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ORIGINAL ARTICLE

Analysis of the cytological features supporting the diagnosis of lobular breast cancer. Factors associated with equivocal diagnoses

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Summary

Purpose: *Lobular carcinoma, the second most frequent type of breast cancer, accounts for 8-14% of all invasive breast cancers and presents a wide spectrum of differences from tumors of ductal origin. Its cytomorphologic features can create diagnostic problems.*

The purpose of this study was to identify the cytological and immunocytological features that support the diagnosis of lobular breast cancer.

Methods: *We retrospectively reviewed and analyzed a series of 46 fine needle aspirates (FNA) of invasive lobular carcinomas confirmed histopathologically. All findings were classified and analyzed in order to identify possible sources of diagnostic failure.*

Results: *Mammographic features were very subtle in most cases. The detailed cytomorphologic analysis revealed mainly discohesive architecture (95%), little or no nuclear atypia (91.3%), smooth regular nuclear membrane (93.47%) and low mitotic rate (97.8%). Loss of E-Cadherin immunoexpression was found in all cases. Estrogen (ER) and progesterone (PR) receptors were positive in the majority of the cases, whereas C-erbB2 (HER2/neu) was negative.*

Conclusion: *Discohesive architecture, low grade of nuclear atypia and plasmatoid appearance were the most important features .The correct preoperative diagnosis of lobular carcinoma permits a more specialized therapeutic approach.*

Key words: *breast, cytomorphology, cytology, lobular carcinoma*

Introduction

Lobular carcinoma, the second most frequent type of breast cancer, is also one of the most difficult types to detect in FNA samples, as well as in body fluids. The distinction between metastatic lobular cancer cells and mesothelial cells can be very difficult [1-3].

Lobular carcinoma that accounts for 8-14% of all invasive breast cancers [4-7] has different cytomorphologic features from tumors of ductal origin.

It has also different biological behavior, clinical and radiological features, molecular profile and several morphologic variations that could create diagnostic problems. Lobular carcinoma has an increased propensity for multifocal and multicentric distribution and for bilaterality and many times it is not detected by regular breast self-exams. This type of breast cancer is less likely to appear on a mammogram and lymph nodes may remain impalpable even if extensively involved [8-10].

Magnetic reasonance imaging (MRI) has been shown to be more sensitive than either mammography or ultrasonography [11].

The recognized lobular carcinoma variants include [12-14]: Tubulo-lobular carcinoma, alveolar lobular carcinoma, solid lobular carcinoma, pleomorphic lobular carcinoma, signet ring lobular carcinoma, and mixed types.

Invasive lobular carcinoma of the breast is reported to have a propensity to metastasize [15,16] to the peritoneum, leptomeninges, retroperitoneum, gastrointestinal tract, reproductive organs and bones [17]. In the literature, the largest series

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reports 0.8% lobular Ca in pleural fluid and 21.6% in peritoneal fluid [18].

It is quite obvious that since lobular carcinoma presents a wide spectrum of differences from tumors of ductal phenotype requires different therapeutic managements.

In the current study we retrospectively reviewed and analyzed a series of 46 FNAs of invasive lobular carcinomas in order to focus on sources of diagnostic failure and identify the cytological and immunocytological features that support the diagnosis of lobular breast cancer.

Methods

From the database of the Department of Clinical Cytology of the "Achilopouleion" General Hospital of Volos we retrieved all malignant breast specimens from January 2007 to March 2014.

We selected 46 cases with FNA cytological diagnosis of lobular carcinoma or suspicious for lobular carcinoma and confirmed the diagnosis of primary invasive lobular breast carcinoma histopathologically.

FNAs were performed with or without ultrasound guidance. The slides were prepared by the Thin Prep 2000 fluid cytology technique and stained with Papanicolaou and May Grunwald Giemsa. Immunocytochemistry for E-Cadherin, ER, PR and C-erb B2/HER2/neu was performed using the Max Bond automatic immunostainer.

Surgical specimens were stained with hematoxylin and eosin.

Lobular carcinoma was classified according to World Health Organization criteria [5].

Cases were examined cytologically, focusing on cellular arrangement, nuclear size and shape, distribution of nuclear chromatin amount of cytoplasm and cytoplasmic and nuclear characteristics. All findings were classified and analyzed in order to identify possible sources of diagnostic failure.

Results

During the study period breast malignancy was diagnosed in 352 samples. The diagnosis of histologically proven lobular carcinoma was suggested in 46 of those samples (13.06%). The lobular carcinoma patients were women aged 43-87. Seven women (15.2%) were premenopausal and 39 (84.7%) postmenopausal. Other lesions such as papillomatosis, ductal epithelial hyperplasia, sclerosing adenosis or collageneous spherulosis were found in 8/46 cases (19.5%).

Mammography

Mammographic features were very subtle in most cases (lack of desmoplastic reaction). The main findings are shown in Table 1.

Ultrasonography

Ultrasonographic findings are shown in Table 2.

Detailed cytomorphological analysis

Cytomorphological features are displayed in Table 3.

Table 1. Mammographic findings in 46 cases

Mammographic features	*Cases, N*	*%*
Architectural distortion or asymmetry compared to the other breast	18	39.1
Poorly defined thickening of the breast	13	28.2
Benign lesion	12	26.0
Small focal mass with microcalcifications	3	6.5

Table 2. Ultrasonographic findings in 46 cases

Ultrasonographic findings	*Cases, N*	*%*
Small densities in the parenchyma separated by non enhancing intervening tissue	32	69.5
Heterogeneous hypoechoic lesion with ill defined margins	9	19.5
Solitary mass with irregular margins	3	6.5
Enhancing fibroglandular breast elements	2	4.3

Table 3. Cytomorphological features in 46 cases

Cytomorphological features	*Cases, N*	*%*
Cellularity generally moderate or poor	35, 11	76, 23.9
Discohesive architecture (Figure 1)	44	95.0
Little or no nuclear atypia	42	91.3
Homogeneously distributed fine chromatin	42	91.3
Light cytoplasm	43	93.47
Low mitotic rate	45	97.8
Smooth regular nuclear membrane	43	93.47
Nuclei placed eccentrically (plasmatoid feature) (Figure 2)	40	86.9
Linear or cordlike arrangement (Figure 3)	28	60.8
Presence of targetoid mucin vacuole, signet ring shape (helpful diagnostic clue)	9	19.5
Intranuclear inclusions	12	26.0
Rosary like pattern	6	13.0
Occasional prominent nucleoli	3	6.5

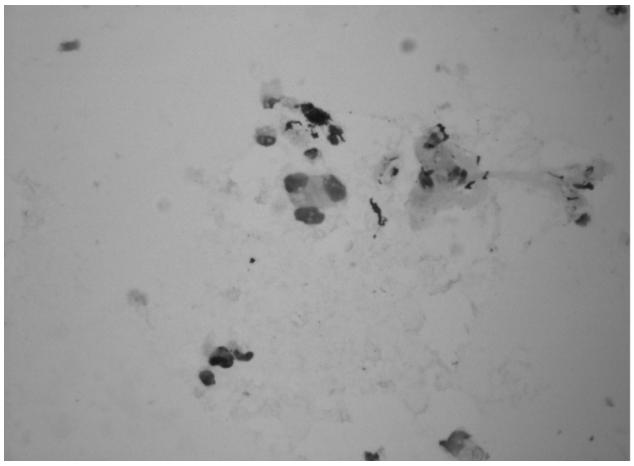

Figure 1. Small and poorly cohesive clusters (Pap stain x40)

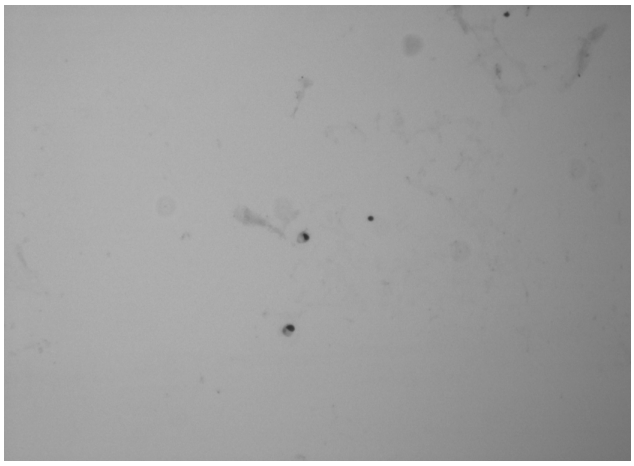

Figure 2. Few small malignant cells with eccentric nuclei (Pap stain x20).

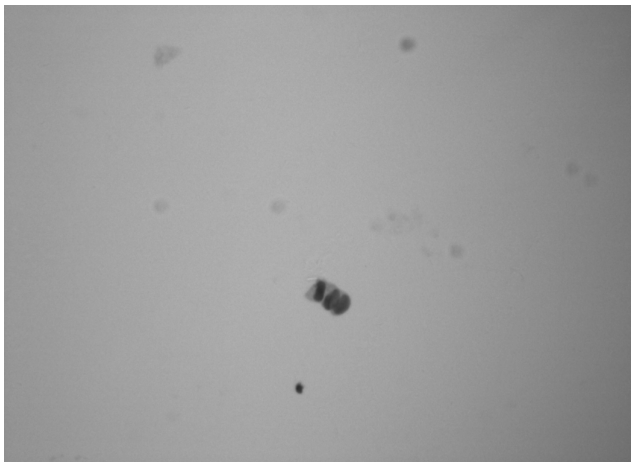

Figure 3. Cordlike arrangement (Pap stain x40).

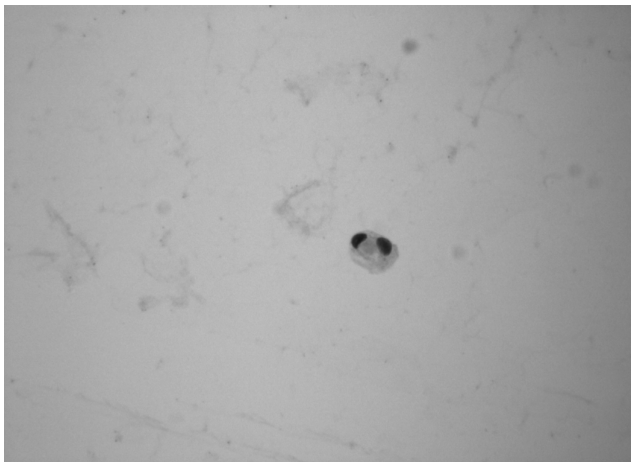

Figure 4. Pleomorphic type of lobular carcinoma (Pap stain x40).

Necrosis was a factor associated with more diagnostic difficulties since it was not easy to identify the bland-looking tumor cells intermingled with degenerated cells and debris interspersed with fatty vacuoles.

E-cadherin

E-Cadherin proved to be useful in 5 cases, for the distinction between lobular and ductal neoplasia. Loss of E-Cadherin immunoexpression was found in all cases.

ER, PR

ER was positive (3+) in 44/46 cases (95.6%). The remaining 2/46 cases (4.3%) showed positivity in a few scattered cells.

PR was also positive in the majority of the cases (42/46; 91.3%). In 3 cases only 8-10% of tumor cells showed positive expression whereas the last case was PR negative and ER positive in only 8% of the tumor cells. The histologic examination revealed a pleomorphic variant of lobular carcinoma.

C-erbB2 (HER2/neu)

Two cases (4.3%) were C-erbB2 positive (2+). The majority of tumors (95.6%) showed negative expression of C-erbB2 oncoprotein.

Discussion

The incidence of lobular carcinoma seems to be increasing and the growing number of postmenopausal women receiving hormonal therapy might be a possible factor.

In our study 84.7% of women with this type of breast carcinoma were postmenopausal, which is in agreement with data from the literature [4,6,7]. A rare case of bilateral invasive lobular breast cancer in a female teenager from Cameroon, where breast cancer is the commonest malignancy, was published [19].

Coexistence of lobular carcinoma with ductal hyperplasia with or without atypia, intraductal papilloma and papillomatosis is not rare [14].

Multifocality is one of its characteristics, so women with invasive lobular breast carcinoma are treated by total mastectomy slightly more frequently than those with ductal carcinoma.

Ductal and lobular carcinomas present quite different metastatic patterns [15-17]. Invasive ductal carcinoma affects the lungs, pleura and CNS, whereas advanced lobular carcinoma is much more likely to involve the peritoneum, gastrointestinal system, meninges and spinal fluid. Atypical symptoms due to metastasis to CNS may be the first sign of clinical presentation.

Invasive lobular carcinoma is one of the difficult types to detect, with failure rates ranging from 4% to 39% [20,21]. The reasons are: high risk for unsampled invasive cancer, especially in classic and pleomorphic types with necrosis, or very fragile samples, bland cytologic characteristics of tumor cells and the presence of several morphologic variations of lobular breast cancer. In case of pleomorphic type of lobular carcinoma the diagnosis of malignancy is easier because of higher cellularity and more marked cellular atypia than the other subtypes (Figure 4) and mainly the classic type.

Differentiation between benign and malignant lesion proved to be problematic in many cases of breast fine needle aspirations. It is obvious that the rate of correct diagnosis depends on the tumor size.

Once again it has to be noted that in cases with body fluid (pleural or peritoneal) positive for malignancy the knowledge of the patient's detailed history is of great importance.

Mutation in E-Cadherin gene leads to loss of function of E-Cadherin which is to maintain cell to cell adhesion. The E-Cadherin protein is located on the cell membrane and has three domains (extracellular, intramembranous and intracytoplasmic) [22,23]. E-Cadherin is also associated with p120 catenin, an inner membrane-bound protein, so that loss of E-Cadherin leads to loss of p120 membranous expression. Lobular carcinoma cells express cytoplasmic p120 because it redistributes to the cytoplasm.

Complete lack of E-Cadherin supports a diagnosis of lobular differentiation, whereas some rare cases may still express the protein but it may not be functional. On the other hand, tumors of ductal phenotype show membranous p120 and E-Cadherin expression.

E-Cadherin immunoexpression can be helpful in distinguishing between ductal and lobular carcinoma.

In addition, immunostain for p120 catenin, a cytoplasmic protein that belongs to the E-cadherin complex and anchors the E-cadherin protein to the cytoplasmic actin filaments, may be complementary to E-cadherin in the evaluation of lobular carcinoma. Positive cytoplasmic staining for p120 catenin supports lobular phenotype.

Presence of extracellular mucin is a characteristic of ductal breast carcinoma, whereas normal ductal epithelial cells do not contain mucicarmine-positive cytoplasm.

Lobular carcinoma cells may present only intracytoplasmic mucin, showing signet ring formations. According to the literature only three cases of lobular carcinomas displaying both extracellular and intracellular mucin have been described [24,25].

ER and PR expression is valuable since it predicts patient's response to adjuvant endocrine therapy [26]. Lobular carcinomas are more frequently steroid receptor-positive where -as they are usually C-erbB2 negative- are diploid and have a lower S-phase fraction.

Overexpression of HER2 is associated with negative ER, PR, bigger sized tumors, intermediate to high grade, positive axillary lymph nodes and poor prognosis [25].

The correct preoperative diagnosis of lobular carcinoma permits an individualized therapeutic approach with assessment of the contralateral breast, preoperative hormonotherapy and more extensive surgical resection margins.

From this analysis it is evident that discohesive architecture, low grade of nuclear atypia and plasmatoid appearance were the most important features to distinguish invasive lobular carcinoma from invasive ductal carcinoma.

References

1. Yoon MJ, Hirschowitz SL, Apple SK. Metastatic lobular carcinoma of the breast in pleural fluid: Diagnostic pitfall for mesothelial cells. Open Breast Cancer J 2011;3:49-52.
2. Kim JH, Kim GE, Choi YD et al. Immunocytochemical panel for distinguishing between adenocarcinomas and reactive mesothelial cells in effusion cell blocks. Diagn Cytopathol 2009;37:258-261.
3. Monaco SE, Dabbs DJ, Kanbour-Shakir A. Pleomorphic lobular carcinoma in pleural fluid :Diagnostic pitfall for atypical mesothelial cells. Diagn Cytopathol 2008;36:657-661.
4. Menet E, Becette V, Briffod M. Cytologic diagnosis of lobular carcinoma of the breast. Experience with 555 patients in the Rene Huguenin Cancer center. Cancer Cytopathol 2008;112:111-117.
5. Ellis IO, Schmitt SJ, Sastre-Garau X et al. Invasive lobular carcinoma. In: Tavassol FA , Devilee P (Eds): World Organization Classification of tumours. Pathology and Genetics of Tumours of the Breast and Female genital organs. Lyon, France: IARC Press 2003,pp 23-26.
6. Arpino G, Bardou VJ, Clark GM, Elledge RM. Infiltrating lobular carcinoma of the breast: Tumor characteristics and clinical outcome. Breast Cancer Res 2004;6:149-156.
7. Molland JG,Donnellan M,Janu NC,Carmalt HL,Kennedy CW,Gillett DJ. Infiltrating lobular carcinoma—a comparison of diagnosis, management and outcome with infiltrating ductal carcinoma. Breast 2004;13:389-396.
8. Krecke KN,Gisvold JJ. Invasive lobular carcinoma of the breast: mammographic findings and extent of disease at diagnosis in 184 patients. AJR Am J Roentgenol 1993;161:957-960.
9. Veltman J,Boetes C,van Die L,Bult P,Blickman JG,Barentsz JO. Mammographic detection and staging of invasive lobular carcinoma. Clin Imaging 2006;30:94-98.
10. 10. Butler RS,Venta LA,Wiley EL,Ellis RL,Dempsey PJ,Rubin E. Sonographic evaluation of infiltrating lobular carcinoma. AJR Am J Roentgenol 1999;172:325-330.
11. Rissanen T,Tikkakoski T,Autio AL,Apaja-Sarkkinen M. Ultrasonography of invasive lobular breast carcinoma. Acta Radiol 1998;9:285-291.
12. DiCostanzo D,Rosen PP,Gareen I,Franklin S,Lesser M. Prognosis in infiltrating lobular carcinoma. An analysis of "classical" and variant tumors. Am J Surg Pathol 1990;14:12-23.
13. 13. Middleton LP,Palacios DM,Bryant BR,Krebs P,Otis CN,Merino MJ. Pleomorphic lobular carcinoma: morphology, immunohistochemistry, and molecular analysis. Am J Surg Pathol 2000;24:1650-1656.
14. 14. Mise I, Vucic M, Maricevic I, Sokcevic M, Curic-Juric S. Histologic subtypes of invasive lobular carcinoma in correlation with tumor status and hormone receptors. Acta Clin Croat 2010;49:275-281.
15. Ferlicot S, Vincent-Salomon A, Medioni J et al. Wide metastatic spreading in infiltrating carcinoma of the breast. Eur J Cancer 2004;40:336-341.
16. Borst MJ, Ingold JA. Metastatic patterns of invasive lobular versus invasive ductal carcinoma of the breast. Surgery 1993;114:641-642.
17. James JJ, Evans AJ, Pinder SE et al. Bone metastases from breast carcinoma: histopathological-radiological correlations and prognostic features. Br J Cancer 2003;18;89:660-665.
18. Antic T, Gong Y, Sneige N. Tumor type and single cell/mesothelial – like cell pattern of breast carcinoma metastases in pleural and peritoneal effusions. Diagn Cytopathol 2012;40:311-315.
19. Enownchong Enow-Orock, Egbe Obinchemti T, Achidi EA et al. Bilateral invasive lobular breast cancer in a female teenager: a rare finding of a common disease – case report and review of literature. Pan Afr Med J 2010;6:2.
20. Tan SM, Behranwala KA, Trott PA et al. A retrospective study comparing the individual modalities of triple assessment in the preoperative diagnosis of invasive lobular breast carcinoma. Eur J Surg Oncol 2002;28:203-208.
21. 21. Hwang S, Loffe O, Lee I, Weisman J, Cangiarella J, Simsir A. Cytologic diagnosis of invasive lobular carcinoma: factors associated with negative and equivocal diagnoses. Diagn Cytopathol 2004;31:87-93.
22. Rajeev Singhai, Vinayak W Patil, Sanjog R Jaiswal et al. E-Cadherin as a diagnostic biomarker in breast cancer. N Am J Med Sci 2011;3:227-233.
23. Goldstein NS. Does the level of E-Cadherin expression correlate with the primary breast carcinoma infiltration pattern and type of systemic metastases? Am J Clin Pathol 2002;118:425-434.
24. Rosa M, Mohammadi A, Masood S. Lobular carcinoma of the breast with extracellular mucin: new variant of mucin producing carcinomas? Pathol Intern 2009;59:405-409.
25. Yu J, Bhargava R, Dabbs DJ. Invasive lobular carcinoma with extracellular mucin production and HER-2 overexpression: a case report and further case studies. Diagn Pathol 2010;15:5-36.
26. Rakha EA, El-Sayed ME, Powe DG et al. Invasive lobular carcinoma of the breast: response to hormonal therapy and outcomes. Eur J Cancer 2008;44:73-83.