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Rare breast malignancies and review of literature: A single centres experience



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ABSTRACT

INTRODUCTION: Breast cancer is a heterogeneous condition, with variants which are less common but still very well defined by the World Health Organization (WHO) classification. With the small number of cases each year large trials are difficult to perform. This series aims to discuss the rare breast malignancies encountered within a breast department and the evidence based approached to their management.

METHOD: Literature search of electronic databases via PubMed and the search engines Google/Google Scholar were used. Emphasis on keywords: breast cancer and the type of histology used to limit search. Searches were screened and those articles suitable had full text versions retrieved. The references to all retrieved texts were searched for further relevant studies.

CONCLUSION: Due to the rarity of some of these breast cancers, systematic evaluation of patient with detailed histopathology will aid accurate diagnosis and management. The series hopes to add the existing understanding of this small percentage of cases.

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1. Introduction

Breast cancer is the commonest cancer in UK [1] and one-third of all new cases of cancer in women [2] with about 55,000 new diagnoses made annually. A large majority of breast cancers (60%) are invasive ductal carcinoma [3] which is often described as no special type with about 10% being invasive lobular carcinoma. However as a heterogeneous condition, there are other variants which are less common but still very well defined by the World Health Organization (WHO) classification [4]. With the small number of cases each year large trials are difficult to perform.

This series aims to discuss the rare breast malignancies encountered within a breast department and the evidence based approached to their management.

2. Lymphoma of the breast

2.1. Case reports 1

A 68 year old lady was recalled from breast screening for a poorly defined opacity in her left lower breast. Mammogram showed a 2 cm lesion and an FNA was reported as C5 suspicious for lymphoma. She underwent a core biopsy of the breast lump. This suggested a B cell mature follicular lymphoma. Lymphoid cells were

B cells expressing CD20 and CD 79a. Reactive T cells CD2, CD3 and DC5 were all positive surrounding the follicles. CD5 restricted to T cells. Lymphoid cells were cyclin D1-negative. Follicular cells expressed CD10, Bcl6 and Bcl2. In situ hybridisation studies for kappa and lambda light chains show scattered plasma cells with a polytypic pattern of light chain expression. She underwent bone marrow biopsy, which showed no evidence of marrow infiltration by follicular lymphoma.

Treatment: She went on to have 8 courses of R-CHOP. After her 5th cycle the vincristine was changed to vinblastine to help with neuropathy. An interval CT showed reduction in size of known lesion in the left breast indicating response to treatment. She was maintained on Rituximab on 2 monthly basis for 2 years.

She remained follow up suggesting no recurrence after 2 years of diagnosis Fig. 1.

2.2. Case reports 2

A 76 year old lady presented with a 9 week history of a rapidly enlarging lump on the sternal notch. On examination there was a 3 cm by 3 cm firm lump palpable on the sternum. Breast examination was unremarkable. Mammogram showed no abnormality in the breast but ultrasound of the mass showed a soft tissue lesion. FNA came back as C4 suspicious of lymphoma and core biopsy showed features suggesting of plasmablastic lymphoma. Staging CT scan confirmed the presternal mass was infiltrating the pectoralis major muscles with no definite bony destruction but high attenuation in the marrow implying marrow infiltration. There was

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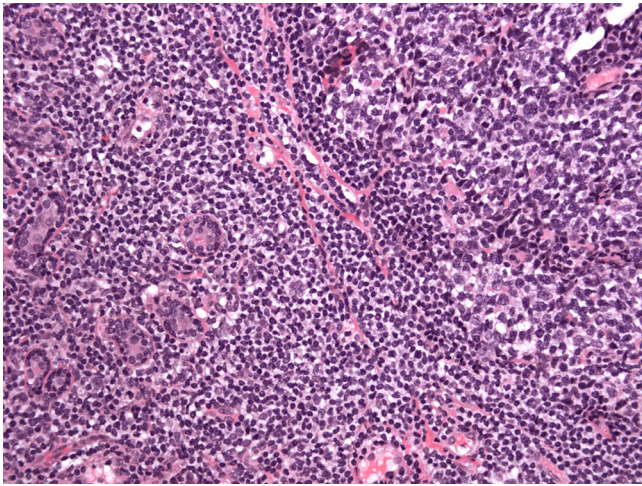


Fig. 1. Immunohistochemistry sample of lymphoma of breast.

no significant lymphadenopathy elsewhere and spleen was normal. Bone marrow aspirate and trephine from the posterior iliac crest had no features to suggest myeloma or marrow infiltration with lymphoma.

A repeat CT 3 months post diagnosis and following chemotherapy showed that the soft tissue mass was completely resolved with no residuum, but there was diffuse ground glass change in both lungs suggesting drug toxicity, intercurrent infection or diffuse lymphoma in the lungs.

2.3. Case reports 3

A 49 year old lady was recalled from screening for an abnormality detected in the left breast. Ultrasound showed a 21 mm mass. FNA was C1 and core biopsy was reported as lymphoid tissue with suspicion of lymphoma B3. Incidentally, she also had a 2 cm by 2 cm firm lump on the right forearm ulnar aspect, firmly adherent to underlying structures. The breast lesion was completely excised for histology. Immunohistochemistry demonstrated expression of the B-cell antigens CD20 and CD79a by the majority of the lymphoid cells, with abundant small reactive T-cells (CD2-positive, CD3-positive, CD5-positive and CD43-positive). There were small numbers of IgD and CD23-positive B-cells consistent with residual mantle zone cells. Larger numbers of Bcl-6-positive cells are identified within the germinal centres but these germinal centre cells are Bcl-2-negative. The Ki67 proliferative fraction is high within the reactive germinal centre fragments. The appearances confirmed B-cell, mature, extra nodal marginal zone lymphoma of mucosal associated lymphoid tissue (MALT). Immunohistochemistry on the wedge biopsy of the lesion on the arm showed expression of the B-cell antigens CD20 and CD79a by the neoplastic cells, in keeping with diffuse large B cell lymphoma which might represent a high grade transformation of the breast lymphoma. Staging CT and PET CT showed involvement of a right axillary node (3.3 cm) and bone marrow examination showed no infiltration.

She has since had 4 cycles of R-CHOP chemotherapy is due for a repeat CT to assess interval progress, with a view to complete 2 further cycles and stop treatment if a final CT and PET show response.

2.4. Review of literature

Malignant lymphomas primarily arising in the breast and in the absence of previously detected lymphoma localizations are termed 'primary breast lymphomas' (PBLs) [5]. PBL accounts for less than

0.5% of breast malignancies [6]. The PBL incidence is 0.04–0.53% of all primary malignant tumours of the breast and 2.2% of extra nodal lymphomas [5]. The most common presentation of PBL is with an incidental breast mass [7,8]. On histology, majority of these are diffuse large B cell lymphoma (DLBCL) with other PBL of low grade histology i.e. follicular lymphoma or extra nodal marginal zone (MALT) lymphoma being rarer [6]. In a series of 37 patients with lymphoma involving the breast at initial presentation, 49% were DLBCL, followed by follicular and MALT representing a combined 38% [7]. Likewise in a Swiss series, 5 out of 7 patient with primary breast lymphoma had DLBCL, one follicular and one a MALT lymphoma [8]. These PBL of low grade histology has been further investigated by the International extra nodal lymphoma study group which studied 60 patients (36 follicular and 24 MALT) [7] most presented with Ann Arbor stage Ie or IIe except for IV_E in 3 patients due to bilateral breast involvement, found on imaging and confirmed on cytology. Only 2 of the 60 presented with B-symptoms [6].

Current treatment of DLBCL following tissue diagnosis is with RCHOP based chemotherapy alone or with radiotherapy. Ganjoo et al. [7] reported a 5 year progression free survival rate of 61% and 5 year overall survival of 82%. In a French series [9] of 19 patients (17 DLBCL, 2 follicular/diffuse grade 3 lymphomas), four patients received local treatment only (resection and local radiotherapy) while the remaining 15 received chemotherapy (CHOP or ACVBP followed by involved field radiotherapy). Three of the four patients treated with local treatment only died of their lymphomas. Among the 11 treated with CHOP, 2 died of their lymphomas. The role of CNS prophylaxis remains unclear as rates of CNS involvements are low. The IELSG series demonstrated a similar behaviour of MALT PBL with primary extra nodal MALT in other locations. However patients with follicular PBL had worse progression-free survival (PFS) and overall survival (OS) compared to limited stage nodal follicular in other locations, suggesting an adverse prognostic role of primary breast localisation [6]. In the Swiss series, of all PBL, five and ten year survivals were 57% and 17%, respectively. In the 3 patients who died, 2 had tumours that was Bcl-2 positive but Bcl-6 negative. All surviving patients have positive Bcl-2 and Bcl-6 immunostaining. This may represent important prognostic factors if proven in a larger study [8].

The role of surgery in this disease should be limited to get a definitive diagnosis [10,11]. While for the staging and the treatment CT scan and chemo radiotherapy are, respectively, mandatory [12,13]. Nowadays, surgical resection plays a therapeutic role only in MALT lymphomas, whereas for large B cell lymphomas has only a diagnostic indication. For such disease, the cornerstone of treatment is systemic chemotherapy [12].

3. Ovarian cancer metastasizing to breast

3.1. Case report

This is an 86 year old lady with known ovarian serous papillary carcinoma of the ovary for which she had undergone total abdominal hysterectomy and bilateral salpingo-oophorectomy and omentectomy a year ago. This was followed by chemotherapy in the form of 6 cycles of Carboplatin. She presented with a lump in her right axilla. On examination there was a 3 × 3 cm lump in the right axilla. Mammogram showed a 30 mm pathological node and FNA was reported as C5, metastatic in nature. Needle fragment from lymph node revealed poorly differentiated carcinoma. A core biopsy of the node showed features consistent with metastatic poorly differentiated serous papillary carcinoma of ovarian or primary peritoneal origin. Tumour expressed pancytokeratins and cytokeratin 7 but not cytokeratin 20. Staining for CA125 showed

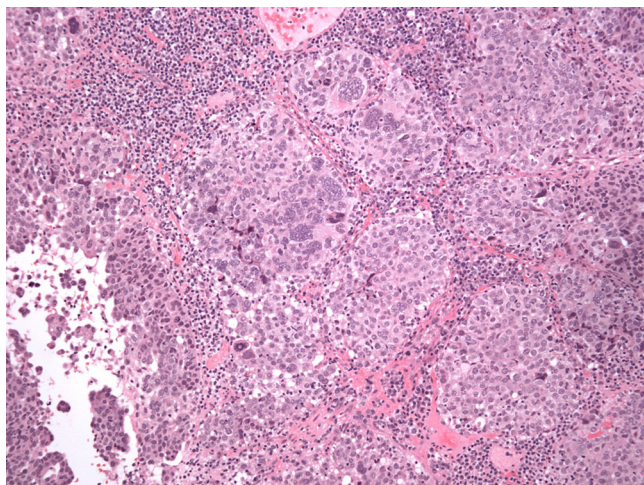


Fig. 2. Immunohistochemistry of metastatic poorly differentiated serous papillary carcinoma.

strong uniform staining for WT1 and P53. Staining for CEA, TTF1 and BRST-2 was found to be negative. A staging CT abdomen and pelvis confirmed disease recurrence [Figs. 2 and 3](#).

Treatment: She went on to receive chemotherapy in the form of Carboplatin and Paclitaxel, the latter was omitted after 1 cycle due to development of neuropathy and lethargy. She completed 6 cycle of Carboplatin given every 3 weeks. She initially responded to the treatment and this was confirmed on the follow up CT.

Unfortunately she had a relapse of the condition after a few months, and was not offered any further treatment due to her frailty. She passed away within 2 years of the initial diagnosis of her axillary metastasis.

3.2. Review of literature

Supradiaphragmatic metastases from ovarian cancer account for less than 1% of all breast malignancies with the most common type being of serous carcinoma. In one paper the majority had evidence of extra mammary malignancy on discovery the breast metastases. Of these cases only 1 out of 32 cases involved primary ovarian carcinoma [\[14\]](#). Although it is very rare Yamasaki et al. [\[15\]](#) reported 30 cases of ovarian malignancy metastatic to the breast. Recine et al. [\[16\]](#) studied a series of 18 patients with metastases to breast of which 14 from serous ovarian carcinomas and 4

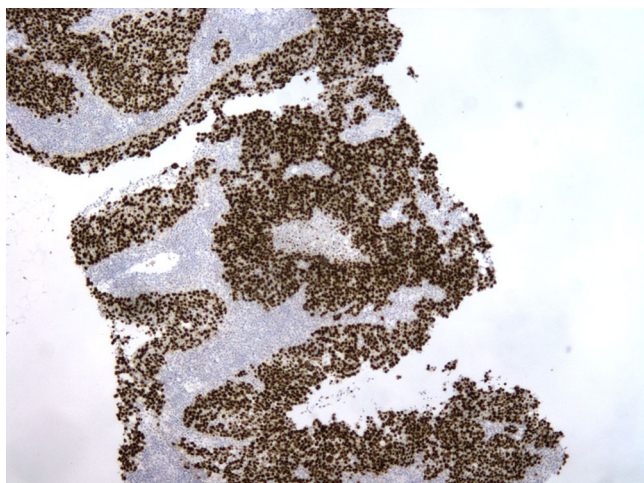


Fig. 3. Staining of WT1 for CA 125.

peritoneal serous carcinomas. The metastases were discovered on average 20 months post presentation with high grade serous carcinomas. These findings are similar to those published previously suggesting most breast metastases of ovarian origin usually occurs with known previous malignancy. Of Recine et al., there were also 3 cases presenting as stage IV having synchronous breast and axillary lymph node metastases. Susini et al. [\[17\]](#) presented a case of ovarian carcinoma detected at screening mammogram initially thought to be intramammary lymph node metastases. The patient had a CA 125 within normal limits but histology following quadrantectomy and axillary dissection suggested that this may have ovarian origin. PET scan showed a small simple ovarian cyst with high FDG uptake which showed turned out to be serous ovarian carcinoma microscopically. As such accurate histology may change management course for the patient. In a separate study by Ozsaran et al. [\[18\]](#), the ovarian cancer metastases to both breasts and axillary lymph nodes. The patient presented with large pelvic mass and pleural effusion. Initial breast examination and mammograms were normal but even with chemotherapy and radiotherapy went on to have bilateral swelling of the areolas, developed nipple retraction and mammogram at that point revealed multiple areas of calcification. This highlights the need for serial examination for breast disease in this group. It is important that metastasis to the breast be differentiated accurately from primary breast cancer, because prognosis and treatment differ significantly [\[18,19\]](#).

4. Primary osteosarcoma of the breast

4.1. Case report

An 81 year old lady presented with a lump in her right breast. On examination there was a suspicious 3 × 2 cm lump on the right breast. This corresponded to a 34 mm irregular mass with micro calcification on mammography. FNA was reported as C5 and core biopsy showed it to be suspicious of either sarcoma or metaplasia. She underwent a right mastectomy. The histopathology report showed that the tumour dimensions were of 30 × 20 × 20 mm. It appeared well circumscribed, relatively uniform with central necrosis. It comprised of osteoid multinucleate giant cells and abundant undifferentiated stroma. There was no evidence of any epithelial component and staining for cytokeratins like 34beta12E and MNF16 were negative. The tumour was also negative for smooth muscle actin. The stromal component was strongly positive for vimentin. There was no vessel space invasion.

Excision was complete by a margin of at least 20 mm. There were no features suggesting any antecedent phyllodes tumour ([Fig. 3](#)). The dissected right axillary lymph nodes showed reactive features only, with no evidence of metastatic carcinoma. Overall, the histological features were those of a Primary Breast Osteosarcoma (PBO) with tumour diameter 35 mm, no vessel space invasion and lymph node negative. She went on to have radiotherapy and at 5 years there had been no evidence of local recurrence. This case has been reported in literature [Fig. 4](#) [\[20\]](#).

4.2. Review of literature

The literature suggests less than 0.1% of breast malignancies are due to primary sarcoma. However 'pure osteosarcoma' that has no epithelial component, not arising from bone and not associated with a benign tumour is rare. This is less than 1% of all soft tissue sarcomas and tends appear in the more elderly compare to skeletal osteosarcomas [\[21\]](#). The Mayo clinic series over 60 years [\[22\]](#) had 24 of 25 patients with primary breast sarcoma which presented with a palpable mass, of which 1 was an osteosarcoma. Coussy et al. [\[21\]](#) described the case of a 61 year old woman who

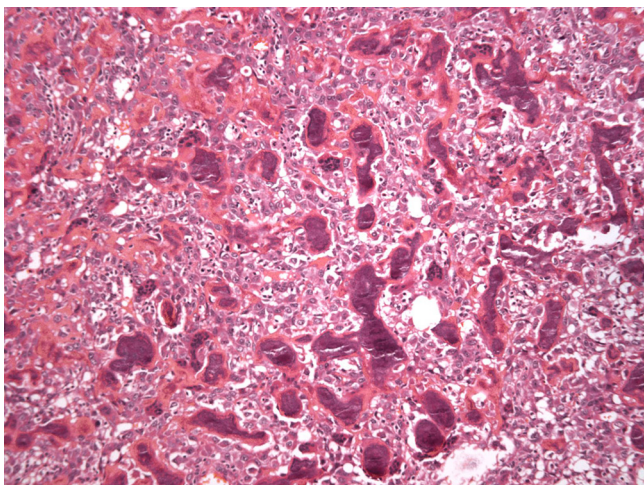


Fig. 4. Slide rich with osteoid multinucleate giant cells and abundant undifferentiated stroma which is positive for vimentin.

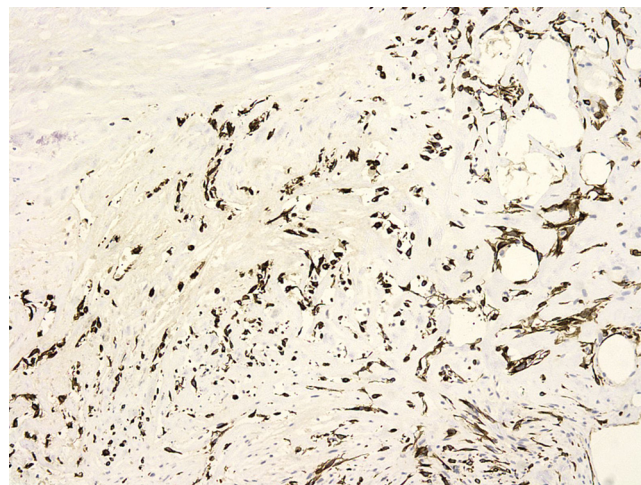


Fig. 5. Staining for CK epithelial marker.

presented with a painless mass which turned out to be osteosarcoma. The mammogram showed a well-defined mass with large macro calcification closely resembling bone as well as peripheral soft tissue mass. An MRI showed low signal intensity of the central mineralised matrix with rapid enhancement of the peripheral mass. The core biopsy confirmed a spindle shaped tumour. Similarly a Japanese case of a 59 year old woman who presented with a left breast lump described mammography which showed crushed stone like calcification. Immunohistochemistry indicated the presence of vimentin without epithelial markers [23]. The diagnostic criteria for osteosarcoma is the absence of epithelial component in the tissue with neoplastic osteoid element [20,24–28].

Recommended management includes total excision with adequate margins but no axillary dissection is required as lymph node involvement is rare and no radiotherapy is required either [21–23]. Treatment is poorly standardised but adjuvant chemotherapy should be considered for patients based on tumour size, histological grade, and histological subtype, with infiltrative margins and necrosis as poor prognostic features. The author [22,23] also summarised that tumour size appeared to be a more valuable prognostic factor for survival rates.

5. Metaplastic carcinomas

5.1. Case report of spindle cell carcinoma

A 58 year old lady presented with a lump in her left breast. She had previously undergone excision of a benign breast lump left breast 10 years ago. On examination there was some induration at the existing scar but mammogram showed 2 new suspicious masses associated to the lumpectomy site. FNA was reported as C5 and core biopsy showed an invasive metaplastic carcinoma with focal hyalinisation of the stroma. It expressed epithelial markers cytokeratin (KAE1/3 and MNF116) and E cadherin indicating a spindle cell carcinoma which was ER, PGR and HER2 negative Figs. 5 and 6.

Treatment: She underwent mastectomy and sentinel lymph node followed by adjuvant chemotherapy in the form of 6 courses of FEC to which she responded very well. This lady developed metastatic recurrence of her breast cancer in left upper lobe of lung after one year and underwent surgical excision of it. A repeat CT in 3 months' time revealed a new left lower lobe nodule, but there was no evidence of liver or bony metastasis. She is currently undergoing palliative chemotherapy in the form of Paclitaxel and Avastin.

5.2. Case report of invasive squamous cell carcinoma

A 74 year lady presented to the symptomatic breast clinic with left nipple inversion associated with a subareolar mass. Her left breast mammogram revealed a 20 mm ill-defined mass highly suspicious of malignancy. She underwent a FNA of the lump, this confirmed malignant cytology C5. A core biopsy of the lump showed a moderately/poorly differentiated squamous cell carcinoma with central cystic and necrotic element. She opted for a mastectomy and sentinel node biopsy. This confirmed as invasive squamous cell carcinoma with no vessel space or skin involvement. The tumour was ER and HER2 negative. There was no evidence of nodal involvement.

No other treatment was offered and she is still under yearly follow up for last 2 years Fig. 7.

5.3. Review of literature

Metaplastic carcinomas of the breast form a heterogeneous group composing of epithelial or mesenchymal cell population admixed with adenocarcinoma and include epithelial only carcinomas as a subtype [29]. This includes biphasic epithelial and sarcomatoid carcinoma and monophasic spindle cell carcinoma [30]. The group still represents less than 1% of all breast malignancies and low grade disease can mimic benign fibrous breast lesions. Most metaplastic carcinomas are sporadic, but there may

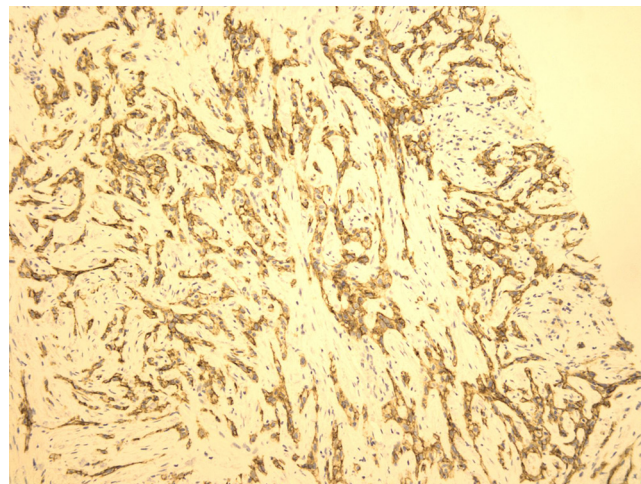


Fig. 6. Staining for E cadherin.

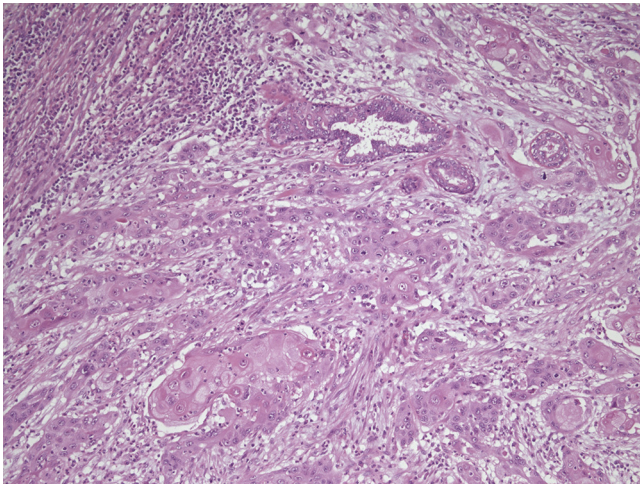


Fig. 7. Histology demonstrating squamous cell carcinoma of the breast.

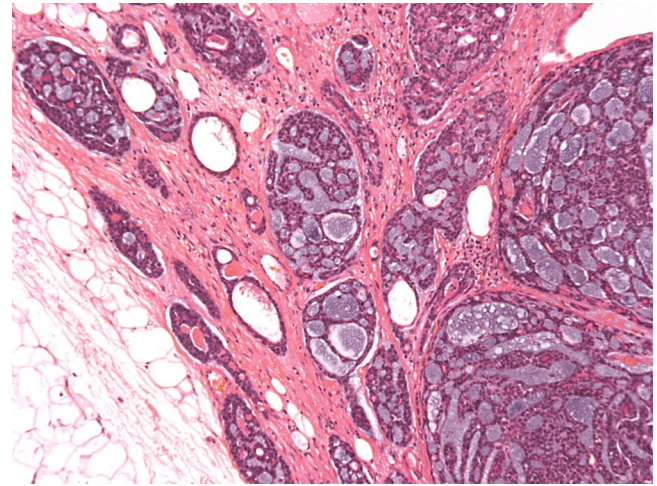


Fig. 8. Specimen demonstrating glandular lumens with eosinophilic material.

be a slight propensity for metaplastic spindle cell carcinoma to arise from pre-existing lesions, including papillomas, complex sclerosing lesions and nipple adenomas [30–32]. A series by Abd el-All [33] of eight patients initially had FNAC define 4 as benign, 2 as suspicious and 3 as malignant but following wide excision biopsy were reclassified into 5 benign and 3 malignant. The common finding on FNAC was the presence of spindle cells without ductal epithelial cells. Immunohistochemistry was helpful in clinching the diagnosis. According to Tse et al. [30] of the 34 sporadic carcinomas identified in his series, oestrogen and progesterone receptors were only positive in 4 (12%) and 3 (9%) of the cases, respectively. Likewise only 5 (15%) had positive expression of C-erbB2 oncogene, which may limit oncological treatment options. Increasingly this is referred to as triple-negative breast cancer (TNBC). Similarly, in a series of 26 Canadian cases, only 5 were ER positive and 2 were PR positive and 1 was HER2/neu positive adenosquamous carcinoma [29].

Another variant seen is squamous cell carcinoma (SCC) of the breast. Not to be confused with the more commonly seen cutaneous squamous cell carcinoma, the diagnosis of these breast lesions constitutes less than 0.1% of all breast carcinomas [34]. SCC of the breast, account for less than 1% of invasive carcinoma [35] and nodal involvement varies from 6–50% depending on source and use of chemotherapy is unclear. In the literature only some small series are reported [36–39]. It does not involve skin or have associated lesion on a second site [36]. Squamous cell metaplasia is also seen in cysts, chronic inflammations, abscesses and adenofibromas [36,38]. This hypothesis is further supported by many cases where primary squamous cell carcinoma is reported after its initial appearance as a benign disorder (abscess or after implantation of a breast prosthesis or after radiation therapy) [38–43]. In the study by Talmor et al. [43], it has been postulated that the origin of the epithelial element could be from the epidermoid cysts deposited during development or due to trauma or during surgery. Like other metaplastic carcinoma they poorly respond to chemotherapy and are an aggressive malignancy with poor outcomes [34].

6. Adenoid cystic carcinoma

6.1. Case reports 1

A 66 year old lady presented with a small lump in her right breast. She had a previous breast cyst and a family history of breast cancer (mother). Her mammogram confirmed highly suspicious lesion in her right breast. FNA was C3 but core biopsy confirmed this to be adenoid cystic carcinoma B5b. She underwent a wide

local excision and sentinel lymph node biopsy. Histology confirmed an 18 × 15 × 20 mm tumour which was moderately differentiated adenoid cystic carcinoma. It was well circumscribed and focally encapsulated tumour. It composed of small basaloid cells and larger cells with vesicular nuclei. Tumour cells were arranged in cribriform pattern but tubular and solid patterns were also noted. Most lumina contained mucin but focally pink hyaline like material was also present. Tumour was ER & PGR and HER 2 negative. There was no lymphovascular or perineural invasion. No lymph node involvement in sampling of axillary nodes was found.

She underwent radiotherapy treatment using standard tangential field arrangement, 6-15MV photons, treating to a dose of 45 Gy in 20 fractions followed by boost to tumour bed right lateral breast using single field 12MeV electrons to a dose of 10 Gy in 5 fractions. 55 Gy in 25 fractions to the tumour bed in view of adenoid cystic histology. There has been no evidence of local recurrence after 5 years of surgery and she has been discharged from surveillance of breast cancer. This case has been reported in literature by Veeratterapillay et al. [44].

6.2. Case reports 2

An 82yr demented lady was found to have a right sided breast lump by her carer for nearly 2 weeks. On examination there was a firm lump palpable in the upper outer right breast and this was confirmed on USS. She refused to undergo a mammogram. She had a core biopsy of the lump confirming an adenoid cystic carcinoma. She underwent right mastectomy and axillary dissection. The histology of the breast and axillary specimen showed a 21 mm well circumscribed adenoid cystic carcinoma. There were predominantly cells with basaloid appearance with crowded monotonous oval nuclei and only minimal cytoplasm. There was also cribriform arrangement with well circumscribed pseudo lumens containing myxoid material as well as very occasional true glandular lumens containing dense eosinophilic material. In other areas the cells form elongated trabeculae and occasional tubules. None of the nodes were involved and tumour was ER and HER2 negative Fig. 8.

She has been discharged from follow up due to her noncompliance with surveillance or clinical examination, but last follows up after 2 years had shown no recurrence.

6.3. Review of literature

ACC of the breast accounts for less than 0.1% of breast malignancies. ACC is most commonly seen as a tumour of the salivary glands

but there are similarities in morphology even though they behave differently. The biggest study on ACC is the population based cohort study by Ghabach et al. [45] This showed no evidence of increase risk of contralateral malignancy compared to the 60% significantly increased risk of contralateral breast cancer reported in the SEER-based study [46]. Due to the rarity of this condition no definite surgical treatment is recommended. There are studies supporting simple lumpectomy with or without radiation, simple to radical to mastectomy [47]. The chance of local recurrence has been high. As such if lumpectomy [47,48] is preferred radiotherapy to the breast is usually recommended. Some studies discourage performing any form of axillary surgery as the risk of nodal involvement is minimal [47,49]. However, unlike its head and neck counterpart it is associated with favourable prognosis with excellent survival in the absence of other cancers [47]. Studies have shown it to be low grade, node negative and receptor negative tumour [49] and one of the only triple negative cancers where there is no role for chemotherapy [50]. Although, lymph node involvement in breast ACC is uncommon [45,47,51], some surgeons still prefer to perform sampling of nodes as seen in both our cases. As this condition is rare, we are unable to not recommend axillary procedures due to the diversity of procedures offered.

Conflict of interests

The author(s) declare that they have no competing interests.

Authors' contributions

CN and TF reviewed the patients selected for discussion and analysed the clinical and histopathology results. CN, NA and TF worked together to perform the literature search and contributed to the writing of the manuscript. All authors read and approved the final manuscript.

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Cases of ACC and PBO have been published previously, the senior author of the publication is also an author of this paper and have given consent for the cases to be publish here.

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