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ORIGINAL ARTICLE

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Carcinoma ex-pleomorphic adenoma of the breast. Report of three cases suggesting a relationship to metaplastic carcinoma of matrix-producing type

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Abstract Three cases of carcinoma ex-pleomorphic adenoma of the breast are reported. Patients were 82, 60 and 56 years old and presented with a breast lump. All tumours showed areas of pleomorphic adenoma adjacent to typical areas of malignant transformation. These cases add to the spectrum of tumours shared by breast and salivary gland. The relationship between these neoplasms and metaplastic carcinoma of matrix-producing type is discussed.

Keywords Pleomorphic adenoma · Breast carcinoma · Metaplastic carcinoma

Introduction

Similarities in the embryogenesis of breast and salivary gland and the dual epithelial–myoepithelial cell differentiation in both anatomical sites account for the occurrence of salivary gland-type neoplasms in the breast [15]. Pleomorphic adenoma is one such benign neoplasm that occurs in both salivary gland and breast. In salivary gland, malignant transformation of pleomorphic adenoma is a well-recognised, albeit relatively, uncommon event. Malignant transformation can take the form of superimposed adenocarcinoma or development of a malignant mixed tumour with dual epithelial and mesenchymal elements [2, 16, 17, 18, 20, 21, 22, 28, 37, 38, 40, 43, 45]. Malignant pleomorphic adenoma has been reported to occur outside of the major salivary glands [11, 18]. To the best of our knowledge, malignant change arising in a pleomorphic adenoma of the breast has not been reported to date in the English language literature available to us for review. One previous record of ductal carcinoma co-existing with pleomorphic adenoma of the breast is noted, but the two tumours were separated from one another by normal intervening breast tissue [23].

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Clinical histories

Case 1

An 86-year-old woman presented with a suspicious palpable breast mass. Fine needle aspiration showed features of carcinoma. A left partial mastectomy was performed, which showed a 25-mm diameter circumscribed tumour, clear of the margin. There was no clinical evidence of metastatic disease to the axillary nodes or distant sites. Post-operative radiation was delivered to the breast and regional lymph nodes. Chemotherapy was not undertaken because of her advanced age and cardiomegaly. The patient remains free of disease 4 months after surgery.

Case 2

The patient was a 60-year-old woman who presented with an isolated nodule in the breast detected on a screening mammogram. A 14-mm circumscribed mass was present within 10 cm of excised breast fatty tissue. An axillary lymph-node dissection was performed, which showed 12 lymph nodes free of metastasis. Of these nodes, 2 contained nevus cells in their capsules. The patient remains free of disease 6 months after surgery.

Case 3

The patient was a 57-year-old woman who presented with a palpable mass in the left breast that she had noticed for about 3 months prior to diagnosis. A routine mammogram 7 months earlier was negative for abnormality. A diagnostic mammogram showed a 25-mm lobulated mass in the 12 o'clock position. Fine needle aspiration biopsy was positive for malignancy. A left modified radical mastectomy was performed, which revealed a 24-mm diameter tumour clear of the margins and ten axillary nodes negative for metastases. There was no clinical evidence of distant metastatic disease. She received a course of chemotherapy using adriamycin and cyclophosphamide. She remains free of disease 4.5 years later.

Materials and methods

All tissues were fixed in 10% buffered formalin, processed and embedded in paraffin wax as per standard histopathology protocols. Haematoxylin and eosin stain was performed on all blocks. Immunohistochemistry was performed on selected blocks using the Dako "EnVision+" biotin-free enhanced labelled polymer method [44] for all except the CD10 stain for which the Immunovision "Powervision" method [29] was employed. Sources and dilutions of the antibodies are reported in Table 1. The chromogenic in situ hybridisation for Her-2 neu was performed using the Zymed subtraction probe technology method [10, 41].

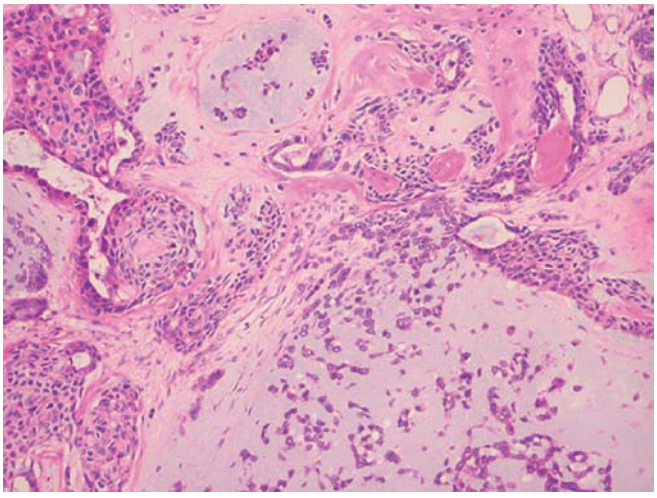

Fig. 1 Case 1. Photomicrograph to show areas of low-grade pleomorphic adenoma similar to that seen in salivary gland (haematoxylin and eosin ×150)

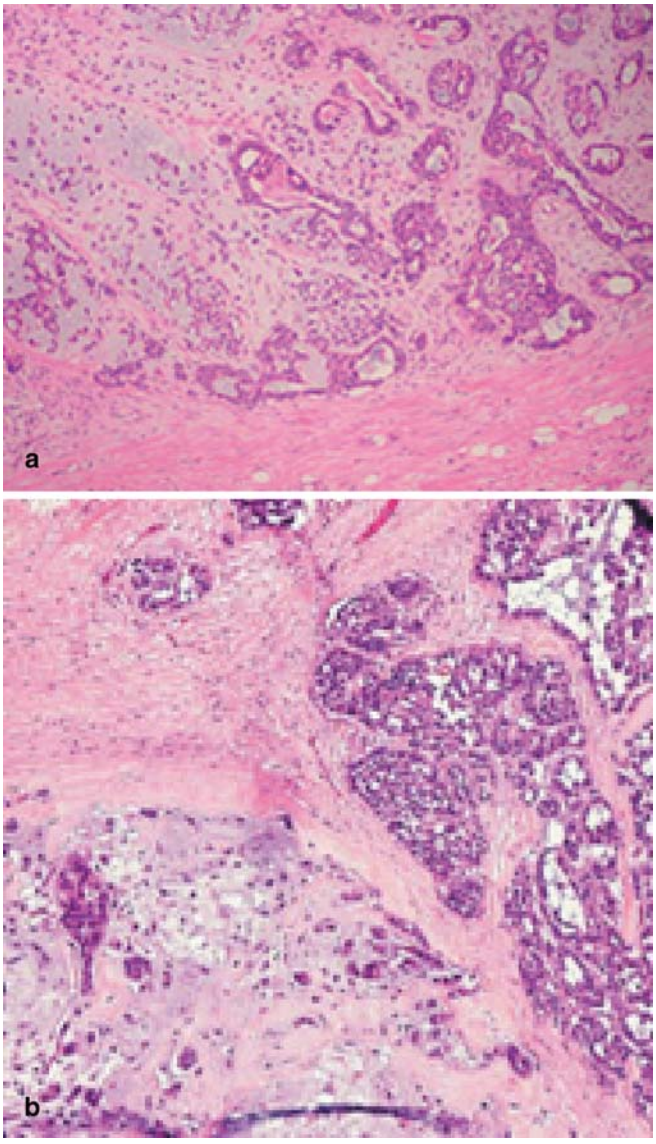

Fig. 2 a, b Cases 1 and 2. Circumscribed border of the benign component (haematoxylin and eosin ×100)

Table 1 Source and dilution of antibodies. *MSA* muscle specific actin, *HC myosin* heavy chain myosin, *K* keratin, *ER* oestrogen receptor

Antibody	Source	Clone	Dilution
P63	Dako	4A4	1:100
CD 10	Novocastra	56C6	1:50
MSA	Dako	HHF-35	1:50
HC myosin	Dako	SMMS-1	1:50
S 100 protein	University of Toronto	N/A	1:1500
Cam 5.2	BD Biosciences	CAM 5.2	Neat
K7	Dako	OV-TL 12/30	1:50
34βE12	Dako	34BE12	1:100
K 5/6	Dako	D5/16B4	1:50
MIB 1	Dako	MIB-1	1:100
P53	Dako	DO-7	1:100
ER	Novocastra	6F11	1:40
Her-2 neu	Dako	A485 polyclonal	1:500

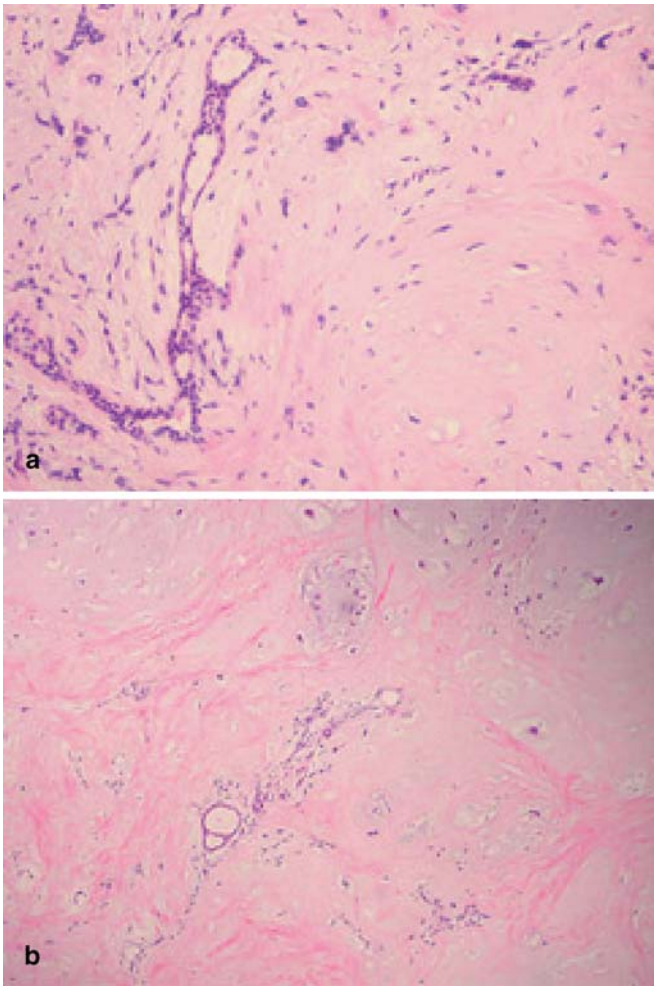

Fig. 3 a, b Case 3: Areas resembling pleomorphic adenoma. Benign-appearing ductal structures, bland periductal spindle cells and chords of epithelioid cells associated with nodules of cartilage (haematoxylin and eosin ×400 and ×200)

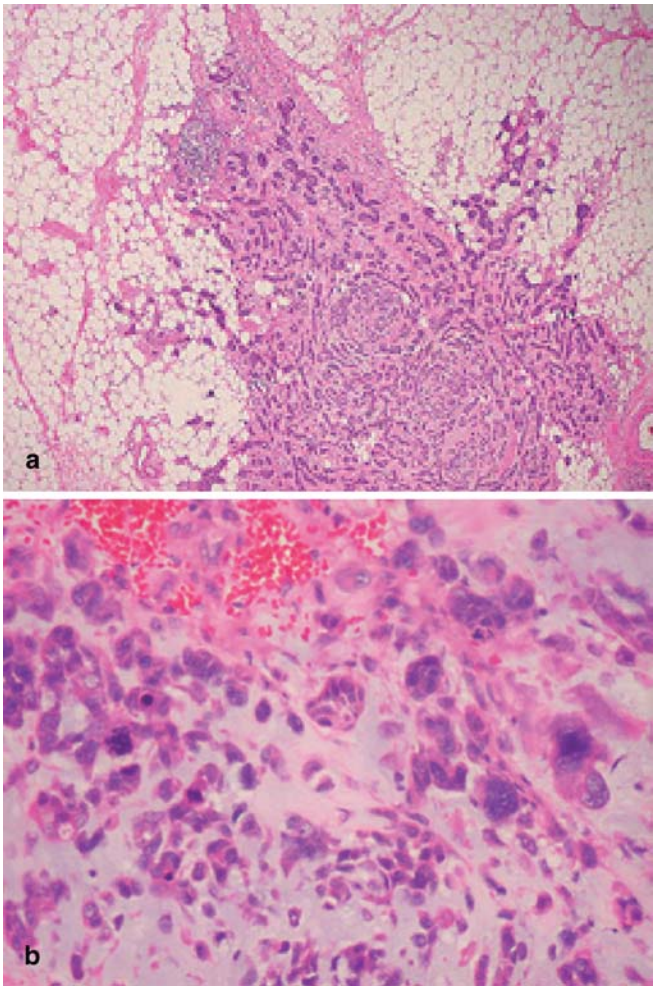

Fig. 4 Case 1. Component B. (**a**) Infiltrative growth pattern resembling invasive ductal carcinoma not otherwise specified (haematoxylin and eosin ×40). **b** Areas resembling high-grade metaplastic carcinoma (haematoxylin and eosin ×200)

Histological features

As all tumours were histologically similar, they will be described together. All three tumours were composed of two components. One component had the features of pleomorphic adenoma (component A), and the other showed features of overt malignancy (component B).

Component A

This component was histologically similar to typical pleomorphic adenoma of salivary gland (Fig. 1) and comprised approximately 60% of the tumour in case 1, a small area in case 2 and about 90% of the total neoplastic proliferation in case 3. This component had a circumscribed border in all cases and was composed of islands of chondroid tissue with interspersed small ductal structures (Fig. 2). Calcification of the chondroid stroma was seen in two of the three cases. Irregular sheets, nests and chords of epithelioid cells were also seen, and bland spindle cells were present between the ducts (Fig. 3). Uniform oval and spindle cells arranged in ill-defined chords and nests were present within the chondroid matrix (Fig. 1). The ductal structures had an internal layer of uniform columnar cells and an incomplete peripheral layer of myoepithelial cells as predominantly seen in cases 1 and 3. In these areas of the tumours, mitoses were very scanty, and necrosis was absent.

Component B

This was characterised by histologically malignant areas. In cases 1 and 3, there were areas that resembled grade-3 invasive ductal carcinoma not otherwise specified (NOS) and areas of high-grade metaplastic carcinoma with chondroid matrix. In case 2, the malignant component was pure high-grade matrix producing metaplastic carcinoma. In all cases, component B was seen at the periphery of neoplastic nodules invading the surrounding fat (Fig. 4 and Fig. 5). In case 1, extensive necrosis was present. At the periphery of the necrotic zones were garlands of markedly atypical epithelial cells showing remarkable nuclear pleomorphism and hyperchromasia. Mitotic figures were numerous, and some atypical mitoses were observed. Focally, an infiltrative border was noted with complex atypical glandular structures, sometimes associated with a desmoplastic stromal reaction, extending into the adjacent fat of the breast in a pattern seen in usual invasive ductal carcinoma NOS (Fig. 4 and Fig. 5). Some of the malignant areas also showed abundant chondroid matrix material resembling metaplastic carcinoma (Fig. 4 and Fig. 6). No malignant spindle-cell component was

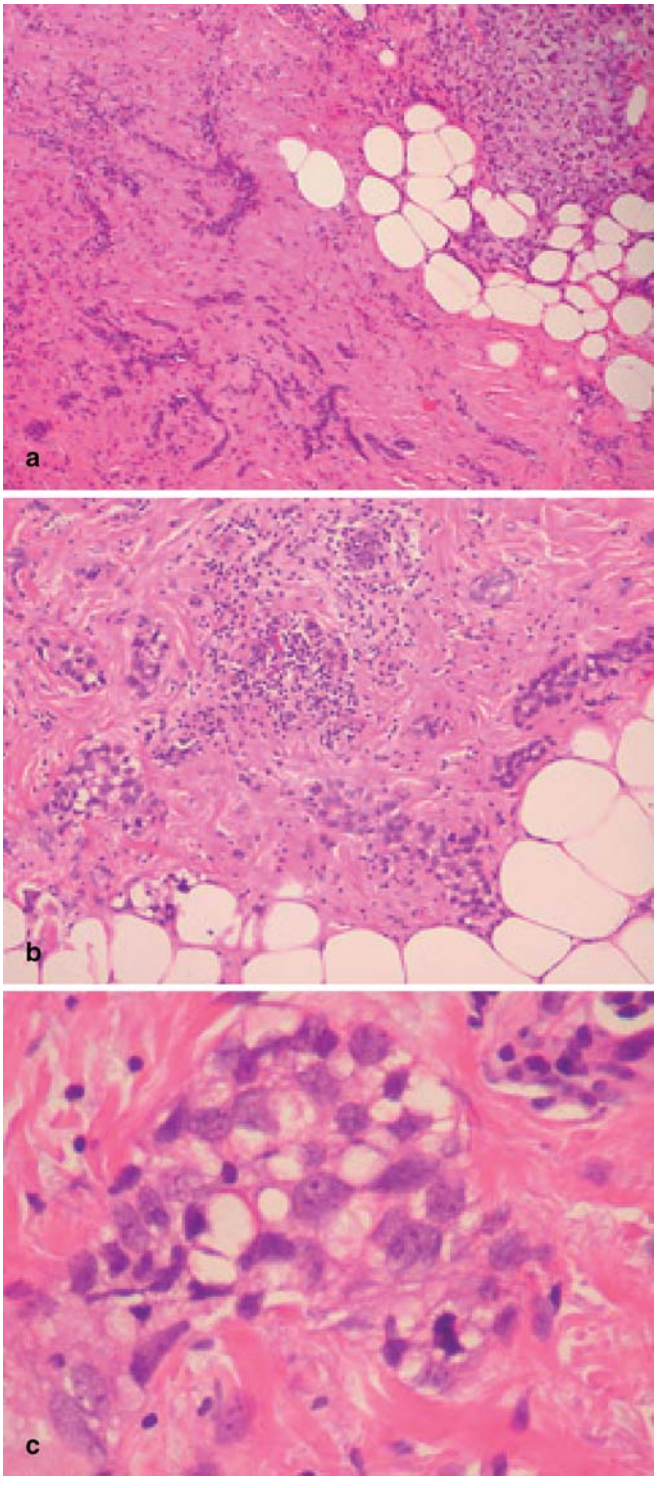

Fig. 5 a–c Case 3: Malignant areas showing infiltrative growth pattern, atypia and mitoses (haematoxylin and eosin ×100, ×200, ×400)

identified. A few ducts adjacent to the tumour contained high-grade solid in situ carcinoma.

In case 2, most of the tumour was composed of markedly pleomorphic cells floating in pools of myxochondroid matrix (Fig. 6). Numerous mitoses were seen in these areas, which resembled high-grade metaplastic carcinoma with matrix production.

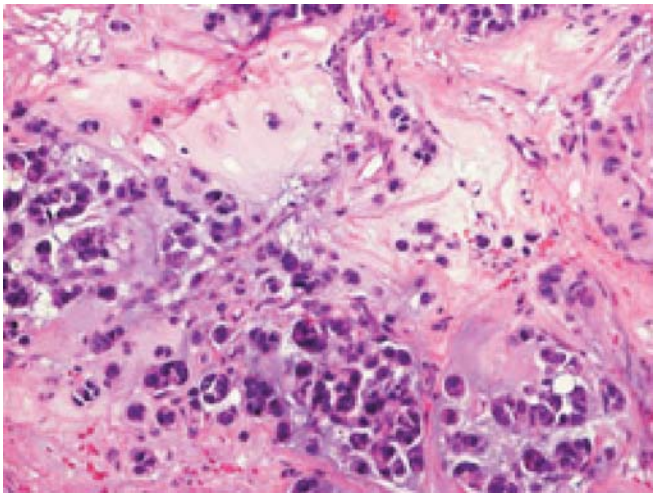

Fig. 6 Malignant areas of case 2 showing disorderly growth pattern and marked cytological atypia (×200)

Some of the malignant cells had an acinar arrangement and were associated with a desmoplastic fibrous stroma. High-grade ductal carcinoma in situ was seen in the adjacent breast tissue.

In case 3, a small peripheral area of the tumour showed features of grade-3 invasive ductal carcinoma NOS, and focal areas resembled high-grade metaplastic carcinoma with chondrosarcomatous differentiation. The chondroid lobules in the malignant component showed hypercellularity, marked cytological atypia, presence of mitoses and extensive necrosis. Between the lobules of atypical chondroid material were irregular groups and chords of pleomorphic epithelial cells exhibiting marked nuclear pleomorphism and hyperchromasia (Fig. 5). Mitoses and apoptotic cells were frequent in this component. No lymphatic or vascular invasion was seen. Within the tumour, a few ducts showed solid, grade-3 intraductal carcinoma.

Immunohistochemical features

Case 1 was studied for immunohistochemistry with all antibodies, and selected markers were employed in cases 2 and 3. Immunostains for p63, CD10, muscle-specific actin and smooth-muscle heavy-chain myosin highlighted myoepithelial cells in the benign component A of the tumours only (Fig. 7 and Fig. 8). Thus, some of the cells at the periphery of the ductal structures were positive for p63 as were many of the cells in the epithelioid nests. The epithelioid cells present in the chondroid matrix of component A were negative for p63. CD10 showed strong positive staining of the intertubular bland spindle cell component and the epithelioid and spindle cells present in the chondroid regions of the benign areas. The stains for muscle specific actin and smooth-muscle heavy-chain myosin showed surprisingly little staining in case 1 but good staining of periductal myoepithelial cells in case 3. Component B (malignant) areas failed to stain for myoepithelial markers except for focal positivity for p63 in the cells of the chondroid component. Both components (A and B) showed positive immunostaining for S-100 protein, but the staining was weak and patchy in the

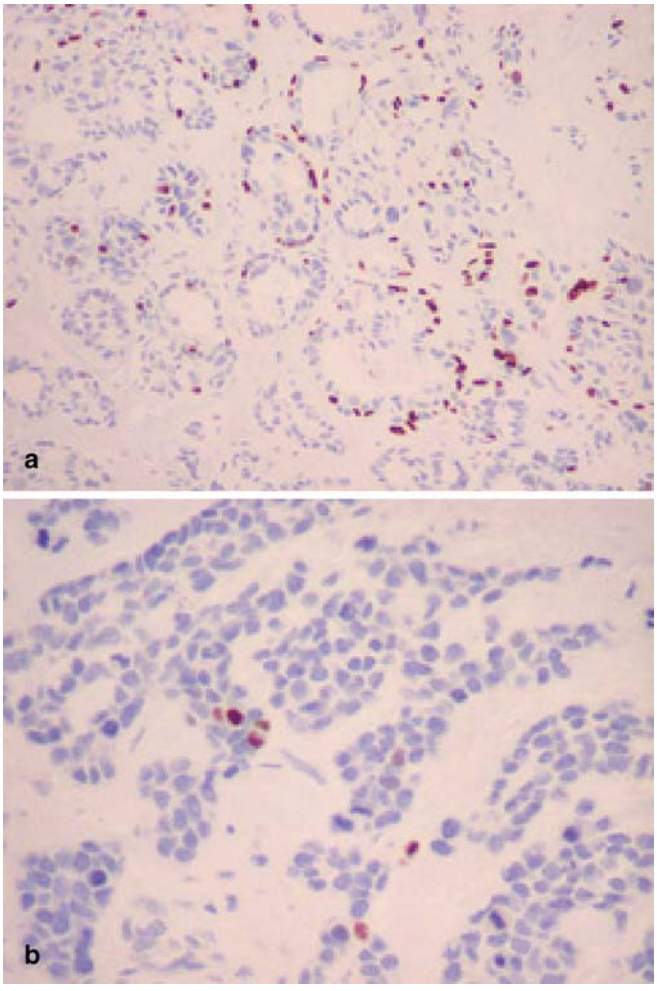

Fig. 7 Immunostain for p63 in case 1 showing a myoepithelial layer around many of the tubular structures in the benign areas (**a**; ×200) and scanty positive nuclei without an orderly arrangement in the malignant areas (**b**; ×400)

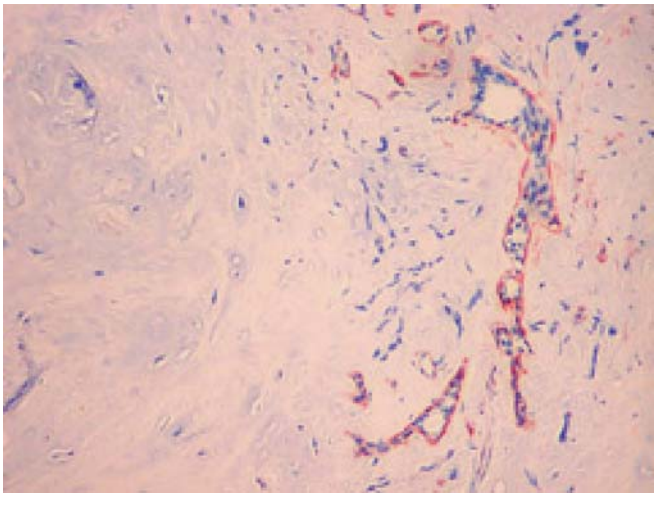

Fig. 8 Immunostain for muscle-specific actin demonstrating a periductal myoepithelial cell layer in the benign component (×200)

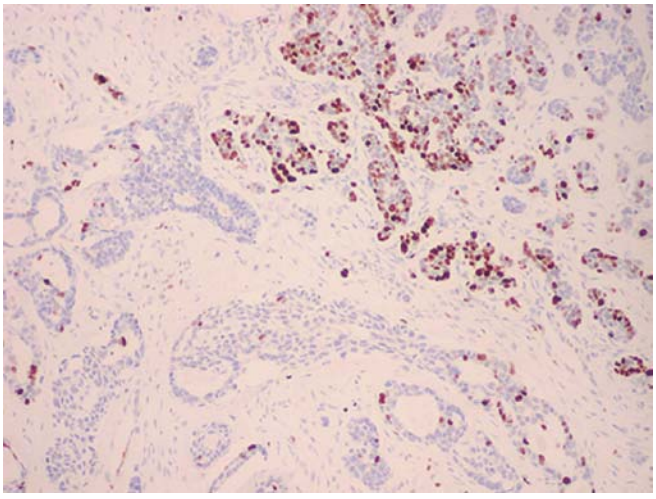

Fig. 9 Immunostain for Mib-1 in case 1. The scanty positive nuclei in the benign areas (*bottom left*) contrast with the numerous positive cells in the malignant areas (*top right*; ×200)

malignant areas of the tumours. In the benign areas, there was positive staining of almost all of the ductal epithelium, the surrounding myoepithelial cells, the epithelioid cell nests, the spindle cells and the chondroid cells. In case 1, staining for CK 5/6 was limited to the luminal cell layer of a few of the ductal structures in the benign areas of the tumour and to the majority of the cells in the malignant areas. The stain for Mib-1 showed scanty positive nuclei in the benign areas and numerous positive nuclei in the malignant areas (Fig. 9). The stain for p53 showed strong positive staining of more than 90% of nuclei in the malignant areas and patchy weak staining of the low-grade areas of the tumour in about 30% of nuclei. Immunostains for oestrogen receptors were negative in both components of the tumours, and Her-2 neu was not overexpressed or amplified in cases 1 and 3.

Discussion

The presence of salivary gland-type tumours in the breast has been known for a long time, but, in recent years, the spectrum of these lesions has been broadened to include oncocytic neoplasms [8], acinic cell carcinoma [9, 31] and mucoepidermoid carcinoma [6, 13, 42]. Although pleomorphic adenoma of the breast has been recognised for many years [1, 3, 4, 5, 7, 12, 19, 23, 25, 26, 30, 36, 46], as far as we are aware, its malignant counterpart has not been reported in the recent pathology literature. The recurrent pleomorphic adenoma of the breast reported by Soreide et al. did not show histological features of malignancy [36]. We believe that the three cases presented above meet the criteria for the diagnosis of carcinoma ex-pleomorphic adenoma, at least as defined in the salivary gland counterpart [17, 32, 33]. All three tumours showed benign or low-grade areas that were identical to pleomorphic adenoma of salivary gland. In addition, areas showing histological features of malignancy were seen

based on an infiltrative growth pattern, necrosis, marked cytological atypia, high mitotic rate, presence of atypical mitoses and high Mib-1 index.

Malignant transformation of pleomorphic adenoma of salivary glands has been shown to be associated with molecular changes, including expression of androgen receptor [27] and the amplification of Her-2 neu gene and overexpression of Her-2 neu protein [24, 35]. In two of the three cases presented above, there was no evidence of Her-2 neu amplification.

The differential diagnoses considered included matrix-producing metaplastic carcinoma, high-grade variant of adenoid cystic carcinoma and malignant adenomyoepithelioma. Part of the malignant areas of the tumours presented above resembled metaplastic carcinoma, but these neoplasms are typically uniformly high grade throughout and do not contain benign areas resembling pleomorphic adenoma. However, since there was no long history of a pre-existing stable nodule showing sudden onset of growth, one cannot entirely exclude the possibility of low-grade differentiated areas that resemble pleomorphic adenoma occurring within metaplastic carcinoma. Also, the usual abrupt transition between benign and malignant components seen in most cases of carcinoma ex-pleomorphic adenoma of salivary gland was less convincing in most of the cases described above, in which some areas of the tumour showed a transition from the benign-appearing areas to the high-grade malignant areas (Fig. 10). Furthermore, some cases of carcinoma ex-pleomorphic adenoma of salivary gland have been reported to show amplification of Her-2 neu gene, which was not apparent in our cases. Although a few tumour cells stained for p63, we were unable to demonstrate a definite myoepithelial component in the high-grade areas of the two cases available for immunohistochemistry. However, as elaborated elsewhere, the absence of a myoepithelial immunotype is not helpful in distinguishing between metaplastic carcinoma and carcinoma ex-pleomorphic adenoma because many metaplastic carcinomas exhibit myoepithelial markers [14], and the carcinoma component arising from malignant transformation of pleomorphic adenoma would not necessarily be expected to retain a myoepithelial immunotype. Similarly, the presence of a few ducts containing intraductal carcinoma adjacent to two of the three tumours is unhelpful in making this distinction. The presence of ductal carcinoma in situ is a useful diagnostic point to indicate the epithelial origin of a pure spindle cell metaplastic carcinoma [14] and to differentiate it from a sarcoma, but this feature is of no use to separate carcinoma ex-pleomorphic adenoma from metaplastic carcinoma. The exquisite organisation of myoepithelial cells at the periphery of ductal structures in the benign pleomorphic adenoma component of these lesions is the most compelling argument in favour of the diagnosis of carcinoma ex-pleomorphic adenoma rather than metaplastic carcinoma, since we believe this degree of organisation would be most unlikely in a metaplastic carcinoma with low-grade areas. Indeed, if such a differentiated change occurs in metaplastic matrix-producing carcinoma, it has not been illustrated in the literature we have reviewed. Furthermore, we believe that pleomorphic adenoma and metaplastic carcinoma of the breast likely represent two ends of a spectrum of neoplasia with potential for multiple lines of differentiation: epithelial,

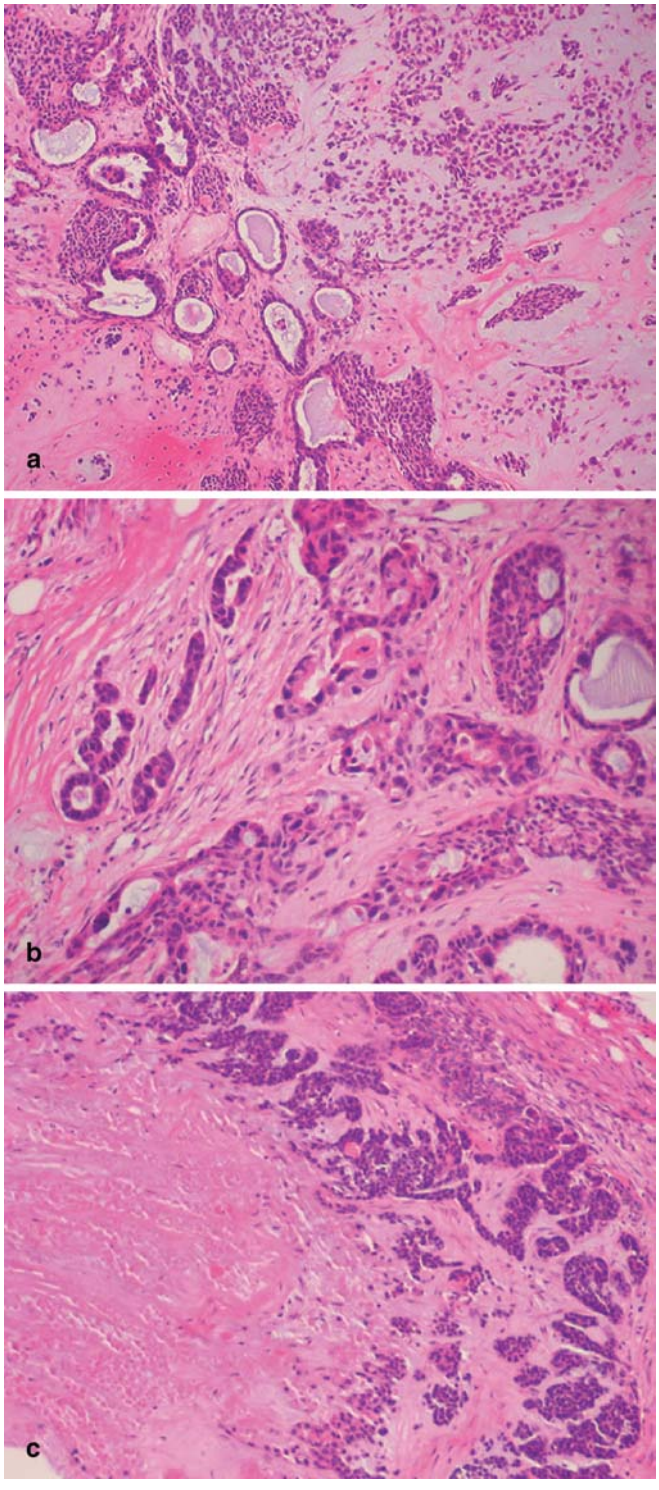

Fig. 10 a–c Panel to show transition from low-grade (**a**; ×100) through intermediate-grade (**b**; ×200) to high-grade (**c**; ×100) areas of the tumour in case 1

myoepithelial and mesenchymal. The transition from benign to malignant appearing areas illustrated in Fig. 10 supports this concept.

Although conceptually within the rubric of malignant epi-myoepithelial tumours (adenomyoepitheliomas), which can occasionally show matrix production [34, 39], the resemblance of the benign areas to pleomorphic adenoma warranted separation of this tumour as a distinct entity. Indeed, case 1 was referred with a suggested differential diagnosis of malignant adenomyoepithelioma or malignant pleomorphic adenoma. A diagnosis of adenoid cystic carcinoma was suggested by the referring pathologist for case 2, but the characteristic ductal structures and nodules of eosinophilic hyaline matrix of adenoid cystic carcinoma were not observed, and the presence of cartilage would be unusual for such a diagnosis.

The small number of cases reported and short clinical follow-up do not allow us to relate the histological features of malignancy to clinical outcome. Nevertheless, we think that the present tumours should be added to the list of neoplasms common to breast and salivary gland.

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