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Myoepithilial Tumours of the Breast

Report of Two Cases

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Abstract

Myoepithelial lesions of the breast are defined as lesions arising from or composed of a dominant pure population of myoepithelial cells. They include adenoid cystic carcinoma, pleomorphic adenoma, myoepitheliosis, adenomyoepithelial adenosis, adenomyoepithelioma and myoepithelioma. The last two can be benign or malignant. Myoepithelial tumours of the breast are extremely rare. The benign myoepitheliomas are composed of a solid proliferation of cells with abundant eosinophilic syncytial cytoplasm. Although the biological behaviour of these remains uncertain, the tumours are considered to be myoepitheliomas with benign features due to mild nuclear pleomorphism, sparse mitotic figures and low ki67 index. Malignant myoepitheliomas represent the malignant end of the spectrum of myoepithelial lesions in the breast, usually arising de novo or in a pre-existing benign adenomyoepithelioma. Myoepitheliomas most often have spindle cell morphology and may mimic benign and malignant lesions. We report two cases of myoepithelial tumours and present a review of the current literature.

Case presentation: The two patients were females aged 60 and 85 years, respectively. One patient had a palpable breast lump and the other presented as a firm mass without palpable axillary lymph nodes. The diagnosis of the first case was myoepithelioma with uncertain biological behaviour since the mitotic rate was 3-4mf/10High Power Field (HPF), and the second a malignant myoepithelioma due to the high mitotic rate.

Conclusion: The patients were treated surgically and remain alive, two years after the initial diagnosis.

Key words:
Breast, Spindle cell tumors, Myoepithelioma - benign, Malignant

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Introduction

The normal breast comprises a duct-lobular system and is lined by two layers of cells: an inner secretory cell during lactation (luminal cells) and an outer contractile cell that helps to push the milk out during breast feeding [1-3]. Despite the fact that breast ducts and lobules are composed of an approximately equal proportion of luminal and myoepithelial(ME) cells, the latter appear to transform infrequently and tumours with myoepithelial differentiation are therefore rare [4].

Myoepitheliomas of the breast are rare tumours. They usually present as palpable nodules with a mammographic density without distinctive features. The age of patients may range from 22 to 87 years. Most tumours are benign; less than 50 malignant cases have been reported in the literature [5, 6]. According to WHO, malignant myoepithelioma (MME) classification is defined as an infiltrating tumour composed purely of myoepithelial cells with identifiable mitotic activity [7].

We report two cases of myoepithelial tumours, whose diagnosis was based on morphologic criteria and immunohistochemical methods, and present a review of the current literature.

Case Presentation

Case # 1

An 85-year-old female patient was admitted, in order to manage a breast lump gradually increasing in size, located in the lateral upper quadrant of the left breast. A mammography (Fig. 1) demonstrated a circumscribed lobulated dense mass in the outer upper quadrant (Bi-RADS 3) and a fine needle aspiration biopsy (FNAB) revealed spindle cells. An open quadratectomy and ipsilateral axillary lymphadenectomy was performed; sentinel lymph node biopsy (SLNB) is not available at our institution. Pathology examined a 12.5cm x 9cm x 6cm specimen of the left breast and identified a whitish, firm mass, with focal cystic degeneration measuring 3.6cm x 3.4cm x 2.8cm. The axillary specimen revealed 12 lymph nodes with a mean diameter of 0.2-2.5cm. Microscopically, the tumour was a myoepithelioma with benign features,

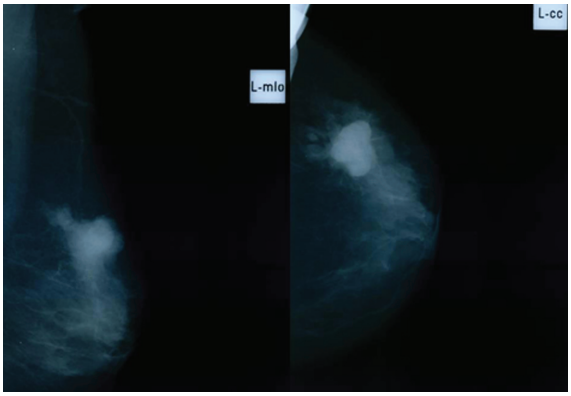

Fig.1 Mammography of the left breast (mediolateral oblique –mlo, craniocaudal – cc) demonstrating a circumscribed lopbulated mass in the outer upper quadrant with high density (Bi-RADS 4 lesion).

such as minor nuclear atypia and low mitotic index (about 2-4/10 HPF). All lymph nodes were negative. Immunohistochemically, the neoplasm displayed the following profile: P63(+), CK903(+), CK5/6(+), CD10(+).ER, PgR, HER2 status was negative. Diagnosis concluded that the tumour was a benign myoepithelioma that did not require adjuvant therapy. Close follow-up was decided on an outpatient basis, and the patient is still alive, two years after surgery.

Case # 2

A 60-year-old female patient was admitted to our hospital after having noticed a palpable mass in her right breast. Physical examination revealed a firm mass without palpable axillary lymph nodes. Mammography showed a lobulated mass with microcalcifications (Bi-RADS 4). Core needle biopsy revealed malignant spindle cells. Thoracic and abdominal computerized tomography (CT) and a nuclear bone scan were unremarkable. The patient underwent a modified radical mastectomy. Gross examination revealed a solid, ill-defined and partly cystic tumour, measuring 6cm in its greatest diameter (Fig. 2). Areas of haemorrhage and necrosis were present. In the remaining breast parenchyma, we found some small cysts. By light microscopy, the tumour displayed an infiltrative growth pattern and was composed mainly of nests of neoplastic cells, intimately admixed with a reactive spindle cell stroma. The tumour cells had an epithelioid appearance with vacuolated cytoplasm (Fig. 3a) or storiform pattern (Fig. 3b). The nuclei were large with prominent nucleoli. Numerous mitotic figures (8/10HPF) and necrosis were noted (Fig. 4). Moreover, some areas revealed neoplastic myoepithelial cells emanating from the myoepithelial layer of entrapped ductules. The sentinel axillary lymph node was examined and was negative. Immunohistochemically, the neoplastic cells were diffusely positive for p63 (Fig. 5), CD10, CK903, CK5/6. About 70% of the tumour cell nuclei were positive for ki67. Additionally, the tumour cells were triple negative [ER, PR (Fig. 6a), HeR2/neu] whereas EGFR was strongly positive (+3) (Fig. 6b). The histological diagnosis was malignant myoepithelioma of the breast. Given the patient's age and absence of other comorbidities, adjuvant radiotherapy was offered without chemotherapy. Follow-up was free of local recurrence and metastasis, and the patient remains alive, 18 months after surgery. *Written informed consent has been obtained from the two patients.*

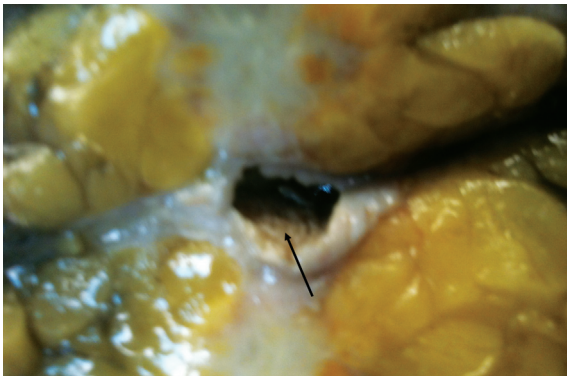

Fig.2 Gross appearance of a myoepithelial carcinoma: the tumor is ill-defined firm

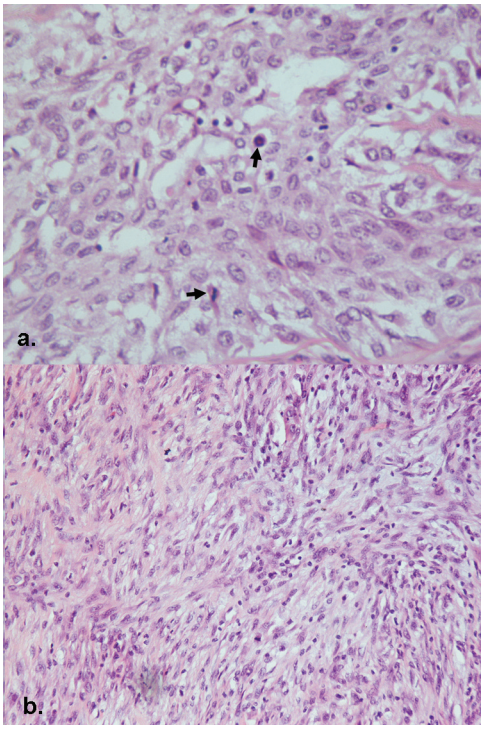

Fig.3 (a) MME with epithelioid appearance and mitosis(H/Ex200), (b) MME with storiform pattern (H/Ex200).

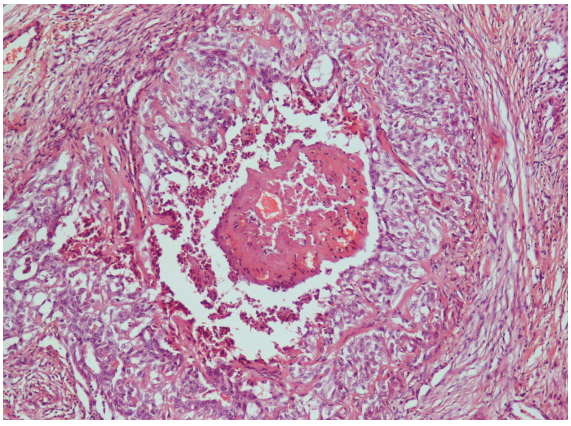

Fig.4 MME with central necrosis (H/Ex200).

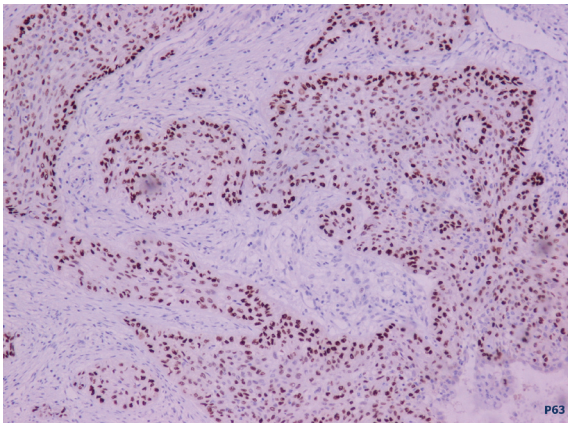

Fig.5 MME: the tumour cells are strong positive for p63(x200).

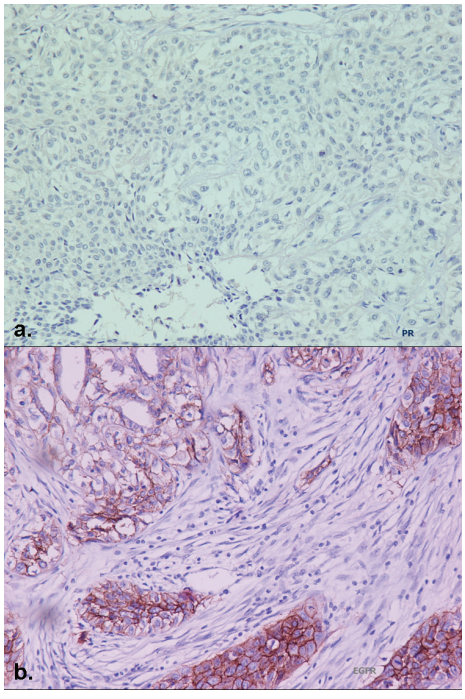

Fig.6 (a) MME: The tumour cells are negative for PR(x200), (b) MME: The tumor cells are intensely positive for EGFR(x200).

Discussion

Myoepithelial cells in the breast form a discontinuous outer cell layer between the luminal epithelial cells and the basement membrane. The myoepithelial cell layer persists in many breast lesions. Histologically, these cells may be difficult to recognize, but their presence and the alterations they undergo can be identified immunohistochemically and by electron microscopy [8,9]. Tumours composed of or deriving from myoepithelial lesions have also been reported in the salivary glands [10].

Classification

Myoepithelial proliferative lesions of the breast are classified as myoepitheliosis, adenomyoepithelial adenosis, adenomyoepithelioma and myoepithelioma [10]. Myoepitheliosis is characterized by the proliferation of spindled to cuboidal myoepithelial cells within and sometimes around multiple ducts. Adenomyoepithelial adenosis (AMEA) is a rare type of adenosis and consists of a diffuse proliferation of round or irregular tubular structures lined by a cuboidal to columnar epithelium which may show apocrine metaplasia. Adenomyoepithelioma is a tumour characterized by biphasic proliferation of both epithelial and myoepithelial cells. Myoepitheliomas are neoplasms of purely myoepithelial origin and may be benign myoepithelioma (ME) or malignant (MME).

The malignant myoepithelioma (MME) represents the malignant end of the spectrum of the myoepithelial lesions of the breast. It may arise de novo or in a pre-existing benign adenomyoepithelioma.

Diagnosis

i. Morphological features

ME and MME are composed purely of neoplastic myoepithelial cells. The tumour cells may form fascicles or anastomosing cords and often appear to emanate from the myoepithelial cell layer of entrapped ductules within the tumour. The differentiation of benign and malignant tumours is based on cytologic features and the presence and number of mitotic figures. Cytologic atypia includes pleomorphism, coarse chromatin and prominent nucleoli[12,13]. Mitotic activity has been evaluated in myoepithelial lesions. Nagao et al referred that all 10 malignant myoepitheliomas in their study had a mitotic rate >7 per high power field (HPF) and a MiB-1 index >10%. Those authors suggested that the latter criteria should be used to diagnose malignancy in myoepitheliomas[14]. Savera et al referred that the mitotic figures did not correlate with outcome because brisk mitotic activity was observed even in low-grade tumours [15]. Hornick and Fletcher in their study of 14 cutaneous myo-

epitheliomas demonstrated that recurrent/metastatic myoepithelial neoplasms had a higher mitotic rate than other lesions [16].

Necrosis and haemorrhage are uncommon; such findings are usually associated with malignancy [14,15,17].

ii. Immunohistochemical features

Immunohistochemically, ME cells are immunoreactive for SMA, CD10, P63, S100, HMWCK. CD10 expression has been reported that is dependent on the type of ME tumour[11,17,18]. ME tumours mimic various benign and malignant lesions, sometimes rendering diagnosis difficult.

Differential diagnosis

The differential diagnosis includes borderline and malignant phylloid tumour and soft tissue sarcomas such as leiomyosarcoma, angiosarcoma, fibrosarcoma, malignant fibrous histiocytoma, and malignant schwannoma. Immunohistochemical stains may be helpful, using a panel of markers which includes antibodies against epithelial and myoepithelial differentiation, mesenchymal, smooth muscle, as well as neural differentiation. Positivity for epithelial and myoepithelial markers would rule out pylloid tumour and all types of soft tissue sarcomas[14,17,19].

Another important differential diagnosis is specific variants of metaplastic carcinoma, such as spindle cell squamous carcinomas and spindle cell adenocarcinomas. The help of immunohistochemistry in these cases is important since spindle cell adenocarcinomas are negative for HMW CKs and positive for CK7. On the other hand, the differential diagnosis of ME carcinomas from spindle cell squamous carcinomas, based on morphological features, is much more difficult. Additionally, there is an overlapping in the immunoprofile of these tumours. Busa et al claim that MME and spindle cell squamous carcinomas are either both derived from the myoepithelial cell layer or they have a common stem cell[20]. Tavassoli et al support that the only distinctive morphological feature of MME is its clear-cut emanation from the myoepithelial cell layer, as this feature has never been described in spindle cell squamous carcinomas or in other types of metaplastic carcinomas of the breast [4,19].

Based on morphological studies, Wagotz et al support the myoepithelial origin of metaplastic carcinomas; the latest immunohistochemical studies seem to confirm this theory [21,22].

In addition, both myoepithelial carcinoma and squamous carcinoma are triple negative and express EGFR[23]. Furthermore, it is well known that normal myoepithelial cells demonstrate strong EGFR expression in contrast to luminal epithelial cells [24]. EGFR overexpression has been shown to correlate with clinical response to anti-EGFR tyrosine kinase inhibitors in patients with non-small cell lung carcinoma. Hence, patients with myoepithelial and metaplastic breast carcinomas may also benefit from targeted therapy against EGFR [25].

Myoepithelial tumours, generally considered benign, can undergo clinical evolution, while MME appears to have haematogenous [lung, bone and brain metastasis] and lymphatic spread.

To date, there is limited published data on the biological behaviour and long-term clinical outcome of these malignant tumours. The prognosis of MME with distant metastasis is very poor at the time of recurrence and varies after the initial diagnosis [26].

Treatment of MME includes wide resection of the suspicious breast mass with concomitant appropriate axillary lymph node harvest. The operative strategy should follow the same principles as in every case of breast malignancy. Adjuvant chemo- or/and radiotherapy is based on clinic-pathological staging and the patient's age and general health status.

In conclusion, myoepitheliomas are neoplasms of purely myoepithelial origin that may be benign or malignant. The latter is a rare neoplasm that represents the malignant end of the spectrum of myoepithelial lesions of the breast and tends to show haematogenous and lymphatic spread. All breast myoepitheliomas should be managed as potentially malignant tumours with appropriate surgical clearance and staging.

Conflict of interest

The authors declare that they have no conflict of interest.

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