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Fibroadenoma of the breast with florid epithelial cells hyperplasia: a case report

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ABSTRACT

Irianiwati, Rahmayani, E. Soekarti, Soeripto, J.L. Peterse - ***Fibroadenoma of the breast with florid epithelial cells hyperplasia : a case report***

Fibroadenoma is a benign biphasic tumor of the breast, composed of an epithelial and a stroma component. Fibroadenoma with epithelial cells hyperplasia may contribute to the higher risk of breast cancer, especially for florid and atypical hyperplasia. The distinction between fibroadenoma with florid epithelial cells hyperplasia, in-situ carcinoma and invasive duct carcinoma of the breast can be difficult morphologically. To solve the problem, immunohistochemical staining with specific andibodies will be helpfull in distinguishing usual duct hyperplasia from ductal carcinoma in situ.
A case of fibroadenoma with florid epithelial cells hyperplasia has been reported. Morphologically, this tumor is difficult to be differentiated from ductal carcinoma. Immunohistochemical staining with High molecular weight cytokeratins 34βE12, Smooth Muscle Actin (SMA), E- cadherin could be used to determine the diagnosis of this tumor.

***Key words**: Fibroadenome - florid hyperplasia - ductal carcinoma - immunohistochemical staining*

ABSTRAK

Irianiwati, Rahmayani, E. Soekarti, Soeripto, J.L. Peterse - ***Fibroadenoma pada payudara dengan hiperplasi florid sel epitel: laporan kasus***

Fibroadenoma adalah tumor jinak bifasik pada payudara yang terdiri dari komponen epitelial dan stroma. Fibroadenoma dengan proliferasi epitel kelenjar meningkatkan risiko menjadi karsinoma payudara, terutama fibroadenoma dengan hiperplasi florid dan atipi. Secara morfologi, fibroadenoma dengan hiperplasi florid sukar dibedakan dari karsinoma payudara in-situ. Pengecatan imunohistokimiawi dengan antibodi tertentu dapat digunakan untuk membedakan tumor-tumor tersebut.
Dilaporkan satu kasus fibroadenoma payudara dengan hiperplasi epithelial florid. Secara morfologi, tumor ini sukar dibedakan dengan karsinoma duktal. Pengecatan imunohistokimiawi dengan antibodi monoklonal anti *High molecular weight cytokeratins 34βE12, Smooth Muscle Actin (SM), E-cadherin* berperan penting dalam menegakkan diagnosis tumor ini.

INTRODUCTION

Fibroadenoma is a benign biphasic tumor that occurs most frequently in women of chlidbearing age, especially those under 30. This tumors composed of both fibrous and glandular tissue. Fibroadenomas are associated with mild increase in the risk of subsequent breast cancer, especially when they are associated with epithelial hyperplasia, nevertheless the occurrence of a carcinoma within a fibroadenoma is uncommon, in fact it occurs in only 0.02 to 0.1% of the cases.[1,2]

Fibroadenoma with very cellular and florid epithelial hyperplasia has also been designed as epitheliosis,[3,4] and papillomatosis.[5] The distinction between epitheliosis, in situ carcinoma and invasive

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duct carcinoma of the breast lesions can be difficult morphologically.[6] To solve the problem, immunohistochemical staining with high molecular weight cytokeratins 34ßE12 and smooth muscle actin (SM), is helpful in distinguishing usual ductal hyperplasia from ductal carcinoma in situ. The identification of myoepithelial cell layers may be helpful in establishing a diagnosis proliferative breast disease vs intraepithelial neoplasia.[7]

A case of fibroadenoma of the breast with florid epithelial cells hyperplasia which has diagnostic problem morphologically and settled immunohistochemically is reported.

CASE REPORT

A 34 year old female presented to the hospital with two painless, well-defined, mobile and two firm masses in her left breast. No enlarged axillary and supraclavicular lymph nodes were palpable. Mammography revealed a well-circumscribed density corresponding to the palpable mass. Fine-needle aspiration yielded benign cells. Lumpectomy of the left breast was done. Gross pathology, there were two masses, 3x2x2 cm and 2x2x2cm, encapsulated, cut surface solid, lobular, white in color and rubbery.

Breast tissue with a pericanalicular and intracanalicular type of fibroadenoma was shown microscopically. On the other part of the fibroadenoma, there were extensive proliferation of epithelial cells forming a solid, tubular, papillary and comedo-like pattern. Some of the cells were atypical, moderate polimorphy with clear and coarse nuclear chromatin and some mitoses. The cells were likely invasive to the surrounding tissue due to scattered myoepithelial cells and indistinct cytoplasmic border. Cellularity of the stroma can be found in some areas. The diagnosis was invasive duct carcinoma within a fibroadenoma of the breast. The block was sent to Academic Medical Center (AMC) the Netherlands in 2006, for diagnostic confirmation. The diagnosis from AMC (Dr. Hans Bras) was phylloides tumor because of the partly cellular stroma, in which a non invasive (in situ) ductal carcinoma (comedo type) was presented. However the answer from the Antoni van Leuwenhook/AVL (Dr. Hans Peterse) was fibroadenoma with florid epithelial hyperplasia, therefore a benign tumor. The arguments for a fibroadenoma was that no striking cellular stroma or stroma overgrowth or differentiation. By using Immunohistochemical (IHC) staining with SMA antibody there was smooth transition of 2-layered (SMA) to semi-solid epithelial cells proliferation with variable cell types, forming syncitial pattern and irregular fenestration pattern. This picture supported the argument for epithelial hyperplasia. High molecular weight cytokeratins (34ßE12) staining showed variant expression and inconsistent expression in the solid areas. E-cadherin staining demonstrated linear, membranous staining of the neoplastic cells. PAS diastase staining demonstrated a positive staining in the necrotic areas (mostly in the lumen of the comedo types) and in the stroma of the tumor.

FIGURE 1. Breast tissue with a pericanalicular and intracanalicular type of fibroadenoma. There were extensive proliferation of epithelial cells forming a solid, tubular, papillary and comedolike pattern. HE staining 40 x.

FIGURE 2. The cells in the solid and cellullar areas are atypi, moderate polimorphy with clear and coarse nuclear chromatin and some mitoses. HE staining 400x

FIGURE 3. The tumor showed two layers of SMA staining that forming syncitial pattern and irregular fenestrations pattern. SMA staining 40 x

FIGURE 4. High molecular weight keratine 34βE12 staining showed variant and inconsistent expression in the solid areas of the tumor 100 x

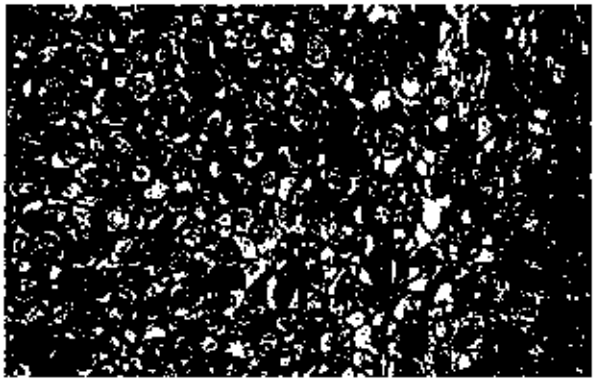

FIGURE 5. E-cadherin staining demonstrates linear, membranous staining of the neoplastic cells. 100x

DISCUSSION

Fibroadenoma, one of the most common benign breast lesions, has a characterisatic age-specific incidence and 50% of the cases is associated with other pathological entities such as sclerosing adenosis, duct ectasia, apocrine metaplasia, florid disease, duct papilomatosis, infiltrating duct carcinoma, duct carcinoma in situ, and invasive lobular carcinoma.[1] Shabtai *et. al.* found that fibroadenoma-associated with pathological entities was found in 48% of the cases, and with florid diseases was found in 12.9%.[8] Washington *et. al.* showed that 75% of breast lesions with foci of hyperplasia, adenosis and apocrine metaphasia were found in postmenopausal women.[9] These tumors originate from the breast lobules and are estrogen-dependent, as they grow during pregnancy and under hormone replacement therapy, participate in lactation and often decrease in the menopause.[1] In this case, the patient was a 34 year, unpregnanct woman, and was not under hormone replacement therapy. The basis of ductal proliferation was not clear, perhaps the neoplastic stromal cell secreted growth factors that effect epithelial cells.[10]

There are no definite clinical criteria to suggest that atypical hyperplasia or malignant change has occurred in a fibroadenoma. Pre-operative diagnosis of these lesion was difficult because their presenting features are similar to those of benign fibroadenoma. Mammography may reveal an abnormality, but rarely indicates malignancy.[11] The mammographic feature that was considered suspected for carcinoma arising from fibroadenoma included large size, indistinct margins, and microcalcification.[12] Mammography of the case revealed a well-circumscribed density corresponding to the palpable mass. Fine-needle aspiration yielded benign cells. In cytological diagnosis, a false negative result can be avoided by recommending histological confirmation by excision biopsy when significant atypic cells are present, even if the overall pattern is a fibroadenoma.[13] The diagnosis is invariably reached on histological examination of the tumor.

Routine staining and morphology examination of the case was difficult, making uncertainty of the diagnosis, because of pronounced cell hyperplasia with solid, tubular, papillary and comedo-like pattern. The cells were atypic, moderate polymorphy with

clear coarse nuclear chromatin, and some mitoses. Indistinct cytoplasmic border made the cells seemed to lie in a syncitial pattern. The cells were likely invasive into the surrounding tissue due to scattered myoepithelial cells. Some mitoses could be found in this tumor. Therefore immunohistochemical staining is important to determine whether it is benign or malignant lesion.

The identification of myoepithelial cell layers has an important role in establishing a diagnosis of proliferative breast diseases on intraepithelial neoplasia. Immunohistochemical stains were employed against SMA, HMW/high molecular weight cytokeratins (34ßE12).

SMA is strongly positive in breast myoepithelial cells. SMA is easier to interprete when used on lesions with minimal reactive stroma. In this case there were two layers of SMA forming syncitial pattern and irregular fenestration pattern. This pattern supported for a benign lesion. In atypical hyperplasia of the breast, the SMA staining identified myoepithelial cells in fine branching fibrovascular layers or scattered cells between other proliferating cells.[6] This pattern is absent in carcinoma in situ.

High molecular weight cytokeratine 34ß12, a monoclonal antibody against basal cell are 90 % - 100% strongly positive for usual ductal hyperplasia. In contrast, this cytokeratine expression is lost or markedly reduced in 81%-100% of ductal carcinoma in situ and atypical hyperplasia. Cytokeratin expression of this case showed characteristically discontinous basal cell layers.[14] Study of epitheliosis of the breast, 34ß12 staining showed strong immunoreactivity in the streaming sheetlike intraluminal proliferation, in contrast of ductal carcinoma in situ that were non reactive for HWM keratin.[4] But, because many normal epithelial cells and a small percentage of usual ductal hyperplasias are negative for this antigen, the absence of high molecular weight cytokeratine expression alone is not diagnostic of atypia or malignancy. Conversely, a positive immunoreaction does not necessarily indicate a benign process, as a small percentage of ductal carcinoma in situ is typically positive for cytokeratine 34ß12. Therefore, although high molecular weight cytokeratine may be useful in the evaluation of difficult intraductal proliferation, these antibodies do not represent a gold standard and must be interpreted in conjunction with the morphology on HE sections.

E cadherin, a monoclonal antibody for detecting cellular adhesion molecule, has proved to be a valuable tool for distinguishing ductal carcinoma in situ (DCIS) and lobular carcinoma in situ (LCIS). In almost all cases of DCIS, E-cadherin demonstrates linear, membranous staining of the neoplastic cells. In contrast, LCIS is nearly always negative for membranous E-cadherin. In this case, the E-cadherin staining supported for the duct type tumor and not lobular type. Vos *et. al.*, in his study revealed that the loss of E-cadherin expression in lobular carcinomas appears to be due to somatic mutation of the E-cadherin gene in some cases. In the normal breast, E-cadherin demonstrates strong membrane staining of luminal cell and more granular membrane staining of myoepithelial cells.[16]

The reason for diagnosis of phylloides tumor (from AMC) of this tumor was its partly cellular stroma. However, there was no intracanalicular growth pattern with leaf-like pattern projected into dilated and cystic lumen, that was characteristic in phyloides tumor.[5]

Loss of heterozygosity (LOH), a genetic change frequently detected in cancer, can also occur in benign epithelial foci in the breast. LOH in breast proliferative lesions was believed to be premalignant, such as atypical hyperplasia and carcinoma in situ.[17] In fibroadenoma case, the frequency of LOH was 10% in mild hyperplasia, 27% in moderate hyperplasia, and 25% in atypical hyperplasia. Total frequency of LOH was statistically higher in carcinoma cases than in fibroadenoma cases.[18] Florid or atypical hyperplasia leads to a moderate increase (1.5-4 times) for development of cancer in the relative risk.[9] In this case no test of LOH test was done.

CONCLUSION

A case of fibroadenoma with florid epithelial cells hyperplasia suggestive of ductal carcinoma has been reported. The used of smooth muscle actin, high molecular weight cytokeratine 34ß12 and Her2-neu staining are very important to differentiate between fibroadenoma with florid epithelial cells hyperplasia and ductal carcinoma.

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