Morphologic and immunohistochemical criteria for the diagnosis of papillary intracystic carcinoma

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Abstract

Microscopically features in papillary intracystic carcinoma are arbitrary but the immunohistochemical characteristics of the tumor provide important information for the diagnosis. SMA, factor VIII, S-100 Protein, Citokeratin together with Calponin can be used to assist in the interpretation of difficult papillary lesions.

***Keywords*:** papillary intracystic carcinoma.

Introduction

Papillary neoplasms are characterized by epithelial proliferations supported by fibro vascular stalks, with or without myoepithelial cell layer. They may occur in the ductal system from the nipple to the terminal ductal or lobular unit. They may be benign, atypical or malignant. The microscopic examination of the lesion, together with the additional immunohistochemical studies provides important information for the diagnosis, which cannot be made on clinical or macroscopically examination.

Material and method

We present the case of a 68 years old woman with left nipple unilateral and sanguineous discharge. On mammographic examination she had a circumscribed retro-areolar mass and on sonographic examination a well-defined smooth-walled cystic lesion with solid component. There was no palpable mass in the left breast. The specimen was fixed in formalin, and for microscopic examination of the tumor, the slides were stained with H-E. The immunohistochemical studies were performed with: Citokeratin, SMA (Smooth Muscle Actin), factor VIII, CEA (carcinoembryonic antigen), S-100 Protein, Calponin, ER, PR.

Results and discussions

Macroscopically examination of the surgery specimen showed a dilated duct containing sanguineous fluid but also a cauliflower-like white mass attached to the duct wall. The diameter of the duct was 2 cm and the maximum diameter of the tumor mass was 1 cm. Microscopically, the tumor located in the distended duct is characterized by proliferation of fibro vascular stalks covered by a proliferation of epithelial atypical cells, disposed on 3–4 layers.

The fibro vascular stalks were elongated or short, and had different dimensions. There were areas were the epithelial cells showed cribriform or solid features, and area were they formed micropapillae. The epithelial cells were round or spindle, with moderate eosinophilic cytoplasm and pleomorphic nuclei. The nucleoli were evident. Many epithelial cells had atypical mitosis (Figure 1).

The identification of myoepithelial cell layer was very difficult and were performed immunohisto-chemical studies: Citokeratin, SMA (Smooth Muscle Actin), Calponin, CEA (carcinoembryonic antigen), S-100 Protein, ER, PR. Epithelial cells were positive for Citokeratin but negative for CEA, and SMA (Figure 2).

SMA was positive at the vascular structures in the papillary fronds and in some myofibroblasts stromal cells. Using SMA there were no myoepithelial cells between the epithelial layer and the basement membrane (Figures 3 and 4).

SMA was also negative in the lining of the duct wall into which the papillary mass proliferated. The duct wall had no epithelial or myoepithelial layers. All the endothelial cells, which delimitates the wall vessels, were positive with factor VIII. Some of these vessels came very close to the basement membrane and sometimes it was difficult to differentiate them from the myoepithelial cells. Using of factor VIII permitted to differentiate them (Figure 5).

Calponin was negative, so the lesion did not contain any myoepithelial cells. Some of the epithelial cells were positive for S-100 Protein (Figure 6). Tumor epithelial cells were also positive for ER and PR (Figure 7). In the surrounding breast there were no pathologic modifications. Because of the aspect of the lesion and the absence of the myoepithelial cells the final morphological diagnosis was: intracystic papillary carcinoma of the breast, low-grade.

Papillary carcinoma *in situ* accounts for approximately 2% of all breast carcinomas [1]. The majority of the patients is in the fifth and sixth decades of life and are women [2]. These neoplasms can be either solitary or central located, corresponding to the intracystic papillary carcinoma or multifocal within the terminal duct/lobular unit and correspond to the papillary type of ductal carcinoma *in situ*.

It is very important to distinguish central papillary carcinoma from the multifocal peripheral variety since the frequency of multifocality in the latter might necessitate a wider excision depending on the extent of the lesion.

Clinically, the nipple discharge in intracystic papillary carcinoma occurs in 22–26% of patients [3]. In almost all the patients a palpable tumor is present. The tumor is generally centrally located. Mamographically the tumor appearance is as a solitary nodule, multiple nodules or dilated ducts. Clinically, mamographically and macroscopic, intracystic papillary carcinoma cannot be distinguished from papilloma or atypical papiloma; only sometimes the intracystic papillary carcinoma is larger.

Papillary intracystic carcinoma is most frequently an *in situ* carcinoma and only in some cases the stromal invasion occurs. In the absence of stromal or vascular invasion, this tumor is an *in situ* carcinoma located in one duct, not correlated with axillary node metastases and with excellent survival rates [4].

The cases associated with stromal invasion are more aggressively [2]. This is the reason because the diagnostic of these tumors must be very correct.

Microscopically, intracystic papillary carcinoma in composed of papillary fibro vascular stalks covered with epithelial cells and proliferating in a dilated duct. The epithelial cells assume a variety of proliferative patterns: solid, micropapillar, and sieve-like, rosette-forming, cribriform growth pattern. The epithelial cells exhibit atypia and abundant mitotic activity, but sometimes they are monotonous in the appearance. Sometimes the epithelial cells may be spindle or may have apocrine features.

Some tumors may produce mucus (positive on Alcian staining) and others may develop neuroendocrine granules (positive on Grimelius staining and on Cromogranin examination). The most important feature for the diagnosis of intracystic papillary carcinoma is the absence of a myoepithelial cell layer in the papillary processes proliferating into the distended duct lumen [5]. Various viewpoints have been presented regarding the presence of myoepithelial cells in papillary carcinoma [4, 6].

Some of the authors have mentioned sporadic myoepithelial cells in some papillary carcinoma, other has seen a prominent myoepithelial cell layer and others have not seen any myoepithelial cells in these lesions [2]. In the papillary intracystic carcinoma according to the O.M.S. 2003 classification of breast tumors, the diagnosis requires that 90% or more of the papillary processes must be devoid of a myoepithelial cell layer, regardless of presence or absence of notable epithelial proliferation [2].

Usually, an experienced pathologist, familiar with the aspect of the myoepithelial cells can easily determine the presence or absence of the myoepithelial cell layer. Sometimes is very difficult and the immunohistochemical examinations may help.

Cytokeratin cocktail antibodies in addition to CK 14 and CK 17 identify myoepithelial cells but they are also positive in epithelial cells, which make it difficult to differentiate myoepithelial cells because of their proximity to the epithelial cells [7].

The myoepithelial cells are positive to the SMA, which is also positive in the vessel walls in the fibro vascular core of the papillary stalks. Some of the vascular spaces may come closer apposed to the epithelial cells, and in association with a positive reaction with SMA they could be misinterpreted as a myoepithelial cell layer. SMA reacts with stromal myofibroblasts in addition to myoepithelial cells and thus is not specific for myoepithelial cells [8, 9].

Wang *et al.* found in a study that Calponin and SMMHC (smooth muscle myosin heavy chain) always detect the myoepithelial cells in the benign papillary lesions of the breast [10, 11].

Calponin and SMMHC rarely react with desmoplastic stromal myofibroblasts, allowing for a more decisive interpretation of the lesion.

The myoepithelial cells are negative with factor VIII but all the endothelial cells are positive with factor VIII and this is very helpful. The use of S-100 Protein is also helpful. S-100 Protein is positive in some of the myoepithelial cells but usually is negative in the endothelial cells. We must take care because S-100 protein may be positive in the epithelial cells [6].

Some of the authors observed positivity for CEA in the epithelial cells in papillary carcinoma but this feature is inconstant and must be not used in discriminating between papilloma and papillary carcinoma [2].

The differential diagnosis of intracystic papillar carcinoma is made with papilloma, papillomatosis, sclerosing papilloma, atypical papilloma and invasive papillary carcinoma. Papilloma is generally a solitary lesion located in the subareolar region or the major ducts, involving one single duct. Clinic, mamographically and macroscopically the aspects are the same as in the intracystic papillary carcinoma.

Microscopically, papilloma is characterized by epithelial proliferation supported by a fibro vascular stroma. The myoepithelial layer (positive with SMA) is invariable present between the epithelial cells and the basement membrane. The epithelial cells do not show atypia but may be disposed in a solid, stratified pattern. Squamous, mucinous, clear cell, sebaceous or apocrine metaplasia or infarctization may occur.

Papillomatosis is a proliferation of papillary fronds supported by fibro vascular stalks within multiple terminal ductal/lobul units, with or without extension in the major ducts. Usually this is a microscopically lesion. Atypia may be present. The myoepithelial layer is present usually, but sometimes, it may be absent, in the areas with atypia. Solitary or multiple papillomas may undergo extensive sclerosis. The lesion is a sclerosing papilloma. Clinical it is on rare occasion associated with nipple discharge.

Macroscopically it may be a solid or an intracystic mass. Microscopically, the sclerotic changes may be focal or diffuse and display distorted tubules imitating invasive carcinoma. There is no atypia and the myoepithelial layer is always present.

Atypical papilloma is a papilloma, which displays focal areas within the papillary processes, with proliferation of a monotonous cells having atypia. Such areas must occupy less then a third of the lesion. Once the necrosis appears the lesion in qualified as carcinoma even it occupies less then one third of the lesion.

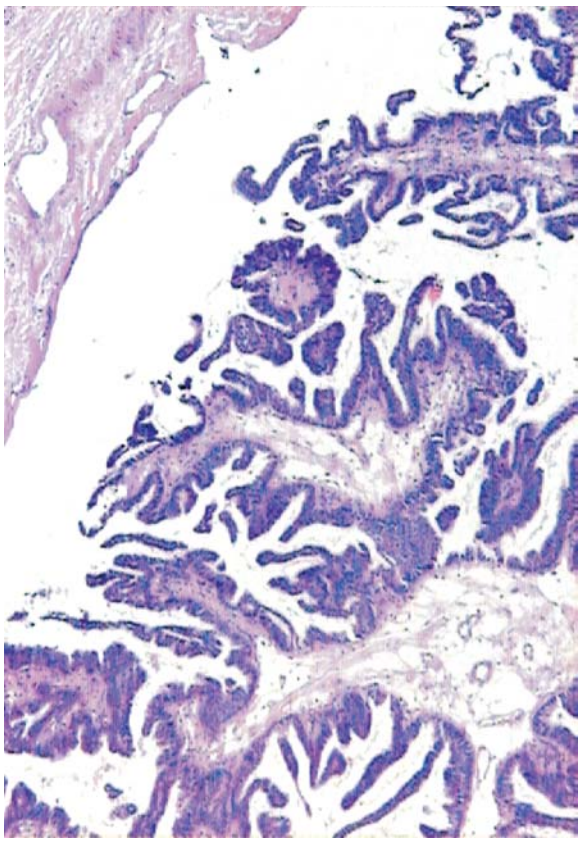

Figure 1 – ***The tumor located in a distended duct. Proliferation of fibro-vascular stalks covered by epithelial atypical cells (HE)***

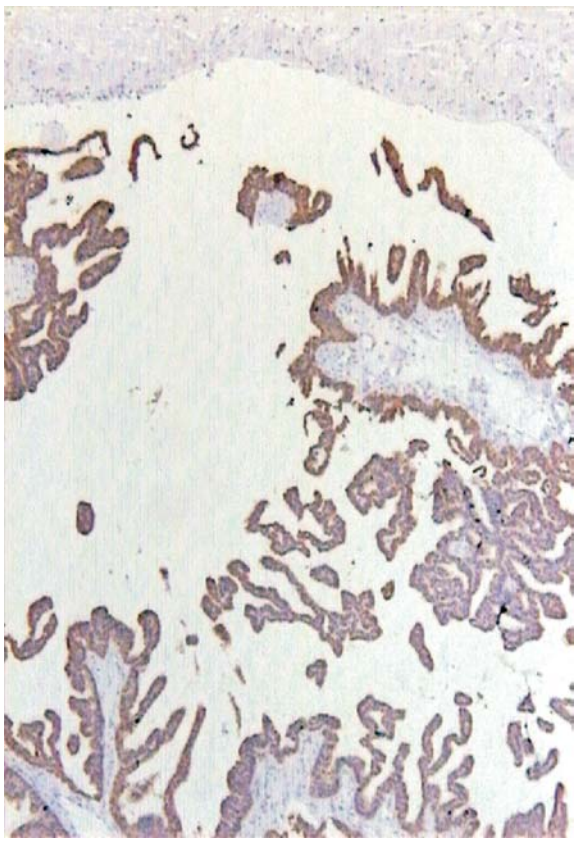

Figure 2 – ***Epithelial cells positive for Cytokeratin***

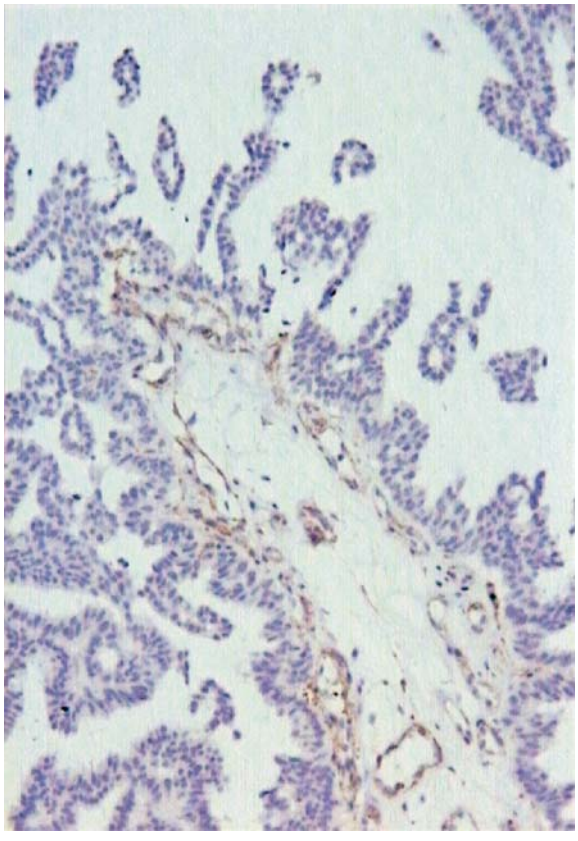

Figure 3 – ***SMA positive in vascular structures in papillary fronds and in some stromal cells***

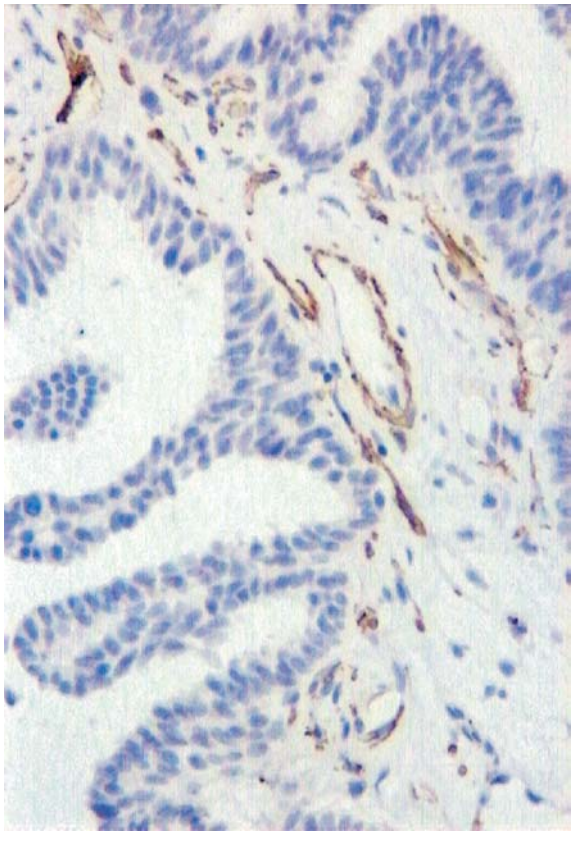

Figure 4 – ***SMA positive in vascular structures in papillary fronds and in some myofibroblasts***

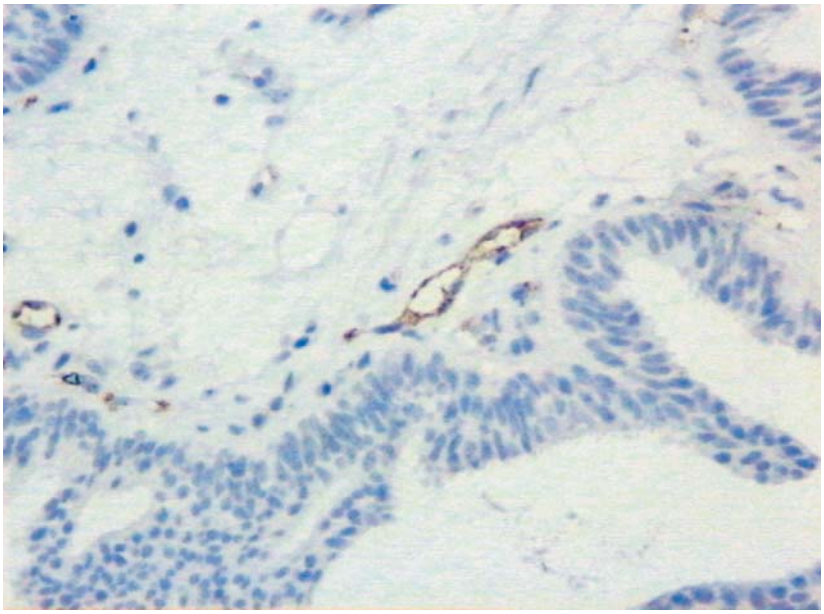

Figure 5 – ***Factor VIII positive in endothelial cells***

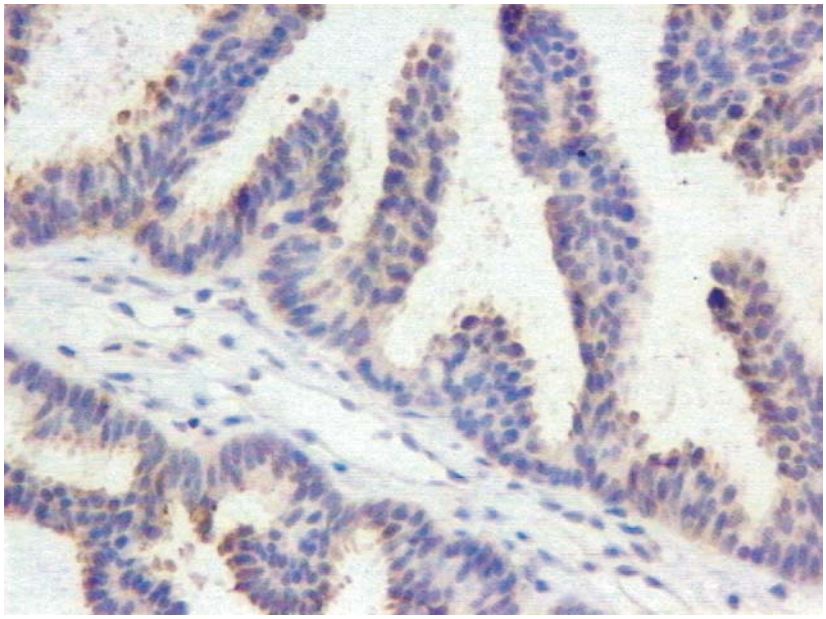

Figure 6 – ***Some epithelial cells positive for S-100 protein***

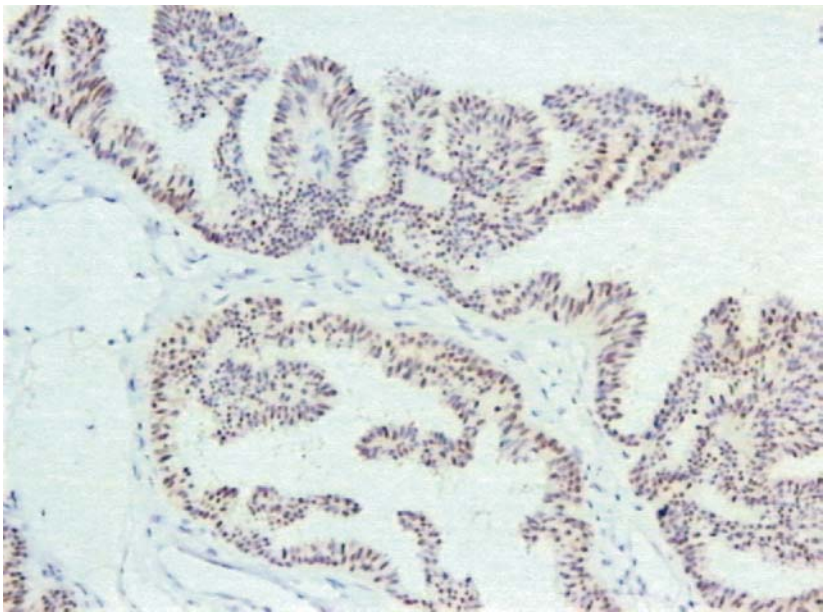

Figure 7 – ***Tumoral epithelial cells positive for ER***

When the epithelial cells present highly atypia with abundant mitotic activity the lesion is qualified as carcinoma, even these areas occupied less then one third of the lesion. The myoepithelial layer may be present in more then 90% of the papillary processes.

Invasive papillary carcinoma is usually a not otherwise specified or a tubular invasive ductal carcinoma occurring in association with an intraductal papillary lesion. Intrusion of tumor cells in cords or clusters into the duct wall where the papillary lesion proliferates is not interpreted as indicative of invasion. Once these cells break through the basal lamina and extend beyond the duct wall without a myoepithelial layer around them, the lesion must be considered an invasive carcinoma. Some papillary carcinomas are accompanied by production of abundant mucoid secretion [12–14].

Rupture of the involved duct wall results in mucus disrupting of the surrounding stroma, sometimes accompanied by small clusters of epithelial tumor cells. This is considered as true invasion but if it has small dimensions does not appear to adversely affect the prognosis [12].

Conclusions

Immunostains for SMA along with S-100 Protein and factor VIII can be used to assist in the interpretation of difficult papillary lesions. More recently, Calponin and SMMHC are used in identification of myoepithelial cells, and their role is important in differentiating myoepithelial cells from desmoplastic stromal myofibroblasts. The criterions used now to differentiate between atypical papilloma and papillary carcinoma is arbitrary, but the future studies will provide significant informations.

Considering the fact that a fully developed papillary carcinoma is an intraductal lesion and not highly aggressive it may be possible in the future to include atypical papilloma and papillary carcinoma in the same category.

The invasive papillary carcinoma is found around the dilated duct containing an intracystic papillary carcinoma and his appearance is that of an invasive ductal carcinoma not otherwise specified. Frozen section analysis of such lesions is notoriously difficult and is not indicated.

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