CASE REPORT

Benign mixed tumour of the breast and breast skin, two cases with diagnostic difficulties

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SUMMARY

We present two cases of pleomorphic adenoma, one that developed in the breast parenchyma and the other in the breast skin, with their histopathological differential diagnosis.

BACKGROUND

Benign mixed tumour is the most common tumour type in salivary glands and diagnosis of this tumour is generally not problematic due to its wide morphological spectrum. However, its occurrence in other locations such as the breast and breast skin is quite uncommon. These unusual presentation sites may mimic malignant tumour clinically and radiologically. Therefore, the exact diagnosis requires histopathological examination. We present two cases of pleomorphic adenoma (PA) and emphasise the lesions in histopathological differential diagnosis.

CASE PRESENTATION

Case 1

A 57-year-old white, postmenopausal woman presented with a non-tender, palpable lump in the inner quadrant of her left breast. No nipple discharge was noted.

Case 2

A 78-year-old white, postmenopausal woman presented with a non-tender, mobile, palpable lump, localised superficially in the right breast.

INVESTIGATIONS

Case 1

Radiologically, a 1.5 cm, lobulated, calcified, hypoechoic solid mass with partially ill-defined borders was seen. The core biopsy of the lesion suggested a benign, mixed epithelial-mesenchymal lesion, reminiscent of benign mixed tumour of the salivary gland ([figure 1](#)).

Case 2

Ultrasonography showed a 1.5 cm, lobulated, hypoechoic solid mass. The core biopsy of the lesion revealed proliferating groups of epithelial cells in a hyalinised, partly myxochondroid matrix. The epithelial component was distributed as single cells, cords, irregular tubuloalveolar or glandular/ductal structures ([figure 2](#)). The glandular foci were lined by one or two rows of epithelial cells. The inner cells showed slightly eosinophilic cytoplasm with cuboidal or polygonal shape and small-medium sized ovoid nuclei. The outer layer was slightly flattened, similar to a myoepithelial cell

Figure 1 Core biopsy of the lesion, rich in cartilaginous matrix (×20 H&E).

([figure 3](#)). No apocrine decapitation secretion was observed in the ductal lumens. Additional focus of follicular or sebaceous differentiation was not determined. There was no mitotic activity, nuclear pleomorphism or tumour necrosis. In order to reveal the phenotypes of cells in these glandular structures, whether luminal epithelial or abluminal (myoepithelial/basal), we used immunohistochemical markers. Glandular structures including inner and/or outer layers of cells showed diffuse positive staining for cytokeratin 7, S-100 and vimentin, however, no immunostaining for smooth muscle actin (SMA), p63 or calponin was noted. Cytokeratin 14 was positive in focal areas. Weak positivity for oestrogen and progesterone receptors was observed in less than 1% of tumour cells. Ki-67 proliferation index was low (<5%).

Figure 2 The proliferated epithelial cells distribute as single cells, cords and irregular tubuloalveolar structures in a myxoid matrix (×400 H&E).

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DIFFERENTIAL DIAGNOSIS

Since PA of the breast is an uncommon benign tumour, it may be mistaken for a malignant tumour clinically, radiologically and even histopathologically, in core needle biopsy materials. Therefore, it is important to differentiate PA from malignant tumours of the breast, such as metaplastic carcinoma, malignant phyllodes tumour and mucinous carcinoma, to prevent unnecessary surgical intervention.^{1 2} At this point, it is better not to over-interpret core needle biopsy materials with osteocartilaginous tissue fragments as 'malignant tumour' unless obvious malignant epithelial and/or mesenchymal elements are determined.³ In metaplastic carcinoma, the epithelial component appears as an invasive carcinoma and mesenchymal component, as a sarcoma with marked atypia.¹ Similarly, the malignant stroma of phyllodes tumour shows fibrosarcomatous appearance with a leaf-like pattern. Mucinous carcinoma, however, can be more problematic due to the bland appearance of the nucleus in the invasive carcinoma component. To distinguish these two tumours, histochemical stains, Alcian Blue and hyaluronidase, have been suggested.² The extracellular mucin in mucinous carcinoma stains positive with Alcian Blue (pH=1 and 2.5) and positivity remains even after applying hyaluronidase. In contrast, Alcian Blue positivity vanishes in PA. None of our cases showed prominent sarcomatous areas or growing patterns of phyllodes tumour. The core biopsy of case 1 showed balanced proliferation of benign ductal epithelial and myoepithelial cells embedded in a bland-looking osteocartilagenous matrix in routine H&E sections. Therefore, microscopic appearance at low power magnification was reminiscent of the benign mixed tumour of the salivary gland. However, the core biopsy of case 2 was different from that of case 1 in many ways. First, the amount of epithelial component (in case 2) was more than the stromal component and this was obscuring the biphasic pattern of the lesion. Second, the epithelial component showed irregular growing patterns such as single cells, cords and small nests or glandular structures. Moreover, myoepithelial cells were not identifiable clearly in H&E sections and immunohistochemical stainings (negative for both p63 and calponin). No nuclear atypia was defined and Ki-67 proliferation index was low (<5%). Therefore, the low power magnification was simulating the appearance of infiltrating low-grade adenocarcinoma. Since there was no extensive mucinous material in the background, we did not consider mucinous carcinoma in case 2. However,

Figure 3 The glandular foci showing one or two rows of epithelial cells. Arrow showing a glandular structure composed of eosinophilic polygonal cells in the inner layer and flattened cells in the outer layer intermittently (×400 H&E).

Figure 4 Main nodule as an 'intraductal papilloma' on the left and one of the small nodules with similar features on the right (×20 H&E).

we could not exclude the possibility of an invasive carcinoma in the core needle biopsy specimen and suggested excision of the lesion with clear margins.

TREATMENT

Cases 1 and 2

The lesions were excised with a cuff of normal breast parenchyma.

OUTCOME AND FOLLOW-UP

Case 1

Grossly, the tumour was circumscribed (10 mm in diameter), solid, grey-white in colour and firm. Two other small nodules (3 and 2 mm in diameters) were seen adjacent to the tumour. Microscopically, the main tumour nodule was seen in a big ductus as an 'intraductal papilloma' (figure 4). This tumour nodule consisted of a calcified, osteocartilaginous core surrounded by a balanced and mixed proliferation of ductal epithelial and myoepithelial cells (p63+, SMA+; figures 5 and 6). No necrosis, mitotic activity or cytological atypia was observed. Adjacent satellite nodules showed similar morphology.

Case 2

Macroscopic evaluation of excision material revealed a well-circumscribed nodular lesion directly beneath the breast skin

Figure 5 Mixed and balanced proliferation of epithelial and myoepithelial cells on the left, and cartilaginous stroma on the right (×400 H&E).

Figure 6 Myoepithelial cells showing continuous p63 positivity (×400).

(figure 7). Microscopic examination revealed similar morphological and immunohistochemical findings, described in core needle biopsy (figures 8–10).

DISCUSSION

PA is the most common tumour type in the salivary gland and is more common in the parotid gland than submandibular and sublingual glands.⁴ It occurs less frequently in other sites such as skin (chondroid syringoma), larynx, lung, lacrimal gland and breast. Less than hundred cases of PA of the breast have been reported in the literature, mostly in the form of single case reports^{3 5} and a few case series including a maximum of 10 cases.^{6–8} Since it is rare in the breast and breast skin, it is possible to misinterpret it as a malignant tumour during clinical and radiological evaluations.⁹ The exact diagnosis requires histopathological examination of the surgical excision material.

Most of the cases of PA were reported in women; however, three cases were of men with an age ranging between 23 and 85 years.⁵ The majority of the women were postmenopausal. The lesions were determined as palpable nodules on routine physical examination or nodular lesions with or without calcification in mammography.^{5–7} An incidentally discovered case during examination of a surgical specimen for breast carcinoma has also been reported.⁶ It shows a tendency to locate in the subareolar/periareolar region of the breast.¹⁰ The tumour sizes ranged from 0.6 to 17 cm with a mean diameter of 2 cm.⁵ Both our patients were also postmenopausal women and presented as

Figure 8 Diffuse positivity for cytokeratin 7 (×200).

palpable, non-tender and nodular lesions. While the nodular lesion was localised in the inner quadrant of the breast in case 1, it was localised superficially under the skin in case 2.

Chondroid syringoma represents the cutaneous counterpart of benign mixed tumour of the salivary gland including varying amounts of epithelial and mesenchymal stromal components.^{11 12} It occurs predominantly in the head and neck region as a slowly growing, painless, nodular lesion.^{11 12} The epithelial cell component consists of bland epithelial cells arranged in the form of tubules, cords and anastomosing glands.^{11 12} Positive immunostaining for cytokeratin, carcinoembryonic antigen, epithelial membrane antigen for inner layer of cells and vimentin, S-100, neuron-specific enolase and glial fibrillary acidic protein for outer layer of cells have been described.^{11 13} However, it has been indicated that two-layered ductal/tubular structures could be scant or even absent in chondroid syringomas,^{11 13} as seen in our case 2. Therefore, negative immunostainings for myoepithelial cell markers do not indicate the invasive nature of the tumour. Chondroid syringoma may also be classified as eccrine or apocrine, due to the morphological appearance of the tumour cells. The mesenchymal stromal component may be myxoid, chondromyxoid, hyalinised or osteoid.¹¹ Case 2 mainly showed hyalinised stroma.

Breast tissue surrounding PA may show some benign variations such as fibrocystic changes, ductal epithelial hyperplasia, sclerosing adenosis, intraductal papilloma or papillomatosis.^{6 7} It is noteworthy that most of the PA cases reported have been in

Figure 7 The low-power appearance of nodule in excision specimen (×40 H&E).

Figure 9 Negativity for calponin with a positive internal control (vessel wall; ×200).

Figure 10 Diffuse positivity for S-100 (×200).

the subareolar–periareolar region of the breast.^{5 10} This suggests that the tumour originates from the large ducts. Because of this, some authors regarded it as a form of intraductal papilloma with cartilaginous and osseous metaplasia instead of a distinct entity,⁸ while others regarded it as PA, mammary counterpart of

similar tumours arising from the salivary gland and dermal adnexal structures.⁶ The lesion was localised in the periareolar region and observed in the background of intraductal papilloma in our first case.

PA can be multifocal and local recurrences are related to multifocality.⁷ Wide-local excision of the lesion with a cuff of normal breast tissue was recommended for treatment.¹⁴ No recurrence was recorded after 27 and 5 months of follow-up for case 1 and case 2, respectively.

Occasionally, malignant transformation of PA of the breast (carcinoma ex-PA) has been reported.¹⁵ Hayes *et al* reported high-grade invasive breast carcinoma in the form of matrix-producing metaplastic carcinoma in three cases. The authors demonstrated PA areas adjacent to typical areas of malign transformation in all cases and commented on the relationship between PA and matrix-producing metaplastic carcinoma.

Competing interests None declared.

Patient consent Obtained.

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Learning points

- ▶ Pleomorphic adenoma (PA) of the breast is an uncommon benign lesion with a tendency to localise in the subareolar region, usually as a non-tender, nodular mass.
- ▶ PA may show multifocality and therefore has a risk for local recurrence. Wide-local excision of the lesion is recommended for adequate treatment.
- ▶ PA of the breast may mimic a malignant tumour clinically and radiologically. Therefore, exact diagnosis requires histopathological examination. At this point, a core needle biopsy specimen including chondromyxoid/osteochondromyxoid areas without evidence of prominent carcinomatous and/or sarcomatous areas should alert the pathologist with regard to PA.
- ▶ Moreover, PA may, very rarely, originate from adnexal structures of breast skin (chondroid syringoma). Since two-layered ductal/tubular structures may be scant or even absent in chondroid syringomas, they may show no immunostaining for myoepithelial cell markers. Being aware of this point will help to prevent misinterpretation of the lesion as 'invasive carcinoma' in core needle biopsy samples and consequently prevent excessive surgical treatment of patients.

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