5].

Tavassolvi described 3 types of these lesions—myoepithelioma, adenoepithelioma and the sinister variant malignant myoepithelioma [6]. Besides the breast other rare sites of malignant myoepitheliomas are reported on the skin, lungs [7], vulva [4] and nasopharynx.

The World Health Organization (WHO) recognised this entity in 1919 and according to this classification; myoepithelial carcinoma is composed almost exclusively of tumour cells with myoepithelial differentiation [6,8].

The mean age of presentation is the 5th decade [5,8] with women presenting with a painless breast lump. Diagnosis is made on immunohistochemistry using antibodies to broad-spectrum keratins, p63 and antibodies to myofilament. Antibodies namely C10, p63, S100 protein, α-smooth muscle actin (SMA), caldesmon are considered the common markers for detecting these lesions. Our case was labelled as malignant myoepithelioma after the immunohistochemistry showed positivity to p63, S100 and SMA; in short it was found to have immunnopositivity for both epithelial and myoepithelial markers, which is typical of myoepithelial carcinoma cells.

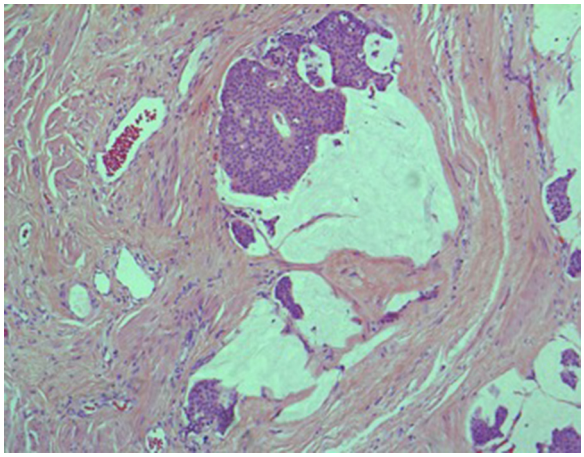

Fig. 2. Invasive mucinous carcinoma composed of sheets of monotonous atypical epithelial cells within dissecting pools of mucin.

Malignant myoepitheliomas tend to be negative for oestrogen receptors [ER] [9] and for this reason Suguna et al. [8] suggested that all ER negative breast cancers should have myoepithelial markers tested as a significant number (29%) of these exhibit these markers [9]. Although the vast majority are ER negative cancer, in our case due to the dual population identified in the lesion with a small tubular structure in the centre which was ER positive, she was commenced on an aromatase inhibitor.

Treatment for myoepitheliomas is surgical excision of the lesion followed by radiotherapy to the breast for breast conserving procedures to prevent local recurrence [4]. In a report by Tsuda [10] 6 patients were treated by local excision and only 1 patient received radiotherapy treatment, as a consequence 3 of the patients developed local recurrence. The dose of radiotherapy is variable and some have recommend 50 Gy radiotherapy in 15–25 fractions. In our case, the patient received 3 weeks of radiotherapy at 15 Gy in 15 fractions and has remained disease free to date.

These cancers have a tendency to metastasize to viscera's like lungs and brain [5,10] and are found to be aggressive in nature [7] despite this, the role of chemotherapy is controversial and there is no consensus of its use [8]. In a study by Behranwala et al. [11], the 2-year and 5-year survival was 88% and 55% respectively.

3. Mucinous carcinoma of the breast

3.1. Case report 1

A 69 year old lady who was identified through breast screening in December 2012 for a new stellate mass found in her left breast which appeared highly suspicious of cancer (M4). She underwent both FNA and core biopsy of this lesion. FNA suggested a moderate yield of malignant cells in crowded clusters with a large amount of mucin in the background. These appearances were in keeping with a special mucinous type breast carcinoma. The core biopsy of the lesion confirmed an invasive mucinous carcinoma which was oestrogens receptor (ER) positive and HER2 negative. A staging scan revealed no abnormal appearance of axillary nodes. She subsequently underwent a wide local excision and sentinel node biopsy. Histology following this, showed a grade 2 invasive mucinous carcinoma comprising of mucin lakes in which small nests of malignant epithelial cells were suspended within the breast tissue as seen in Fig. 2. There were also associated micro calcification as well as high grade DCIS with a cribriform architecture; associated with this was lymphovascular space invasion in the tissue. In summary, she had

a grade 2 invasive mucinous carcinoma which measured 9.6 mm with a whole tumour size including DCIS of 11 mm. The 2 sentinel nodes that were removed were found to be free of metastasis.

She was subsequently referred for radiotherapy treatment with the oncologist and was also started on Letrozole 2.5 mg to be taken once a day. She received 40 Gy in 15 fractions to the left breast over a period of 3 weeks.

The patient remains well and after 3 years of follow up there is no evidence of local recurrence or distant metastasis.

3.2. Case report 2

A 48 year old lady presented to the symptomatic clinic with 6–7 month history of left breast pain. On examination she had tethering of the skin on the left breast most noticeable when raising her arm. A 5 cm firm lump underneath the left sub areola area was identified and she underwent mammography which identified a 46 mm ill-defined opacity of unclear nature (M3). On ultrasound the lesion looked more like a haematoma (U2). Following this she had a FNA and a core biopsy; FNA cytology revealed dispersed monomorphic small to medium sized atypical cells with hyperchromatic nuclei and moderate cytoplasm containing intra nuclear vacuoles, with mucin present in the background. The appearances were suggestive of a mucinous carcinoma (C5). The core biopsy of the lump confirmed features of invasive mucinous carcinoma grade 2 (B5b). Due to the size of the lump she underwent mastectomy and axillary node sampling. Microscopy of the specimen revealed a well circumscribed and partially encapsulated tumour composed of tumour cell nests floating within lakes of mucin measuring 35 mm. The appearances were most in keeping with a grade 1 invasive mucinous carcinoma. There was possible lymphovascular space invasion seen and tumour was found to be oestrogen positive (ER) and HER 2 negative. 1 out of 3 sentinel nodes removed showed metastatic carcinoma and therefore she underwent axillary clearance but no further malignancy was found in the nodes. After discussing her case in the breast MDT she was recommended to undergo chemotherapy treatment followed by 5 years of endocrine treatment. She had chemotherapy in the form of 6 courses of 5 Fluorouracil (FU), Epirubicin and Cyclophosphamide. She initially accepted to take part in the SUPREMO trial (Selective Use of Postoperative Radiotherapy aftEr MastectOmy) which randomises patients with 1–3 positive nodes to either chest wall radiotherapy versus no further treatment. She has since refused to undergo any further treatment and currently remains well four years after her original operation and has also underwent breast reconstruction.

3.3. Case report 3

A 63 year old lady was identified from breast screening in November 2011 with a poorly defined opacity in the right upper inner breast. On mammogram there was a 13 mm stellate lesion and had features consistent of a carcinoma (M5) but an ultrasound of the breast was not able to identify this area. A FNA of the lesion was performed which revealed paucicellular specimen containing a few benign ductal epithelial cells only. However, on the core biopsy performed a special type mucinous carcinoma was identified which was oestrogen receptor positive (ER) and HER2 negative. She underwent a wide local excision and sentinel node biopsy and histology of the tissue removed showed a 20 mm grade 1 invasive mucinous adenocarcinoma with presence of lymphovascular invasion. 1 of the sentinel lymph node showed positive staining with S100, HMB45 and melan-A indicating there were melanocytes present. This patient previously had a nodular malignant melanoma excised early that year and the features suggested metastatic malignant melanoma. Fortunately, there was no evidence of mucinous adenocarcinoma metastasis to the axilla. Her case was discussed in MDT and she was referred to the melanoma team for axillary block dissection. She also received postoperative radiotherapy 40 Gy in 15 fractions over 22 days to the right breast. After 4 years of follow up since her original surgery she remains symptom free.

3.4. Literature review

Mucinous carcinoma of the breast is estimated to account for less than 5.5% of all breast cancers [12]. The incidence for this type of cancer in literature is variable due to histological variability with some carcinomas being purely mucinous and others being mixed in nature.

Mucinous carcinoma is defined as tumour containing a mucinous component of 50% or more [9,13]. Although some describe the amount of mucin could be lower than that (>33–50%) and still be considered as mucinous carcinoma [9]. On histology these cancers have clusters of neoplastic cells suspended in extra cellular mucin [14]. There are 2 broad classifications based on the amount of mucin present; one is a pure mucinous breast carcinoma (PMBC) and the other type is a mixed mucinous breast carcinoma (MMBC). WHO has defined PMBC as consisting exclusively of tumour tissue with extracellular mucin production while MMBC is a tumour where there are area of both mucinous and infiltrating ductal epithelial component [12]. Pure mucinous cancers are seen in 2–3% of all invasive cancers and majority; like all our cases reported belong to the mixed mucinous group.

This is a helpful distinction as it has been suggested that pure and mixed carcinomas differ significantly with respect to prognostic factors. Rasmussen et al. [15] found that patients with pure mucinous carcinomas had fewer lymph node metastases at the time of primary operation and a longer recurrence-free survival times than those with mixed carcinomas. The same conclusion was reported by Komaki et al. who showed the 10-year survival rate of PMBC being 90.4% compared to 66.0% in MMBC.

Age of presentation is variable but generally it affects older population with a median age of 55–60 years [9,16].

The presentation of mucinous carcinoma is highly variable and there is debate about common characteristics on mammography. One study examining PMBC found that although majority of the lesions (87%) were palpable clinically but 1/3rd (17%) of these were not visible on mammogram [15]. They can have well defined margins on the X-rays unlike the classical ill-defined margins of a cancer and could mislead for benign lesions.

Surgical treatment involves local excision of the lump or mastectomy with sentinel node mapping. This is followed by chemotherapy, adjuvant radiotherapy in case of breast conserving surgery and endocrine treatment. The drug of choice for chemotherapy is anthracycline based.

The prognosis for patients with mucinous breast cancer is generally favourable with a 10 year survival of more than 90% for pure mucinous cancer [17]. When compared to ductal carcinomas, mucinous carcinomas tend to be of a lower grade at time of detection [18] and have a low incidence of lymph node metastasis and recurrence rate. A wide ranging study using the Netherlands Cancer Registry showed that there was a better age, stage and grade adjusted prognosis for patients with mucinous carcinoma when compared to invasive ductal carcinomas [19].

Positive nodal status has been reported as being the most significant predictor of worse prognosis [20]. As far as the tumour size is concerned, there is debate on whether the tumour size has an impact on survival or not. There are studies correlating larger size with a poorer prognosis compared to others where no significant impact on survival based on tumour size has been found [21]. This is potentially because the volume of mucin surrounding the tumour can mean the true size of the tumour can be difficult to determine. Although size of the tumour is not an important factor to

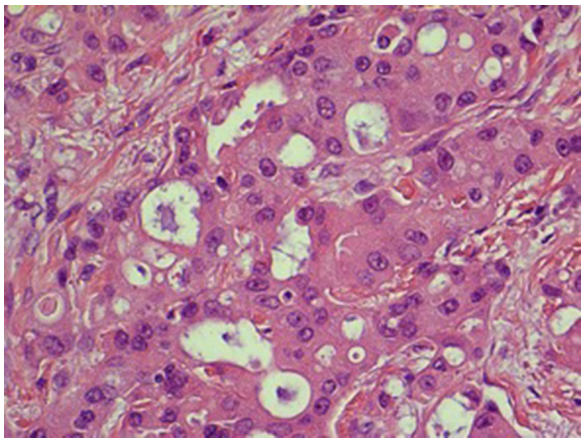

Fig. 3. Invasive apocrine carcinoma composed of cells with abundant eosinophilic and finely granular cytoplasm.

determine the prognosis as the bulk of the tumour is given by the mucin which is considered to overestimate the tumour size. However the presence of mucin is found to give resistance to Transtuzumab and these cancers are found to be HER 2 negative [13]. Although nodal status is a sign of poor prognosis but nodal involvement is rare in such cancers with nodal disease from 12 to 19% reported [9]. For this reason there have been suggestion to avoid nodal dissection when removing the mucinous cancer [21].

4. Invasive apocrine breast cancers

4.1. Case report 1

This 60 year old lady was seen at the screening clinic in February 2011 after being diagnosed with right breast cancer on screening mammogram. The tumour measured 5 mm on mammogram (M3) but was not visible on ultrasound. FNA was not performed but she underwent a vacuum-assisted core biopsy (VACB) of this area. This showed pieces of generally markedly hyalinised breast tissue with evidence of active chronic inflammation, associated with atypical apocrine appearing areas. These were markedly atypical, with areas of calcification seen within it. The appearances suggested an apocrine high grade DCIS. In addition, there were areas of atypical cells present as cords and columns within the stroma and the sample was interpreted as an invasive ductal carcinoma grade 2, with apocrine features. After discussing her case in the breast MDT she was recommended to undergo breast conserving surgery and sentinel node biopsy. Histology of the breast tumour removed showed a small focus of residual high grade DCIS with micro papillary and comedo growth patterns. There was a 5 mm focus of invasive carcinoma composed of solid islands of tumour cells which have abundant eosinophilic cytoplasm and round nuclei with prominent central nuclei as seen in Fig. 3. The appearances were those of a grade 2 invasive apocrine carcinoma which was oestrogen receptor negative (ER) but HER2 positive. 2 sentinel nodes were removed and these were found to be free of metastasis. She only underwent postoperative radiotherapy of 40 Gy in 15 fractions over 22 days to the right breast even though it was recommended for her to have chemotherapy and Herceptin treatment. She has remained disease free four years since her treatment.

4.2. Case report 2

This 67 year old lady was referred to the symptomatic clinic with a chance finding of a lesion identified in her left breast on her CT chest organised for investigation of upper GI symptoms. This showed an ill-defined enhancing nodular area in the outer aspect of the left breast measuring 16 mm. Clinically there was no palpable lump but on mammography an 18 mm irregular density in the left upper outer breast was identified which looked suspicious for cancer (M4). An ultrasound scan of the left breast was also performed and revealed this lesion to be a 16 mm irregular solid mass consistent with malignancy (U5). A FNA and core biopsy of the lesion was performed. The FNA examination revealed a cellular specimen with the best preserved cells seen with numerous sheets of apocrine cells and variable nuclear pleomorphism. There appeared to be myoepithelial cells in the background raising the possibility of an apocrine variant of ductal carcinoma. A core biopsy of this area showed invasive ductal carcinoma grade 2 with apocrine architecture and the tumour was found to be ER and Her2 negative. This lady opted for wide local excision and sentinel node biopsy. Her final histology confirmed a 12 mm grade 2 invasive apocrine carcinoma and the sentinel nodes removed were free of metastasis. MDT recommended radiotherapy and chemotherapy treatment for this lady. She completed 6 cycles of FEC (Fluorouracil, Cyclophosphamide and Epirubicin) followed by radiotherapy to the breast in the form of 40 Gy in 15 fractions only.

4.3. Literature review

Apocrine carcinoma of the breast is seen in women between 6th and 7th decade. It is a rare cancer and its incidence is reported between 0.3–4% of all female breast cancer [22] unlike a much higher quoted incidence of 62% in one study [23]. This variation is simply due to the fact that in the past there were no strict criteria available to describe these lesions till Rosen [24] suggested that apocrine cancers should be reserved for 'neoplasms in which all or nearly all the epithelium has apocrine cytological features [24]. Japaze et al. [25] proposed a strict criteria to diagnose apocrine lesions; this included 75% cells containing apocrine features and the cells to be large in size containing eosinophilic cytoplasm with sharply defined borders. The cells have a nucleus to cytoplasm ratio of 1:2 and contain large nucleoli.

Both our cases had typical features of apocrine tumours as the criteria suggested with abundant eosinophilic cytoplasm in the cells and nuclear pleomorphism.

One misconception regarding these tumours was the source of its origin which was initially thought to arise from apocrine sweat glands but this was proved to be wrong and the true origin of the apocrine cells was later confirmed to arise in the terminal duct-lobular unit [23]. These cancers do not express oestrogens or progesterone receptors but there is over expression of human epidermal growth factor and therefore these lesions are found to be HER 2 positive except to occasional negativity to it as has been reported by Tsutsumi [26]. The current recommendation now is to test these cancers for androgen expressivity so the management could be more targeted in the form of anti-androgens. This tumour is assessed immunohistochemically and in majority of cases it expresses GCDFP-15 (76–100%) [22] which is a 15,000 Dalton monomer glycoprotein and is considered a specific tissue marker of apocrine epithelium [27]. Interestingly, the levels of GCDFP-15 decreases with advanced disease and also for node-positive apocrine carcinoma [28].

Prognosis of these cancers is reported as same as the infiltrating ductal cancers [29,30], but some studies have suggested a better 5 year survival than a non-apocrine carcinoma [22].

Conflicts of interest

The authors declare that they have no competing interests.

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Ethical approval

Informed consent provided by patient and in cases of impaired ability to consent, consent was provided by next of kin.

Author contribution

T.F. reviewed the patients selected for discussion and analysed the clinical and histopathology results. L.W. and T.F. worked together to perform the literature search and contributed to the writing of the manuscript. C.N. performed final revisions and editing of final manuscript. All authors read and approved the final manuscript.

Guarantor

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