Review

Invasive Pleomorphic Lobular Carcinoma of the Breast: Pathologic, Clinical, and Therapeutic Considerations

Khalid Al-Baimani,[1] Amy Bazzarelli,[2] Mark Clemons,[1,3] Susan J. Robertson,[4] Christina Addison,[3] Angel Arnaout[2,3]

Abstract

Pleomorphic lobular carcinoma is an uncommon form of breast cancer and a subtype of invasive lobular carcinoma. It has unique histopathologic features that translate to a more aggressive phenotype with an associated poor prognosis. Unlike classical invasive lobular carcinoma, it can lose estrogen and progesterone receptor expression and demonstrate *HER-2/neu* amplification. It remains to be determined, however, whether the pleomorphic histology independently predicts a worse outcome or whether other known associated negative prognostic factors such as larger tumor size, increased metastatic disease, and associated worse molecular subtypes commonly present in pleomorphic carcinoma account for the poor prognosis. Here we present an updated review of the unique pathologic and clinical features of pleomorphic lobular carcinoma needed to guide management for women with this subtype of cancer.

Clinical Breast Cancer, Vol. ■, No. ■, ■-■ © 2015 Elsevier Inc. All rights reserved.

Keywords: Breast cancer, Diagnosis, Histopathology, Invasive lobular cancer, Management, Pathogenesis, Pleomorphic

Introduction

Breast cancer is the one of the most common types of cancers, resulting in 500,000 deaths globally each year.[1] It has a variety of pathologic subtypes, which results in widely different prognosis and management.[1] After invasive ductal carcinoma (IDC), invasive lobular carcinoma (ILC) of the breast is the second most common type of invasive breast carcinoma, accounting for 8% to 14% of all breast cancers.[2-7]

ILC is pathologically, clinically, and biologically unique among breast cancers.[2] Traditionally, ILC presents as a number of histologic subtypes based on morphology.[8] Pleomorphic lobular breast carcinoma (PLC) is a uncommon but clinically important form of ILC.[9] First described by Page and Anderson[10] in 1987 and initially classified by Dixon et al[11] as a mixed subgroup of ILC, PLC was segregated from other cancers as a result of its apparently more aggressive behavior and associated worse outcomes compared to other breast cancer subtypes.[9,12,13] Not until 2003 did the World Health Organization (WHO) officially recognize PLC as a variant of ILC.[14]

In this review, we present an updated review of the unique pathologic and clinical features of PLC that are needed to guide management for women with this cancer.

Epidemiology

Pleomorphic lobular carcinomas represent less than 1% of all breast cancers[15,16] and approximately 15% of ILCs.[5-7] PLC has been associated with older age and postmenopausal status.[9,15,17,18] It has also been shown to be more commonly represented in *BRCA2* carriers.[19] *BRCA2* mutations have been detected in 40% of PLC in one study.[20] Another study showed that there was a statistically significant increase in the rate of tumors of the pleomorphic subtype in *BRCA2* mutation carriers (7 of 9) compared to the rates of PLC present in *BRCA1* mutation carriers (0 of 10) or non-*BRCA*-mutant patients (6 of 21).[19] The link between *BRCA* and PLC may not be confined to *BRCA2*, however, as it has also been shown that 27% to 32% of PLC had loss of heterozygosity of *BRCA1*.[18]

Histopathologic Considerations

According the WHO, ILC is subdivided into classic, solid, alveolar, tubulolobular, and pleomorphic subtypes according to

[1]Division of Medical Oncology, Ottawa Hospital Cancer Center, Ottawa, ON, Canada
[2]Division of General Surgery, Ottawa Hospital, Ottawa, ON, Canada
[3]Division of Cancer Therapeutics, Ottawa Hospital Research Institute, Ottawa, ON, Canada
[4]Department of Anatomical Pathology, Ottawa Hospital, Ottawa, ON, Canada

Submitted: Apr 11, 2015; Revised: Jun 11, 2015; Accepted: Jun 15, 2015

Address for correspondence: Angel Arnaout, MD, MSc, FRCSC, FACS, CW 1606, Ottawa Hospital—General Campus, 501 Smyth Road, Ottawa, ON, Canada K1H8L6
E-mail contact: anarnaout@toh.on.ca

1526-8209/$ - see frontmatter © 2015 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.clbc.2015.06.010

their morphology and their clinical features.[21] Classic, solid, alveolar, and tubulolobular subtypes are separated on the basis of architecture, while the pleomorphic subtype is separated mostly on the basis of nuclear morphology.[14,22] The pleomorphic subtype has been further classified into apocrine, histiocytic, or signet-ring cell types.[21] In a series of cases used by the WHO as the basis for morphologic features of PLC,[23] cells are arranged in a "targetoid" pattern often seen in single-file arrangements similar to classic ILC.[23,24] Some cases also exhibit alveolar formations. PLC is, however, distinct from ILC on the bases of increased nuclear size, nuclear pleomorphism, nucleolar prominence, and increased mitotic activity.[9,24] Some of the cases demonstrate foamy cytoplasm as a result of a high number of vacuoles and are called histiocytoid, while others have eosinophilic cytoplasm and appear to overlap with apocrine carcinoma. As nuclear atypia increase, the nuclear features approach those of IDC, and there can be difficulty distinguishing cytologically the nuclear characteristics of ILC cells from cells of IDC.[20,24-26]

With respect to immunohistochemically defined pathologic features, all subtypes of lobular carcinoma are characterized by deficient expression of E-cadherin. E-cadherin is a transmembrane intercellular adhesion glycoprotein responsible for cell–cell adhesion,[27] and this loss of expression of E-cadherin on immunohistochemistry is a defining feature found in most ILCs compared to IDC, which, in contrast, demonstrate a 98% expression rate.[28] Decreased expression of E-cadherin in ILC is usually associated with reduced or absent catenins that connect it to the actin microfilament network within the cell in normal function.[27,29] The characteristic loss of cohesion seen between ILC cells is the result of the loss of E-cadherin function.[27,29] PLC shares this loss of E-cadherin expression in 80% to 100% of cases.[9,26,30] The distinctive genetic alterations associated with diminished E-cadherin expression including loss of heterozygosity at the E-cadherin gene (*CDH1*) have also been demonstrated in both PLC and ILC—again, in contrast to IDC.[26] Therefore, although PLC is similar in nuclear characteristic to IDC, it demonstrates both histologic and genetic alterations that link it most closely with ILC.

There are additional immunohistochemical differences between classic ILC and PLC. These include differences in gross cystic disease fluid protein 15 (GCDFP-15) and *p53*. GCDFP is one marker associated with apocrine differentiation.[18,26,31] GCDFP expression is commonly negative in classical ILC despite frequent androgen receptor expression but has been demonstrated to be positive in a greater number of PLC tumors.[12,18,23,26,31,32] Thus, there is an overlap of some PLC with apocrine carcinoma histologically.[23,31]

p53 is a tumor suppressor gene involved in maintaining normal cell cycle and cell growth.[31] Expression of *p53* is rare (0%-5%) in classic ILC; however, more pleomorphic cancers demonstrate its expression 10% to 45% of the time.[18,31] *p53* expression is associated with more aggressive tumors, and this may also help explain why PLC tumors appear to behave in a worse fashion than classic ILC tumors.

Pathogenesis of PLC

There has been considerable debate in the literature regarding whether PLC is a subset of lobular or ductal carcinoma. This arises from the high grade and more aggressive nature of PLC compared to ILC, and the question becomes whether PLC is a type of IDC that has lost E-cadherin versus a more aggressive type of ILC. Most evidence, however, now points to PLC having a lobular origin that has developed a more aggressive phenotype.[33-35]

Functional loss of the E-cadherin gene (*CDH1*, found at the locus 16q22.1) as seen in ILC is related to methylation of the gene promoter, frame-shift mutations, and loss of heterozygosity.[33,35-37] Normal structure and function to the E-cadherin molecule is essential to many cellular events within epithelial cells. It permits cells to adhere to one another by interactions between the molecules. Within the cell, it is associated with catenins that integrate their function with the actin cytoskeleton.[36] This complex is termed the E-cadherin–catenin complex, and its disruption is an important step in the pathogenesis of both classical ILC and PLC.[34,35]

Simpson et al[20] demonstrated that genomic gains in chromosomes 1q and 16p and losses in 11q and 16q occurred most of the time (over 80%-90%) in PLC, which closely resembles changes seen in ILC.[32] In addition, PLCs had high *HER-2* and *C-MYC* amplification as well as decreased estrogen receptor (ER) frequency on genomic sampling.[18,20,31] Additional losses of *p53, BRCA1, BRCA2,* and *ESR* loci have also been identified to be present in PLC.[18] It has also been shown that combined inactivation of E-cadherin and *p53* in mice led to the development of an invasive and metastatic breast cancer that closely mimicked PLC in humans, thus clearly identifying a pathway for the development of PLC.[1]

Clinical and Diagnostic Imaging Presentation of PLC

Compared to IDC patients, PLC patients tend to be older, to have larger tumors, and to exhibit more axillary lymph node involvement (higher T and N stages) by the time of presentation.[15,16] Median tumor size in one series was 20 mm compared to 15 mm for classical ILC.[9] In addition, PLC often displays evidence of lymphovascular invasion and a higher proliferative index.[4,38] Compared to ILC, PLC patients have a higher incidence of distant metastases,[9] with a pattern of spread similar to ILC[9,32,39,40]—namely to the bone, peritoneum, and ovaries. Taken together, these indicate a more aggressive phenotype at presentation.

Very few studies detailing the radiographic features of PLC have been performed. PLC is similar to ILC in that it can be mammographically occult, with up to 19% of associated mammograms being negative.[16] However, PLC has a higher detection rate on mammography compared to ILC[16]; and similar to ILC, the most common presentations are of a mass or architectural distortion. It is rare to have microcalcifications in PLC compared to 6% in the ILC group. PLC is similar to ILC in exhibiting higher rates of multifocality and multicentricity,[11,41] but a higher number of PLC tumors require mastectomy compared to ILC.[9]

In terms of ultrasound imaging, there do not appear to be any differences between PLC and ILC, with most lesions presenting as a spiculated mass.[16] As with ILC, magnetic resonance imaging may be helpful to add to traditional breast imaging such as mammography and ultrasound in excluding the presence of multicentric disease.[16]

Download English Version:

https://daneshyari.com/en/article/5881960

Download Persian Version:

https://daneshyari.com/article/5881960

Daneshyari.com