Portion of E-DCIS Lesion Coexisting With Intraductal Papilloma of the Breast
—Immunohistochemistry of Synaptophysin for Diagnosis by Core Needle Biopsy—

Ichiro Maeda¹, Yoshihide Kanemaki², Tomoko Uejima³, Shinya Tajima¹,
Satoi Nagasawa¹,³, Ryoko Ohi¹,³, Koichiro Tsugawa³, and Masayuki Takagi¹

(Received for Publication: March 13, 2015)

Abstract

Immunopositivity for neuroendocrine markers [NEs: synaptophysin (syn), chromogranin A (CGA), CD56, CD57, and neuron-specific enolase] is evidence of the presence of tumor cells with neuroendocrine cell differentiation in the breast. It has been reported that a certain type of breast cancer is immunopositive for NEs; such a breast cancer type has been named carcinoma with endocrine features or endocrine ductal carcinoma in situ (E-DCIS). Here, we report a case of a patient in whom a portion of the E-DCIS lesion coexisted with intraductal papilloma. A 38-year-old woman had an irregular hypoechoic lesion of the right breast on ultrasonographic examination, and core needle biopsy (CNB) of mass lesion was performed. Histopathologically, the CNB specimen showed a fibrovascular core with ductal hyperplasia, indicating that the lesion was most likely an intraductal papilloma (IDP) with ductal hyperplasia. However, immunohistochemistry revealed that the CNB specimen from the right breast was focally positive for syn. We determined this lesion to be of the “indeterminate” type. An excisional biopsy of this right breast lesion was performed. This lesion was diagnosed as an E-DCIS lesion coexisting with intraductal papilloma. As such, the case presented suggests that immunopositivity for syn was a useful indicator for E-DCIS diagnosed by CNB.

Key words
breast, DCIS, papilloma, neuroendocrine marker, synaptophysin

Introduction

Immunopositivity for neuroendocrine markers [NEs: synaptophysin (syn), chromogranin A (CGA), CD56, CD57, and neuron-specific enolase] is evidence of the presence of tumor cells with neuroendocrine cell differentiation in the breast¹-³. It has been reported that a certain type of breast cancer is immunopositive for NEs, and such a breast cancer type has been named carcinoma with endocrine features or endocrine ductal carcinoma in situ (E-DCIS). In immunohistochemistry, benign lesions are immunopositive for high-molecular-weight keratins (HMWKs: CK5, CK5/6, CK14, and 34betaE12) with an intense mosaic staining, whereas low-grade malignant lesions are negative for these molecules. Furthermore, almost all benign lesions are focally immunopositive for the estrogen receptor (ER), whereas low-grade malignant lesions are diffusely immunopositive for ER⁴.

In this manuscript, we report the case of a patient in whom a portion of the E-DCIS lesion coexisted with intraductal papilloma in the right breast. However, immunopositivity for syn is a useful indicator for E-DCIS diagnosed by core needle biopsy (CNB).
Case Report

Patient: A 38-year-old woman.

Clinical course: The patient visited our hospital presenting with a palpable left breast mass. The mass was diagnosed as invasive carcinoma of no special type (NST) by ultrasonography and CNB. Although no mass was palpable in the right breast, ultrasonographic examinations revealed an irregular hypoechoic lesion, measuring 17 mm in diameter in the outer portion of the right breast (Fig. 1). Magnetic resonance imaging (MRI) revealed a nonmass lesion with clustered ring enhancement in the right breast (Fig. 2). CNB of the right breast lesion was performed.

Histopathological findings of the right breast lesion: Histopathologically, the CNB specimen showed a fibrovascular core with ductal hyperplasia, indicating that the lesion was most likely an intraductal papilloma (IDP) with ductal hyperplasia (Figs. 3, 4a, 4b, 5a). Immunohistochemical analysis was performed in this specimen to eliminate the possibility of DCIS. The analysis revealed an intense mosaic staining of CK14 (Figs. 4c, 5c), and the CNB specimen from the right breast was partially immunopositive for ER (Fig. 5d) and focally positive for syn (Fig. 5b). This CNB specimen almost entirely showed an intense mosaic staining of CK14 without apocrine cell differentiation with a sufficient number of myoepithelial cells immunopositive for p63. These findings indicated that the lesion was benign. However, a few portions of the specimen were focally immunopositive for syn. These findings indicated that the lesion might be malignant. We determined this lesion to be of the “indeterminate” type. An excisional biopsy of this right breast lesion was performed. A specimen of this lesion showed E-DCIS coexisting with intraductal papilloma (Fig. 6). In immunohistochemistry, the part of intraductal papilloma showed intense mosaic staining of CK14 without apocrine cell differentiation and was focally immunopositive for syn with a sufficient...
Fig. 4. Portion of needle biopsy specimen of the right breast

(a) HE staining (medium-power field)
- Papillary lesion with wide fibrovascular core and ductal hyperplasia

(b) HE staining (high-power field)
- Ductal hyperplasia with apocrine cell differentiation

(c) Double immunohistochemistry of CK14 and p63
- Ductal hyperplasia tumor cells show a mosaic staining and immunopositivity for CK14 in the cytoplasm, but the portion showing apocrine cell differentiation is immunonegative for CK14. The myoepithelial cells around ductal hyperplasia cells are immunopositive for p63 in the nuclei.

(d) Synaptophysin
- Ductal hyperplasia tumor cells immunonegative for synaptophysin

number of myoepithelial cells immunopositive for p63 (Fig. 7). The part of DCIS was immunonegative for CK14 and focally immunopositive for syn with some myoepithelial cells immunopositive for p63 (Fig. 8)

Histopathological findings of the left breast mass:
Histopathologically, the CNB specimen showed the features of invasive carcinoma of NST. Partial mastectomy of the left breast with the mass lesion was performed. The mass lesion showed the feature of invasive carcinoma of NST (Fig. 9).

Discussion

Cross et al.5) first reported on endocrine DCIS in 1985. Tsang and Chan2) have described a large series of 34 cases and stated, “E-DCIS was frequently accompanied by papillomas in the vicinity and may present as nipple discharge.”

The distinction between benign and malignant intraductal papillary lesions is not always straightforward, due to the architectural variety accompanying occasional IDPs6). It should be considered that malignant lesions are occasionally immunopositive for NEs in the papillary lesions. Furthermore NEs are useful as a marker of breast cancer4, 7). Tse et al.4) describe that the sensitivity and specificity of syn are 94.7% and 54.5%, respectively, in the papillary lesion of the breast.

There has been confusion on whether differentiated neuroendocrine cells are absent in the normal breast tissues8, 9). Many studies showed the association of breast cancer with differentiated neuroendocrine cells immunopositive for NEs2, 10), but a few studies showed the association of benign lesions with such cells10, 11). We reported that there are IDPs immunopositive for CD5610). It was also shown that
IDPs are immunopositive for syn and CGA in a few studies. Omi et al. reported that three patients with IDPs with neuroendocrine cell differentiation were immunopositive for syn; however, on re-examination, it was found that one patient had tumor recurrence, one had atypical ductal hyperplasia, and the remaining patient had DCIS\(^1\). In malignant tumors, the percentage of syn-immunopositive cells is higher than that of chromogranin A-immunopositive cells\(^2, 12\).

The specimen from the right breast of our patient was determined as the “indeterminate” type, because the HE staining features of the specimen indicated IDP with ductal hyperplasia rather than DCIS, but certain portions of the specimen were focally immunopositive for syn. E-DCIS coexisted with IDP in excisional biopsy specimens. On the basis of these findings, we propose two theories that may explain the association of E-DCIS with IDP. One theory is that E-DCIS arises from IDP and the other is that E-DCIS spreads into IDP.

The coexistence of E-DCIS with IDP should be considered, when CNB specimens are immunopositive for syn.

**Conclusion**

We report the case of a 38-year-old woman in whom a portion of the E-DCIS lesion coexisted with intraductal papilloma in the right breast. Immunopositivity for syn is a useful indicator for E-DCIS diagnosed by CNB.

**Conflict of interest**

The authors have no conflicts of interest to declare, including specific financial interests, relationships, or affiliations relevant to the subject matter or material discussed in the manuscript.
Fig. 6. Excisional biopsy specimen from the right breast (HE staining)

(a) Low-power field
(b) Upper left portion of Fig. 1-a
   Needle scar is present.
(c) Upper right portion of Fig. 1-a
   Intraductal papilloma with focal apocrine differentiation.
(d) Lower right portion of Fig. 1-a
   Cribriform-type DCIS is present.

References
Fig. 7. Papilloma in biopsy specimen excised from the right breast

(a) HE staining
Intraductal papilloma with ductal hyperplasia and focal apocrine differentiation

(b) Immunohistochemistry of synaptophysin-
Ductal hyperplasia tumor cells focally positive for synaptophysin.

(c) Double immunohistochemistry of CK14 and p63
Ductal hyperplasia tumor cells showing mosaic staining and immunopositivity for CK14 in the cytoplasm. However, ductal hyperplasia tumor cells with apocrine differentiation show immunonegativity for CK14. Some myoepithelial cells are immunopositive for p63 in the nuclei.

**Fig. 8.** DCIS in biopsy specimen excised from the right breast
(a) HE staining
DCIS, cribriform type
(b) Immunohistochemistry of synaptophysin
DCIS cells focally immunopositive for synaptophysin.
(c) Double immunohistochemistry of CK14 and p63
A few DCIS cells show staining and immunopositivity for CK14 in the cytoplasm. Some myoepithelial cells around the dilated ducts are immunopositive for p63 in the nuclei.

**Fig. 9.** Microscopy image of partial mastectomy specimen of the left breast (HE staining)
(a) Low-power field
Invasive carcinoma with fat tissue infiltration
(b) High-power field
Invasive carcinoma of no special type (scirrhou type)