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

Smaroula N. Divani¹, Nikolaos D. Kardasis²
¹Department of Clinical Cytology, Volos General Hospital, Volos, Greece; ²Chartered financial analyst, Zurich, Switzerland

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 immunexpression 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

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

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 resonance 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

Correspondence to: Smaroula N Divani, MD. Department of Clinical Cytology, Volos General Hospital, 164 Gallias street, Volos 38221, Greece. Tel: +30 24210 25922, E-mail: smarouladivani@hotmail.com
Received: 16/06/2014; Accepted: 05/07/2014
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 adenosin 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>
<thead>
<tr>
<th>Table 1. Mammographic findings in 46 cases</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mammographic features</strong></td>
</tr>
<tr>
<td>Architectural distortion or asymmetry compared to the other breast</td>
</tr>
<tr>
<td>Poorly defined thickening of the breast</td>
</tr>
<tr>
<td>Benign lesion</td>
</tr>
<tr>
<td>Small focal mass with microcalcifications</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 2. Ultrasonographic findings in 46 cases</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ultrasonographic findings</strong></td>
</tr>
<tr>
<td>Small densities in the parenchyma separated by non enhancing intervening tissue</td>
</tr>
<tr>
<td>Heterogeneous hypoechoic lesion with ill defined margins</td>
</tr>
<tr>
<td>Solitary mass with irregular margins</td>
</tr>
<tr>
<td>Enhancing fibroglandular breast elements</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 3. Cytomorphological features in 46 cases</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cytomorphological features</strong></td>
</tr>
<tr>
<td>Cellularity generally moderate or poor</td>
</tr>
<tr>
<td>Discohesive architecture (Figure 1)</td>
</tr>
<tr>
<td>Little or no nuclear atypia</td>
</tr>
<tr>
<td>Homogeneously distributed fine chromatin</td>
</tr>
<tr>
<td>Light cytoplasm</td>
</tr>
<tr>
<td>Low mitotic rate</td>
</tr>
<tr>
<td>Smooth regular nuclear membrane</td>
</tr>
<tr>
<td>Nuclei placed eccentrically (plasmatoid feature) (Figure 2)</td>
</tr>
<tr>
<td>Linear or cordlike arrangement (Figure 3)</td>
</tr>
<tr>
<td>Presence of targetoid mucin vacuole, signet ring shape (helpful diagnostic clue)</td>
</tr>
<tr>
<td>Intranuclear inclusions</td>
</tr>
<tr>
<td>Rosary like pattern</td>
</tr>
<tr>
<td>Occasional prominent nucleoli</td>
</tr>
</tbody>
</table>
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 plasmoid appearance were the most important features to distinguish invasive lobular carcinoma from invasive ductal carcinoma.
References


