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Triple-Negative Breast Cancer: Clinical and Histological Correlations

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Keywords
Breast cancer, molecular subtypes

Summary
Triple-negative breast cancer (TNBC) is characterized by the lack of estrogen and progesterone receptors and the lack of HER2 expression or amplification. Much interest has recently been focused on these triple-negative (TN) subtypes because they may be aggressive and are more likely to recur and metastasize than other subtypes of breast cancer. TNBC accounts for approximately 10–24% of all breast cancer cases, and typically it occurs in younger patients and in patients with BRCA1 mutation. There is a substantial heterogeneity of TNBCs both at the morphological and the molecular level, but there are also common features, such as low tumor grade and accelerated tumor proliferation. Morphologically, TNBC may present as invasive ductal, metaplastic, medullary, apocrine, or other types. Molecularly, they are most frequently associated with a basal phenotype, but there is a distinct subgroup of cancers that are not of basal type and belong to the claudin-low or molecular-apocrine type. The basal phenotype is frequently associated with the loss of BRCA1.

Schlüsselwörter
Mammakarzinom, molekulare Subtypen

Zusammenfassung
Das tripel-negative Mammakarzinom (TNBC) ist charakterisiert durch die fehlende Expression von Östrogen- und Progesteronrezeptoren sowie durch die fehlende Überexpression bzw. Amplifikation von HER2. Aufgrund der generell höheren Aggressivität und Rezidivhäufigkeit im Vergleich mit anderen Phänotypen des Mammakarzinoms ist das TNBC in den Mittelpunkt des Interesses gerückt. Das TNBC macht etwa 10–24% aller Fälle von Brustkrebs aus und tritt am häufigsten bei jüngeren Patientinnen und bei Patientinnen mit BRCA1-Mutation auf. Es besteht eine erhebliche Heterogenität der TNBCs sowohl auf der morphologischen als auch auf der molekularen Ebene, es gibt aber auch gemeinsame Eigenschaften wie ein geringer Differenzierungsgrad und eine erhöhte Proliferationsaktivität. Morphologisch kann sich das TNBC als invasiv-duktaler, metaplastischer, medullärer, apokriner oder anderer Phänotyp präsentieren. Auf molekularer Ebene ist das TNBC am häufigsten mit einem basalen Phänotyp assoziiert, seltenere molekulare Varianten des TNBC betreffen den Claudin-low und den molekular-apokrinen Typ. Der basale Phänotyp ist nicht selten mit einem Verlust von BRCA1 assoziiert.

Introduction

Breast cancer is a highly heterogeneous disease at both the molecular and the clinical level. The histopathologic World Health Organization (WHO) classification of breast cancer [1] stratifies tumors based on their morphological tumor characteristics, with little reference to non-morphological (immunohistochemical or molecular) features. This builds upon the traditional classification of breast cancer, but its prognostic and predictive relevance is rather limited. Tumors with identical type, grade and stage can have markedly different outcomes, and as a result, some patients may be overtreated or undertreated. For the success of targeted therapy and individualized medicine, a predictive rather than purely prognostic classification system would be required.

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In the last few years, the study of gene expression by microarray and related technologies (since 2000) has led to the definition of molecular phenotypes of breast cancer and has provided a more precise profile of the disease aiming at resolving the complexity of breast cancer and identifying related entities that share specific molecular alterations and are sensitive to specific treatments. The phenotypic classification of breast carcinoma has been based on unsupervised clustering of gene expression data [2] and basically distinguishes 5 main subtypes. The 2 most frequent subtypes are the estrogen receptor (ER)-positive luminal A and luminal B tumors, and the other 3 subtypes include ER-negative tumors with normal breast-like, human epidermal growth factor receptor 2 (HER2)-related, and basal-like groups. The luminal C subtype [2] could not be identified consistently. More recently, rare subtypes such as the molecular apocrine subtype [3] and the claudin-low subtype [4] of breast cancer were identified.

In contrast, the term triple-negative (TN) breast cancer is a pragmatic, clinical term, which correlates with the molecular classification but cannot be used to identify one or more molecular subtypes. For various reasons, TN breast cancers (TNBCs) have attracted the attention of both pathologists and oncologists. This is because they were reported to be more aggressive in general and more likely to recur and metastasize than other subtypes of breast cancer [5]. Secondly, they may differ from ER- and HER2-positive tumors in histogenesis, although their true origins and developmental mechanisms seem to be elusive [6]. Unlike common breast cancers, TNBC is resistant to our current HER2-targeted therapies such as trastuzumab and hormonal therapies such as tamoxifen and aromatase inhibitors. Thirdly, most TNBCs are basal-like breast cancers, which have distinct molecular and biological characteristics [7–10]. We will discuss TNBCs, and the term 'basal-like' will be used in our review as an important subgroup of TNBCs.

Definition and Risk Factors of TNBC

TNBCs are defined as breast cancers lacking both ERs and progesterone receptors (PgRs), and HER2 expression by immunohistochemistry. They account for approximately 10–24% of all breast cancers [5, 11–15]. Because of their frequent expression of basal markers, such as basal cytokeratins, TNBCs are sometimes lumped together with basal-like breast cancers. However, it is important to bear in mind that these are overlapping but by no means identical groups of breast cancer.

TN and basal-like subtypes occur more commonly in the African-American population than in Caucasians and have a particular predominance in premenopausal women [16, 17], with younger age at diagnosis [5, 18–21]. Other risk factors include lifestyle factors such as an increased body mass index (obesity), sedentary lifestyle, and alcohol consumption [22, 23]. Dolle et al. [24] reported that the TNBC risk was 2.5 times increased in women who had used oral contraceptives for more than 1 year compared to women who had used oral contraceptives for less than 1 year or never.

Histopathological Features

TN and basal-like tumors have been characterized by several aggressive histopathological features, including high histological and nuclear tumor grade, large tumor size, elevated mitotic count, area of central fibrosis and necrosis, pushing margin of invasion, poor tubule formation, lymphocytic stromal response, and high nuclear-cytoplasmic ratio [9, 16, 25–30]. The majority of TNBCs are invasive ductal carcinomas of no special type [31]; however, there are several other and mostly rare histological types that may frequently be TN. This includes atypical or typical medullary-like cancers [27, 32], apocrine carcinomas and pleomorphic lobular carcinomas [9], metaplastic carcinomas [27, 33], and adenoid cystic carcinomas [34]. The majority of metaplastic and medullary-like cancers also show a basal phenotype, which is rarely found in other special types of breast cancer [32, 35, 36].

Molecular Features in TN and Basal-Like Breast Cancers

The triple-negative phenotype of breast cancer tumors significantly overlaps with the basal-like phenotype. The majority of, but not all, TNBCs (66–90%) are associated with a basal phenotype and, conversely, a majority of, but not all, basal-like tumors have a TN phenotype [8, 37, 38]. On the other hand, it was shown that a small but significant subgroup of basal-like breast cancers may express either hormone receptors or HER2 [38–40]. In fact, TNBCs represent a rather heterogeneous group at the molecular level. Gene expression studies have shown that TNBCs mostly belong to three distinct molecular classes: the basal-like group, the claudin-low group, and the molecular-apocrine group. The claudin-low tumors are characterized by stem cell features and features of epithelial-mesenchymal transition (EMT). They lack cell-cell junction proteins, including E-cadherin, and they frequently have an intense lymphocytic cell infiltrate [4]. The molecular-apocrine subtype is also consistently seen in TN breast cancers, but also in HER2-overexpressing cancers [3, 41]. This subtype characteristically is positive for the androgen receptor and may be seen in patients with germ-line PTEN mutations (PTEN = phosphatase and tensin homolog) [42].

Basal-Like Subtype

The most frequent molecular subtype of TNBC is the basal-like subtype. This basal phenotype accounts for approximately 16–18% of all invasive breast cancers [43, 44].

Although TN and basal-like breast cancers share many molecular and morphological features, TN and basal-like are not identical terms [13, 45–47]. The term TN is a term based on clinical assays for ER, PgR, and HER2, whereas the term basal-like is based on microarray gene expression assays [2, 48]. At the immunohistochemical level, basal-like breast cancers are characterized by the expression of proteins normally found in basal/myoepithelial cells of the normal breast, including high-molecular-weight (basal) cytokeratins (CK5/6, CK14, and CK17). Therefore, the term 'basal-like' stems from the similarity between the molecular profile of these tumors and that of basal/myoepithelial cells of the normal breast [48].

Tumors expressing basal cytokeratins are thought to originate from CK5-positive epithelial progenitor cells of the breast [49–51]. Although several definitions [27, 52] of basal-like carcinomas have been proposed, there is no internationally accepted consensus on this. Most of the previous studies in the breast have defined the basal phenotype as the group of tumors expressing high-molecular-weight (basal) cytokeratins including CK5/6 [43, 53], CK14 [54], or both [55]. By contrast, other studies [56] showed that 76% of the tumors could be classified as basal-like on the basis of ER and HER2 negativity in conjunction with expression of CK5/6 and epidermal growth factor receptor (EGFR).

Basal-like breast cancers usually show high p53 protein expression [53, 57, 58], or a high rate of *p53* gene mutations [2, 31, 59], and high expression of EGFR [27, 31, 56, 57, 60]. Also they may be associated with germ-line *BRCA1* mutations [45, 61] and often express genes associated with proliferation, such as those coding for cyclin E1 and proliferating cell nuclear antigen (PCNA) [2, 48, 62]. Association of basal-like breast cancer with elevated mRNA levels of p16 and cyclin E with lower levels of retinoblastoma (Rb) and cyclin D1 compared to other tumor subtypes suggests that *Rb* inactivation is integrally linked to basal-like tumors [59]. In addition, the myoepithelial markers smooth muscle actin (SMA), p63 and CD10 are generally expressed [27].

The basal-like subtype has been associated with poor clinical outcome [14, 45]. This probably reflects the subtype's association with a high proliferative capacity, a high histological grade, and the lack of systemic therapy, since basal-like tumors express a low level of ER and do not overexpress HER2 [44, 63]. In addition, Potemski et al. [64] have revealed that poor prognosis associated with the basal-like phenotype of breast cancer was determined not by CK5/6 or CK17 expression, but instead by ER absence and cyclin E expression.

BRCAness in TN Cancers

The two major contributors to hereditary breast cancer are the cancer susceptibility genes *BRCA1* and *BRCA2* [65]. *BRCA1* is a tumor suppressor gene expressed in the cells of breast and other tissue, where it helps repair damaged DNA and destroy cells when the DNA cannot be repaired. If *BRCA1* itself is damaged, the damaged DNA can allow the cell to duplicate without control, resulting in cancer [66]. This gene is responsible for most cases of hereditary breast and ovarian cancer. *BRCA1*-associated cancers are typically high grade and TN, and share common pathologic features such as positive EGFR immunostaining [67–69]; also, Foulkes et al. [61] found that the majority of these *BRCA1*-associated cancers that are ER negative (81%) are more likely to develop at a younger age (before age 45), compared to 62% of cancers in women diagnosed after age 65. Furthermore, the proportion of *BRCA1*-associated cancers that are of the basal phenotype has been estimated to be 88% and 57% by Foulkes et al. [61] and Lakhani et al. [67], respectively.

In addition, a number of studies have shown that BRCA1-positive disease and TNBC/basal-like breast cancer share certain characteristics, including ER negativity, HER2 negativity, high nuclear grade, high Ki-67 labeling index, basal marker expression (CK5/6, 14, 17, EGFR), and tumor protein 53 (tp53) mutation [53, 61, 67, 70, 71]. Furthermore, Young et al. [72] have reported that young women with high-grade TNBC and with no family history of cancer are likely to carry a *BRCA1* mutation. Microarray gene expression studies have also shown a similarity between sporadic basal-like tumors and those familial tumors harboring a *BRCA1* mutation [45, 73]. In addition, Turner et al. [74] have suggested that tumors expressing more than one basal cytokeratin are more likely to have a dysfunctional BRCA1 pathway. Immunohistochemical profiling using tissue microarrays has identified that a group of tumors characterized by basal cytokeratin expression are also characterized by low expression of BRCA1 [58]. Indeed a basal phenotype is one of the hallmark features of 'BRCA-ness' (sporadic cancers that look like those from *BRCA1* or *BRCA2* mutation carriers) and might have important implications for management [71].

Metastasis and Pattern of Recurrence

TNBCs and basal-like cancers are more likely than others to metastasize to the brain [75, 76], and vice versa [77]. In a study of 55 patients with invasive breast cancer who developed brain metastases, the frequency of ER-negative, CK5/6-positive, and EGFR-positive tumors was higher than that observed in a comparison group of patients who did not have brain metastases [78]. Also, the incidence of central nervous system (CNS) metastases has been observed in African-Americans and BRCA1 mutation carriers, and these two populations of patients have a relatively higher incidence of TN/basal-like tumors [79]. In particular, the risk of visceral recurrence within 5 years of diagnosis is significantly higher in TNBC patients, although the risk of bone recurrence in the same interval is significantly lower [80]. Also, tumors expressing basal markers are associated with more lung and brain metastases than comparable tumors not expressing basal markers [81].

Patients with TNBC exhibit a distinct pattern of recurrence, which is characterized by a rapidly rising rate in the first 2 years following diagnosis and a peak at 2–3 years, followed by a decline in recurrence risk over the next 5 years, and a very low risk of recurrence thereafter [5, 19]. The risk of distant recurrence and death due to breast cancer within 5 years of diagnosis is significantly higher in TNBC patients than in other patients with non-TN breast cancer [5].

Prognosis

Molecular subtypes of breast cancer are associated with different clinical outcomes [82]. Patients with basal phenotype [77] or TN tumors [5, 83] generally have a shorter disease-specific survival and overall survival than those with non-basal, non-TN, or luminal A tumors. In addition, Liu et al. [84] have reported that, although the TN phenotype is related to poor prognosis in the whole breast cancer population, those positive for CK5/6 or CK17 had an even worse clinical outcome in the TN phenotype. Also, it was reported that TNBCs are associated with more advanced stage [85] and higher grade [46, 86], which are associated with worse prognosis in breast cancer. However, it is not clear if the poor prognosis of TNBCs and basal-like breast cancer is due to poor therapy options or inherent aggressiveness [82].

Disclosure Statement

None of these authors have personal financial interests or conflicts of interest to declare.

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