Mucoepidermoid carcinoma of the breast

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Received August 1, 2006

Mucoepidermoid carcinoma of the breast is a very rare type of neoplasm with a very distinct histology, immunohistochemistry as well as prognostic characteristics. Two cases of this type of breast carcinoma are presented. Both tumors were microscopically composed of intermediate, epidermoid and glandular cells. The first case was a high grade tumor with focal necroses, where epidermoid and mucinous cells were found only as isolated elements. The second case was of low grade, the squamous cells showed keratinization and glandular cells formed distinct small lumina. The prognostic characteristics, differential diagnosis, grading system and immunohistochemical profile of these rare neoplasms are described.

Key words: Mucoepidermoid carcinoma – breast – salivary glands tumor – basal cell phenotype

Mucoepidermoid carcinoma (MEC) is a rare neoplasm of the breast. As both mammary and salivary glands share some similar morphological features, it is not so surprising that salivary gland-like tumors can be found also in the breast. These tumors can be subdivided into two groups: the tumors with myoepithelial differentiation (myoepithelioma, mixed tumor, adenoid cystic carcinoma, adenomyoepithelioma) and tumors devoid of or with only scanty myoepithelial differentiation (acinic cell carcinoma, oncocytic carcinoma, MEC) [1]. Although MEC is frequent in salivary glands, only about 24 cases have been described in the breast so far [2]. We report herein two cases of this rare lesion and discuss the differential diagnosis.

Patients. First patient was a 63-year-old female with impalpable circumscribed lesion measuring 18 mm, located in the upper outer quadrant of the right breast, detected at screening mammography. A core cut biopsy was performed with a diagnosis "ductal carcinoma in situ". The patient underwent partial mastectomy with axillary lymph node dissection. She was treated by adjuvant chemotherapy (5-fluorouracil, doxorubicin, cyclophosphamide) and subsequent radiotherapy. Eighteen months later, she is well and without disease. The patient has no lesion in salivary glands.

Second patient was a 30-year-old female. She underwent mastectomy because of a large tumor mass in the left breast with subsequent axillary lymph node dissection. No lymph node metastasis was identified. The patient was treated by chemotherapy and radiotherapy; five years later, she is without recurrence or metastasis. The patient does not have any other tumor lesion.

Material and methods

Both cases were retrieved from the consultation files of one of the authors (A.R.). In the first case, both partial mastectomy specimen and axillary fat were examined, whereas, in the second case, only the mastectomy specimen was available and the information about negative result of lymph node examination was obtained from the patient's chart.

The tissue was fixed in 10% formalin, routinely processed and embedded in paraffin. Four micrometers thick sections were cut and stained with hematoxylin and eosin, alcian blue and periodic acid-Schiff (PAS). Deparaffinized sections were also examined immunohistochemically by the streptavidin-biotin method using polyclonal primary antibody against S-100 protein (1:4000, Bio-Genex, San Ramon) and vascular endothelial growth factor (VEGF) (1:200, Neo markers, Westinghouse) and by monoclonal primary antibodies against smooth muscle actin (SMA) (1A4, 1:200, Dako, Glostrup), CD 10 (56C6, 1:100, Novocastra, Newcastle), p63 (4A4, 1:200,

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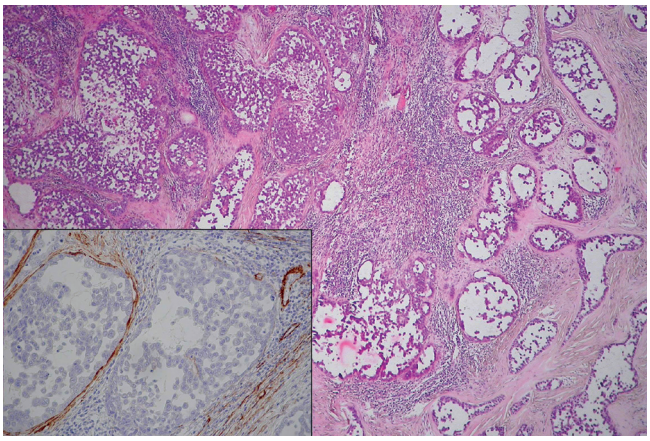

Figure 1. Predominantly solid and intraductal tumor with focal necroses. The stroma is infiltrated by lymphocytes (H&E). Inset: immunohistochemical demonstration of smooth muscle actin highlights predominantly intraductal growth of the tumor. Neoplastic cells are negative (case 1, 40x, inset 100x).

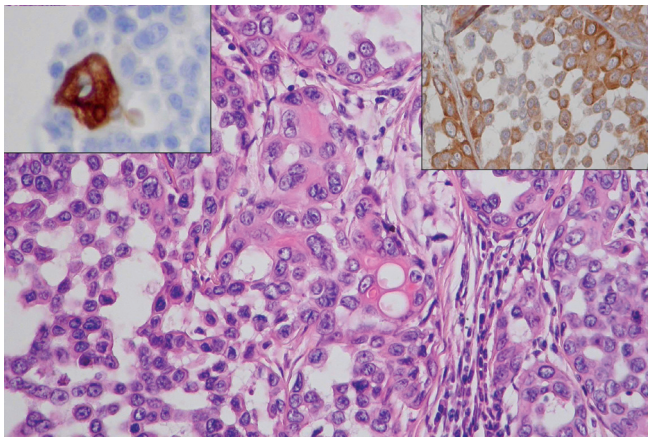

Figure 2. Demonstration of three cell types in mucoepidermoid carcinoma. Intermediate cells are on the left, squamous and mucinous cells are localized centrally (H&E). Inset – left hand corner: positivity of cytokeratin 18 in mucinous cells. Inset – right hand corner: expression of cytokeratin 5/6 in intermediate cells (case 1, 200x, insets 200x and 400x).

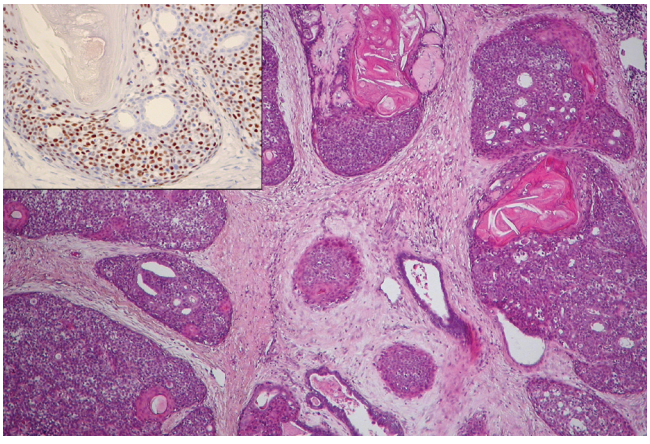

Figure 3. The tumor shows solid non-infiltrative growth pattern. The intermediate cells are dominant, the squamous cells show keratinisation, the glandular cells are in minority (H&E). Inset – expression of p63 in intermediate cells (case 2, 40x, inset 200x).

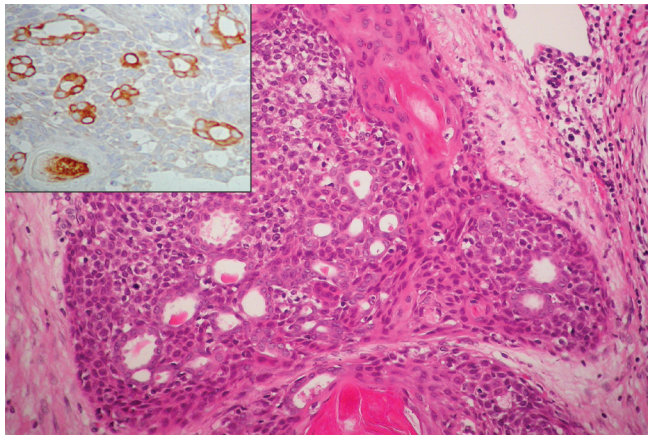

Figure 4. The detail of three cell types of mucoepidermoid carcinoma, note low degree of anisonucleosis (H&E). Inset – expression of cytokeratin 7 in glandular cells. (case 2, 200x, inset 200x)

Dako), E-cadherin (NCH-38, 1:100, Dako), high molecular weight cytokeratin (34ß E12, 1:100, Dako), cytokeratin 5/6 (D5/16 B4, 1:200, Dako), cytokeratin 7 (OV-TL 12/30, 1:100, Dako), cytokeratin 18 (DC 10, 1:50, Dako), cytokeratin 19 (RCK 108, 1:100, Dako), estrogen receptors (1D5, 1:75, Dako), progesterone receptors (PgR636, 1:300, Dako), Ki-67 (MIB-1, 1:30, Dako), p53 (DO-7, 1:150, Dako).

A streptavidin-biotin peroxidase detection system (EnVision, Dako) was used. For detection of HER-2/neu protein and epidermal growth factor receptor (EGFR) were used kits – HercepTest™ (Dako) and EGFRpharm Dx™ (Dako). Appropriate tissue specimens were used as positive controls.

Results

Case one: Grossly, two nodular lesions were found within the breast tissue, measuring 18 mm and 15 mm. Both lesions were well circumscribed. No connection of either nodule with the overlying skin was identified.

Microscopically, the larger lesion was the primary tumor and the smaller one was an intramammary lymph node with a tumor metastasis. Seventeen lymph nodes identified within the axillary fat were free of metastasis.

The primary tumor was relatively well circumscribed, however, focal invasion into surrounding tissue was identified.

The tumor showed mainly solid pattern with predominantly intraductal growth. (fig. 1) There were three cell types: intermediate, epidermoid and glandular cells. The intermediate cells formed the vast majority of the tumor. (fig. 2) They were poorly differentiated, small and ovoid, with high mitotic activity. The epidermoid and glandular cells were in minority, localized mainly in the central part of the tumor. The epidermoid cells had polygonal shape, larger nucleus and eosinophilic cytoplasm. The glandular cells had vacuolated cytoplasm; the content was PAS positive. These cells occasionally formed small lumina filled with PAS and alcian blue positive material. Focal necroses were found in the central parts of the tumor. The stroma, prominent particularly at the periphery of the tumor, had lymphocytic infiltration. The lymph node metastasis was composed of the intermediate cells only.

Immunohistochemically, the vacuolated cells and the cells forming small lumina expressed strongly cytokeratin 18 and weakly cytokeratin 7. Cytokeratin 19 was negative. Most intermediate and epidermoid cells expressed strongly cytokeratin of high molecular weight, cytokeratin 5/6 and weakly p63; Other markers of myoepithelial differentiation, such as – SMA, S 100 protein and CD 10, were negative. Tumor cells expressed weakly E-cadherin; they did not express hormonal receptors (neither oestrogen, nor progesterone) and HER-2/neu protein. Tumor cells, in particular the intermediate ones, showed strong membranous expression of EGFR and weak expression of VEGF. Ki67 was positive in 25 % and p53 in 20 % of tumor cells.

Case two: Grossly, the tumor measured 82x65x50 mm, it was well circumscribed, without any connection to the skin.

Histologically, the tumor grew in slightly hypocellular stroma in solid well-circumscribed foci, sometimes lined with sparse myoepitheliar layer. Neither obviously infiltrative growth pattern nor necroses were observed.

The tumor was composed predominantly of intermediate and squamous cells, the latter were localized in small nests and often showed keratinisation. (fig. 3) The glandular cells were in minority, they formed small lumina. Neither cell type showed distinct cytological atypia or nuclear polymorphism. The intracellular mucin-containing vacuoles were not identified. (fig. 4) The mucus (using alcian blue and PAS reaction) was demonstrated only in extracellular location within glandular lumina or between intermediate cells. Rarely, obvious sebaceous differentiation of tumor cells with multivacuolated cytoplasm and scalloped nuclei was found. The mitotic count was quite high (3 mitoses per high power field, at maximum), namely in the intermediate cells.

Immunohistochemically, the cells forming small lumina expressed cytokeratin 7 and 18, cytokeratin 19 was negative, the squamous cells and intermediate cells expressed cytokeratin 5/6; p63 was strongly expressed in all intermediate cells and in some squamous cells. EGFR showed predominantly cytoplasmatical positivity localised in the intermediate cells only. All three tumor cell types expressed high molecular weigh cytokeratin. SMA, S 100 protein, CD 10 and E-cadherin were negative. Similarly to the first case, tumor cells did not express hormonal receptors (neither oestrogen, nor progesterone) and HER-2/neu protein. Oncoprotein p53 was positive in 15 %, Ki67 was focally positive even in 40 %, tumor cells did not express VEGF.

Discussion

Mucoepidermoid carcinoma (MEC) is a salivary gland tumor arising predominantly in major salivary glands and, less frequently, in minor salivary glands of oral [3] or nasal [4] cavity, oesophagus [5] and bronchial tree [6]. Rarely, it has been diagnosed also in other locations in the head and neck region, e.g. thyroid gland [7], thymus [8], mandible [9], or ear [10, 11]. Origin of these "ectopic" tumors might be related to embryological development of the head and neck. Exceptionally, MEC has been described in other exocrine glands – pancreas [12], lacrimal gland [13], breast, skin adnexa [14], bile duct [15] and intestinal mucosa [16]. Classification of tumors in this group is rather problematic, not only due to rarity of these cases, but also because confusing use of overlapping terms mucoepidermoid and adenosquamous carcinoma.

All tumors located outside the salivary glands share the same morphological and even immunohistochemical features as MEC of the major salivary glands [2, 7, 15, 17]. In addition, MEC sometimes preserve expression of certain organ specific markers, e.g. MEC of thyroid gland expresses thyroglobulin [7].

MEC of the breast is an extremely rare tumor with only 24 cases reported so far [1, 2, 17 – 22]. Some of them showed an intraductal component, sometimes accompanied with "classical" ductal carcinoma in situ [2, 2]. The hormonal receptor status was studied in one case only [19] – both the oestrogen and progesterone receptors (studied biochemically) were negative. Similarly, in the herein reported cases, neither oestrogen, nor progesterone receptors have been demonstrated immunohistochemically. Oestrogen receptors in the salivary gland MEC are not expressed too [23].

MEC of the breast has been graded either by the same grading system as applied for MEC of the salivary glands [3], or by the grading system used for other breast carcinomas [24]. Some authors use the grading system distinguishing only either low-grade or high-grade tumors [1], whilst others use a three step grading system [2]. However, this is more or less a problem of terminology, as the moderately differentiated MECs belong biologically into the low-grade group of salivary gland tumors and behave in a similar way to the well-differentiated tumors [3].

The low-grade MEC of the breast are well circumscribed, sometimes containing cystic lesions, filled with mucin. The epidermoid or mucus secreting cells are usually found in the central areas of the lesion [1,2]. This group has generally a good prognosis; axillary metastases were described in one

patient only; no distant metastases were reported [1]. According to the last review by di Tommaso et al. [2], 12 cases of low grade MEC have been described so far.

The criteria for the diagnosis of high grade MEC are not well defined. These tumors represent a heterogenous group of different lesions composed of a complex admixture of glandular structures with mucin production, foci of squamous differentiation, and primitive-looking undifferentiated intermediate cells. Neoplasms of this group show usually aggressive behaviour; metastases to axillary lymph nodes and distant organs are frequent [1]. Nine cases have been reported so far [2].

It is possible that the low-grade MEC are more frequent, however, they are easily misinterpreted as mammary carcinomas with mucinous differentiation and/or squamous metaplasia [18]. The clue to the diagnosis of the high grade MEC is identification of specific squamous and mucin secreting cells in the tumor; these elements are sometimes sparse and extremely difficult to find, thus it can be expected that these high grade MEC are underdiagnosed too. These tumors can be misinterpreted as solid variant of high grade ductal carcinoma in situ, as histiocytoid lobular carcinoma [24] or as solid papillary carcinoma with neuroendocrine differentiation [25], all of which superficially resemble high grade MEC composed of small undifferentiated intermediate cells.

The distinction from ductal carcinomas not otherwise specified is needed; tumors with basal cell phenotype (expression of cytokeratin 5/6 or 14) or combined basal and luminal phenotype (expression of cytokeratin 5/6 together with 8, 18 or 19) have more aggressive behaviour than tumors with luminal differentiation (expression of cytokeratin 8, 18 or 19). Tumors with basal cell phenotype represent 15 – 25 % of invasive breast carcinomas. They are usually high grade, have areas of necrosis, they are often p53 and EGFR positive, ER and HER2/neu negative and they have BRCA1 mutation more frequently than other breast carcinomas (26, 27). Both herein reported cases have this immunohistochemical profile (CK5/6 and focal CK 7 and 18 positive; p63, p53, EGFR positive, ER and HER2/neu negative), but both cases – especially the low grade one (similarly to the cases reported previously by di Tommaso [2]) seem to have quite a good prognosis. Hypothetically, this could be explained by the comparison of ductal and mucoepidermoid carcinomas of the breast at one side with salivary duct and mucoepidermoid carcinomas of the salivary glands on the other side.

In salivary glands, about one third of salivary duct carcinomas (similarly to breast ductal carcinoma) express basal cell markers [28] and the prognosis of these tumors is usually unfavourable. On the other hand, well or moderately differentiated MEC have much better prognosis [3]. Thus, the different prognosis of these lesions may be estimated more by histological features than by mere expression of basal cell markers. Another example supporting the proposition that expression of basal cell markers is associated with bad prognosis in ductal carcinoma, but not in other tumors of the breast, is the fact that other salivary gland-like tumors of the breast (such as adenoid cystic carcinoma) are regarded as tumors with very good prognosis, despite their basal-cell phenotype [1].

To show, that breast MEC have less aggressive behaviour than ductal carcinoma with basal cell phenotype, we have used demonstration of VEGF. Its expression is considered a prognostic marker associated with angiogenesis and metastatic potential of the tumor. The first case (high grade) showed weak expression and the second case (low grade) showed no VEGF expression at all. This is similar to the degree of expression of VEGF in MEC of salivary glands [29]. In contrast, ductal breast carcinoma with basal cell phenotype shows high expression of VEGF, similarly to salivary duct carcinoma [29,30].

Thus, we conclude that MEC and other salivary gland like carcinomas of the breast represent a specific category with good prognosis and should not be included in the group of breast carcinomas with basal cell differentiation.

For the distinction of MEC from other carcinomas with basal cell phenotype, a typical growth pattern as well as characteristic fashion of expression of basal and luminal cytokeratins in the three cell types is of particular importance.

In conclusion, we report herein two cases of MEC of the breast (one high-grade, the other one low-grade). The primary mammary origin of the tumors is supported by the absence of other primary lesion elsewhere, particularly within salivary glands. We stress the need to distinguish MEC and other salivary gland-like breast carcinomas from the group of ductal carcinomas with basal cell phenotype, because of their much better prognosis.

This study was supported by Ministry of Health Czech Republic, grant IGA MZ NR 8392-3/2005.

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