

Intraductal papilloma of the breast: Short-review

Abstract

Intraductal papilloma is a common disease in the breast with clinical manifestation of nipple discharge. Hence many Core Needle Biopsy (CNB) is done in suspected intraductal papilloma. However, in the CNB specimen, sometimes it is difficult to determine whether the tumor is benign or malignant. In such situations, myoepithelial markers of p63 and calponin are useful immunostaining. And also high-molecular weight cytokeratins of CK5/6 and CK14 are helpful staining.

Recently the report of two cases entitled "Nuclear inverse polarity papillary lesion lacking myoepithelial cells" is reported. This lesion resembles intraductal papilloma and thought to be at the most a tumor of uncertain malignant potential. Hence to diagnose intraductal papilloma, one should be careful even though problematic cases.

Keywords: Myoepithelial cell • CK5/6; CK14 • p63 • calponin • MUC3

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Introduction

The most major benign papillary lesion in the breast is intraductal papilloma. Intraductal papilloma is divided into two types. One is large duct papilloma (central papilloma). Central papilloma is centrally located and often solitary. And Central papilloma originates from lactiferous sinus or large mammary ducts. The other is small duct papilloma (peripheral papilloma). Peripheral papilloma is peripherally located and often multiple. And peripheral papilloma is involved terminal duct lobular units [1]. Hence, these two types of intraductal papillomas are thought to be different and distinctive lesions. Although both lesions reveal similar histology which is characterized by luminal epithelial cells of papillary proliferation lined by fibrovascular stroma.

In operation specimen, the feature of intraductal papilloma is comparatively well recognized for its papillary structure lined by myoepithelial cells. However, in core needle biopsy, usually fragmented and could be difficult to evaluate intraductal papilloma on daily pathological diagnoses. In such a situation, immunohistochemistry can be helpful because it is easily detected in the myoepithelial cell layer. To confirm the presence of myoepithelial cells at periphery and in fibrovascular stroma is important for the diagnosis of intraductal papilloma.

To detect myoepithelial cells in immunohistochemistry, many myoepithelial markers exist. Hilson JB et al. evaluated seven myoepithelial cell markers (smooth muscle actin, calponin, smooth muscle myosin heavy chain, p63, CD10, cytokeratin 5/6, and p75) in benign breast lesions. And they concluded calponin and p63 are most useful markers for detecting myoepithelial cells [2]. Regarding this article, we use calponin and p63 for myoepithelial cell markers in our hospital. And we think the most reliable myoepithelial cell marker is p63 because other myoepithelial markers are cytoplasmic stainings, however, p63 is nuclear marker. On the other hand, Nikolay KP et al. evaluated the low-affinity neurotrophin receptor (p75NTR) in breast benign and malignant lesions. And they concluded p63 pattern of staining in the myoepithelial cells was quite similar to that of p75NTR [3]. This type of staining might be thought to be useful for detecting myoepithelial cells, however It isn't popular even at present. Hence, we think p63 is the most important staining for myoepithelial cells in daily pathological diagnoses.

One more important immunostaining to discriminate between a benign and malignant lesion in breast papillary lesion including intraductal papilloma, High-Molecular-Weight Cytokeratins (HMWCKs) such as CK5/6, CK14 and CK34betaE12 are thought to be important. It is reported that the combination of HMWCKs of CK14 and estrogen (ER) immunostainings are useful [4-6]. In using these immunostainings, almost all of the papillary lesions are diagnosed benign or malignant excluding apocrine papillary lesion. Because, benign papillary lesions including intraductal papilloma will show mosaic positive pattern of CK14 and ER will not demonstrate diffuse positive pattern (heterogeneous pattern), on the other hand, malignant intraductal lesion including Ductal Carcinoma *In Situ* (DCIS) cases, CK14 will be negative and ER will reveal diffusely positive (homogenous pattern) in immunohistochemistry. Taking into consideration these immunostaining patterns on intraductal papilloma, it will indicate heterogeneity cell, proliferation might be existed and not monotonous like malignant lesion.

As mentioned above, HMWCKs of CK14 and ER are available for detecting intraductal papilloma. Ichiro M et al. evaluated HMWCKs of CK5/6, CK14 and CK34betaE12 for discriminating between intraductal papilloma and solid papillary carcinoma *in situ*. And they concluded CK34betaE12 is especially useful for distinguishing solid papillary carcinoma from intraductal papilloma [7]. And another report, Takuya M et al. reported that most DCIS cases were diffusely positive for luminal cell markers (CK8, CK18, CK19), but negative for HMWCKs of CK5/6 and CK14. And they concluded not only CK14 but also CK5/6 was useful for detecting benign lesions including intraductal papilloma [8]. Hence, which of HMWCKs is the best for detecting intraductal papilloma is truly controversial. However, in our experience of daily pathological diagnoses, CK5/6 might be the most useful for detecting intraductal papilloma. However, we think the truth of which of CK14 or CK5/6 is the best is future problem.

On relation to the immunostainings of HMWCKs, Furuya et al. advocated the Differential Index using Allred Score: $([ER \text{ total score}] + [MUC3 \text{ total score}]) / ([CK5/6 \text{ total score}] + [p63 \text{ total score}])$ [9]. If this score is less than 1, it is thought to be benign lesion. This formula is useful for discriminating between benign and malignant papillary lesions including intraductal papilloma if CK14 and ER are not

available. MUC3 immunostaining is thought to be useful and important when diagnosing the difficult breast papillary lesion including intraductal papilloma and papilloma with atypia [4-6].

Loss of myoepithelial cells in breast tumors are commonly thought to be malignant and invasive lesions. In the past, Tramm T and Cserni G et al. reported that benign and non-invasive apocrine papillary lesions which demonstrate reduction and occasional complete loss of myoepithelial cells [10,11]. These lesions are thought to be benign lesion, however lacking myoepithelial cells. And it is thought that apocrine papillary lesions are special distinct lesions. Recently, Shinya T et al. reported that the two cases of “Non-apocrine papillary lesions lacking myoepithelial cells¹²” which is at a glance resembling intraductal papilloma on H and E histology. These two lesions showed epithelial papillary proliferation with nuclear inverse polarity, absence of nuclear atypia lined by the fibrovascular stroma, and lack of myoepithelial cells. In immunostainings, CK14 and ER were both negative. Hence, they tried the

Differential Index, and the lesions were considered to be at the most a tumor of uncertain malignant potential [4-6,12]. Because of these breast lesions’ name is too long and of its distinctiveness, someone indicates the name of “Tajima tumor” might be appropriate. Then, taking into consideration of these things, it might be thought that there is the breast papillary lesion between non-invasive and invasive lesion. We think that it might exist middle stage between *in situ* lesion and invasive lesion. In the future, the report of breast lesions lacking myoepithelial cells which behave as benign or at the most tumor of uncertain malignant potential (not equal to malignancy) will be increased if pathologists pay attention to subtle findings [4-6].

Conclusion

Discriminating between intraductal papilloma and malignant papillary lesion of the breast is sometimes problematic and challenging. In that situation, immunohistochemistry might be a helpful tool. Hence, we have to diagnose the breast papillary lesion including intraductal papilloma attentively, even though it might be difficult case.

Executive summary

Intraductal papilloma is a common disease in the breast with clinical manifestation of nipple discharge. Hence many-Core Needle Biopsy (CNB) is done in suspected intraductal papilloma. However, in CNB specimen, sometimes it is difficult to determine whether benign or malignant. In such situations, myoepithelial markers of p63 and calponin are useful immunostaining. And also high-molecular weight cytokeratins of CK5/6 and CK14 are helpful staining.

Recently the cases that the name of "Nuclear inverse polarity papillary lesion lacking myoepithelial cells" is reported. This lesion resembles intraductal papilloma and thought to be at the most a tumor of uncertain malignant potential. Hence to diagnose intraductal papilloma should be careful even though problematic cases.

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