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Inflammatory Breast Cancer: A Panoramic Overview

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ABSTRACT

Inflammatory breast cancer (IBC) is a unique breast cancer with a highly virulent course and low 5- and 10-year survival rates. Although IBC only accounts for 1-5% of breast cancers it is estimated to account for 10% of breast cancer deaths annually in the United States. The accuracy of diagnosis and classification of this unique cancer is a major concern within the medical community. Multimodality treatment includes preoperative chemotherapy, mastectomy, and radiation therapy is the therapeutic mainstay and has been shown to improve prognosis. The potential for inaccurate diagnosis and misclassification in cases of IBC is increased by many factors. This includes the misleading initial symptoms of IBC. The early signs of IBC will present in women who have inflammation of the skin of the affected breast, as well as red or purple coloration of the inflamed area. Molecular studies have shown unique signature genes that are hallmarks of IBC. The current article reviews multiple aspects of primary inflammatory breast cancer.

Keywords: Inflammatory breast cancer; metástasis; tumor emboli; dermal lymphatics; stem cells

Introduction

Primary Inflammatory Breast Cancer (IBC) is an unusual and highly aggressive form of epithelial breast cancer[1-3]. This breast cancer subtype is characterized by rapid progression and poor prognosis: the disease is mainly diagnosed at stage IIIB-C or IV with a 5- and 10-year disease-free survival rates of 38% and 18%, respectively[3-5]. Although IBC is estimated to account for 1-5% of breast cancer annually it the United States, it is thought to account for nearly 10% of breast cancer deaths[6, 7]. Overall survival of IBC patients is significantly less than non-IBC patients when diagnosed with distant metastases[8]. Younger women across all ethnicities with an average age of approximately 55 years are especially affected by IBC[9]. The term "inflammatory" is due to the clinical presentation of this disease. IBC patients present with several skin changes such as erythema, edema and peau d'orange, which resemble an infection and was first coined in 1924 by Lee and Tannenbaum[10]. The presentation and prognosis derive from the fact that IBC patients do not have a solid tumor. Instead, they present with intralymphatic tumor emboli that form sheets and cords in the dermal lymphatics of the breast[4, 5]. Patients who have undergone treatment, typically surgery, for non-inflammatory breast cancer can recur with secondary inflammatory breast cancer[11]. Typically,

primary and secondary IBC are distinguished by a short history and sudden onset of the skin changes mentioned above versus skin changes that occur after a long history of non-inflammatory breast carcinoma.

Current Clinical Challenges

A challenging characteristic of IBC to physicians is the lack of a collective tumor mass. Instead of a solid mass, the tumor appears as sheets or cords throughout the breast, thus mammography is typically not useful for diagnosis[5]. The best way to confirm a diagnosis of IBC is through a skin biopsy of the affected breast [12]. Another hallmark characteristic of IBC is how the tumor cells invade the dermal lymphatic tissue of the breast. This leads to the formation of tumor emboli, which have the ability to spread throughout the body[4, 5]. IBC tumors are diagnosed as T4d tumors, but in about 1/3 of cases are found after the tumor has formed distant metastases[4, 13].

The need for accurate diagnosis of IBC becomes increasingly important when considering how the cancer can become metastatic within 6 months of diagnosing the initial symptoms[14]. The risk for misdiagnosis of IBC is unusually high and increased by many factors. One factor being that the clinical and pathological symptoms does not exist uniformly in all cases of IBC[12]. Some IBC patients present with both breast inflammation and dermal lymphatic invasion, while other IBC patients may only have one of these symptoms. Another complicating factor is that IBC is not diagnosed by analysis of histopathology characteristics, but instead is based on the discovery of the previously mentioned combination of clinical symptoms[12].

The current consensus in the field is that IBC is not only phenotypically different, but also molecularly different from other forms of breast cancer[1, 2, 15]. The study conducted between multiple research groups in the International Inflammatory Breast Cancer Consortium has found a 75 gene signature profile that is closely associated with IBC[2]. Therefore, both physicians and pathologists must think of IBC separately from other forms of breast cancer.

Until the late 1990's patients diagnosed with IBC were being treated similarly to Locally Advanced Breast Cancer (LABC) patients. It became clear that surgery and radiation treatment had little effect on the progression of IBC[16]. The discovery that lymphatic invasion and distinct metastasis occur during initial presentation led to the thinking of IBC as a systemic disease, and not a locally advanced cancer.

A Community Cancer Center Surgeon's Perspective

Physicians and surgeons outside of major medical centers are challenged by IBC. Clinical symptoms of IBC are a painful, swollen red breast, with peau d'orange. However, the majority of women with those symptoms have a breast abscess or non-inflammatory locally advanced breast cancer (LABC), thus appropriate diagnosis of the disease is difficult. Treatment strategies have also changed.

Over the past 50 years, treatment has gone from surgery alone, to no surgery at all for IBC and then around 1974, surgery following induction chemotherapy[17]. In the 1960's and 1970's, guidelines prohibited surgery for IBC because of the average 4% five year survival rate and 22 month mean survival and 50% local recurrence rates[18]. Indeed, most IBC patients in the 1970's presented with totally unresectable disease. Almost half of patients with IBC have matted nodes or supraclavicular nodes at presentation[19, 20]. In the mid 1970's, when chemotherapy began to be used for breast disease, many patients were rendered resectable, and up to 33% of patients who had resections after induction chemotherapy had no residual cancer in the breast or axilla[21-23]. The use of "induction" chemotherapy resulted in a dramatic change in patterns of treatment for IBC. In the 70's, at MD Anderson Cancer Center, only 15% of IBC patients received surgery. In the 80's, 99% received surgery, and that pattern has persisted[17]. Since one third of patients have no cancer cells in surgical specimens after induction chemotherapy, some have questioned whether surgery is necessary after complete clinical response to chemotherapy. Li et al reviewed results of 4 studies, and found distinctly better 5 year disease free survival and 5 year overall survival in patients receiving surgery than in patients not receiving surgery[24].

Both the National Comprehensive Cancer Network and the Consensus Statement from 2008 International Expert Panel recommend modified radical mastectomy for IBC (if there is clinical response to induction chemotherapy[12, 25]. Breast conserving therapy has no role in IBC, because of documented 61% local failure rate[26]. Margins of resection must be clear and all secondary skin changes must be removed. Post-operative radiation is important, but it cannot compensate for failure to achieve clear margins. Sentinel lymph node biopsy is not recommended for patients with IBC, based on a 40% false negative rate in a small (8 patients) series by Stearns[27].

Because of the very high doses of radiation recommended post operatively in IBC (66Gy, often given in BID fractions), IBC patients are also discouraged from having immediate reconstruction[3, 12]. Cristofanilli has shown that the biologically distinct entity, IBC, has a 5 years local recurrence rate of 15.1% versus 6.6% rate for non-IBC LABC[28, 29]. There is very little that can be done when local recurrence occurs in IBC, and it is emotionally devastating for the patient, the family and often for the treating team.

Incidence and Risk Factors

Although the occurrence of IBC is infrequent, estimated at 1-5% of all breast cancer cases, the number of diagnosis have doubled between 1975 and 1977 and 1990 and 1992[16,

[30]. The number of breast cancer cases since 1975 have rose steadily, but the number of IBC cases has risen 50% while non-IBC cases have increased only 25%[30, 31]. However, in a survey of the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) data from 1992-2009, the incidence of IBC remained stable[9]. Additionally, IBC is found in younger women when compared to other forms of breast cancer (mean age of 62 years), with a mean age of diagnosis at 57 years[16, 30-33]. IBC has been diagnosed in girls as young as 12 years old[34]. African-American women are diagnosed with IBC at a significantly higher rates than white women of both Hispanic and non-Hispanic origins[32]. According to the SEER program, among both Caucasian and African American women IBC patients were younger at diagnosis than non-IBC patients and among those with IBC, African American women tended to be younger than white women with an average age of 52 years old[9, 16, 31]. This trend continues when comparing the higher diagnosis rate and lower mean age of Hispanic women compared to non-Hispanic white women. In recent studies it has been found that Hispanic women have the lowest mean age of diagnosis of 53 years[32]. Arab-Americans have been found to have a diagnosis of IBC in 1.7% of all breast cancer cases, and this is higher than the 1.3% diagnosis in breast cancer cases of Caucasian women[35]. The population with the lowest occurrence of IBC is Asians with 1.2% of breast cancer cases[35].

There are several discreet risk factors that have been established for IBC[36, 37]. Reproductive risk factors are very prevalent for IBC[38]. It has been found that women who have an earlier age of menarche, and earlier birth of first child are at a higher risk of being diagnosed with IBC[38, 39]. Furthermore, it has been discovered in a study that breast-feeding exceeding duration of 24 months increases the risk of IBC diagnosis[40]. This is enigmatically opposite for cases of non-inflammatory breast cancers[36, 41]. Menopausal status can also affect IBC risk[42]. One example is how obesity has been uncovered to be a risk factor for IBC only in pre-menopausal women[42, 43].

As stated above, the estimated number of IBC cases diagnosed annually in the United States is 1-5% of all breast cancer cases[44]. The percentage of IBC cases is significantly higher Northern Africa[45, 46]. In Tunisia, it has been reported that IBC is estimated to be 5-7% of all breast cancers in the country[47, 48]. Also, in a population-based study Egypt reported that IBC represented 11% of all breast cancers[48]. The confounding deviation of incidence rates between countries may be caused by different diagnostic tools, definition of diagnosis, and varying risk factors in each region.

Misdiagnosis

The exchange of information and data between countries regarding IBC is complicated by of the unique and unusual presentation of IBC. The standards that a diagnosis must meet to be registered in databases as a case of IBC have changed multiple times over the past few decades[16, 30, 31]. The International Classification of Diseases for Oncology in 2007 stated that a diagnosis should only be registered as IBC when dermal lymphatic invasion has occurred, and the pathologist report has confirmed specifically the presence of an inflammatory carcinoma[19]. In 2004 the American Joint Cancer Committee (AJCC) characterized the diagnosis of IBC by the peau d'orange, skin erythema, and edema. The AJCC did not require the discovery of a mass underlying most of the breast for a diagnosis to be registered as IBC[19]. In December 2008 at the first international IBC consortium meeting a consensus statement on diagnosis was formed. This was between expert physicians from throughout the world[12]. The lack of a uniform definition for the diagnosis of IBC leads to unreliable statistics on the number of IBC cases around the world. Utilizing the clinical criteria for IBC a study found that 8.1% of the breast cancer cases at a comprehensive care center in Detroit, Michigan[49]. This figure was reached without the requirement of dermal lymphatic invasion being present. This figure establishes that IBC is underestimated in the United States, but when using other definitions for IBC this figure can vary widely.

The key to increasing the accuracy of diagnosis and classification of IBC may be continuing medical education (CME) within the medical community. The largest obstacle IBC patients face is how unfamiliar general and gynecological physicians are with the initial symptoms of IBC. It has been found that a general physicians misdiagnoses over 90% of women with IBC during their initial evaluation[6]. As discussed at first international IBC consortium meeting, many physicians and breast specialists unaware of IBC, mainly because of its classification as a rare form of breast cancer[12]. Underreporting of IBC is caused when small cancer centers and community hospitals often list cases of IBC generically as, "Breast Cancer" on pathology, patient records, and death certificates. Part of this may stem from the fact that there is currently no insurance code for IBC. The generic ICD10 code is used for IBC and all other forms of breast cancer. This misclassification of IBC contributes to the underreporting of IBC, and this leads to a lack of acknowledgment by the medical community. Thus, demonstrating a clear need for continuing education about the symptoms of IBC to physicians. The time lost by misdiagnosis or misclassification of IBC hampers the chances of survival to patient who is fighting a very aggressive cancer.

Improved literacy when it comes to IBC could greatly improve the way that the disease is managed. Over the past few decades, advocacy group-led educational programs have proven to be effective in educating primary care and

gynecological physicians[50, 51]. A mandatory CME program for physicians that contains uniform information about IBC could greatly decrease the rate of misdiagnosis, similar to how CME has led to reduction in breast cancer mortality by screening mammography[51-53]. The creation of a mandatory CME program may help eliminate the culture within the medical community that labels IBC as a rare cancer that will not be seen. It is widely agreed upon that CME is essential to maintain a high level of patient care in a quickly developing field of medicine[50, 54-56].

Pharmaceutical and life science companies underwrite large portions of CME courses, however this support is being cut back each year[57]. These cutbacks may have the largest impact on poor and rural communities. This would cause a major setback in IBC education because these regions are the most at risk for having physicians unfamiliar with IBC. The IBC community, particularly IBC advocacy groups, has pushed for CME education. However, without major underwriting it will be nearly impossible to reach the target audience of general practitioners and breast specialists.

Research and Progress

Since its identification and classification, IBC has remained a misunderstood and underrepresented form of breast cancer in terms of research focus. Its distinction as a distinct entity has been argued for the better part of a half-century. A detailed review of the literature over the span of 80 years starting from 1924 suggests that the infrequency of IBC coupled with its misdiagnosis, as 'mastitis' could be the main contributing factors of IBC being an understudied entity for such a long period of time[10, 58-61]. Most early investigations included individual or a small number of IBC samples incidentally, along with conventional breast cancers. These studies attempted to relate IBC to conventional breast cancers and most molecular studies focused on expression of genes and proteins associated with breast cancer. Few investigators had the insight to focus on IBC as distinct entity, however some of these types of studies were performed.

As examples, initial studies performed by Paradiso et. al. showed that the percentage of ER+ and PR+ cases were lower in IBC compared to stage matched LABC (ER+, 44% versus 64%; PR+, 30% versus 51%, respectively), pertaining to both premenopausal and postmenopausal women[62]. A similar study using immunocytochemical analysis on frozen sections of IBC samples using antibodies against pHER-2/neu, ER and PR demonstrated that all tumors were strongly pHER-2/neu positive and less than 40% were slightly ER, PR immunoreactive[63]. Expression of the ER and PR genes, c-myb, HER-2 (pHER-2/neu), c-myc, c-fos, the epidermal growth factor receptor (EGFR) gene, and pS2 (a small secreted protein isolated from MCF7 cells after induction by 17β-estradiol) were analyzed in that study. The IBC specimens were found to be positive for the EGFR gene (58%) and HER-2 (60%). Expression of c-myb was found to correlate inversely with c-erb2 expression, and was higher in non-IBC samples (63% versus 38%). Lastly, Moll et. al. screened 27 cases of IBC for the presence of p53 protein. Among the 27 cases, three groups were detected. 8 cases had higher levels of p53 in the nucleus, 9 cases had a complete lack of staining and 10 cases showed cytoplasmic staining with no nuclear staining at all. Further, sequencing analysis showed that nuclear staining was associated with mutated p53 expression and overall weak signal for wild type p53 as shown in 9 cases. The last thirty-seven percent of specimens had accumulated p53 in the cytoplasm and in almost all cases revealed wild-type p53 sequences. Therefore, the study concluded with the finding that IBC cases show two distinct mechanisms for p53 function; direct mutation and cytoplasmic sequestration of the wild type p53 protein[64].

Our laboratory was the first to directly focus on IBC as a unique entity. Performing a modified differential display technique, we identified RhoC GTPase and WISP3 as being uniquely up and down regulated, respectively, in IBC versus non-IBC tumors[65]. Since that initial study, research on IBC has progressed greatly over the past 20 years and has identified a number of unique molecular characteristics of IBC such as expression of E-cadherin, caveolin-1 and -2, ALK and a number of others[7, 15].

Recent research has focused on the origins of IBC. A major step in this direction has been the finding of evidence that supports cancer stem cells playing a role in the robustness of IBC[66, 67]. Tumor cells isolated from the SUM149 and MARY-X models of human IBC have been found to express both embryonal markers (Nestin, Rexl, and Stellar) and the classic breast cancer signature (CD44+/CD24-/CD133+/ aldehyde dehydrogenase-1 (ALDH1)+[68]. Furthermore, 74% of human IBC samples contain a genetic signature compatible with a high composition of a high cancer stem cell composition. This is significantly higher than the 44% of non-IBC cells that yielded a similar result[66].

Researchers have been attempting create a set of definitive diagnosis criteria that would allow for more accurate diagnosis of IBC. The current diagnostic process is through clinical observation of symptoms. Van Laere et.al. have presented the integration of three Affymetrix expression datasets collected through the international IBC consortium allowing them to interrogate the molecular profile of IBC using the largest series of IBC samples ever reported[2]. An IBC-unique 75-gene signature was identified. The study suggests that IBC is transcriptionally heterogeneous and the molecular profile of IBC, bearing molecular traits of aggressive breast tumor biology, shows attenuation of transforming growth factor beta (TGFβ) signaling.

The Role of TGFbeta in IBC

Although significantly different diseases, IBC and melanoma share a number of similarities both in presentation and progression. Both cancers spread via dermal lymphatics, form intralymphatic emboli and have a propensity to form cutaneous metastases[5, 69, 70]. Melanoma can also present as "inflammatory melanoma", which resembles IBC phenotypically[71]. Thus, new leads for studying cutaneous metastasis can be gathered from the melanoma literature. Studies demonstrate a role for TGFβin the etiology of melanoma cutaneous metastasis[72, 73]. TGFβ promotes tumor cell invasion and its expression can be induced in the stroma by radiation treatment[74-79]. Recent studies describe low expression of TGFβ in IBC patients, which may promote cohesive invasion of IBC cells[2, 80]. Stimulation of IBC cells with TGFβ causes altered tumor cell behavior such as stimulating single cell invasion[80]. Study have shown that cells from the emboli are able to invade in clusters via RhoC GTPase-dependent amoeboid movement and this invasion by clusters of IBC cells is disrupted by exposure to TGFβ[80].

Transcriptional analysis of EMT-associated genes in preclinical models of IBC shows loss of multiple genes within the TGFβ signaling pathway[81]. The study has demonstrated that E-cadherin expression was associated with both loss of ZEB1 and diminished expression of multiple genes within the TGFβ signaling pathway, with retention of expression of transcription factors and surface markers consistent with maintenance of a cancer stem cell phenotype, as has been reported to be a characteristic of IBC tumors. TGFβ signaling switches the activity of breast cancer cells from cohesive to single cell motility, similar to what was demonstrated by the Sahai group for non-inflammatory breast cancer[77]. Cells restricted to collective invasion were capable to lymphatic invasion but not blood borne metastasis[77]. Analysis of genes overexpressed in IBC after 4 hours of TGFβtreatment reveals a protein-protein interaction network with MYC, TP53, ESR1 and GSK3b as the most central components[2]. IBC is characterized by a pattern of elevated nuclear SMAD2 expression and attenuated nuclear SMAD3 expression. SMAD staining pattern is even more pronounced in tumor emboli. Moreover, cell motility inducing effect of TGFβ is specifically reduced in IBC cells. Also, TGF β signaling in non-inflammatory breast cancer cells is propagated through SMAD3-dependent pathways. Treatment of IBC cells with TGFβ results in activation of MYC, a known antagonist of SMAD-signaling.

Summarium

IBC is a unique disease with a distinct course of progression. Although IBC appears to have a relatively low incidence rate, it accounts for a disproportionate number of breast cancer deaths annually in the United States. Despite its dire prognosis, awareness of IBC by the public and even heath providers remains low. However, progress in both treatment and understanding the molecular basis of the disease has progressed over the past two decades. With the establishment of the Inflammatory Breast Cancer International Consortium (ibcic.org), IBC awareness, progress in research and development of new treatments and therapeutics will increase dramatically.

Conflict of interest

The authors have no conflict of interests to report.

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