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Inflammatory breast cancer (IBC): A revisit

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Abstract
Inflammatory breast cancer (IBC) is the most aggressive variant of breast cancer resulting in high morbidity and mortality. Management involves the coordination of multidisciplinary management and usually includes neoadjuvant chemotherapy, ablative surgery, and locoregional radiotherapy. The median overall survival among women with IBC is still poor. This article presents a comprehensive review of the English-language literature on IBC with emphasis on the epidemiology, diagnosis, and multidisciplinary treatment of inflammatory breast cancer.

Keywords: inflammatory breast cancer; trimodality therapy; mastectomy; prognosis; survival; triple negative

Introduction
Inflammatory breast cancer (IBC) is an aggressive variant of breast cancer, characterized by rapid progression, higher metastatic potential, and early recurrence [1]. IBC represents about 0.5 % to 2 % of all cases of breast cancer [2] but contributes to 7 -10 % of the deaths caused by breast cancer. Sir Charles Bell in 1814 published the first recorded description of IBC in the scientific literature [3]. Studies have shown that IBC is more common in North Africa as compared to other parts of the world. In Tunisia, it represents 5% to 7% of all breast cancers whereas, in Egypt, the figure is as high as 11 % [4]. The median overall survival of patients with IBC is significantly lower as compared to non-inflammatory breast cancers (NIBC) but the coordinated multidisciplinary management modalities have improved the prognosis over the past three decades [3, 5].
The present article is compiled to provide a brief overview of the clinical, bio molecular, and therapeutic specificities of IBC.

Methods
The articles in the English language, dealing with the IBC were reviewed in PubMed, Research Gate HINARI, Google Scholar, and Web of Science after search on the keywords: Inflammatory breast cancer. Time limits were set from January 2000 to June 2021. Few articles from before January 2000 were considered only due to their significant historical importance.

Definition and Diagnostic criteria
The American Joint Committee on Cancer (AJCC) guidelines define IBC as a separate clinicopathologic entity with erythema and edema occupying at least one-third of the breast surface, that can extend to the whole breast and even to the contralateral breast, the mediastinum, the upper extremities, and the neck area [6]. There are no specific molecular or pathological diagnostic criteria and hence, the diagnosis is predominantly based on clinical features.

Clinical criteria: In the 7th American Joint Committee on Cancer (AJCC) Tumor, Node, Metastasis (TNM) staging system, IBC is designated as T4d.
The criteria that must be met to reach a diagnosis of IBC include all of the following [6]:

1. Rapid onset of breast erythema, edema and/or peau d'orange, and/or warm breast, with or without an underlying palpable mass. A mass may be palpable in only one-third of cases.
2. Duration of signs and symptoms no more than three months.
3. Erythema occupying at least one-third of the breast.
4. Pathologic confirmation of invasive carcinoma.

These criteria are important to distinguish the cutaneous changes of IBC (T4d) from the skin changes that may occur in a neglected noninflammatory breast tumor (T4a-c) as the two are distinct clinicopathologic entities [7].

Pathological criteria: IBC does not have any specific diagnostic pathological criteria and IBC is mostly ductal carcinoma with a high histological nuclear grade [5]. About 17 % to 30% of IBC cases are found to be triple-negative and 18% to 60 % are epidermal growth factor receptor 2 (HER2) positive [5, 8]. Dermal lymphatic emboli are detected in approximately 75% of cases and the absence of dermal emboli does not rule out IBC. Furthermore, there is no direct correlation between the presence, number, or size of emboli and the degree of cutaneous changes [9].
Molecular criteria: Results of the recent studies state that IBC does not have a specific molecular signature though certain cell proliferation genes have been identified that may be contributing to the aggressive phenotype of IBC.
Kleer et al. found that about 80% of IBC samples are characterized by a loss of WNT1-inducible-signaling proteins 3 pathway (WISP3). These are cysteine-rich proteins believed to play a role in inhibiting the invasive potential and the angiogenesis of IBC cells in tissue cultures and animal models [10].

In some other studies, IBC cells were found to display overexpression of several genes, such as homologs of the C-guanosine triphosphatase family (RhoC-GTPase) and E-cadherin that plays a critical role in the progression of metastasis [11-12]. Activation of NF-kappaB in inflammatory breast cancer (IBC) is believed to be associated with loss of estrogen receptor (ER) expression, indicating potential crosstalk between ER and NF-kappaB. Van Laere et al. [13] examined the activation of NF-kappaB in IBC and non-IBC concerning ER and epidermal growth factor receptor (EGFR) and/or ErbB2 expression and Mitogen-activated protein kinase (MAPK) hyperactivation. They concluded that the inverse correlation between NF-kappaB activation and ER activation is due to EGFR and/or ErbB2 overexpression, resulting in NF-kappaB activation and ER downregulation [13].

Classification

In 1938, Taylor and Meltzer classified IBC into two types [14]: primary or secondary as shown in Figure 1. The natural history of primary IBC is similar to that of secondary IBC.

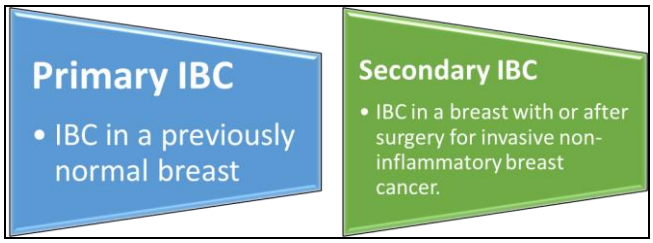

Fig 1: Classification of Inflammatory Breast Cancer (IBC)

Epidemiology

IBC is rare and accounts for 0.5 to 2 percent of invasive breast cancers diagnosed in the United States, but is reported to be more common in North Africa. The most recent estimates suggest that in Tunisia, IBC represents 5% to 7% of all breast cancers [14], 4% to 5 % in Morocco [15], while in Egypt the percentage is as high as 11% [4, 16]. However, the confounding deviation of incidence rates between regions may be due to varying risk factors in each region (e.g., westernization of the population habits) as well as the difference in the diagnostic tools and the definition of diagnosis. In the United States, as per the survey of the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) data from 1992-2009, the incidence of IBC remained stable but substantial differences have been noted in age at diagnosis, age-specific incidence rates, and survival outcomes as per the ethnicity [17]. For IBC, the mean age of diagnosis is 57 years and this is lower when compared to NIBC (mean age of 62 years) and African-American women are diagnosed at a significantly higher rate than white women of both Hispanic and non-Hispanic origins. This racial trend continues when comparing the higher diagnosis rate and lower mean age of Hispanic women (53 years) compared to non-Hispanic white women. In Arab-Americans, IBC forms 1.7% of all breast cancer cases, and this is higher than the 1.3% in Caucasian women and 1.2 % in Asians [18].

IBC is also rarely reported in men. When compared with women, men are typically older when they are diagnosed with IBC [19-20].

Risk factors

Several factors have been established to have an etiological relationship with IBC [21]. Obstetric risk factors have a role as was concluded in an extensive study by Atkinson et al. The study found that females who have an earlier age of menarche, and earlier birth of a first child are at a higher risk of being diagnosed with IBC [22]. Furthermore, it has been discovered in a recent study by Stecklein et al. [23] that a lack of breastfeeding history in parous women with IBC may predict worse prognosis and it was speculated that breastfeeding-induced alterations in the breast microenvironment may alter the aggressiveness of IBC. The prognostic significance of breastfeeding was found to be most pronounced in women with triple-negative IBC. Overweight or obese status is an important modifiable risk factor that has been linked to IBC. Chang et al. in a study conducted at the University of Texas MD Anderson Cancer Center suggested that factors associated with higher body mass index (BMI) at diagnosis may contribute to shorter IBC survival among postmenopausal women but not premenopausal women, who were found to have poorer survival regardless of body size [24].

Clinical features

Patients with IBC typically present with pain or redness associated with itching and enlargement of the breast. The erythema may be extensive and even involve the neck, upper limb, and the opposite breast. Most have axillary lymphadenopathy at presentation, and about one-third have distant metastasis. Hence, the chief complaint may be an axillary lump or a localized pain due to metastases. The onset of symptoms is rapid, ranging from weeks to a few months. Most patients give a history of initial treatment with antibiotics for presumed mastitis or abscess but with no clinical improvement. On physical examination, the breast shape might be distorted, and the skin appears like the skin of an orange (Peau d'orange), warm and thick to touch. Nipple involvement in form of crusting, erythema, flattening, blisters, or retraction may be present. A discrete palpable mass may be present only in one-third of cases. Axillary examination usually reveals lymph node involvement. Rarely, IBC may manifest in form of some paraneoplastic syndrome. Boshier et al. in 2016 reported a case wherein a patient of high-grade triple-negative IBC demonstrated clinical features of the systemic inflammatory response syndrome (SIRS) in the presence of a negative septic screen [25]. The classic and clinical description was provided by Lee and Tannenbaum in 1924 when they cited: 'The rate of growth is startling in its rapidity and often fills the entire breast in a few weeks … the overlying skin is reddened and brawny and its blush may extend far beyond the limits of the mammary gland … the inflamed area presents a distinctly raised periphery after the fashion of erysipelas. The infiltration is so marked that the examiner, with his eyes closed, can distinguish readily the sharp contrast between normal and affected tissue' [26].

Imaging modalities in IBC

Significant advances in imaging techniques in recent decades have been immensely helpful in the evaluation of IBC. These techniques help to facilitate diagnosis, characterization of the tumor, biopsy, delineation of locoregional disease in the ipsilateral and contralateral breast and the regional lymph node basins, and evaluation of

the response to treatment [27-29]. Besides, imaging may also be useful in the identification of distant metastases as it is well documented that 20% to 30% of newly diagnosed IBC have distant metastases at presentation [27].

Mammography is the current standard imaging but in IBC, the optimal compression may be limited due to pain. The various changes that may get revealed include skin thickening, nipple retraction, stromal coarsening, diffusely increased breast density, malignant-type microcalcifications, and/ or architectural disorganization. In about 25% of cases, no tumor mass is detectable [27].

Ultrasound (US) also provides valuable information by showing changes including skin thickening, parenchymal echogenicity changes, dilated lymphatic channels, solid mass, pectoral muscle invasion, focal areas of parenchymal acoustic shadowing, and lymphadenopathy (axillary and supraclavicular) [30].

Breast magnetic resonance imaging (MRI), has the highest sensitivity in the detection of cutaneous abnormalities and primary mammary parenchymal lesions. On MRI, the global cutaneous thickening and multiple small, confluent, heterogeneously enhancing masses are key features of IBC. MRI can thus be utilized as a reliable imaging modality for differentiating primary IBC from secondary IBC. A study by Le-Petross et al. [31] demonstrated that for IBC, breast MRI identifies 98% of breast parenchymal lesions, ultrasound identifies 95% of lesions while mammography identifies only 68% of such lesions. Due to its high sensitivity, MRI is highly recommended in patients suspected of IBC to reach the diagnosis and to monitor the response to chemotherapy.

Positron Emission Tomography/Computed Tomography (PET/CT) is a newer imaging modality and should be considered in the initial staging of IBC wherever available, as the technique provides valuable information on locoregional and distant disease. In a study by Carkaci et al. [29], the cases of 41 women with newly diagnosed unilateral IBC who underwent 18F-FDG PET/CT at diagnosis were retrospectively reviewed. PET/CT showed hypermetabolic uptake in the skin in 98%, in the ipsilateral axillary nodes in 90%, and the ipsilateral subpectoral nodes in 44%. 49% cases were found to have distant metastases at staging though 17% were not known to have metastases before undergoing PET/CT. Disease sites included bone, liver, contralateral axilla, lung, chest wall, pelvis, and the subpectoral, supraclavicular, internal mammary, mediastinal, and abdominal nodes.

Differential Diagnosis

Several conditions may be confused with inflammatory breast cancer and extreme caution must be exercised to avoid potentially avoidable delays in diagnosis and treatment [32].

Infectious mastitis and breast abscess: The major differential diagnosis for IBC is infectious mastitis, with or without an abscess formation. Mastitis often manifests as breast erythema, pain, and fever and can have a similar physical examination and mammographic findings. Focal lump or fluctuance are signs of an accompanying abscess. If there is no response or an incomplete response to antibiotic treatment/abscess drainage within 1–2 weeks, malignancy such as IBC should be considered.

Noninflammatory breast cancer (NIBC): It is at times, difficult to differentiate inflammatory breast cancer from locally advanced breast cancer (LABC) when it involves the skin, causing secondary erythema and skin induration.

IBC typically develops rapidly within 3 months or less, manifests in a younger patient population (average age at diagnosis, 58 years), spreads quickly, and is associated with a 20%–40% rate of distant metastases at presentation [1-2]. In contrast, locally advanced NIBC has a protracted course of onset, manifests in an older patient population (average age at diagnosis, 66 years), Progresses more slowly, and has a 10% rate of distant metastases at presentation [2]. Other malignancies like breast lymphoma or leukemia may also present similar to inflammatory breast cancer and can be differentiated with histopathological findings.

Mammary duct ectasia: This is a benign non-proliferative breast disease in middle-aged women, affecting the large duct system. When complicated with secondary bacterial infection, the cutaneous features may mimic IBC [33].

Gynecomastia: IBC in men should clinically be differentiated from gynecomastia which is a much more common but benign condition [19-20].

Dermatitis: When dermatitis (atopic, contact, dyshidrotic, and seborrheic) affects the skin of the breasts, symptoms include redness, swelling, pruritis, and pain and hence can resemble IBC. Unlike IBC, breast dermatitis is generally bilateral and tends to affect only the skin of the breast, rather than the underlying breast tissue.

Treatment

Optimal management to achieve the best local control and survival outcome of IBC requires a multidisciplinary approach and close coordination between oncologists, surgeons, and radiation therapists to execute the current standard of care via a tri-modality approach comprising of chemotherapy, surgery, and radiotherapy. The guidelines for care were approved in December 2008 at the First International Conference on Inflammatory Breast Cancer [34]. Efforts are ongoing at an international level to formulate better diagnosis, treatment, and research as the survival of patients with IBC has shown only minimal improvement, and to date, there are no therapeutic agents that specifically target IBC [35].

Nonmetastatic IBC-stage III

The treatment of Stage III (nonmetastatic) IBC is similar to Stage III noninflammatory locally advanced breast cancer (LABC) with a major difference, that breast conservation and sentinel lymph node not preferred in IBC due to the extent of the disease [36]. The standard therapy includes neoadjuvant chemotherapy, followed by locoregional treatment (modified radical mastectomy with axillary dissection) and post-mastectomy radiation [37]. For candidates not fit for surgical intervention, radiotherapy is given. The success of chemotherapy in stage III IBC is gauged by the pathologic response and the patients achieving complete pathologic response have significantly improved outcomes compared with those who do not.

Due to a high risk of early recurrence (20%) and poor overall prognosis, immediate breast reconstruction following mastectomy is to be avoided.

Metastatic IBC-stage IV

About one-third of patients with inflammatory breast cancer at the time of diagnosis have stage IV (metastatic) disease. The treatment is based on chemotherapy with/without target

therapy. Surgery and radiotherapy have a palliative role aimed at alleviation of symptoms, control of local disease, and optimization of the quality of life (QOL) [5].

Certain studies, however, do mention the possible role of aggressive combined modality management in stage IV like in Stage III. Dawood et al. [38] in their study found that the subgroup of women with stage IV disease who underwent surgery of their primary had a 51% decreased risk of death compared with those who did not undergo surgery.

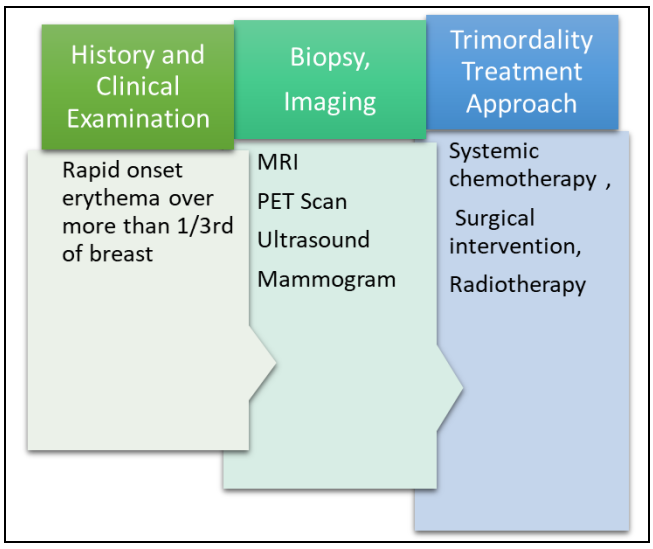

Fig 2: Management of Inflammatory Breast Cancer (IBC)

Role of Targeted therapy

In IBC, there is a significant overexpression of HER2 in 18% to 60% of cases and hence theoretically, there is potential for early HER-2 directed therapy (such as the monoclonal antibody trastuzumab) to improve the outcome in this poor prognosis cancer [5, 8, 39].

In a study by Gianni et al., the addition of neoadjuvant and adjuvant trastuzumab to systemic chemotherapy has shown improvement of the pathological complete response (pCR) rates (38% versus 19%, P = 0.001) and the event-free survival (3-year event-free survival 71% versus 56%, HR 0.59, P = 0.013) [40].

In another randomized multicentre trial, Gianni et al. found that the use of double blocking with trastuzumab and pertuzumab in the neoadjuvant setting showed some improvement in the rate of pCR when compared with that given trastuzumab. without substantial differences in tolerability [41].

The anti-angiogenic therapies (bevacizumab and semaxanib) have shown only modest clinical effects in the clinical trials and the studies with lapatinib, a tyrosine kinase inhibitor of EGFR and HER-2, failed to demonstrated efficacy [42].

Prognosis

The prognosis of patients with IBC is still dismal when compared with that of NIBC. Increased tumor size, lymph node involvement, negative hormone receptor status, and distant metastases drastically decrease the probability of survival. Trimodality therapy incorporating neoadjuvant chemotherapy, surgery, and radiation therapy has improved the relative survival rates in the last few decades through the improvement is still minimal as compared to that in the field of NIBC. In Netherlands, the relative survival for IBC significantly improved from 17.2% (1989-1997) to 30.0 % and 38.9% for the last two time periods (1998-2006: P < 0.001; 2007-2015: P < 0.001) [43].

Harris et al. [44] on analysis of data from the University of Pennsylvania, Philadelphia found the 5- and 10-year overall survival rate in Stage III to be 56% and 35%, respectively; the corresponding relapse-free survival rates were 49% and 34%. Patients achieving the state of pCR after chemotherapy with or without preoperative radiotherapy had better 5- and 10-year overall survival rates (65% and 46%, respectively) and 5- and 10-year relapse-free survival rates (59% and 50%, respectively) compared with patients without a pathologic complete response. Locoregional failure at 5 and 10 years was 8% and 19%, respectively. However, in the study, patients with disease progression on induction chemotherapy were excluded and that factor may account to some extent for the apparent positive results.

Conclusion

IBC is a unique variant of breast cancer with a distinct course of progression. Although IBC has a relatively low incidence rate in most parts of the world except North Africa, it accounts for a disproportionately high number of breast cancer deaths. Some level of progress in both treatment and understanding of the molecular basis of the disease has been witnessed over the past few decades and a tri-modality approach comprising of chemotherapy, surgery, and radiotherapy is considered as the current standard of care. However, there is a strong need for newer therapies designed specifically for IBC, and there are many questions that however remain unanswered.

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