Adenoid cystic carcinoma arising in association with an intraductal papilloma of the breast

To the Editor,

Adenoid cystic carcinoma (AdCC) is a rare ‘salivary gland-like’ type of breast carcinoma with generally indolent biological behaviour in its classic form. This tumour features a biphasic epithelial-myoeipithelial cell population comprising luminal cells that line glandular or cribriform spaces and abluminal myoepithelial or basal cells that form pseudo-glandular spaces containing basement membrane material.1 Although the immunomolecular phenotype is often triple-negative [negative expression for oestrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2)], the vast majority of patients have a good prognosis; therefore, it is important to distinguish it from conventional triple-negative disease with adverse prognosis. Most AdCCs possess MYB gene abnormality, especially MYB-NFIB fusion. AdCC of the breast can be accompanied by other breast lesions, including microglandular adenosis2 and ductal carcinoma in situ (DCIS).3 To our best knowledge however, AdCC arising in association with an intraductal papilloma has not been reported. We now document a unique case of an AdCC that appears to arise from an intraductal papilloma.

A 69-year-old female presented with a 1.0 cm firm lump in the left breast at 9–10 o’clock which appeared suspicious on ultrasonography. An ultrasound core biopsy was performed which found focal cytarchitectural atypia in an intraductal papillary lesion, following which the entire lesion was excised.

The core biopsy comprised five to six cores containing an epithelial proliferative lesion displaying a papillary architecture with anastomosed and coalesced papillary fronds supported by fibrovascular cores. Some detached fragments showed part of the cystically dilated duct from which the papillary lesion arose (Fig. 1A). Several areas displayed relatively rigid luminal spaces amongst the epithelial islands (Fig. 1B), which were either empty or contained small amounts of pink secretions. There was stromal sclerosis, interpreted as sclerosis of the intraductal papillary lesion (Fig. 1C). While the architectural atypia manifested by the cribriform spaces would have required adjunctive immunohistochemistry (IHC) for elucidation, upon discussion with the surgeon, it was felt that complete excision of the entire lesion would be required in any case, hence it was agreed that further workup could be conducted after evaluating the excision specimen.

The excision specimen measured 3.0×2.5×2.5 cm. Macroscopic appearance showed a relatively well-circumscribed, vaguely lobulated, greyish nodule with ill-defined contours (Fig. 2), measuring a maximum diameter of 11 mm.

In the excision specimen, a solidified papillary lesion was present, with several foci of rounded cribriform basoloid epithelial protrusions into surrounding adipose tissue. The basoloid cribriform foci appeared to merge imperceptibly with a morphologically benign intraductal papillary process (Fig. 1D). Within the cribriform areas, the luminal spaces contained both pink secretions as well as watery greyish, mucinous type material. The luminal spaces appeared lined by both polarised and flattened cells (Fig. 1E,F).

IHC performed in the excision specimen revealed mostly negative staining for ER (Fig. 1G). PR and HER-2 were negative. CK7 defined the luminal epithelial with negative reactivity for the outer layer of cells. CD117 showed patchy reactivity of luminal cells. CK5/6 disclosed both positivity in the luminal cells around some of the round spaces, as well as other non-luminal cells. P63 showed a well-defined layer of myoepithelial cells around the cribriform islands (Fig. 1H), while smooth muscle myosin heavy chain (SMMHC) also demonstrated an intact rim of myoepithelial cells. Ki-67 proliferation was less than 10% in lesional areas.

Fluorescent in situ hybridisation (FISH) showed no disruption of the MYB gene (Fig. 1I).

The final diagnosis was regarded as an intraductal papilloma with an epithelial-myoeipithelial lesion consistent with AdCC.

AdCC is an invasive carcinoma composed of epithelial and myoeipithelial neoplastic cells arranged in tubular, cribriform and solid patterns, associated with basophilic matrix and basement membrane material, frequently linked to MYB-NFIB fusion. The major MYB gene alteration of AdCC possesses the MYB-NFIB fusion gene.4 Although the majority of AdCCs will show this fusion, those without the MYB-NFIB fusion gene may display MYBL1 rearrangements or MYB amplification. In our case, we did not detect breakage of the MYB gene on FISH. MYB gene abnormality may be the initiating factor in the pathogenesis of AdCC,5 though it is not an essential criterion and MYB gene abnormality is not always present in all cases, with limited prognostic significance.6 Apart from the classic form of AdCC as seen in our case, solid basoloid AdCC is another subtype which can be more aggressive, with a third subtype that shows high grade transformation.7

The differential diagnoses on core biopsy include atypical ductal hyperplasia (ADH) and low grade ductal carcinoma in situ (DCIS) in view of the cytarchitecturally atypical cribriform proliferation residing within portions of a benign intraductal process. In a papillary lesion, ADH is distinguished from low grade DCIS by extent using a 3 mm threshold. If IHC was conducted on the core biopsy material with a panel of ER and high molecular weight keratins, both ADH and low grade DCIS would display diffuse ER and diminished high molecular weight keratin expression.8 For our case, ER would have been negative and high molecular weight keratin positive, leading away from a consideration of ADH/DCIS, and raising a differential of adenomyoepithelioma which is an epithelial-myoepithelial lesion with prominent myoepithelial cells. The adenomyoepithelioma has both ER-positive and ER-negative forms and may display overlapping histology with AdCC, but it shows more prominent myoepithelial cells which are often clear and epithelioid, contrasting against the basaloid appearance of AdCC (Table 1). MYBL1 rearrangements are not found in adenomyoepithelioma.9

In the excision specimen, the pink spherules may raise consideration for collagenous spherulosis which is usually not mass forming and an often incidental finding within a background of usual ductal hyperplasia or an intraductal...
papilloma. It has been reported that CD117 can distinguish collagenous spherulosis from AdCC, the latter being positive.10

The existence of an in situ component of AdCC has been debated at length. In Rosen’s Breast Pathology,11 it is stated that in situ AdCC can be recognised by the absence of a periductal cuff of bluish hypercellular or slightly myxoid stroma that typically surrounds invasive nests. Additionally, partial duct involvement, myoepithelial cells around affected ducts disclosing a similar uniform distribution and cellular

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Table 1 Comparison of clinicopathological features of adenomyoepithelioma (AME) and adenoid cystic carcinoma (AdCC)

<table>
<thead>
<tr>
<th>Clinicopathological features</th>
<th>AME</th>
<th>AdCC</th>
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<tbody>
<tr>
<td>Cellular composition</td>
<td>Epithelial-myoepithelial tumour with prominent myoepithelial cells</td>
<td>Epithelial-myoepithelial tumour with frequent basoloid appearance</td>
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<tr>
<td>Architectural patterns</td>
<td>Tubular, lobulated, spindle cell, papillary variants</td>
<td>Cribriform/tubular or solid basoloid growth patterns</td>
</tr>
<tr>
<td>Cytomorphology</td>
<td>Myoepithelial cells are enlarged with clear cytoplasm. Small epithelium-lined spaces with inner luminal ductal cells</td>
<td>Myoepithelial cells tend to be smaller, more hyperchromatic and basoloid appearing and have much less cytoplasm, lining pseudolumina in addition to bilayered tubules with true lumens</td>
</tr>
<tr>
<td>Immunohistochemistry</td>
<td>ER+ or −, CD117− or focal +</td>
<td>ER−, CD117+</td>
</tr>
<tr>
<td>Clinical behaviour</td>
<td>Can be benign or malignant</td>
<td>Malignant</td>
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</tbody>
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density as myoepithelium in adjacent non-neoplastic ducts, may be used as histological evidence of in situ disease.

In terms of clinical behaviour, AdCC is a low grade triple-negative disease with favourable behaviour and should not be treated like other triple-negative breast cancers which are more aggressive. Recurrence and distant metastasis are rare. It often presents at an early stage with better survival than invasive breast carcinoma.12 Radical surgery is curative. It must be noted that the solid basaloid form is more aggressive.

In summary, we present a unique case of AdCC appearing to arise from an intraductal papilloma, with histological challenges posed particularly on core biopsy, with the final diagnosis achieved on excision.

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