Pathology (August 2019) **51(5)**, pp. 529–561

CORRESPONDENCE

Primary squamous carcinoma of breast – a rare entity: report of two cases and review of the literature

Sir,

According to the World Health Organization (WHO) classification of tumours of breast,[1] primary squamous cell carcinoma (SqCC) of the breast is classified as metaplastic breast carcinoma. It is rare, with an estimated prevalence of <0.1% of all breast carcinomas. The diagnostic criteria include the presence of more than 90% of tumour cells with squamous differentiation, exclusion of metastatic disease from elsewhere and absence of origin from skin or nipple.[1] Metaplastic carcinomas, including squamous carcinomas, are usually large in size and poorly differentiated with high histological grade. They metastasise less commonly than other breast cancer types to regional lymph nodes and are usually hormone receptor negative.[2] SqCC of the breast carries a poorer prognosis than most other breast malignancies. Most of these cancers present as a cystic lesion or as an inflammatory mass and do not have any particular diagnostic features on imaging, rendering preoperative diagnosis of SqCC difficult. We report here two cases of primary SqCC of breast from a regional hospital in New South Wales, Australia.

A 55-year-old woman presented with a persistent firm lump of several months duration in the axillary tail of the left breast in March 2009. Core biopsy of the lesion showed features of benign fibrocystic change. The lesion increased in size on follow up ultrasound and mammogram showing increased internal calcifications. Fine needle aspiration cytology (FNAC) of the lesion in October 2010 showed malignant cells with squamous differentiation. Ultrasound of the axilla showed multiple enlarged lymph nodes. The previous core biopsy of the left breast lesion was reviewed and the diagnosis remained unchanged as fibrocystic change. The patient underwent wide local excision of her breast lump along with axillary node dissection. Histology showed a moderately differentiated squamous cell carcinoma with a small focus of glandular differentiation (1 mm) surrounded by breast tissue in the axillary tail (Fig. 1). The tumour measured 36 mm in maximum dimension with a histological grade of 3 [Bloom–Richardson–Elston (BRE) grading system]. Ductal carcinoma *in situ* was absent. Thirteen of the fifteen dissected axillary lymph nodes showed metastatic squamous cell carcinoma, with the largest metastasis measuring 20 mm with extensive extra nodal spread. The tumour was ER, PR and HER2 negative by immunohistochemistry. The patient underwent mastectomy in view of an inadequate margin excision. Histopathology showed residual squamous cell carcinoma around the excision cavity and extensive lymphovascular invasion. The patient was treated with adjuvant chest wall and regional nodal irradiation to a dose of 50.4 Gy along with concurrent carboplatin chemotherapy, followed by six cycles of adjuvant fluorouracil, epirubicin and cyclophosphamide (FEC) chemotherapy. Less than 4 months after completing adjuvant chemotherapy, the patient developed chest wall recurrence and was treated with five cycles of docetaxel. Her cutaneous metastases continued to progress rapidly to involve the anterior and posterior chest wall despite sequential therapies including capecitabine/cisplatin, topical immunosensitising diphenylcyclopropenone (DCP), mitomycin/fluorouracil, cisplatin/gemcitabine, bevazicumab and additional chest wall radiotherapy. Molecular profiling by next generation sequencing (NGS) showed evidence of a phosphoinositide-3-kinase (PI3K) mutation (H1047R). Everolimus and aspirin were added to target the mTOR pathway. Unfortunately, the disease progressed despite treatment and the patient died within 4 years of tissue diagnosis.

A 60-year-old woman with a family history of breast cancer affecting her mother and maternal grandmother presented in December 2015 with a 6 month history of increasing left nipple discharge. Ultrasound of the left breast showed a 6 mm retro-areolar rounded intraductal lesion with a dilated duct containing a solid component. There was soft tissue extension into the dilated duct with internal vascularity in the solid component. Core biopsies from the left breast at initial presentation were consistent with a diagnosis of benign papilloma. Imaging of the right breast showed features favouring a complex cyst and benign fibroadenomas. Two years later the nipple discharge recurred and the intraductal lesion had increased in size to 12 mm on ultrasound. Subareolar duct excision of the left breast showed moderately differentiated squamous cell carcinoma of keratinising and clear cell type arising from a dilated duct wall that also contained an intraductal papilloma (Fig. 2). The duct wall showed chronic inflammation and areas of squamous metaplasia. The tumour grading was 3 (BRE) and it was triple negative on immunohistochemistry with a Ki-67 index of 35%. It also showed positive staining for P63 and basal markers (e.g., CK5/6 and CK14). It was classified as a primary squamous cell carcinoma based on the predominant squamous differentiation (>90%). The lesion measured 20 mm and involved margins of the excision biopsy. The patient subsequently underwent mastectomy and sentinel lymph node biopsy. Both the breast tissue and lymph node were devoid of residual tumour. She is currently being treated with adjuvant sequential anthracycline and taxane chemotherapy, followed by radiotherapy to the chest wall.

Primary SqCC of the breast was first reported in 1908 by Troell.[3] The histogenesis of this tumour is still controversial, and considered to potentially arise from squamous metaplasia occurring in cysts, hyperplastic ducts or in papillomas.[4] There are several case reports of primary SqCC of breast presenting as an abscess, cysts or in association with chronic mastitis, supporting the theory that chronic inflammation leading to squamous metaplasia plays an important role in development of this malignancy.[5] This theory is supported in our second case where SqCC occurred in association with chronic inflammation, mastitis and squamous metaplasia of ducts containing the papilloma.

Metaplastic carcinomas are known to arise within papillomas. The reported incidence of such lesions is varied, ranging between 5 and 60%.[6] However, only papillomas with atypia have an increased risk of carcinoma. In a retrospective review of medical records and imaging findings in 130 papillary lesions, Wiratkapun *et al.* reported none of the benign papillary lesions

Print ISSN 0031-3025/Online ISSN 1465-3931

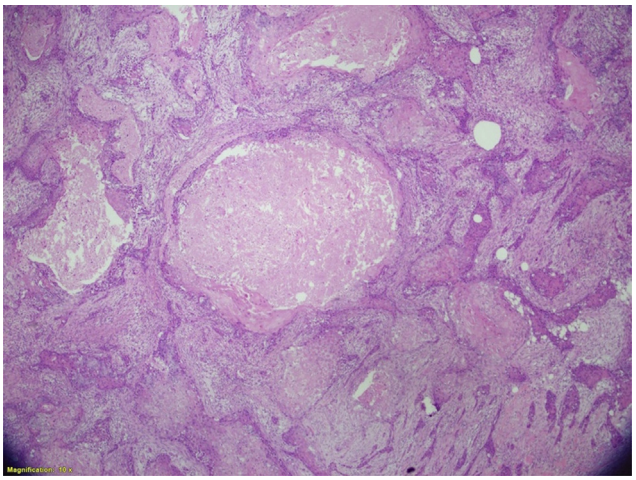

Fig. 1 Tumour showing squamous differentiation with necrosis (H&E).

were upgraded to malignancy. Approximately 20% of benign lesions upgraded to atypical papillary lesion while 31% of atypical lesions were upgraded to malignancy.[7]

Pareja *et al.* evaluated the rate of upgrade to carcinoma at excision in patients with intraductal papilloma (IDP) without atypia in radiological and pathological concordant core needle biopsies.[8] An upgrade rate of 2.3% was noted in this study. Presence of concurrent ipsilateral breast carcinoma and fragmentation of papilloma at histological examination had significant association with upgrade rate. There was no significant difference in upgrade rate between central and peripheral IDP. Some of the previous studies reported higher rate of upgrade at excision in papillomas with atypia varying between 20% and 60%. However, most of these series did not take radiological features into consideration.

SqCCs are distinguished from other metaplastic carcinomas by their predominant squamous differentiation. Origin from an *in situ* SqCC component in a cyst wall or duct can be identified in some cases. SqCC of the breast shares microscopic features of SqCCs of other sites. Some tumours can have a spindle cell component or cytoplasmic clearing. Other histological patterns such as keratinising, non-keratinising, cystic, papillary, clear cell and acantholytic patterns[9] have also been reported.

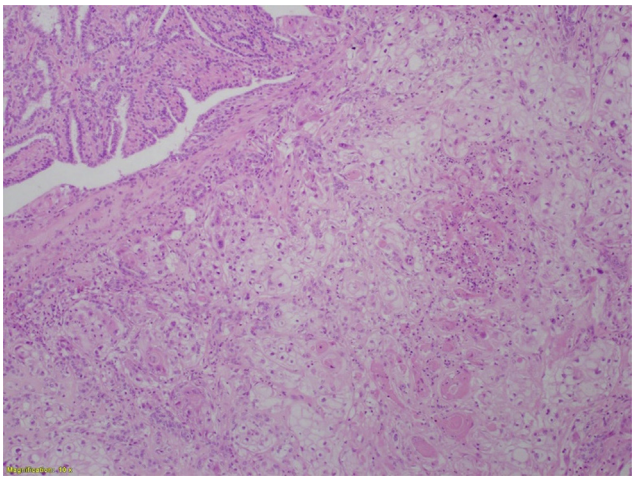

Fig. 2 Squamous cell carcinoma adjacent to a duct containing an intraductal papilloma (H&E).

Like other breast cancers, SqCC has a female preponderance and tends to occur in the seventh decade, with a reported range of 24−91 years. Most patients present with a painless breast lump, although presentation as an abscess is not uncommon.[10] The size of primary SqCC tends to be larger than other breast cancers with a reported range of 1−13 cm (median 5 cm). Cystic degeneration can occur in larger tumours. There are no mammographic features specific to SqCC, although the tumour may present as a cyst on ultrasound. The first patient described herein presented with a lump and the second patient presented with nipple discharge. Both had benign diagnoses on imaging. Compared to other subtypes, FNAC is less often accurate in the pre-operative diagnosis of SqCC.[11] In the study by Guo *et al.*, correct preoperative diagnosis was made in only 18.2% of cases. Specific imaging features on nuclear magnetic resonance imaging (MRI) in combination with ultrasound and core biopsy improves diagnostic accuracy. Surgical excision biopsy is recommended for definitive diagnosis.

Primary SqCC of the breast are most often negative for ER, PR and HER2 although a small proportion can show positivity for hormone receptors (9−12% for ER and 7−9% for PR).[3] They show positive staining for P63, P40, CK5/6 and 34βE12. Both our cases were triple negative and showed positive staining for P63, P40 and CK5/6. Several studies found overexpression of EGFR in these tumours. Guo *et al.* found 79% of tumours to be EGFR positive[11] by immunohistochemistry. Studies analysing ultrastructural features of SqCC showed the presence of both squamous and glandular elements in the same tumour leading to the conclusion that SqCC of the breast is a morphological continuum of adenocarcinoma with extensive squamous metaplasia, typified by the presence of a small amount of glandular differentiation in our first case and squamous metaplasia of duct wall in close association with tumour in the second case. In a recent article on genomic profiling of metaplastic breast carcinomas,[12] metaplastic carcinomas including squamous type were found to have frequent PIK3CA/PIK3R1 (61%) and Ras-Map kinase (25%) pathway aberrations, compared with non-selected triple negative breast cancers from The Cancer Genome Atlas, 14% and 7% respectively.

Most cases of primary SqCC of the breast are treated with surgical resection, either segmental or modified radical mastectomy. Hennessy *et al.* from MD Anderson Cancer Centre showed in a study that half of their patients had node positive tumours.[3] Review of cases from California Cancer Registry[5] found 52% of cases presented with localised disease, 32% with regional disease and 8.5% with metastasis at presentation. In a series of 21 cases of primary SqCC of the breast, 19% had axillary lymph node metastasis at the time of surgical resection.[13] One of our patients had extensive lymph nodal involvement. The median overall survival (OS) at 5 years is 40% and 26% at 10 years.[3] Neoadjuvant chemotherapy did not affect the overall survival.[3] Hormone therapy was used in ER positive tumours and ER positivity was associated with improved relapse free survival. According to the California Cancer Registry, relative cumulative survival of SqCC patients was 68% at 5 years and 60% at 10 years, whereas non-SqCC patients had a better survival rate of 84% at 5 years and 77% at 10 years. Nayak *et al.* showed patients had minimal response to neoadjuvant therapy with 5 year OS of 51%.[9] SqCC is often relatively radioresistant.[10] Our first

patient received both adjuvant chemotherapy and chest wall radiotherapy with only minimal response.

Nayak *et al.* analysed the prognostic features and reported age over 60 years, tumour non- keratinisation and presence of a spindle cell component as adverse prognostic factors. Lymph node metastasis and high pathological stage were significantly associated with poor OS of patients.[5]

To conclude, breast SqCC is a rare and aggressive disease associated with frequent local and distant metastasis and death. Current adjuvant treatment options are limited because of lack of expression of hormone receptors and HER2 over-expression. These tumours are genetically distinct from other triple negative breast cancers and genomic profiling can be of help in the management of some of these tumours. New therapeutic regimens including EGFR tyrosine kinase/mTOR pathway inhibitors and cisplatin based adjuvant chemotherapy may play a role in treatment of these aggressive tumours.[5]

Acknowledgements: The authors would like to acknowledge Dr Stephen Hayes and Dr William Mackie for providing clinical information and tissue for diagnosis.

Conflicts of interest and sources of funding: The authors state that there are no conflicts of interest to disclose.

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DOI: https://doi.org/10.1016/j.pathol.2019.03.003

The utility of a targeted gene mutation panel in refining the diagnosis of breast phyllodes tumours

Sir,

Phyllodes tumours (PTs) of the breast are uncommon biphasic fibroepithelial neoplasms that comprise 0.3–1.0% of all primary breast tumours. Morphologically resembling intracanalicular fibroadenomas, PTs are characterised by a leaf-like architecture consisting of bilayered epithelium with hypercellular stroma. On the basis of assessment of five histological features (stromal cellularity, stromal atypia, stromal overgrowth, tumour borders, and mitotic activity), PTs are graded as benign, borderline, and malignant.[1]

Accurate diagnosis of PTs can be challenging. Despite seemingly straightforward guidelines for PT grading, the actual application can be problematic. The manner in which assessment of the various histological parameters is amalgamated to establish the final grade can also be subjective. Furthermore, differential diagnoses may arise during diagnostic evaluation. At the benign end of the histological spectrum, it may be difficult to differentiate some benign PTs from fibroadenomas, while at the malignant end, a high grade spindle cell lesion raises histological considerations of malignant PT, spindle cell metaplastic breast carcinoma (SCMBC) or primary/secondary breast sarcoma.[2]

Previously, we studied the genomic alterations of fibroepithelial tumours and found recurrent mutations in *MED12* and *RARA* in both fibroadenomas and PTs, with additional aberrations observed in the latter, especially in the borderline and malignant grades where derangements in cancer driver genes are seen.[3] From this study, 16 of the most frequently mutated genes in fibroepithelial tumours (*MED12, TERT, SETD2, KMT2D, RARA, FLNA, NF1, PIK3CA, EGFR, RB1, PTEN, ERBB4, BCOR, TP53, IGF1R*, and *MAP3K1*) that were compiled into a customised panel, were found to be helpful as diagnostic adjuncts when applied to two challenging cases of PTs.

In Case 1, a 35-year-old Caucasian female was diagnosed with malignant PT of the breast on excision biopsy of a right breast lump. She sought a second opinion at our institution, where a diagnosis of borderline PT was rendered based on histology. The tumour was composed of epithelium-lined fronds with myxoid and variably cellular stroma. Stromal cellularity ranged from mild to moderate, with foci of relatively densely packed fascicles of spindle cells that were reminiscent of fibrosarcoma. Mitoses averaged about 3 per 10 high-power fields (HPF) (field diameter 0.6 mm), although in one section, mitoses that numbered up to 12 per HPF were observed amongst cellular stroma with inflammatory cells.