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Review

Lobular breast cancer: Clinical, molecular and morphological characteristics

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ABSTRACT

Infiltrating lobular breast cancer (ILBC) is the most common special breast cancer subtype. This review provides a comprehensive description of ILBC characteristics, including epidemiology, clinical features, molecular genetics and histomorphology. Twenty detailed supplemental data tables guide through primary data of more than 200 original studies. Meta-analyses indicate that ILBC is at least twice as common in the Western world as it is in other geographic regions. ILBC is over-represented in so-called interval carcinomas and in primary metastatic breast cancer. ILBC is also associated higher age, higher pT stage and hormone receptor (ER/PR) positivity. Pathological complete response rates after neoadjuvant chemotherapy are low, ranging between 0% and 11%. Positive resection margins after breast-conserving surgery are comparatively frequent and 17% to 65% of patients undergo a second surgical intervention. Depending on the morphological stringency in the diagnosis of ILBC, lack of E-cadherin expression is observed in 55% to 100% of cases. *CDH1*/E-cadherin mutation detection rates vary between 12% and 83%. Various additional molecular factors, including *PIK3CA*, *TP53*, *FOXA1*, *FGFR1*, *ZNF703* and *BCAR4*, have been implicated in ILBC or progression of lobular carcinoma *in situ* (LCIS) to invasive cancer and are discussed in detail. Eight instructive figure plates recapitulate the histomorphology of ILBC and its variants. Furthermore, we draw attention to rarely addressed histological details, such as two-sided nuclear compression and fat-avoiding growth at the invasion front. Last but not least, we discuss future translational research directions and emphasize the concept of synthetic lethality, which promises new options for targeted ILBC therapy.

Contents

Abbreviations: AR, androgen receptor; ALH, atypical lobular hyperplasia; BC, breast cancer; BCS, breast-conserving surgery; CCND1, cyclin D1; CDH1, gene symbol for E-cadherin; CGH, comparative genomic hybridization; CTNNA1, gene symbol for α-catenin; CTNND1, gene symbol for p120-catenin; DGC, diffuse gastric cancer; EMT, epithelial mesenchymal transition; ER, estrogen receptor; FISH, fluorescence *in situ* hybridization; GEM, genetically engineered mouse; HER2, epidermal growth factor receptor 2, ErbB2; HDGC, hereditary diffuse gastric cancer; IBTR, ipsilateral breast tumor recurrence; ILBC, infiltrating lobular breast cancer; LCIS, lobular carcinoma *in situ*; LIN, lobular intraepithelial neoplasia; LN, lobular neoplasia; NGS, next generation sequencing; NST, breast cancer of no special type; p120, p120-catenin; PR, progesterone receptor; SNP, single nucleotide polymorphism; US, United States; WHO, World Health Organization.

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1. Introduction

Breast cancer (BC) is the most frequent malignancy among women with an estimated 1.67 million new cases diagnosed each year worldwide [1]. Infiltrating lobular breast cancer (ILBC) is the most common special BC subtype. Historically, these tumors were first described as acinar or scirrhous spheroidal cell carcinomas [2,3]. Early microscopic illustrations were provided by Cornil in 1908 (reprinted in Rosen et al., 1978) [2,4]. The term "lobular" carcinoma was coined by Stewart and Foote in the 1940s [5]. These authors and others highlighted the association of lobular carcinomas with a distinct non-invasive lesion, namely lobular carcinoma *in situ* (LCIS), and endorsed mastectomy even for pure LCIS lesions [5,6]. In the 1990s, molecular analyses revealed an almost uniform loss of the E-cadherin cell adhesion molecule by somatic mutation in ILBC and LCIS, but not in other BC subtypes [7–10]. On the one hand, this affirmed the paradigm that distinct cancers arise from distinct precursors and on the other hand, this showed that molecular pathology unfolds its significance only in the light of histomorphology. Therefore, ILBC is a prime example of the principles of modern clinical oncology. The sections below provide a detailed account of ILBC characteristics.

2. Epidemiology and risk factors

In the Western world, ILBC accounts for 10–15% of all BC cases and its incidence increased disproportionately between 1975 and 2000 (almost ten-fold in some regions, to approximately 20/100,000 women per year) [11–15]. This rise was linked to the increasing use of menopausal hormone replacement therapy rather than to improved early detection. Between 2000 and 2004, the ILBC incidence declined and this was attributed to the dramatic decrease in hormone replacement prescriptions in these years [16]. Since then, ILBC incidence has increased again and the reason for this trend is not known [17,18].

Several BC risk factor preferentially promote ILBC development (Supplemental Table 1) [19–26]. For instance, late age at first birth, menopausal hormone replacement therapy or late age at menopause confer a higher risk for ILBC than for non-lobular BC [20,26]. The relevance of steroid hormones for ILBC development is also documented by the interrelationship of age-adjusted ILBC incidences and menopausal status. In the 50-year age group, ILBC is significantly more common in premenopausal compared with postmenopausal women [26]. Another important risk factor is a first-degree relative with ILBC, which suggests a predisposing genetic component [19]. In line with this, genome-wide single nucleotide polymorphism (SNP) association studies have identified genetic polymorphisms associated with ILBC but not non-lobular BC [27]. One of these polymorphisms is located at chromosome 7q34 (rs11977670), but it is unclear how it contributes to ILBC development [27].

Compared with the Western world, the relative frequency of ILBC is much lower in the Middle East, in Africa and in Asia. In these geographic regions, ILBC accounts for only 5% of BC cases [28–31]. Strikingly, ILBC also accounts for <5% of BCs in Asian Americans and Pacific Islanders living in the US, which is probably due to genetic factors [32,33].

Many human tumors have their equivalents in veterinary pathology. However, ILBC is essentially a human disease. To our knowledge, <10 cases of ILBC or LCIS have been described in free-range or domestic animals in the published literature, so far [34,35]. Accordingly, ILBC is not included in standard veterinary breast tumor classifications [36,37].

3. ILBC as a form of hereditary BC

Compared with sporadic cases, hereditary ILBC is rare and occurs as a secondary tumor type in patients or families with the hereditary diffuse gastric cancer (HDGC) syndrome [38–45]. The HDGC syndrome is caused by germline mutation of the *CDH1* tumor suppressor gene, which encodes the E-cadherin protein. Recent studies have also identified *CDH1* germline mutations in some patients diagnosed with ILBC or early onset bilateral LCIS (age <50 years), but without a family history or manifestation of gastric cancer (Supplemental Table 2) [46–52]. Accordingly, clinical criteria for recommending genetic counseling or *CDH1* sequencing is the subject of an ongoing debate and may include patients with a family history of ILBC or early onset bilateral LCIS [46,47].

ILBC is rare in other hereditary tumor syndromes (Supplemental Table 3) [39,40,42,47,49,53–63]. In particular, ILBC accounts for <5% of BCs in *BRCA1* or *TP53* germline mutation carriers.

4. Clinical characteristics

The detection sensitivity of mammography screening is lower for ILBC than for BC of no special type (NST, commonly known as ductal BC). Hence, ILBC is significantly over-represented in so-called interval carcinomas, which become clinically apparent within a period of 24 months after a negative mammography screening result (Supplemental Table 4) [64–68]. ILBC is also slightly over-represented in primary metastatic BC and among mammary carcinomas with clinically inapparent, microscopic tumor cell dissemination in the bone marrow [69–73].

ILBC is associated with a higher age at diagnosis, higher pT stage, higher percentage of multifocal, multicentric and bilateral cases, lower histological grade, higher rate of hormone receptor (ER/PR)-positivity (>95% of cases in recent series), lower rate of HER2 positivity (<5% of cases in recent series) and low tumor cell proliferation (Supplemental Table 5) [74–93]. Some of these associations persist in case series matched for hormone receptor status, histological grade, pT stage or age (Supplemental Table 5) [79,82,84,86].