Adenomyoepithelioma of the breast - A rare case report with a brief literature review emphasising differential diagnosis

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Abstract

Adenomyoepithelioma of the breast is an unusual tumor characterized by the presence of a dual population of cells: luminal cells and myoepithelial cells. A spectrum of histologic patterns can be seen in these lesions and even in different areas of the same tumour. These tumors can be a diagnostic challenge, especially in core needle biopsy samples, because of their morphologic heterogeneity. Recognising the biphasic cellular components and the characteristic architecture of the tumors along with immunohistochemical features are essential to arrive at the right diagnosis. Most tumors have benign behaviour. Very occasional tumours have been reported to exhibit local recurrences, malignant change, and distant spread. Malignant adenomyoepithelioma with distant metastases has been noticed to exhibit significant cytologic atypia and increased mitotic rates. Hence, adequate sampling of the lesion to identify these cytologic features is essential. Complete excision with adequate margins has been reported to lower the risk of local recurrence and distant metastasis.

1. Introduction

Adenomyoepithelioma (AME) was first described by Hamperl in 1970. AME is a biphasic neoplastic proliferation of luminal epithelial and myoepithelial cells (Hamperl 1970). AME is noticed to exhibit a heterogeneous histologic pattern due to variations in the proportion of epithelial and myoepithelial cells (Tavassoli 1991). Papillary configuration is noticed in many lesions, and hence, AME is regarded as a variant of intraductal papilloma (Rosen 1987). Prominent histological heterogeneity, like papillary architecture or multi nodularity, especially in a limited biopsy sample, (Hoda and Rosen 2004; Zhang et al. 2004; McLaren et al. 2005) may be easily

missed and result in misdiagnosis of malignancy (Rosen 1987). Most AMEs exhibit benign behaviour. Occasional malignant AMEs with distant spread have been recorded in previous literature (Tavassoli 1991; Loose et al. 1992; Simpson et al. 1998; Ahmed and Heller 2000). Exact diagnosis and prediction of clinical behavior of the tumor are essential for the proper management of the patient.

2. Case report

A 36-year-old female presented with complaints of lumps on both the breasts. The lumps were irregular, firm and unfixed. Fine needle aspiration was inconclusive. Excision of the lesions were carried out. The swelling from the right breast was measuring about 1.5x0.6cm and the swelling from the left breast was measuring about 2.1x2cm in dimension. Both the lesions were firm in texture and greywhite in colour. Microscopic examination of the right breast lump showed benign hyalinised intracanalicular fibroadenoma. Microscopic examination of the left breast lump showed infiltrating cords, trabecular and glandular elements of benign ductal epithelial cells with a very predominant myoepithelial component throughout. Individual ductal cells with relatively bland appearing uniform nuclei, admixed with myoepithelial components were seen traversing the stroma [Fig1, Fig2]. No mitotic figures noticed. A diagnosis of benign adenomyoepithelioma was made and further immunohistochemical examination was carried out to confirm the same. Positivity of p63 and SMA (smooth muscle antigen) immunohistochemical positivity of the lesion are characteristic of adenomyoepithelioma [Fig3].

3. Discussion

Patient age usually ranges from 22 to 92 years with a mean age of occurrence of 59 years (McLaren et al. 2005). Most patients have been females, although occasional cases have been recorded in men (Tamura et al. 1993). Common clinical presentation is a solitary palpable nodular breast mass (McLaren et al. 2005). The lesions tend to occur in the periphery of the breast (Rosen. 1987), although the central lesions have been reported (Jabi et al. 1988; Tavassoli 1991). Tenderness and serous nipple discharge are infrequent findings (Tavassoli 1991). In mammography, AME is seen as a lobulated or round, dense, usually circumscribed mass lesion. Occasionally, margins might be

partially indistinct (Hayes 2011). Calcifications and cystic change are not frequently found (Trojani et al 1992).

The mass size of AME varies from 0.3 cm to 7 cm, with a mean size of 2.5 cm (Tavassoli 1991; McLaren et al. 2005). The tumors are palpated to be round or lobulated firm masses that are often well-circumscribed (Rosen 1987; Tavassoli 1991). Multinodularity, papillary architecture and focal cystic changes have been recorded (Laforga et al, 1998; Papaevangelou et al. 2004; McLaren et al. 2005). The recurrent lesions usually have irregular margins and with size ranging from 2 cm to 6 cm (Loose et al. 1992). The cross-section is usually pink-white to gray-tan firm tissue with focal or diffuse translucency (Tavassoli 1991; Loose et al. 1992). Areas of hemorrhage and focal necrosis have also been seen in the lesions (Zarbo and Oberman 1983; Rosen 1987; Zhang et al. 2004). The AME tumor has biphasic histology, containing cuboidal to columnar epithelial cells arranged in tubules enclosed by myoepithelial cells (McLaren et al. 2005). However, a varying spectrum of histologic patterns has been noticed among various reported cases and even in different areas of the same tumour (Rosen 1987). These variations were noticed because of the difference in distribution of epithelial and myoepithelial cells, the altering spindle and polygonal morphology of myoepithelial cells, the presence of papillary element, and the extent of fibrosis (Rosen 1987). Three histologic variants of AMEs have been described in literature (Tavassoli 1991). The first is the tubular variant, which is composed mainly of tubules with unusually prominent proliferation of myoepithelial cells. The second is the spindle cell variant, which is predominated by spindle shaped myoepithelial cells admixed with epithelial tubules. Finally, the third is a lobular variant containing solid nests of myoepithelial cells enclosing epithelial tubules. The solid nests of myoepithelial cells are often surrounded by dense fibrous tissue (Tavassoli 1991).

AMEs are often found to have papillary architecture and, hence, often regarded as a variant of intraductal papilloma or an evolution of intraductal papilloma (Rosen 1987; Loose et al. 1992; Rosen 2009). Myoepithelial cells often form nests or sheets and exhibit a spindle to myoid shape containing clear cytoplasm. This solid pattern is seen to often obliterate, compress, or displace the tubules, leading to zones that lack epithelial components (Tavassoli 1991; Rosen 1987; McLaren et al. 2005). These regions, if prominent, may result in a misdiagnosis of myoepithelioma. The

myoepithelial cells might sometimes exhibit pink to amphophilic cytoplasm or have a plasmacytoid shape with dense, hyaline like eosinophilic cytoplasm with peripheral nucleus (Jabi et al. 1988; Tavassoli 1991; Rosen 2009). Myxochondroid substances synthesised by the myoepithelial cells may be seen resembling pleomorphic adenomas (Jabi et al. 1988; McLaren et al. 2005). Dense, hyaline like, collagenous matrix can be noticed in the basement membranes (Fukuoka 2001) [18]. Epithelial cells might have darker nuclei and dense eosinophilic or amphophilic cytoplasm, when compared to myoepithelial cells (Rosen 2009). Apocrine, squamous and sebaceous metaplasia of epithelial cells may be noticed variably (Tavassoli 1991; Cai and Tan 2005; Rosen 2009). Atypical features such as brisk mitosis, cellular pleomorphism, prominent nucleoli, hyperchromasia, and necrosis, if noticed, indicate the possibility of recurrence or malignant behaviour (Tavassoli 1991; Loose et al. 1992; Ahmed and Heller 2000).

Immunohistochemical characteristics are unique for epithelial and myoepithelial components. The epithelial cells show uniform cytoplasmic positivity for cytokeratins like CK7, cytokeratin AE1/3 and CAM 5.2 (McLaren et al. 2005; Loose et al. 1992). The luminal surfaces of the epithelial cells show positivity for the epithelial membrane antigen (Rosen 2009). Myoepithelial cells do not show positivity for epithelial membrane antigen and often show subtle reactions to cytokeratin AE1/3 (Loose et al. 1992; McLaren et al. 2005). The myoepithelial cells exhibit p63, smooth muscle myosin heavy chains, CD10, CK5, actin, calponin and S100 positivity (Loose et al. 1992; McLaren et al. 2005; Rosen 2009; Dewar et al. 2011). p63 is often seen to produce the best results with intense persistent nuclear staining (McLaren et al. 2005). Actin staining is prominent in spidle shaped myoepithelial cells rather than polygonal shaped ones (Rosen 2009).

Smooth muscle myosin–heavy chain is considered most sensitive due to its ease to interpret when compared with smooth muscle actin and muscle-specific actin, and because it does not usually cross react with myofibroblasts (Werling et al. 2003; Rosen 2009; Dewar et al. 2011). Calponin is very sensitive in identifying myoepithelial cells with its unique cytoplasmic staining. However, calponin positive myofibroblasts is seen in around 74% of breast proliferative lesions differentiated by subtle, patchy staining (Dewar et al. 2011). All myoepithelial cells express S100 with varied intensity (Rosen, 2009; Loose et al, 1992; Dewar et al. 2011). Epithelial cells are usually S100 negative, but occasional positivity can be noticed in the epithelial cells, in which

case, the diagnostic utility of this myoepithelial marker may be limited (Dwarakanath et al. 1987; Gillett et al. 1990; Nayar et al. 1999; Rosen 2009). The myoepithelium specific markers exhibit various ranges of cross-reactivity and variable proportion of protein expression, particularly in the neoplastic myoepithelial cells when compared with normal myoepithelial cells (Rosen 2009; Dewar et al. 2011). Hence, a panel consisting of two or more myoepithelial markers is suggested to be employed in order to mitigate the chances of misdiagnosis (Rosen 2009; Dewar et al. 2011). Proliferative markers such as Ki-67 are present in both elements of the lesion but could be higher in the myoepithelial component than it is in the epithelial cells (Koyama et al. 1997). Estrogen immunostaining is seen to be either negative or weak patchy positive (Jabi et al. 1988). Progesterone and ERBB2 immunostain have been consistently recorded to be negative in the literature (Rosen 1987; Jabi et al. 1988).

AMEs are considered variants of intraductal papilloma by some researchers (Rosen 1987). AMEs can be differentiated from papilloma with prominent myoepithelial components on the basis of pattern, architecture, and extent of myoepithelial cell proliferation (McLaren et al. 2005). The lesions that exhibit only myoepithelial cells that are seen to line the papillae and form the basal layer below the epithelial cells and without forming nests, nodules or an increased amount of myoepithelial component are referred to as papillomas with prominent myoepithelial cells (McLaren et al. 2005). Myoepithelial immunohistochemical markers indicate the prominence of myoepithelial cells within the papillae and also at the periphery of the lesion (Dewar et al. 2011). When the fibrovascular core of the papillae is dense or exuberant, nuclear immunostains, like p63 or maspin, must be included in a myoepithelial marker panel to avoid picking up cross-reaction with myofibroblasts located in the fibrovascular core (Dewar et al. 2011). A diagnosis of AME is considered only if the myoepithelial cell proliferation is extensive and diffuse seen throughout the lesion (Jabi et al. 1988). Nipple adenoma could sometimes resemble AME, but the identification of florid epithelial hyperplasia and the pseudo infiltrative appearance of stromal sclerosis enclosing tubules without any trapped fibrous tissue or fibrovascular cores are helpful in differentiating the former (McLaren et al. 2005). Clear cell carcinoma may occasionally resemble AMEs, but that may be distinguished by identifying both epithelial and myoepithelial components and confirming the same using immunohistochemical stains, if needed (McLaren et al. 2005). Metaplastic tumors associated with papilloma should also be included in the differential diagnoses of AMEs (Gobbi

et al. 2003). A rare adenosis variant of AME is seen to have an infiltrative growth that mimics microglandular adenosis. Microglandular adenosis can be differentiated by an absence of myoepithelial cells and S100 positivity (Rosen 2009).

When the lesion largely exhibits a spindle shaped myoepithelial cell component, it may histologically mimic leiomyoma or myoid hamartoma (Tavassoli 1991). Intense positivity for S100 and p63, and low staining for actin and cytokeratin in AME are useful in distinguishing the two lesions (Tavassoli 1991; Rosen 2009). Myoid hamartomas show increased expression for CD34, whereas CD34 is negative in AME. Tumors that solely contain benign myoepithelial cells indicate myoepithelioma (Hamperl 1970; Tavassoli 1991; Rosen 2009). Extensive sampling of the lesion to detect the tubular epithelial element is essential to differentiate AMEs from myoepithelioma.

AMEs may contain focal areas that mimic adenoid cystic carcinoma of the breast, but that have infiltrative margins and a characteristic cribriform pattern in most cases. The myoepithelial cells in an adenoid cystic carcinoma are found to be smaller, darker, and basaloid and have less amount of cytoplasm than the myoepithelial cells of an AME (Jabi et al. 1988). Also, adenoid cystic carcinoma may be ruled out by the absence of the two types of mucin and the identification of apocrine epithelial metaplasia (McLaren et al. 2005). Pleomorphic adenomas have overlapping features with AMEs, but a distinct hyaline matrix containing chondroid areas and encapsulation is more conspicuous in pleomorphic adenoma (Jabi et al. 1988; McLaren et al. 2005; Rosen 2009).

Diagnosing AME on a needle core biopsy can be difficult due to its morphologic heterogeneity. In limited biopsy samples, the retrieved tissue may mimic invasive carcinoma, especially in lesions that exhibit compressed tubules with clear cell epithelioid like myoepithelial proliferation (Rosen 1987; Hoda and Rosen 2004; Zhang et al. 2004; Rosen 2009). Regularly spaced, round or oval glands, streaming of the glands in one direction and predominant spindle cell or clear cell myoepithelial cells are some histologic clues that help in diagnosing AME (Hoda and Rosen 2004). Immunohistochemical stains for myoepithelial cells, especially p63, are useful for accentuating the excess myoepithelial elements (Hoda and Rosen 2004). Atypical features, like prominent nuclear pleomorphism, brisk mitotic activity, necrosis, infiltrative growth, and the excess

proliferation of one of the two components of the tumour may be difficult to recognise in the needle core biopsy samples. Hence, an excision biopsy is recommended to exclude a carcinoma arising in an AME (Hoda and Rosen 2004).

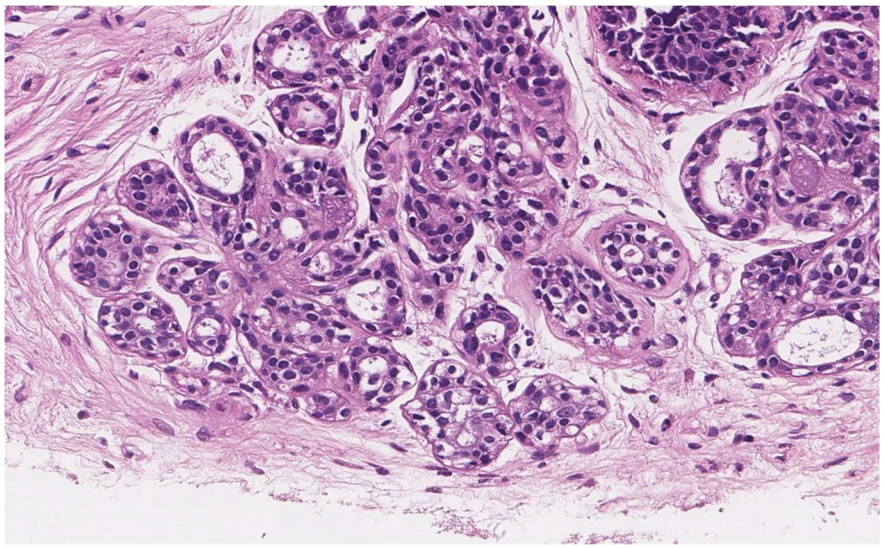

Fig. 1: Ductal and myoepithelial cells proliferation; 20X

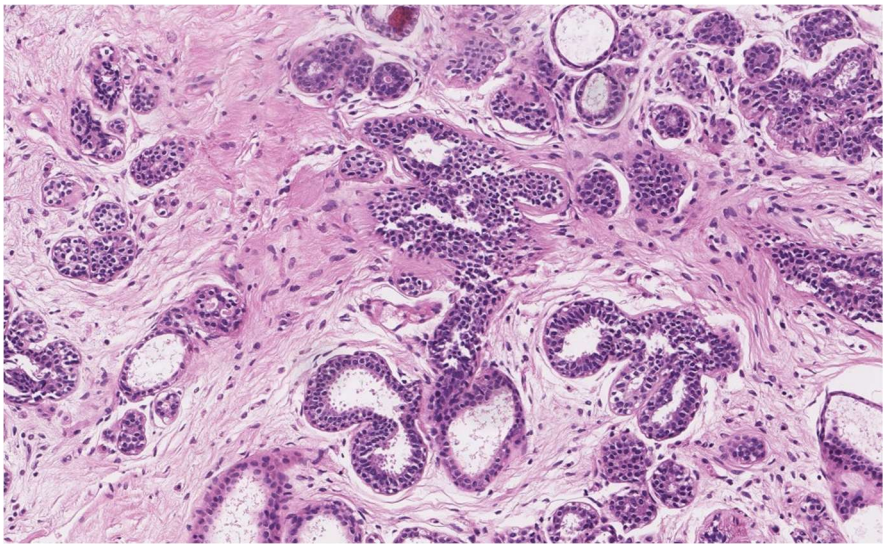

Fig. 2: Ductal and myoepithelial cells proliferation; 20X

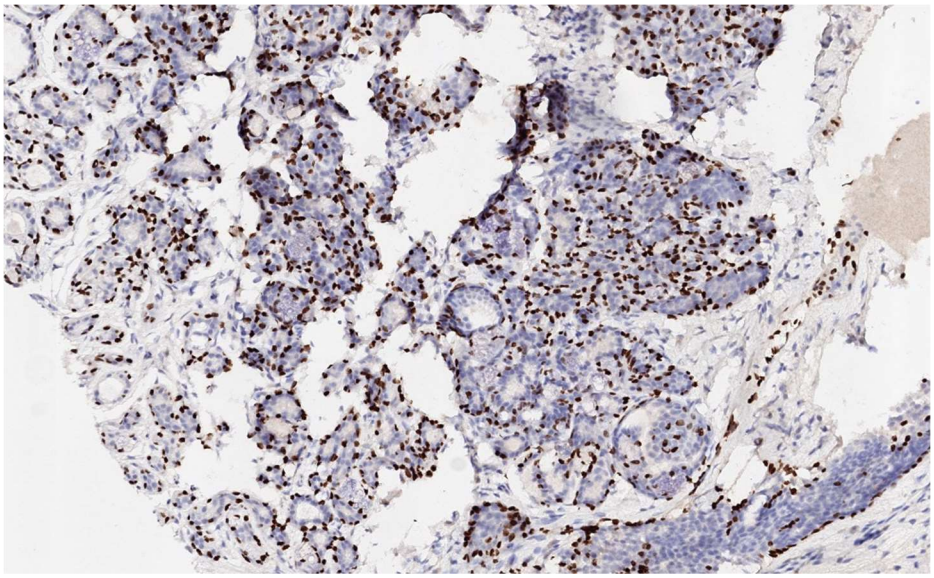

Fig. 3: p63 in myoepithelial cells; 20X

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