Institute of Experimental Morphology, Pathology and Anthropology with Museum
Bulgarian Anatomical Society

Acta morphologica et anthropologica, 28 (1-2)
Sofia ● 2021

Eosinophilic Metaplasia in Benign Breast Epithelium: a Case Report

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The aim is to present an extremely rare epithelial lesion of the breast with detailed description of its immunophenotype. A 73-year-old woman with invasive ductal carcinoma with conventional intralobular hyperplasia without atypia demonstrated a massive diffuse, PAS-D positive, granular eosinophilic transformation of the cell cytoplasm. The lesion was assessed as eosinophilic (acinar) metaplasia and showed a phenotype, proving its mammary origin. In addition, the eosinophilic and granular cytoplasm was MUC1 positive, similar to prostatic eosinophilic metaplasia. The data in the literature were compared with the presented unique finding in diagnostic and differential diagnostic aspects.

Key words: breast, eosinophilic metaplasia, acinar metaplasia, MUC1.

Introduction

Metaplasia is a process, representing the transformation of one tissue into another, related to the first (initial) one [10]. Such conversion is possible only between tissues originating from a single embryonic layer. Metaplasia is a sign of tissue adaptation towards changed conditions or requirements to them.

Only a few cases of eosinophilic metaplasia (EM) in the breast have been described in the English literature so far [1]. The authors call them Paneth cell like changes or acinar cell differentiation (metaplasia) and are found mainly in tumor mammary epithelium [1,6]. From the described in the literature cases, only one concerns intraductal hyperplasia without atypia in which granular eosinophilic transformation of the cellular cytoplasm is observed. In this case, both extensive expression of lysozyme and the presence of multiple zymogenic granules ultrastructurally confirm the acinar cell-like phenotype [6].

A case of EM in a non-tumor mammary parenchyma, adjacent to ductal carcinoma is presented.

Case report

Surgical specimen from partial right mastectomy of 73 year-old woman was observed. Histological investigation showed an invasive ductal carcinoma (NOS) with size of 8 mm, grade II according to Elston & Ellis grading system, pT1b, negative sentinel lymph nodes (TNM 2017). It is combined with ductal carcinoma *in situ* in the right breast with size of 8 mm, with low grade. As an accompanying lesion in both breasts, a fibrocystic mastopathy with and without atypia was also observed.

EM was found in foci of fibrocystic mastopathy without atypia. It was presented by well-defined benign lobules, adjacent to the tumor parenchyma. Hyperplastic benign lobular epithelium was polygonal in shape and with abundant cytoplasm, filled with eosinophilic cytoplasmic granules (**Fig. 1**). The granules were round in shape, measuring 2 to 5μm and filled the entire cellular cytoplasm (**Fig. 2**). The nuclei were centrally located, with no evidence of cellular atypism, with small, non-prominating nucleoli and without mitoses (**Fig. 2**). Eosinophilic secretion was observed in the lumens of the acini (**Figs. 1 and 2**).

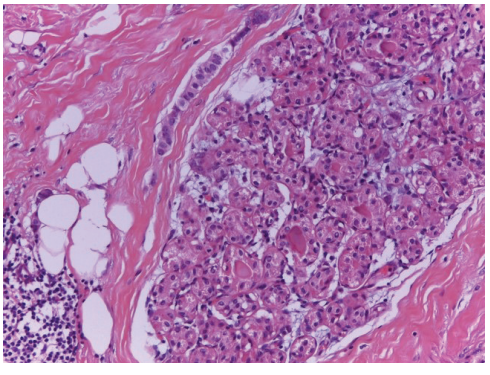

Fig. 1. EM in benign hyperplastic mammary lobule in the context of chronic inflammation (at the bottom left) and carcinoma (at the top left – lymphatic tumor embolus). HES, 200.

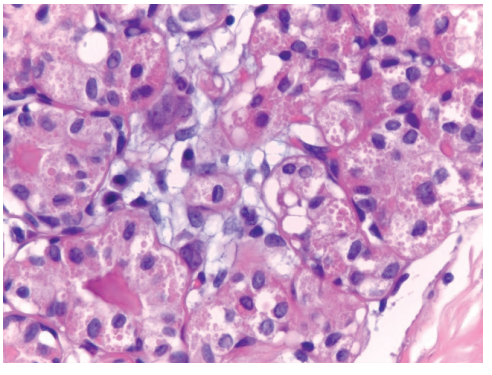

Fig. 2. EM in benign hyperplastic mammary lobule on higher microscopic magnification. HES, ×630.

Histochemically, with staining of periodic acid-Schiff reaction (PAS) and PAS-D – periodic acid-Schiff reaction with diastase, the granules showed a non-constant weak positive reaction (**Fig. 3**).

Immunihistochemically, the granules were GATA-3, estrogen and progesteron receptors (ER and PR) positive (**Figs. 4-6**). They were also cytokeratin 7 positive and Her2 negative (data not shown). Eosinophilic cytoplasmic granules were positive for epithelial membrane antigen (EMA or MUC1) (**Fig. 7**). The surrounding context was of chronic inflammation (**Fig. 1**).

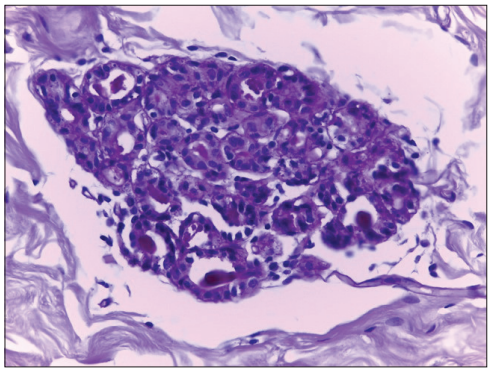

Fig. 3. Weak to moderate PAS-D positivity of EM. PAS-D, ×400.

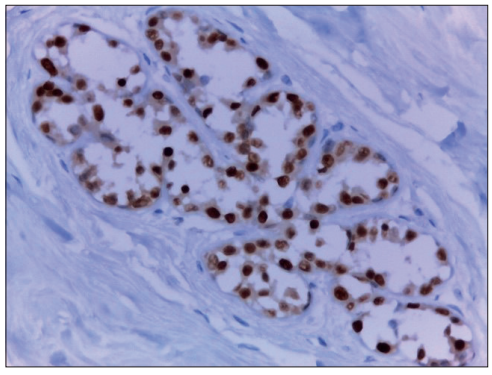

Fig. 4. Pronounced nuclear immunostaining of EM-epithelium for GATA3 in favor of mammary phenotype. Immunohistochemistry, GATA3, ×400.

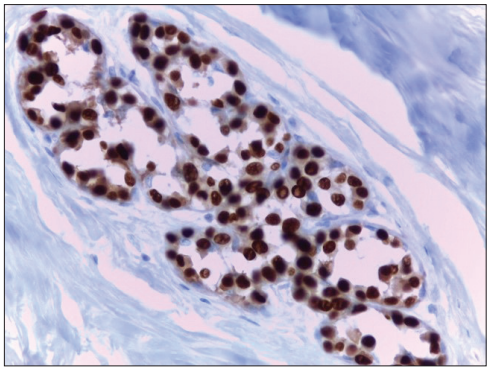

Fig. 5. Pronounced nuclear immunostaining of EM-epithelium for ER in favor of mammary phenotype. Immunohistochemistry, ER, ×400.

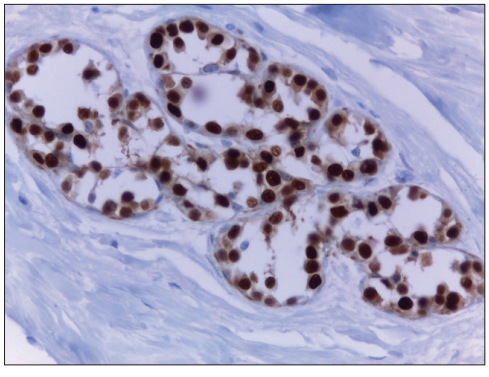

Fig. 6. Pronounced nuclear immunostaining of EM-epithelium for PR in favor of mammary phenotype. Immunohistochemistry, PR, ×400.

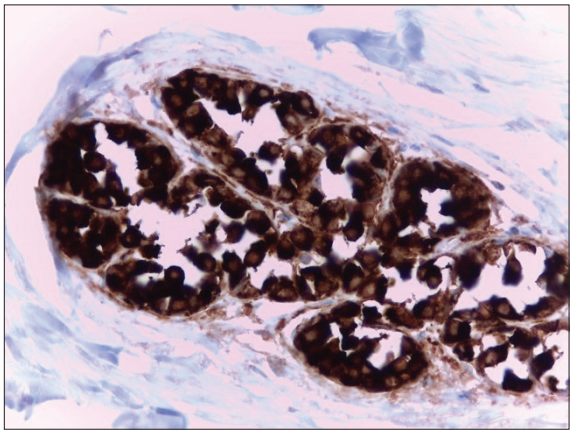

Fig. 7. Pronounced cytoplasm immunostaining of EM-epithelium for MUC1. Immunohistochemistry, MUC1, ×400.

Discussion

EM represents the presence of different in size, intensivelly eosinophilic intracytoplasmic granules in benign epithelium [7]. The process is described in a number of glandular organs and mucus membranes – uterine endometrium [12], prostate [1,14] and breast [6]. EM is a phenomenon in which the glandular epithelium is replaced by another similar type of epithelium, which is either not found or is very rarely observed in normal glands. From all organs, the process in the prostate gland has been studied in most details. In this organ, EM is represented by secretory cytoplasmic granules with both exocrine and lysosomal character [7]. These granules have different size and mainly ductal localization [9]. Eosinophilic cytoplasmic granules in prostatic EM express MUC1, which can serve as a reliable immunohistochemical marker for the EM phenotype [8]. From a general pathological point of view, prostate EM is an indirect (phenotypic type) metaplasia [7]. EM in the prostate is accompanied by banal or granulomatous chronic inflammation [3] and prostate adenocarcinoma [4].

It is well known that breast and salivary gland tissues share embryologic similarities. Similar to the salivary glands, the breast has modified sweat or apocrine glands, and some tumors arising in the breast are subject of development of salivary type tumors, such as pleomorphic adenoma, adenoid cystic carcinoma, adenomyoepithelioma and acinar cell carcinoma (ACC) [5]. Matoso et al. emphasized that breast tumors with salivary gland differentiation originate from a malignant transformation of terminal duct-lobular units with metaplastic changes. Furthermore, the immunohistochemical profile of the tumor is identical to the salivary ACC. The significance of acinar cell differentiation in breast carcinomas is not clear [11].

Most of the described cases with such changes were of acinar cell carcinoma or lesions, associated with micronodular adenosis. ACC of the breast with features of acinar-type differentiation was first described by F. Roncaroli et al. in 1996 as the breast counterpart of identical tumors of the parotid gland [13]. This carcinoma shows diffuse infiltrative growth pattern of small glandular structures and is composed of cells with a coarse glanular or clear cytoplasm resembling acinar cells of the salivary glands or Paneth cells. Histologically small acinar or glandular structures mixed with solid nests are seen. Most of the tumor is comprised of monotonous round cells with a finely granular, weakly eosinophilic or clear vacuolated cytoplasm resembling acinar cells of the salivary glands. Morphologically distinct cells show dark eosinophilic granules, resembling Paneth cells. The lumen of some small acinar or glandular structures contains red colloid-like material and microcalcifications. Other solid nests, similar to *in situ* carcinoma and invasive ductal carcinoma are focally observed. These large solid tumor nests revealed central comedo-like necrosis, reminiscent of ductal carcinoma *in situ* and were originally interpreted as an "ordinary" invasive ductal carcinoma (similar to another case of invasive ductal breast carcinoma with acinar cell metaplasia descriped in the literature), but these cells are cytologically and immunohistochemically closely similar to typical acinar cells [13]. Peridic acid-Schiff (PAS) stain demonstrates strong staining of cytoplasmic granules with diastase resistance. Immunohistochemically, both the glandular and solid tumor cell populations are strongly positive for lysozyme, a-1-antitrypsin an MUC1. Intense expression with E-cadherin and focal cytoplasmic positive reaction for S-100 protein are demonstrated. Chromogranin is also expressed focally in the areas of the granular acinar cells. Focal neoplastic cells are weakly positive for cytokeratin 7, compared to a strongly

positive reaction in normal ducts and lobules. The other areas are negative for estrogen receptor, progesterone receptors, GCDFP 15, cytokeratin 20, MUC2, MUC5A, MUC6, neuron specific enolase, CD68, smooth muscle actin, and human epidermal growth factor receptor-2 (HER2 / neu) [1, 13].

Electron microscopy, performed on formalin-fixed tissue, demonstrates numerous variable sized electron dense granules in the cytoplasm, which are consistent with zymogenic granules [1,13].

Damiani et al. investigated acinar cell differentiation in salivary gland tumors and defined the presence of zymogen-type granules. Zymogen is only one of the components in ACC, as amylaze, lysozyme and a1-antichymotrypsin are also constituents of salivary gland acinar cells. They found amylaze expression in all breast tumors, as well as in all cases of ACC of the studied parotid glands. Amylaze expression was negative in "ordinary" breast carcinomas. [2].

In the presented case EM was localized in hyperplastic benign mammary epithelium and the results showed that similar to the prostate EM [8], EM in benign mammary epithelium was PAS-D+/MUC1+. In adition, in the presented case, the immunihistochemical study showed an organ-specific mammary phenotype: GATA3+/ck7+/RO+/RP+/Her2-. Cytoplasmic granules in EM are negative with PS-100 staining [14], while in apocrine metaplasia a moderate staining is observed [1]. Immunohistochemical staining with GCFP15 is found in areas with apocrine metaplasia [1]. These results can also be used in the differential diagnosis with salivary-gland type differentiation in the conventional ductal hyperplasia or malignancy of the breast.

Conclusion

Similarly to prostate and endometrium, EM in the breast can be observed in benign hyperplastic and neoplastic epithelium, where they may be associated with other types of epithelial metaplasias [1, 4, 5]. The presented observation is the first detailed immunohistochemical study of the phenotype of EM in benign mammary epithelium. EM in the breast may be part of a benign hyperplastic lesion and accompany mammary carcinoma.

References

1. **Chang, E. D., E. J. Lee, A. W. Lee, J. S. Kim, C. S. Kang.** Primary acinic cell carcinoma of the breast: a case report with an immunohistochemical and ultrastructural studies. – *J. Breast Cancer*, **14**, 2011, 160-164.
2. **Damiani, S., G. Pasquinelli, J. Lamovec, J. L. Peterse, V. Eusebi**. Acinic cell carcinoma of the breast: an immunohistochemical and ultrastructural study. – *Virchows Arch*., **437**, 2000, 74-81.
3. **Dikov, D. I., M. S. Koleva, J. F. Boivin, T. Lisner, V. T. Belovezhdov, V. Sarafian.** Histopathology of nonspecific granulomatous prostatitis with special reference to eosinophilic epithelial metaplasia: Pathophysiologic, diagnostic and differential diagnostic correlations. – *Indian J. Pathol. Microbiol.*, **63**(Supplement), 2020, S34-S40.
4. **Dikov, D. I., M. S. Koleva, Z. K. Peshev, V. T. Belovezhdov.** Nonspecific granulomatous prostatitis in association with eosinophilic epithelial metaplasia and prostatic adenocarcinoma. – *Indian J. Pathol. Microbiol.,* **60**, 2017, 409-411.

5. **Foschini, M. P., T. Krausz.** Salivary gland-type tumors of the breast: a spectrum of benign and malignant tumors including "triple negative carcinomas" of low malignant potential. – *Semin. Diagn. Pathol.,* **27**, 2010, 77-90.
6. **Kinkor, Z., A. Skálová.** Acinic cell-like differentiation in invasive ductal carcinoma and in ductal hyperplasia of the breast-report of two cases. – *Cesk Patol.*, **41**, 2005, 29-33.
7. **Koleva, M.** Eosinophilic metaplasia in prostatic epithelium: main characteristics, morphology, morphogenesis. *PhD thesis*, Medical University-Plovdiv, 2020, 7-80 pp.
8. **Koleva, M, D. Dikov, V. Belovejdov, V. Sarafian**. Expression of MUC1 in eosinophilic metaplasia of the prostate. – *Prostate,* **79**, 2019, 622-627.
9. **Koleva, M. S., D. I. Dikov, V. T. Belovezhdov, V. Sarafian**. Eosinophilic metaplasia in transurethral resection of the prostate. – *Indian J. Pathol. Microbiol.,* **63**, 2020, 423-426.
10. **Lugo, M., P. B. Putong**. Metaplasia. An overview. – *Arch. Pathol. Lab. Med*., **108**, 1984, 185-189.
11. **Matoso, A., S. E. Easley, D. R. Gnepp, S. Mangray**. Salivary gland acinar-like differentiation of the breast. – *Histopathology,* **54**, 2009, 262-263.
12. **Moritani, S., R. Kushima, S. Ichihara, H. Okabe, T. Hattori, T. K. Kobayashi, S. G. Silverberg.** Eosinophilic cell change of the endometrium: a possible relationship to mucinous differentiation. – *Mod. Pathol.,* **18**, 2005, 1243-1248.
13. **Roncaroli, F., J. Lamovec, A. Zidar, V. Eusebi**. Acinic cell-like carcinoma of the breast. – *Virchows Arch.,* **429**, 1996, 69-74.
14. **Weaver, M., F. Abdul-Karim, J. Srigley, D. Bostwick, J. Ro, A. Ayala**. Paneth cell-like change of the prostate gland. A histological, immunohistochemical, and electron microscopy study. – *Am. J. Surg. Pathol.,* **16**, 1992, 62-68.