



Inflammatory Breast Cancer: a Separate Entity

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Abstract

Purpose of Review Inflammatory breast cancer (IBC) is an uncommon but highly aggressive subtype of breast cancer that contributes significantly to breast cancer-related mortality. In this review, we provide an overview of the clinical and molecular characteristics of IBC, and highlight some areas of need for ongoing research.

Recent Findings The disease is characterized by florid tumor emboli that obstruct dermal lymphatics, leading to swelling and inflammation of the affected breast. Recent studies have focused on tumor cell intrinsic features, such as signaling through pathways involved in growth and stem-like behavior, as well as extrinsic features, such as the immune system, that can be leveraged to develop new potential therapies.

Summary Key efforts have led to an increase in awareness of the disease as well as new insights into IBC pathogenesis. However, there is a strong need for new therapies designed specifically for IBC, and many unanswered questions remain.

Keywords Inflammatory breast cancer · Locally advanced breast cancer · Tumor emboli · Dermal lymphatic invasion · Clinical trials

Introduction

Inflammatory breast cancer (IBC) is a clinicopathologic diagnosis, the essential features of which have not changed significantly since 1978 when Lucas and colleagues described eight clinical parameters for the diagnosis of IBC [1]. Pathologic confirmation of invasive breast cancer is essential. Currently, the AJCC 7th edition requires diffuse erythema and edema (or peau d'orange) of greater than or equal to one-third of the breast for a T4d classification of IBC [2]. If these features occupy less than one-third of the breast, it is a T4b classification. The AJCC 8th edition continues to require the quantifier of clinical involvement of one-third of the breast, but will also include grade since IBC is predominantly a high-grade cancer [3]. Additional diagnostic recommendations incorporate the rapid onset of symptoms, with a duration of less than 6 months [4].

Importantly, data have shown that the specific set of criteria used to define IBC can have a significant impact on the rate of diagnosis, suggesting that the incidence of IBC is likely underestimated in the USA. For example, analysis of IBC cases at one academic institution showed significantly more cases of IBC (8.1% versus 2.1%) using less rigid clinical criteria, i.e., erythema, edema, and peau d'orange, compared with the number of cases identified using the standard SEER definition of IBC, i.e., comparable with the AJCC criteria [5].

Clinical Features

Both overdiagnosis and underdiagnosis are potential problems with IBC. Overdiagnosis can occur when non-inflammatory locally advanced breast cancer (LABC) involves the skin and is challenging to differentiate from IBC [6]. Underdiagnosis can occur because the clinical features of IBC are variable in presentation. For example, erythema can wax and wane over time. In addition, as awareness of IBC increases, IBC patients are presenting earlier in their disease course. At the time of initial presentation, erythema and edema may occupy only a minimal region of the breast, or the erythema may be absent completely, yet the other characteristics of IBC remain present. In addition,

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erythema may be difficult to detect in dark-pigmented skin. The lack of prompt recognition leads to delays in the initiation of treatment as well as improper treatment [6].

Proper diagnosis of IBC is particularly important because it indicates a worse prognosis compared with non-inflammatory LABC. Older data from the surveillance, epidemiology, and end results program (SEER) compared clinical outcomes and found the median survival time of IBC was 2.9 years compared with 6.4 years for LABC and > 10 years for non-T4 breast cancer [7]. IBC is enriched for the HER2-positive and the triple-negative (negative for estrogen receptor (ER), progesterone (PR), and HER2) subtypes of breast cancer (approximately 40% of IBC are HER2 positive and 30% of IBC are triple negative, compared with 25% and 15% of non-IBC, respectively) [7–10]. But across all subtypes, IBC patients have worse outcomes compared with non-IBC patients [8, 11]. Although the prognosis has improved with better recognition of the disease as well as improvements in systemic therapy, particularly the development of HER2-directed therapy, further progress is needed [12–14].

Certain pathologic features can provide supporting evidence, but are neither necessary nor sufficient for a diagnosis of IBC. Dermal lymphatic invasion is one such feature; it can occur in all stages of breast cancer, but in IBC dermal lymphatic emboli are often more numerous and larger in size [15••]. Two skin punch biopsies to identify dermal lymphatic invasion should be attempted whenever possible, but this finding is confirmed in only 75% of biopsy samples, and is not required for the diagnosis [6]. Similarly, radiologic criteria can be highly suspicious for IBC and can provide support for a clinical diagnosis. These include diffuse skin thickening on mammogram or breast MRI (compared with nodular or focal skin thickening that can be associated with locally advanced breast cancer), increased vascularity of the tumor on breast ultrasound, trabecular thickening on mammogram, and extensive non-mass-like enhancement within the breast parenchyma and involvement of regional and contralateral lymph nodes on MRI [15••, 16].

There is also increasing evidence supporting a role for PET-CT in staging IBC, and further research in this area is needed [15••, 17]. Greater than 90% of inflammatory breast cancers are FDG-avid [15••]. Of note, 25–30% of patients with IBC present with distant metastases, as opposed to 5–10% for non-IBC [18, 19]. PET/CT increases the clinical stage in > 40% of cases, and improves subsequent mapping for radiation therapy in ~ 18% of cases [16, 20].

Additional clinical, radiologic, and pathologic features that can assist in distinguishing IBC from non-inflammatory LABC should be considered whenever possible. There is currently no single pathologic or molecular feature of IBC that is sufficient for its diagnosis. Clearly, a collection of both pathologic and clinical criteria needs to be developed which can result in a more accurate diagnosis of IBC.

Principles of Therapy

Optimal treatment of inflammatory breast cancer requires a multidisciplinary approach. The standard of care for treatment of IBC is trimodality therapy with upfront systemic therapy, including chemotherapy, followed by total mastectomy and axillary lymph node dissection, then post-mastectomy radiation to the chest wall and regional draining lymph nodes. Data from the National Cancer Database show that in non-metastatic IBC the use of trimodality therapy is an independent predictor of survival even after controlling for potential confounding variables [21]. However, even with recent improvements in the use of trimodality therapy, it remains underutilized with incidences ranging from 58.5 to 73.4% annually when assessed between 1998 and 2010 [21].

Neoadjuvant Systemic Therapy

The purpose of neoadjuvant systemic therapy (NST) is to convert the initially inoperable inflammatory breast cancer into disease that is surgically resectable, in addition to controlling microscopic disseminated disease. Choices of chemotherapy are generally based on non-IBC treatment regimens. For Her2-positive disease, standard NST includes dual Her2-directed therapy, i.e., both trastuzumab and pertuzumab with a taxane chemotherapeutic regimen, preferably followed by an anthracycline-containing regimen. In trials of neoadjuvant HER2-directed therapy, there were limited numbers of IBC patients enrolled (6% in TRYPHAENA and 7% in NeoSphere); therefore, the use of these data to support a standard of care approach for IBC is based upon extrapolation, yet pathologic complete response (pCR) rates were high among the general breast cancer patients treated with these published regimens, 64% and 40% respectively [22, 23]. As of yet, we do not have an optimal chemotherapy backbone for dual anti-HER2 therapy for HER2-positive IBC [24, 25]. Because of concerns over extrapolating therapeutic efficacy from LABC trials to the treatment of IBC, an IBC-specific NST study of paclitaxel, pertuzumab, and trastuzumab (reserving anthracycline and cyclophosphamide for the adjuvant setting) has been studied in a recently completed clinical trial demonstrating comparable pCR rates with the NeoSphere trial [26••].

Neoadjuvant therapy for ER-positive and triple-negative IBC remains anthracycline and taxane-based chemotherapy as standard of care, e.g., dose-dense adriamycin and cyclophosphamide followed by paclitaxel. Recent or ongoing NST studies for triple-negative IBC include an assessment of the EGFR inhibitor panitumumab in combination with chemotherapy, which demonstrated a pCR rate of 42% for the triple-negative subset in a pilot trial for HER2-negative IBC [27••] (ongoing, <https://clinicaltrials.gov/ct2/show/study/NCT01036087>), as well as an ongoing Translational Breast Cancer Research Consortium (TBCRC)–sponsored study exploring the JAK

1/2 inhibitor ruxolitinib in combination with standard NST chemotherapy (ongoing, <https://clinicaltrials.gov/ct2/show/study/NCT02876302>) [28, 29]. The TBCRC trial is based upon preclinical studies that showed active JAK/STAT signaling in cancer stem cells which are enriched in models of IBC [28, 30].

Surgery

The standard of care for surgical treatment of IBC is modified radical mastectomy, i.e., total mastectomy with complete axillary lymph node dissection (MRM). Multiple recent studies have confirmed an improvement in locoregional control with MRM compared with breast-conserving surgery [31–33]. In addition, MRM has been shown to be associated with an improved median survival of 59 months, compared with 47 months after breast-conserving surgery [34]. A few recent studies have revisited the role of breast-conserving surgery in IBC; however, these were retrospective studies often with small sample sizes or potential confounding variables, and generalizations cannot be made based upon their results [35–37]. Therefore, outside of a clinical trial, all patients with non-metastatic inflammatory breast cancer should receive, when possible, a modified radical mastectomy as their surgical intervention following NST.

Sentinel lymph node biopsies are considered inadequate for staging in IBC. False-negative rates from sentinel node biopsies are significantly higher in IBC compared with locally advanced non-inflammatory breast cancer (40% in IBC and 6% in LABC) [38]. Identification rates for sentinel lymph node sampling are also extremely low in inflammatory breast cancer which may be the result of aberrant lymphatic drainage associated with IBC [39]. Given the extent of axillary lymph node involvement in inflammatory breast cancer and the challenges associated with sentinel lymph node sampling in this disease, all patients with IBC who undergo mastectomy should receive a complete level 1 and level 2 axillary lymph node dissection as standard of care.

Given the extensive skin involvement with IBC and the requirement of skin sparing with immediate reconstruction, there is an increased risk of complications and increased risk of delay of subsequent radiation therapy when breast cancer reconstruction is performed at the time of mastectomy [40, 41]. In addition, immediate reconstruction often interferes with optimizing radiation fields. Reconstruction is not absolutely contraindicated in this disease; however, delayed reconstruction 6–12 months post-completion of radiation therapy is an acceptable approach [42].

Radiation Therapy

Even with the completion of trimodality therapy, local regional disease recurrence can occur in up to 40% of patients with

non-metastatic inflammatory breast cancer [14]. There are special considerations for post-mastectomy radiation therapy in IBC, which targets the chest wall and includes the regional lymph nodes. These include the use of acceleration, bolus, and/or increased total dose specifically in the setting of IBC [43]. Data from M.D. Anderson Cancer Center suggest improvement in locoregional control with hyperfractionated dose escalation in patients with positive margin status, disease that responds poorly to chemotherapy, or age of less than 45 years [44]. Identification of potential radiosensitizers in this disease is an area of active research. There is experimental evidence for simvastatin as a radiosensitizer in IBC [45]. In addition, the ability of the PARP inhibitor veliparib to act as a radiosensitizer has been evaluated in a pilot trial supported by the TBCRC and showed promise [46••], supporting the ongoing phase II randomized trial investigating the benefits of olaparib as a radiosensitizer in inflammatory breast cancer (ongoing, <https://clinicaltrials.gov/ct2/show/study/NCT03598257>).

Adjuvant Systemic Therapy

The role of adjuvant therapy in IBC is dependent on the specific cancer subtype and is extrapolated from data which involves primarily non-inflammatory breast cancer patients. As in non-IBC, in ER-positive IBC endocrine therapy is given with or without ovarian suppression depending upon menopausal status. Premenopausal patients should receive ovarian suppression in addition to an aromatase inhibitor, given their high risk of recurrent disease, which is extrapolated from studies involving non-IBC [47]. For triple-negative breast cancers, the CREATE-X study showed that patients with residual disease after neoadjuvant chemotherapy have a 5.6% improvement in overall survival if they receive 8 cycles of capecitabine in the adjuvant setting [48]. Subgroup analyses suggested that there was no significant benefit to the addition of capecitabine in hormone receptor-positive breast cancer, but there was a benefit in triple-negative disease. At this time, adjuvant capecitabine can be considered for triple-negative IBC patients with residual disease after neoadjuvant chemotherapy.

Finally, for HER2-positive IBC, adjuvant anthracycline-based chemotherapy should be given if not given in the neoadjuvant setting. HER2-directed therapy is then continued for a total of 1 year in duration, as in non-IBC HER2-positive disease. In the setting of pCR, adjuvant pertuzumab and trastuzumab can be given. This is supported in part by the results of the APHINITY trial, which showed that the addition of adjuvant pertuzumab to adjuvant trastuzumab yields a small absolute benefit in disease-free survival, and a greater benefit in node-positive disease [49]. In the absence of pCR, adjuvant trastuzumab emtansine for 14 cycles should be considered, based on the results of the recent KATHERINE study where the risk of recurrence of invasive breast cancer or death

was 50% lower in patients with residual invasive breast cancer after NST who received trastuzumab emtansine compared with those who received trastuzumab alone [50]. In addition, the ExteNET trial examined the benefit of extending adjuvant HER2 therapy with the use of the oral small molecule HER2 inhibitor neratinib for 1 year after the completion of trastuzumab-based adjuvant therapy, showing a 2.5% increase in invasive disease-free survival, with higher increases in hormone receptor-positive and lymph node-positive diseases [51]. Adjuvant neratinib can be considered for IBC patients if they did not receive pertuzumab as part of their NST, since prior therapy with pertuzumab was not permitted in the ExteNET trial.

Metastatic Disease

Given the rarity of IBC, most patients with metastatic disease have enrolled in clinical trials focusing on non-inflammatory breast cancer; therefore, the current treatment of IBC in the metastatic setting is currently approached similarly to that of non-IBC. One exception is the approach to palliative local-regional therapy. Unlike non-IBC, palliative mastectomy, axillary lymph node dissection, and post-mastectomy radiation therapy may reduce the risk of severe morbidity associated with local regional disease progression in IBC [52, 53]. In addition, there is an increased risk of brain metastases in patients with metastatic IBC, suggesting a role for screening brain MRI in patients with stage IV IBC at the time of disease progression [54].

Cellular and Molecular Pathogenesis

The key pathologic hallmark of IBC is the presence of tumor emboli within the papillary and reticular dermis of the skin of the breast (i.e., dermal lymphatic invasion (DLI)). As mentioned above, inflammatory breast cancer tumor emboli can be larger and more frequent than those present in LABC. It is thought that the dermal lymphatic emboli block the local lymphatics in the skin of the breast, and this contributes to the inflammatory infiltrate and characteristic edema in IBC. In addition, the emboli are a source of local dissemination for IBC, and some models raise the question as to whether or not distant metastases can originate from tumor emboli in addition to the primary tumor [55, 56].

It is worth noting that in many cases of IBC there is no single dominant tumor mass. Instead, tumor cells are loosely infiltrative in the stroma as groups of cells. Whether in the stroma or in the lymphatics, IBC cells exist in clusters [57]. Experimental evidence shows that IBC cells disseminate as clusters rather than as single cells [57]. Interestingly, recent studies suggest that non-IBC cancers can also invade vessels and metastasize as clusters rather than single cells, potentially

via a different mechanism [58]. IBC tumor emboli maintain high levels of E-cadherin during invasion and metastasis, in contrast to non-inflammatory breast cancers that lose E-cadherin when they undergo epithelial-to-mesenchymal transition [57]. Paradoxically, although E-cadherin is traditionally described as a tumor suppressor, it may act to promote tumor progression in IBC [59].

It has been challenging to model these clinicopathologic features of IBC in the laboratory. While some patient-derived xenograft models of IBC have been established and have yielded important insights into IBC pathogenesis, most models are not associated with the classic skin involvement or with the finding of loose stromal invasion/lymphovascular invasion associated with IBC. Woodward and colleagues have found that the addition of mesenchymal stromal cells to human IBC cells upon introduction into the murine mammary gland results in tumors that better recapitulate the histologic features of IBC [60••]. A significant amount of investigation in IBC occurs among dogs that can develop a type of breast cancer with many clinical features similar to human IBC. These canine cancers are tightly linked to the estrus cycle, suggesting an important role for the hormonal milieu in the initiation of this disease [61, 62].

In addition to cell line models, IBC tumor emboli can be cultured in vitro under conditions in which only emboli from IBC survive [63]. This method has generated important insights into the pathogenesis of IBC including a role for RhoC GTPase-dependent amoeboid movement in mediating invasion, in a manner that can be disrupted by TGF β [63]. Recently, organoid technology has been used to grow human breast cancers [64]. We have also found that IBC tumors can be grown using this method, resulting in the preservation of molecular features of IBC, and enabling comparison between IBC and non-IBC tumors and modeling of interactions between tumor cell clusters and stromal cell types in vitro [65].

Additional studies have focused directly on patient samples, using different technologies to search for molecular features that are unique to IBC. Although attempts to identify an RNA expression signature unique to IBC have resulted in the identification of genes of interest in patient samples, including those that correlate with response to therapy, gene expression signatures of IBC overlap with those present in non-inflammatory breast cancers [66••, 67]. Somatic tumor-associated mutations have also been studied in IBC. No unique mutation associated with IBC has been identified to date. Genes which are commonly mutated in IBC include *TP53*, *MYC*, *PIK3CA*, *HER2*, and *FGFR1*, but these genes are also frequently mutated in non-inflammatory breast cancers [68, 69].

The key role of stromal cells in IBC pathogenesis has also suggested that a permissive microenvironment within the breast may play a role in the development of IBC [70]. Several studies have focused on key differences in the

microenvironment of IBC. Analysis of normal breast tissue adjacent to areas of inflammatory breast cancer clusters has found an increase in cells possessing stem cell markers such as CD44, CD49f, and CD133/2, as well as macrophages associated with the marker CD68 [71••]. Lower pretreatment mast cell density in inflammatory breast cancer tissue, as well as more stromal tumor-associated lymphocytes, has been found to correlate with response to NST [72]. Intriguingly, PDL1 expression is also frequent in IBC and is predictive of disease response to NST [73••]. Differences in infiltrating immune cells in IBC versus non-IBC, such as in tumor-associated macrophages and CD4⁺ T cells, among others, support the need for further research and have generated interest in clinical trials of immunotherapies in IBC [74–77].

There are also notable molecular features of the IBC cells themselves. Inflammatory breast cancers contain a significant component of cells which have characteristics of progenitor cells and can be identified as being CD44⁺ CD24⁻, ALDH1⁺, or CD133⁺ [30, 78]. There are also a number of signaling pathways which play important roles in the pathogenesis of IBC, such as the RhoC GTPase, EGFR, JAK2/STAT3, and VEGF receptor family and angiogenesis pathways [30, 79–82]. Activation of these pathways critically affects the ability of IBC cells to grow and survive, invade lymphatics and blood vessels, and disseminate locally and distantly. Many of these pathways converge on two key concepts in IBC: (1) an increase in stem cell markers both in adjacent normal tissue and within IBC tumors, and (2) the importance in tumor invasion and lymphangiogenesis as early mediators of inflammatory breast cancer growth and dissemination.

Based on these findings and research into IBC, one can develop a model of the multiple factors that contribute to and are necessary for the development of IBC. Alterations in signaling pathways promote the development of an aggressive breast cancer. Early in the disease course, tumor emboli develop, invade, and block local lymphatic vessels, leading to tissue damage and immune infiltration which further promotes tumor growth. These changes occur in the background of a permissive stromal microenvironment that develops due to a combination of genetic and environmental exposures, and likely contributes to IBC dissemination. This combination of events leads to breast cancer with a high propensity for rapid growth and early metastasis, and supports the ongoing need for active investigation into this disease.

Conclusions

IBC is a rare but highly aggressive subtype of breast cancer associated with increased mortality rates compared with LABC. Trimodality therapy with neoadjuvant systemic therapy, modified radical mastectomy, and post-mastectomy radiation therapy remain the standard of care, but new clinical trials

focus on investigational agents that can augment response to therapy. New insights into aspects of IBC development and biology, including intrinsic properties of the tumor cells, tumor emboli, and the role of the microenvironment, will pave the way for new therapies for this disease.

Compliance with Ethical Standards

Conflict of Interest Jennifer M. Rosenbluth declares that she has no conflict of interest.

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Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors. If this does pertain to clinical trials for IBC, Dr. Overmoyer has designed these studies which are mentioned in the article.

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