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Inflammatory Breast Cancer; Diagnostic and Therapeutic Challenges

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ABSTRACT

Inflammatory Breast Cancer (IBC) is an aggressive form of breast cancer with dermal manifestations. This is due to the direct effect of the breast cancer cells which block the lymphatic channels of the skin. Consequentially, it appears to have an inflammatory appearance of skin overlying the breasts. Hence, it can often be confused with infection of the breast and may cause diagnostic challenges to clinicians as most of the non-inflammatory breast cancer (non-IBC) commonly presents with just a discrete breast mass. This review addresses the challenges in diagnostic pathway. Due to its aggressive nature, a rapid treatment with trimodality approach is the corner stone of effective therapy. Throughout the 90s, despite IBC incidence rose, the overall survival only improved marginally to 30-50% 5-year survival rate. We examine the current treatment and its challenges. There is an urgent need to delineate the IBC molecular changes to enable eradication with the use of IBC-specific targeted therapies. We also highlight the potential new avenues for therapeutics.

INTRODUCTION

Inflammatory breast cancer (IBC) is a rare type of breast cancer, corresponding to approximately to 1-5% of breast cancers in the western world [1,2]. In the UK, it has lower incidence than in American series [3]. It mainly affects the skin of the breast in which the tumour grows along the lymphatic channels of the skin. In most cases, the IBC cells do not necessarily form the conventional form of breast cancer, where asolitary breast lump is found. It tends to block the vessels resulting in the symptoms associated with an inflammation of the breast [4]. It is not uncommon that the breast may feel hot to touch and sometimes it may look pitted with classical description of orange peels. In the initial stage the breast may appear as ridges and raised marks on the skin overlying the breast.

Since these symptoms are not classical of non-IBC, sometimes the diagnostic process is challenging. In addition, the disease behaves very aggressively with fast progression [4]. Trimodality treatment, which includes the use of systemic therapy first, followed by surgical and radiation treatments is strongly recommended [5,6]. This review addresses the diagnostic challenges and the controversies surrounding treatments.

DIAGNOSTIC PATHWAY AND ITS CHALLENGES

The symptoms of IBC can be similar as an infection of the breast with a classical presentation of mastitis. Therefore, oedema and erythema that affects a third or more of the breast are the commonest symptoms [4]. Sometimes general practitioners have tried to treat these clinical presentations with repeated courses of antibiotics and it is

often refractory to the anti-microbial therapy. Major pitfalls of the diagnostic process are that mastitis is very uncommon in women who are not pregnant or breast-feeding and that mastitis is particularly rarer in women who are past in the menopause. IBC is attributed to the build-up of lymph in the skin of breast as the cancer cells have blocked lymphatic vessels, preventing the normal flow of lymph [4].

Other symptoms include discolouration of breast, appearing pink, reddish purple and bruised [4]. The dermal layer of breast may have ridges and appear pitted with classical description of *peaud'orange* [4]. Sometimes the symptoms would be very subtle with rapid increase in size of breast, sensation of heaviness, tenderness of breast or inverted nipple [4]. Perhaps the regional manifestation with swollen lymph node in axillary or supraclavicular regions, may be noted [4]. All symptoms can be easily confused with signs of other conditions such as an infection, injury or another form of locally advanced breast cancer [4].

Standard diagnostic tests such as digital mammography, punch biopsy of the skin with or without dermoscopy [7], fine needle aspiration and/or high resolution ultrasonography with Doppler capability of breast and regional lymph nodes are useful in establishing the diagnosis [8]. Establishing diagnosis can be difficult as often there is no lump that can be elicited during the physical examination and/or a screening mammography. Most challenging of all, most women with IBC have dense breast tissue and this makes detection in a screening mammography more difficult. Due to its aggressive nature[4], it can arise between scheduled screening mammograms. Furthermore, high mammographic breast density has been shown to have increased risk of IBC [9].

Following the diagnosis of IBC, it is routinely staged with the standard TMN and staging systems [10]. Staging tests in the form of positron emission tomography-computed tomography with or without FGD-PET [11], bone scan and magnetic resonance imaging are recommended to exclude the disease in systemic organs. Proper diagnosis and staging of IBC can help to develop the best treatment plan and estimate the potential outcome of the disease.

Challenges in staging with IBC is that the TNM classification does not distinguish patients on the basis of the presence of inflammatory criteria [10]. Evidence have shown that the patients with IBC have significantly reduced overall survival. Among those are the ones who present with distant metastasis at diagnosis (stage 4) [10], but this factor has not been taken into account by TNM classification.

Most IBC are invasive ductal carcinomas which progress rapidly, often within the duration of weeks or months, hence at diagnosis it is often at Stage III or stage IV of disease. Compared with other BC, IBC tends to be diagnosed in younger women of African heritage [12-14] or women with higher body mass index (BMI) [15]. BMI increases IBC risk irrespective of menopausal status and oestrogen receptor (ER) expression [9]. It can also occur in men usually at an older age than women [16]. Prevalence and diversity of germline genetic mutations among patients with IBC suggests the genetic component of this disease [17,18]. However, there is no clear association observed between BRCA pathogenic variants and IBC [19].

Activation of inflammatory markers such as nuclear factor-kappaB (NF-kB) is associated with IBC [20-22]. Indeed, hyperactivation of non-canonical drivers of NF-kB directed inflammation such as tyrosine phosphorylated receptor-interacting protein kinase 2 (pY RIPK2) is noted in IBC [23]. RIPK2 activity correlated with advanced tumour, metastasis, and group stage as well as BMI to indicate that RIPK2 might be a useful prognostic marker for IBC [23]. Generally, the combined receptor tyrosine-protein kinase/CD340 (ErbB2)-overexpressing and basal-like cluster is more expressed in IBC compared to non-IBC, whereas the combined luminal A, luminal B and normal-like cluster was more pronounced in non-IBC compared to IBC [24]. Conversely, IBC cells tend to behormone receptor (HoR) negative. It has been suggested that the inverse correlation between NF-kB activation and ER activation is due to Epithelial Growth Factor receptor 2(EGFR2/Her2) and/or ErbB2 overexpression and its downstream signaling that directly activates the NF-kB pathway and down regulates the ER expression [20]. Phenotypically IBC cells tend to over-express EGFR and down-express ER.

CURRENT TRIMODALITYTREATMENTS

IBC can spread quicker than non-IBC so it normally imposes treatment straight away [8,25]. The treatment includes systemic chemotherapy with anthracycline and taxane drugs if the patients are fit to undergo neoadjuvant chemotherapy [26].

This is firstly to treat and to control the disease in the breast and to consequentially reduce the swelling. Multimodal approach with the aid of neoadjuvant radiotherapy can sometimes be recommended, if surgically challenging even after the neoadjuvant chemotherapy [5,27]. Indeed, this approach has shown to have a better response to therapy and longer survival [28].

Targeted therapies may be indicated. 60% IBC express a large amount of EGFR2(Her2) and/or ErbB2 [20]. The treatment specifically designed to treat Her2-expressing IBC is trastuzumab (Herceptin) [29]. This primarily function by locking on to EGFR on the IBC cells so that the cells cannot be stimulated by EGF to grow. Herceptin is usually given as a subcutaneous injection or alternatively as intravenous infusion. It is normally started together with chemotherapy. When given together, it has been shown to be more effective at shrinking the cancer than either treatment alone. This anti-Her2 therapy is continued after the completion of chemotherapy for at least 12 months including the period during postoperative radiation therapy.

Alternatively, "HER dimerization inhibitor" such as pertuzumab which inhibits the dimerization of HER2 with other HER receptors and prevents them from signalling in ways that promote cell growth and proliferation is also indicated [30]. In fact, in context of chemotherapy, dual-Her2 targeting agent has shown significantly improved pathological complete response rate compared with trastuzumab without substantial differences in tolerability [31,32]. Pertuzumab and trastuzumab without chemotherapy eradicated Her2-positive IBC in a proportion of women and showed a favourable safety profile [31,32]. Targeting Her1 receptor with panitumumab has been studied in randomized phase 2 study in triple-negative IBC [33].

The treatment is then followed by surgery in form of modified radical mastectomy with removal of affected skin and most or all lymph nodes in axilla [26,27]. Often, the lining over the underlying chest muscles is also removed, but the chest muscles are preserved. Sentinel lymph node biopsy (SLNB) and skin-sparing mastectomy are not recommended for patients with IBC [34]. One study has indicated that SLNB was unsuccessful in most IBC patients [35]. Breast reconstruction is not usually done at the same time of mastectomy in IBC women [26]. Lately some centres have offeredan immediate reconstruction [36,37].

Due to the importance of radiotherapy and the potential complications of immediate reconstruction that may delay it, many surgeons recommend a delayed reconstruction for IBC.

IBC has higher risk of cancer in the contralateral breast than comparably staged non-IBC [38]. Absolute risks following IBC and non-IBC were 4.9 vs. 1.1% at 2 years, 6.0 vs. 2.2% at 5 years, and 7.7 vs. 6.1% at 20 years after diagnosis [38]. Some may argue for contralateral prophylactic surgery with these risks, however, these risks are probably lower than systemic relapse risk to indicate for any contralateral preventative interventions.

Post mastectomy radiotherapy to chest wall under the breast that was removed is part of multimodal therapy (if not given before the surgery) for IBC [26,27]. If there is axillary involvement, radiotherapy to regional areas such supraclavicular and intercostal spaces may be indicated [26,39]. Optimal loco-regional therapy for women with non-metastatic IBC continues to be radiation therapy [40]. Whether breast-conserving surgery could be preferable in some selected groups of patients with clinical complete response is still a debated question [39,41]. In this case, external beam radiotherapy is mandatory but how the boost to be administered has a huge question mark [39]. Excitingly the use of radio-sensitizing agent such as Veliparib (poly(ADP-ribose) polymerase inhibitor has been studied in the phase I trial [42].

The challenges with trimodality treatment is that it is often underused in treatment of IBC [26]. So far the data suggest that use of trimodality therapy is only increased marginally with time in USA [6]. There are specific barriers to the care of the patient with IBC despite that it is a significant independent predictor for survival for patients with IBC (55.4% with trimodality vs 37.3% single modality) [6]. Lately an addition to trimodality approach has been studied. For example, phase II trial of Bevacizumab plus weekly Paclitaxel, Carboplatin, and metronomic Cyclophosphamide with or without Trastuzumab is currently recruiting for IBC [43].

PROGNOSIS OF IBC

Many factors can influence the prognosis, including the type and location of the cancer, the stage of the disease, the patient's age and overall well-beings, and the extent that the disease responds to the multimodal approach of treatment [44,45]. On the whole IBC usually develops quickly and

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spreads aggressively to other systemic organs, IBC tends to poorer prognosis than non-IBC [10,46]. Having said that, survival statistics are based on large numbers of patients, however an individual prognosis could be better or worse, depending on many factors such the biology of cancer (subtype biology) and the individual well-beings.For example, recent study indicated that overall survival is related to age of menarche, metastasis at diagnosis and pathological complete response (pCR) [47]. Other has shown that negative margin surgery, systemic therapy, HoRand HER2-positive IBC as factors associated with improved outcomes [48].

Throughout the 1990s, IBC incidence rose, and survival improved modestly with 40-50% 5-year survival rate [2,27]. HoR and HER2 molecular subtypes had limited predictive and prognostic power in the IBC population [29]. One study has shown that the HoR+/HER2- subtype shows poorer survival outcome than HoR+/HER2+ subtype [49]. IBC is a heterogeneous disease similar to the conventional non-IBC [50]. Despite this, the triple negative subtype population has the worst prognosis than luminal A, Luminal B and Her2-subtype [14,51]. Lately it has been shown that CD20(+)TILs/PD-L1(+)TILs status represents an independent favourable prognostic factor in IBC and TN IBC, suggesting a critical role for B cells in antitumor immune responses [52]. This allows the exploration of using anti-PD1/PD-L1 and B cell activating immunotherapies in IBC.

Other subtype for IBC such as theprostanoid receptors such as EP3 and EP4 differentially regulated activities of the IBC cells. EP4 expression regulates the invasion of IBC, whereas EP3 controls vasculogenic mimicry and increases MMP-2 enzyme activities [53,54].

CONCLUSION

IBC can represent a diagnostic challenge to clinicians. Once diagnosed, quick and rapid treatment using multimodal approach is essential to control the progression of disease. IBC has a high risk of recurrence with poor survival despite contemporary multi-modality therapy [3].

Current evidence suggests that several major inflammatory signalling pathways are constitutively active in IBC. For example, NF-kB, COX-2, and JAK/STAT signalling systems seem to play a major role in the tumorigenesis of IBC [55]. Interleukin-6 (IL-6), tumour necrosis factor alpha (TNF-a), and gamma interferon (INF), IL-18 [56] have been shown to contribute to malignant transformation in preclinical studies of IBC, while transforming growth factor-beta [57], IL-8 and IL-1beta, as well as TNF-a appear to control proliferation, survival, epithelial-mesenchymal transition, invasion, and metastasis [55]. Targeting inflammatory axis may represent the novel therapeutic targets for treatment of IBC.Other pathways such as WNT1-inducible signalling pathway protein 3, Ras homolog gene family member C guanosine triphosphatase, EGFR, and p27(kip1) also have been studied as potential targets in IBC [58].

Molecular targets in vasculolymphatic processes (including the angiogenesis, lymphangiogenesis, and vasculogenesis) have demonstrated greater potential in IBC than in non-IBC [59]. Although loss of E-cadherin is a hallmark of epithelial-to-mesenchymal transition and may correlate with the promotion of metastasis, paradoxically, E-cadherin is overexpressed in IBC through an unknown mechanism [58]. Alternatively, targeting tumour emboli using class I HDAC inhibitor can induce destruction of IBC tumour emboli and lymphatic vascular architecture may be represent the new dawn for effectively targeting the skin involvement and rapid metastasis of IBC [60].

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AUTHORS' CONTRIBUTIONS

FI contributed toward the preparation of the manuscript. PHT provided guidance and mentorship in writing and revising the manuscript.

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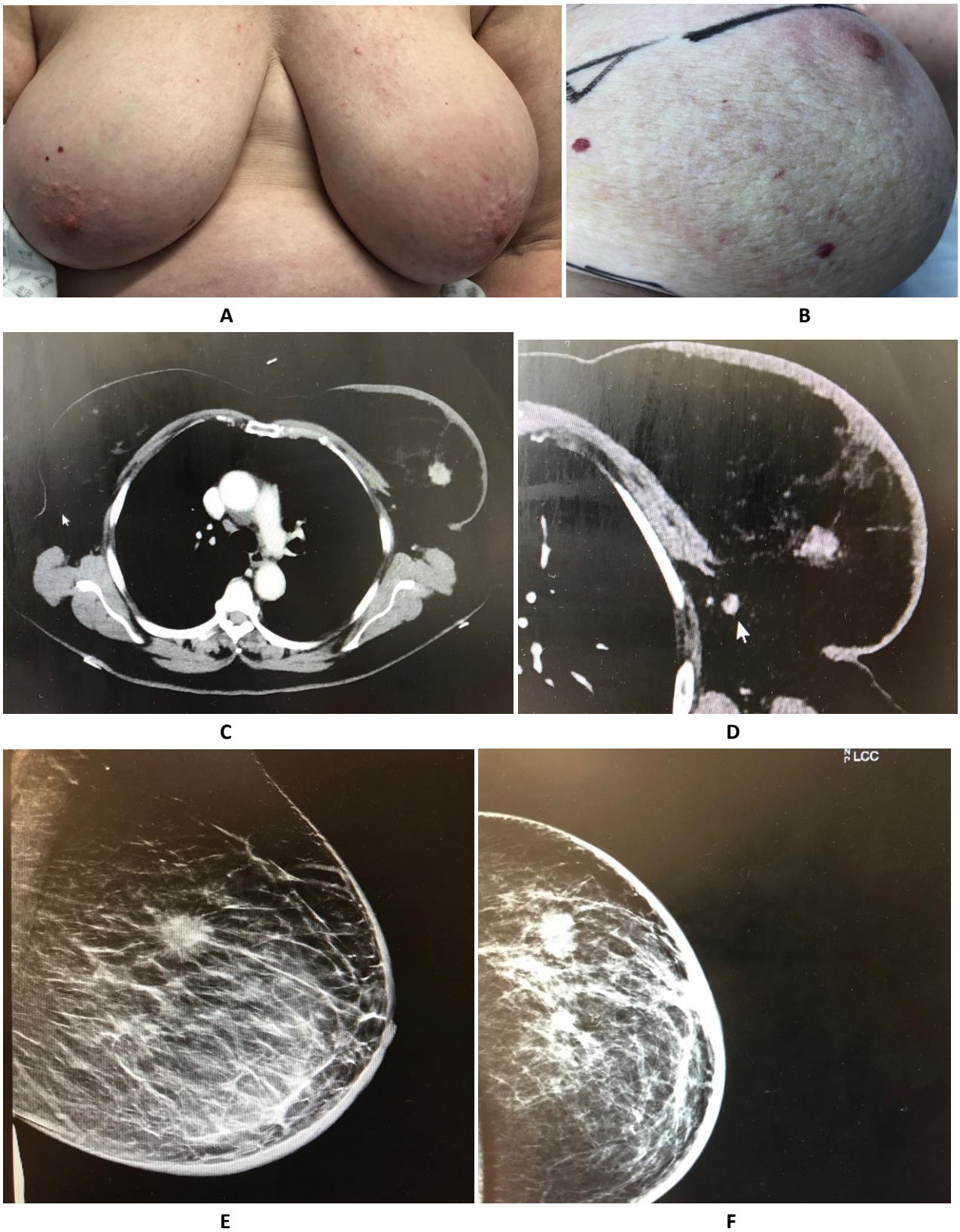

Figure 1: Inflammatory breast cancer appearance on clinical examination and imaging tests

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FIGURE 1:

The following clinical presentations on one patient with IBC are shown. A) The photography taken on the patient with left breast inflammatory breast cancer with left breast slightly more inflammatory than the contralateral breast. Dermal layer of the left breast appears to be red and inflamed. B) The zoom photography of inflammatory breast (left). The appearance of pitted skin known as peaud'orange is illustrated. C) Computerised tomography (CT) scan of thorax shows that overlying the left breast, there is a thickened dermal and subcutaneous layer. D) The zoom view of CT scan of left breast clearly illustrates a thickened layer of skin and subcutaneous tissues. E) Mammography view on the Medial Lateral Oblique (MLO) view shows alesional calcification representing the tumour and the oedematous dermal and subcutaneous layers. F) Mammography view on the cranial-caudal (CC) view demonstrates the calcified tumour and the congestion within the dermal and subcutaneous layers.

Table 1
Common symptoms
Sudden onset
Red and inflamed
Firm
Swollen
Hot to touch
Other symptoms
Ridges or raised marks on skin of the breast
Pitted skin known as *peaud'orange*
A lump or thickening in the breast
Pain in the breast or nipple
Discharge from the nipple
Younger women [2,12]
Women with African heritage [12,13]
Women with higher BMI [9,15]

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