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Analysis of breast true-cut biopsies by applying immunohistochemical study of myoepithelial markers

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Abstract

Objective: Breast pathologies are very common in women. Breast cancer is the most common and most frequent cause of death in women. The most common type of breast cancer is invasive ductal carcinoma. Histopathological examination of the tissue taken with a fine needle aspiration biopsy or true-cut biopsy is the main diagnostic method when clinical examination of breast and/ or radiological mass is detected. The definitive diagnosis of benign and malignant lesions of the breast is important in the form of treatment. The most important features in the diagnosis of breast cancer are atypical cellular features such as invasion, desmoplasia, pleomorphism, hyperchromasia, nuclear irregularity, prominent nucleoli, high mitosis count. Loss of myoepithelial layer in the malignant cases is a very important feature in the diagnosis. Aim of this study is to evaluate the benign and malignant breast pathologies with the immunohistochemical panel.

Material and Methods: The 52 breast true-cut biopsy materials in the archives of Department of Pathology at Faculty of Medicine, Erzincan Binali Yıldırım University between 2015-2017 were re-examined with the immunohistochemical panel. The immunohistochemical staining markers such as estrogen, progesterone, cerb-B2, E-cadherin, P63, CD10, calponin, CK5/6 have been applied in all cases.

Results: Cases including a benign disease such as fibroadenoma, adenosis, fibrosis, fibrocystic changes, and intraductal papilloma were 23. Cases including a malignant epithelial tumor were 29.

Conclusion: In the diagnosis of breast cancers, mainly cellular properties are determinative. The evaluation with the immunohistochemical panel will reduce the risk of diagnostic error when the cases that difficultly diagnosed with cellular properties.

Key words: Breast, cancer, immunohistochemistry

Introduction

The breast is composed of two main components of tissues. These are glandular tissues and stromal tissues. Glandular tissues consist of the milk-producing glands called lobule and the ducts that allow the passage of milk. Stromal tissues include fatty and fibrous connective tissues. Glandular structure is including epithelial and myoepithelial layer (1).

Benign breast disease is very common in women (2). Benign breast diseases include mainly fibroadenoma, adenosis, fibrosis, fibrocystic changes, intraductal papilloma and inflammatory diseases (3).

Fibroadenoma is the most common benign tumor of the breast. It consist of increased stromal component and epithelial component trapped within the stromal component (4).

Adenosis is a benign proliferative breast condition. It includes a milk-producing glands called lobule. The lobules are enlarged in adenosis. There are more glands than usual. (5). Adenosis is often found in biopsies of women who have fibrosis or cysts in their breasts (6). Fibrocystic change is characterized by the development of fluid-containing cysts surrounded by fibrous tissue (7). Histological cystic lesion prevelance about 50-60 % among the women (8). Fibrosis is the formation of scar-like connective tissue. It is a common finding in the breast (7). Intraductal papilloma is a benign epithelial tumor. It constitutes less than 10% of benign breast lesions (9). Microglandular adenosis is a very rare benign lesion. There is a loss of staining in the myoepithelial layer, unlike other benign lesions. In microglandular adenosis, histologically, there is a haphazard infiltration of small and uniformly round glands in fibrous tissue.

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Its differential diagnosis was made from cancer with the absence of cellular atypia and the absence of the staining with estrogen and progesterone receptors (10-12). It is often confused with a tubular carcinoma (13).

The most important features in the diagnosis of breast cancer are atypical cellular features such as invasion, desmoplasia, pleomorphism, hyperchromasia, nuclear irregularity, prominent nucleoli, and high mitosis count. Loss of myoepithelial layer in the malignant cases is very important feature in the diagnosis (14).

Breast cancer comprises approximately 10% of all cancer in women. It is the second most common cancer after lung cancer except skin cancer in all population. Breast cancer is the most common cause of death in women. It is the fifth most common death cause depending on cancer in all population. It is about 100 times more common in women than in men. Males have poorer outcomes due to delays in diagnosis (1).

Most breast malignancies are histologically adenocarcinoma. It constitutes more than 95% of breast cancers (15).

The main types of breast cancer are ductal carcinoma in situ, invasive ductal carcinoma (invasive carcinoma of no special type (NST) or invasive ductal carcinoma not otherwise specified (NOS)), lobular carcinoma in situ, invasive lobular carcinoma (1).

Ductal carcinoma in situ is the most common histologic type of non-invasive breast cancer. It is confined to the ducts of the breast (1). It is the precursor of invasive ductal carcinoma (16). The incidence of ductal carcinoma in situ associated with invasive ductal carcinoma is high (17).

Invasive ductal carcinoma (invasive carcinoma of no special type (NST) or invasive ductal carcinoma not otherwise specified (NOS)) is the most common histologic type with a rate of 70-80% of all invasive breast cancers (18-20). It includes subtypes such as tubular, medullary, papillary, mucinous, and cribriform carcinoma. Invasive tubular carcinoma, medullary carcinoma, cribriform carcinoma, and invasive mucinous carcinoma have a better prognosis, while invasive papillary carcinoma has a poor prognosis (21,22). It has a 5-year relative survival of 79% (23). Estrogen and progesterone expression of tumor cells is associated with good prognosis (24).

Lobular carcinoma in situ is the second common histologic type of non-invasive breast cancer. In lobular carcinoma in situ, there is a sharp increase in the number of cells within the milk glands called lobule in the breast (1). It is the precursor of invasive lobular carcinoma. The incidence of lobular carcinoma in situ associated with invasive lobular carcinoma is high, as is the case with ductal carcinoma in situ associated with invasive ductal carcinoma (17). It is multicentric in approximately 70% of cases. It is bilateral in 30–40% of cases (25).

Invasive lobular carcinoma is the second common histologic type with a rate of 5-15 % of all invasive breast cancers. (19,20,26,27) It has a 5-year relative survival of 84% (23).

Paget's disease is a cancer of nipple and comprises 1% of breast cancers (1).

Breast sarcoma, excluding phyllodes tumor, is an extremely rare and heterogeneous group of malignancies. It constitutes less than 1% of all breast malignancies (28).

Benign lesions such as fibroadenoma are more common in the early decades with a peak in the third decade while the incidence of malignancy is higher in advanced decades (29).

When there are diagnostic difficulties with cellular features, evaluation with an extensive immunohistochemical panel is helpful in the diagnosis.

This study aimed to share the result of our breast true-cut biopsy materials with the literature and to emphasize the importance of evaluation with an immunohistochemical panel in cases with difficulty in the differential diagnosis.

Material and Methods

Ethics committee approval was received on June 25, 2019 with numbered 07/03. In the archives of Department of Pathology at Faculty of Medicine, Erzincan Binali Yildirim University between 2015-2017, 52 breast true-cut biopsy materials were re-examined with the immunohistochemical panel. Most of the patients were diagnosed with breast mass and true cut biopsy. The cases reported as malignant epithelial tumors were 29. The cases reported as a benign disease such as fibroadenoma, adenosis, fibrosis, fibrocystic changes were 23. Paraffin blocks of breast true-cut biopsy specimens were supplied from the pathology archive and 4-micron-thick sections were taken from these blocks. After deparaffinization, the sections were stained with Hematoxylin-Eosin stain. The immunohistochemical panel was performed in all cases. 4-micron-thick sections were taken from the blocks of tumor suspected preparations on positively charged slides. The immunohistochemical staining markers such as estrogen (2019/10, ER1/20, Leica, Lot: 61037), progesterone (2020/03, ER2/20, Leica, Lot: 63037), cerb-B2, (2021/09, ER1/20, Dako, Lot: 20062529) E-cadherin (2020/08, ER1/10, Dako, Lot: 10148034), P63 (2020/07, ER2/10, Dako, Cod: IR662), CD10 (2020/08, ER2/20, Dako, Lot: 56C6), calponin (2020/12, ER1/5, Biogenex, Lot: AM3330817), and CK5/6 (2021/03, ER2/20, Thermo, Lot: 1803A) have been applied in all cases. The sections were stained using a fully automated immunohistochemistry device (Leica BOND-MAX®; Leica Biosystems, Melbourne, Australia). Immunohistochemical studies of calponin, P63, CD10, and CK5/6 showed that the myoepithelial layer disappeared in the malignant cases.

Data were evaluated by simple statistical method. The results were expressed as percentages.

Results

The age range was 19-64 year in benign cases and 33-81 in malignant cases. The mean age was 33.6 in benign cases and 57.5 in malignant cases. The most common age group was between 40-50 years in benign cases and between 50-60 years in malignant cases. (Table 1).

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The distribution of cases according to benign disease types was as follows: Of the 23 cases, 10 were a fibroadenoma, 8 were fibrocystic changes, 3 were adenosis, 1 was fibrosis, and 1 was intraductal papilloma (Graphic 1). There were no atypical histopathological features in benign diseases, the myoepithelial layer was observed with the myoepithelial marker in benign diseases like sclerosing adenosis (Figure 1).

The distribution of cases according to malignant tumor types was as follows: Of the 29 cases, 27 were invasive ductal carcinoma, 1 was invasive lobular carcinoma, and 1 was ductal carcinoma *in situ* (Graphic 1).

There were atypical histopathological features such as pleomorphism, hyperchromasia, nuclear irregularity in the ductal carcinoma *in situ*, the myoepithelial layer was observed with the myoepithelial marker in more areas. There was no stromal invasion (Figure 2).

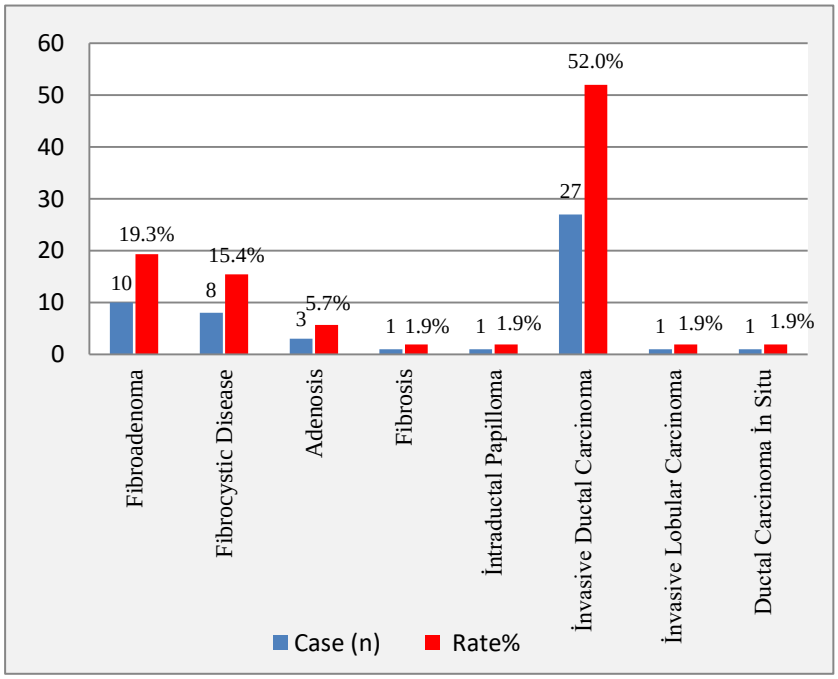
There were atypical histopathological features such as pleomorphism, hyperchromasia, nuclear irregularity in the invasive ductal carcinoma, loss of the myoepithelial layer was observed with myoepithelial marker, unlike benign breast diseases and ductal carcinoma *in situ*. E-cadherin positivity was applied in the differential diagnosis of lobular carcinoma of the breast (Figure 3).

The showing of myoepithelial layer with CD10, P63, CK5/6, and calponin in a case with cellular atypia was usefull in the differential diagnosis of ductal carcinoma *in situ* from invasive carcinoma. The absence of staining with estrogen and progesterone receptors was useful in the differential diagnosis of microglandular adenosis than a carcinoma, such as tubular carcinoma, with low cellular atypia.

Demonstration of myoepithelial layer loss by CD10, P63, CK5/6, and calponin in the invasive carcinoma cases, and the detection of myoepithelial layer with these markers in the benign cases was helpful in the diagnosis.

Table 1: The distribution of 52 breast true-cut biopsies.

Diagnosis	Case (n)	Rate%	Mean Age	
Benign	Fibroadenoma	10	19,3	33.6
	Fibrocystic Disease	8	15,4	
	Adenosis	3	5,7	
	Fibrosis	1	1,9	
	İntraductal Papilloma	1	1,9	
Malignant	Invasive Ductal Carcinoma	27	52,0	57.5
	Invasive Lobular Carcinoma	1	1,9	
	Ductal Carcinoma İn Situ	1	1,9	



Graphic 1. The distribution of 52 breast true-cut biopsies.

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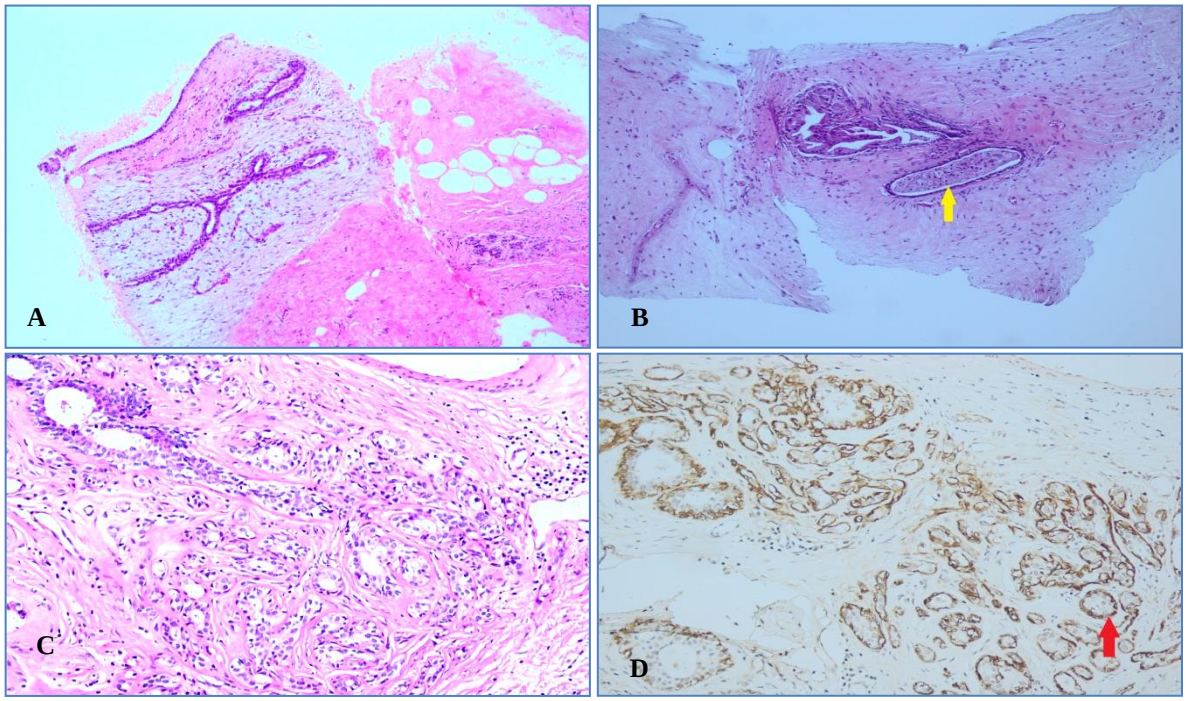

Figure 1: The histopathologic view of benign breast diseases. **A-** Fibroadenoma. (HEX100) **B-** Fibrocystic change including cyst with histiocytes (yellow arrow).(HEX100) **C-** Sclerosing adenosis. (HEX200) **D-** The showing of the myoepithelial layer with CD10 in sclerosing adenosis (red arrow). (X200)

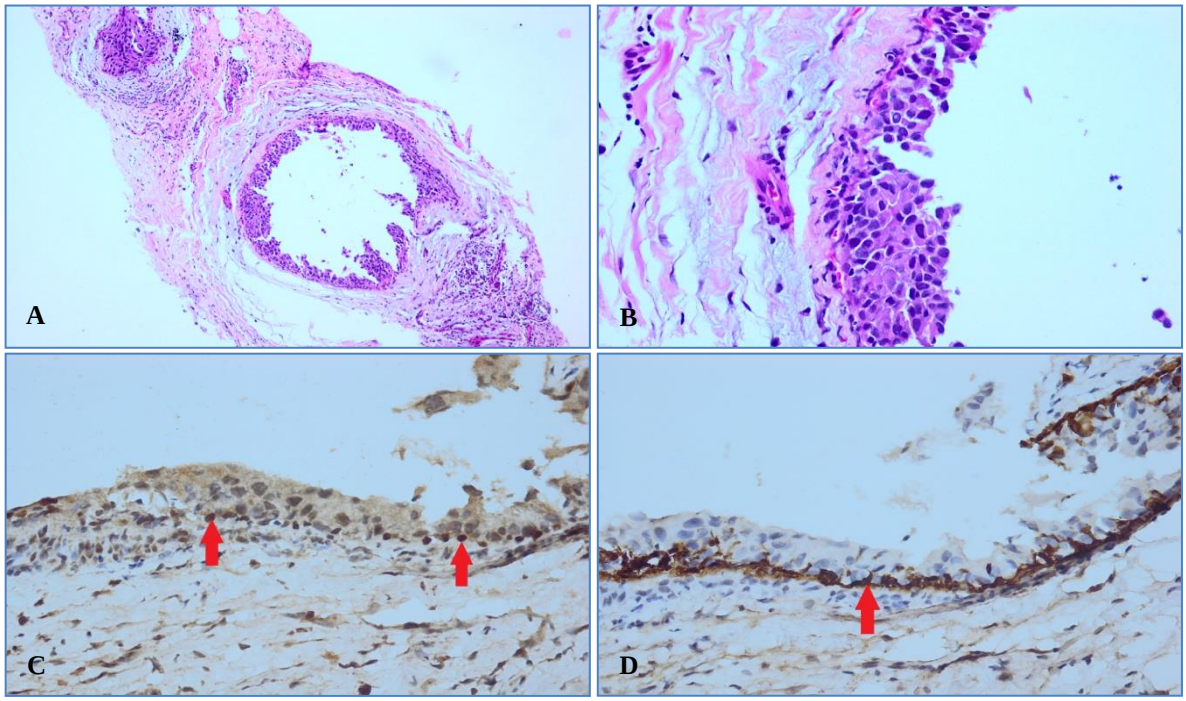

Figure 2: The histopathologic view of ductal carcinoma *in situ* in the breast. **A-** (HEX100) **B-** (HEX400) **C-** The nuclear staining of the myoepithelial layer with P63 (red arrows). (X400) **D-** The showing of the myoepithelial layer with CD10 (red arrow). (X400)

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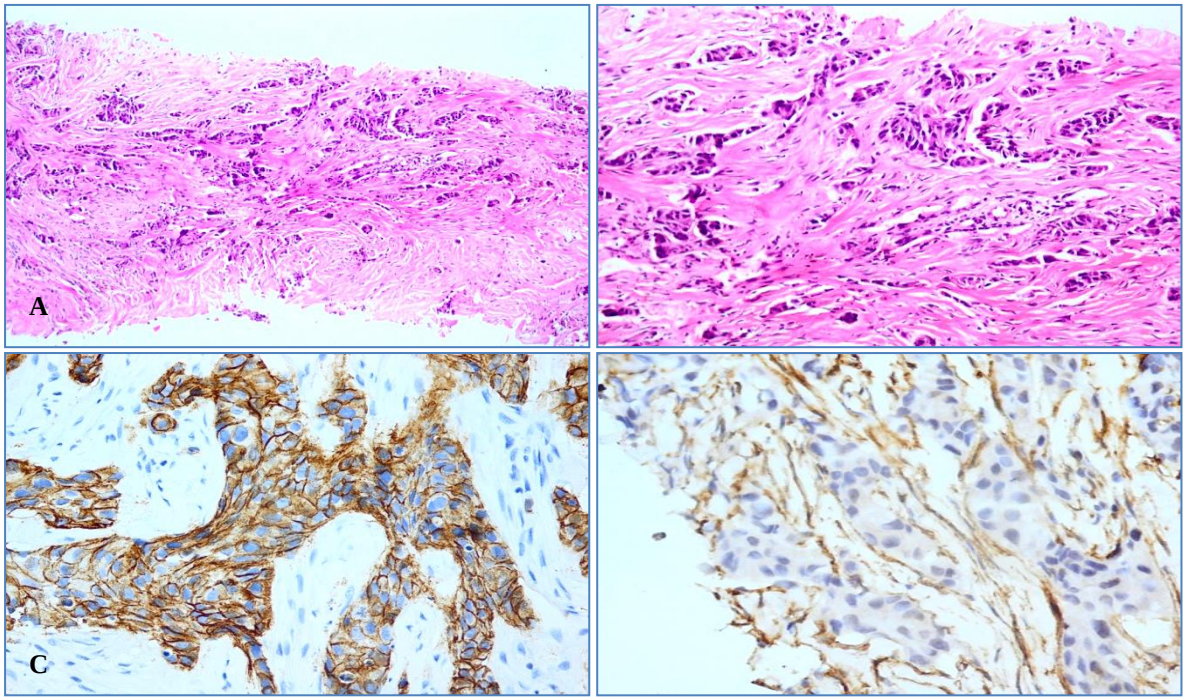

Figure-3. The histopathologic view of invasive ductal carcinoma in the breast. **A-** HEX100. **B-** HEX200. **C-** E-cadherin positivity in invasive ductal carcinoma of the breast. **D-** The loss of myoepithelial layer. Staining is observed only on the ground. (CD10X400)

Discussion

Breast pathologies are very common in women. Benign lesions are more common in the early decades. Benign breast diseases include mainly fibroadenoma, adenosis, fibrosis, fibrocystic changes, intraductal papilloma and inflammatory diseases (3).

The main types of breast cancer are ductal carcinoma in situ, invasive ductal carcinoma (invasive carcinoma of no special type (NST) or invasive ductal carcinoma not otherwise specified (NOS)), lobular carcinoma in situ, invasive lobular carcinoma (1). While benign lesions are more common in the early decades with a peak in the third decade, the incidence of malignant lesions is higher in advanced decades (29).

The most important features in the diagnosis of breast cancer are atypical cellular features such as invasion, desmoplasia, pleomorphism, hyperchromasia, nuclear irregularity, prominent nucleoli, high mitosis count. Loss of myoepithelial layer in the malignant cases is a very important feature in the diagnosis (14). Immunohistochemical stains such as calponin, P63, CD10, and CK5/6 are important in the identity of myoepithelial layer (30,31).

In this study, there were 10 fibroadenoma cases and 8 fibrocystic change cases among 23 benign breast disease cases. The rate of fibroadenoma cases was 43% and the rate of fibrocystic change cases was 35%. In the study including 352 benign breast disease cases of Sagiroglu et al., it was revealed that the rate of fibroadenoma cases was 53%, the rate of fibrocystic changes was 21% (32).

In both studies, the percentage of fibroadenoma was greater than fibrocystic change. In this study, the rate of fibroadenoma cases was slightly lower than the rate in the study of Sagiroglu et al. The rate of cases with fibrocystyc change was slightly higher than the rate in the study of Sagiroglu et al. However, in both studies, the percentages of fibroadenoma and fibrocystic change were relatively consistent.

In this study, the mean age was 33.6 in benign cases and 57.5 in malignant cases. In the study including 2118 ductal carcinoma cases of Wang et al, the mean age was 57.3 (33). In the study including 174 breast cancer cases of Balekouzou et al, the mean age was 45.8 (34). In the study including 76 breast cancer cases of Mansouri et al, the mean age was 51.3 (35). In this study, this result was compatible with the literature. In this study, the mean age was closer to the result in the study of Wang et al. than others.

In this study, the age range was 33-81 in malignant cases. In the study of Balekouzou et al, the age range was 16-90 year (34). In this study, the age range is narrower according to the result of Balekouzou et al. The limitation of this study, the number of cases were less. If the number of our cases were greater, this range could be wider.

In this study, the most common age group was between 40-50 years in benign cases and between 50-60 years in malignant cases. In the study of Balekouzou et al, the most common age group was between 45-54 years (34). In this study, this result was compatible with the literature. In this

study, the most common age group in benign cases was close to the result in the study of Balekouzou et al.

Microglandular adenosis is a benign lesion with loss of myoepielial layer and therefore may be difficult to diagnose with cancer. Lack of staining with estrogen and progesterone receptors is a supportive finding (10-12). In this study, one of the cases was microglandular adenosis. There was a loss of staining in the myoepithelial layer. Histologically, there was a haphazard infiltration of small and uniformly round glands in fibrous tissue. Its differential diagnosis was made from carcinoma with the absence of cellular atypia and the absence of the staining with estrogen and progesterone receptors. The histopathological diagnosis was confirmed by demonstrating the myoepithelial layer in microglandular adenosis using immunohistochemical markers such as CD10, P63, CK5 / 6, and calponin.

Ductal carcinoma in situ is the most common histologic type of non-invasive breast cancer (1). The showing myoepithelial layer with immunohistochemical markers is important in differential diagnosis than invasive carcinoma. In addition, the absence of stromal desmoplasia and invasion are important in the differential diagnosis. In this study, the showing of myoepithelial layer with CD10, P63, CK5/6, and calponin in a case with cellular atypia was usefull in diagnosis.

The results of our own laboratory were shared with the literature and it was emphasized that the evaluation with a large immunohistochemical panel in breast tru cut biopsy materials would reduce the risk of diagnostic errors in cases difficult to diagnose with cellular features.

Conclusion

In the diagnosis of breast cancers, mainly cellular properties are determinative. The evaluation with the immunohistochemical panel will reduce the risk of diagnostic error when the cases that difficultly diagnosed with cellular properties.

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