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ARTICLE

Revealing the Aspects of Inflammatory Breast Cancer: From Potential Dangers to Therapeutic Strategies

Hoang Huynh, Nhung Le, Chau Anh Nguyen, and Phong Hoang*

Vietnam National Cancer Institute and Hanoi Medical University, Hanoi, Vietnam
*Corresponding author: hoangh.nh491@hmu.edu.vn

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Abstract

It provides a comprehensive exploration of inflammatory breast cancer (IBC), a rare and aggressive form of breast cancer characterized by rapid onset and distinctive clinical features. IBC poses significant challenges in early detection and treatment due to its aggressive nature and propensity for metastasis. The article elucidates the clinical presentation, diagnostic criteria, and underlying molecular mechanisms that distinguish IBC from other breast cancer subtypes. The research investigates current therapeutic approaches and emerging strategies tailored specifically for IBC. These include targeted therapies, immunotherapies, and innovative treatment modalities aimed at overcoming resistance mechanisms and improving patient outcomes. Special attention is given to the role of genomic profiling and biomarker identification in guiding personalized treatment strategies for IBC patients. The article discusses ongoing challenges in managing IBC, such as late-stage diagnosis, limited treatment options, and the need for multidisciplinary care approaches. It emphasizes the importance of early recognition, prompt intervention, and comprehensive patient care to mitigate the aggressive progression of the disease. By synthesizing current research findings and clinical insights, this article aims to enhance understanding of the complexities surrounding IBC and contribute to the development of effective therapeutic paradigms that improve survival rates and quality of life for affected individuals.

Keywords: Aggressive breast cancer; Biomarker identification; Diagnostic criteria; Immunotherapy; Inflammatory breast cancer; Molecular mechanisms; Targeted therapies; Therapeutic strategies

Abbreviations: BMI: Body mass index, CT: Computed Tomography, IBC: Inflammatory breast cancer, MRI: Magnetic Resonance Imaging, PET: Positron Emission Tomography

1. Introduction

Inflammatory breast cancer is a rare and aggressive form of the disease, accounting for only 1-5% of all breast cancer cases. This type of inflammatory breast cancer spreads rapidly, making early detection and prompt treatment crucial for managing its progression. Swollen lymph nodes are often one of the first noticeable signs, along with redness, swelling, and warmth in the affected breast [1, 2, 3]. Inflammatory breast cancer's exact causes remain unknown, but certain risk factors increase its likelihood, such as genetic predisposition and exposure to hormones like estrogen. Diagnosis involves a biopsy to confirm the presence of cancer cells, followed by staging to determine the extent of spread. Treatment typically involves a multidisciplinary approach combining chemotherapy, surgery, radiation therapy, and targeted therapies like trastuzumab for HER2-positive cases. Clinical trials also offer opportunities to access cutting-edge therapies (Fig. 1) [4, 5, 6, 7].

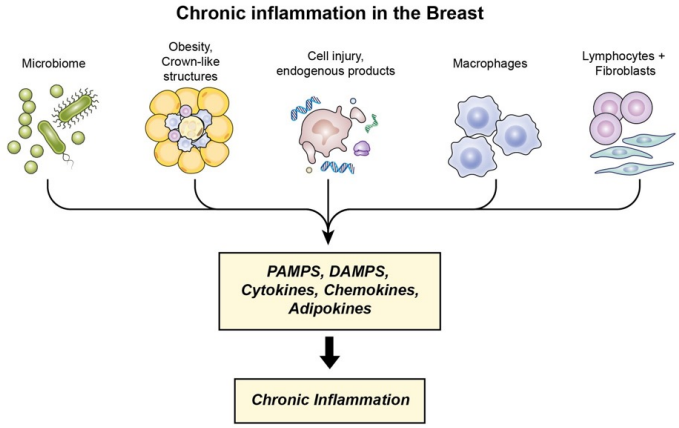

Figure 1. Chronic Inflammation in the Development of Breast Cancer.

2. Breast Cancer Basics

Inflammatory breast cancer (IBC) is a rare and aggressive form of invasive breast cancer, accounting for only 1-5% of all breast cancer cases. It differs from other breast cancers in several ways:

- IBC often does not cause a distinct lump, making it harder to detect through self-exams or mammograms.
- It tends to occur more frequently in younger women (under 40), Black women, and women who are overweight or obese.
- IBC is more aggressive, growing and spreading more rapidly than other breast cancer types.

IBC develops when cancer cells acquire genetic mutations that cause them to break away and travel through the lymphatic vessels in the breast skin. This blockage of the lymph vessels leads to the characteristic skin changes and swelling associated with IBC. The cancer can originate either in the milk ducts or the glandular tissue where milk is produced (Fig. 2) [8, 9].

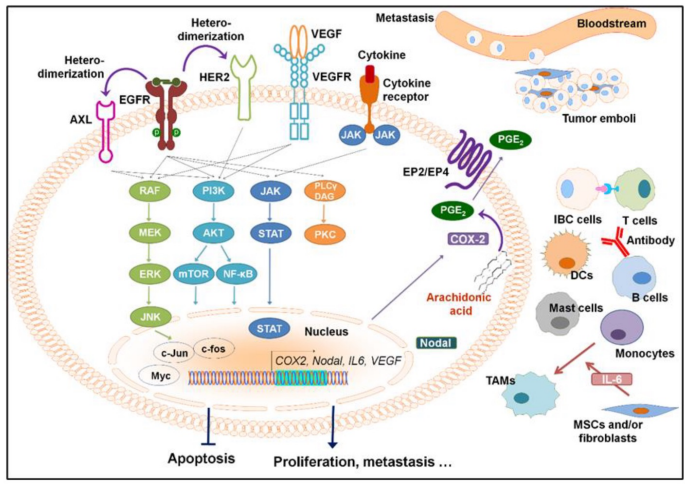

Figure 2. Overexpressed or activated signaling pathways in inflammatory breast cancer.

Unlike other breast cancers, IBC is always at least stage III when diagnosed, as the cancer has already spread to the skin. Alarmingly, in about one-third of cases, the cancer has metastasized to distant sites in the body by the time of diagnosis.

- Swollen lymph nodes
- Inflammatory
- Chemotherapy - Biopsy
- Tamoxifen
- Radiation therapy
- Clinical trials
- Trastuzumab

2.1 Causes and Risk Factors

The exact causes of inflammatory breast cancer (IBC) remain unknown, but several risk factors have been identified that increase an individual's likelihood of developing this aggressive form of breast cancer.

- **Gender:** Being female is a major risk factor, as women are much more likely than men to get IBC.
- **Age:** IBC is more frequently diagnosed in younger individuals, typically those in their 40s and 50s.
- **Race:** Black women have a higher risk of developing IBC compared to white women. The incidence and mortality rates of IBC are higher among Black women, and they tend to be diagnosed at a younger age [10, 11, 12, 13].
- **Body Weight:** Being obese or having a high body mass index (BMI) increases the risk of developing IBC [14]. Obesity is considered an independent risk factor for IBC [15].

Other potential risk factors that require further investigation include:

- Viral infections
- Chronic inflammation
- Younger age at first live birth
- Smoking
- Breastfeeding history [16]

Interestingly, inherited genetic mutations and family history have not shown a clear association with IBC [17, 18]. While a family history of breast cancer in general may increase the risk, no specific genetic mutations or changes have been identified for this type of breast cancer [19]. It's important to note that the risk factors for IBC are largely the same as those for other forms of breast cancer, but the specific factors that can raise the risk of developing IBC are not yet fully understood [20, 21].

3. Signs and Symptoms

Inflammatory breast cancer (IBC) is a rare and aggressive form of breast cancer that presents with distinct symptoms that differ from other types of breast cancer. The onset of symptoms is rapid, often occurring within a few weeks or months. The primary signs and symptoms of IBC include (Fig. 3):

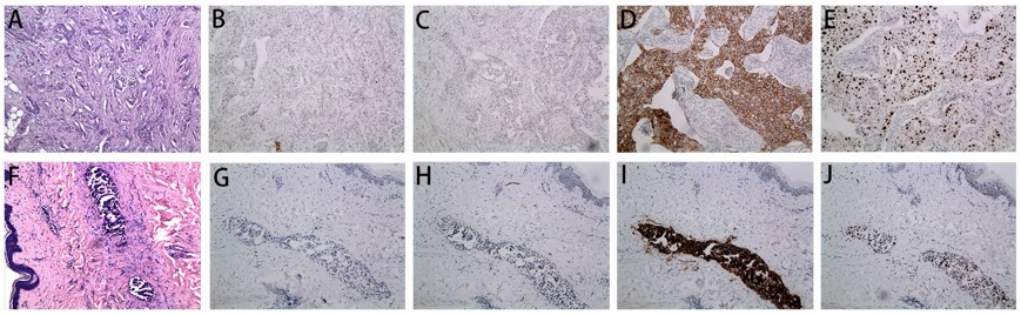

Figure 3. Microscopy examination of the breast specimen.

- **Breast Swelling and Redness:** One of the most noticeable symptoms is sudden and significant swelling, redness, and warmth in the affected breast. The redness can cover up to one-third or more of the breast's surface area.
- **Skin Changes:** The skin of the affected breast may appear thick, pitted, or ridged, resembling the texture of an orange peel (a condition known as "peau d'orange"). This is caused by the blockage of lymph vessels by the cancer cells.
- **Nipple Retraction or Inversion:** The nipple may become inverted or retracted, pulling inward towards the breast.
- **Breast Tenderness or Pain:** Some women may experience tenderness, heaviness, or a burning sensation in the affected breast.
- **Enlarged Lymph Nodes:** Swollen or enlarged lymph nodes under the arm, above the collarbone, or near the breast may be present, indicating the spread of cancer cells.

It's important to note that IBC often does not cause a distinct lump or mass in the breast, which can make it challenging to detect through self-exams or mammograms. Additionally, the symptoms can resemble those of a breast infection or injury, leading to potential misdiagnosis or delayed diagnosis [22, 23, 24]. The diagnostic criteria for IBC include:

1. Rapid onset of breast erythema (redness) and edema (swelling)
2. Peau d'orange appearance of the skin
3. Pathologic confirmation of invasive carcinoma

For a diagnosis of IBC, symptoms must have been present for less than six months, and the erythema (redness) must cover at least one-third of the breast's surface area [25, 26].

4. Diagnosis and Staging

Inflammatory breast cancer (IBC) is diagnosed through a combination of clinical examination, imaging tests, and a biopsy to confirm the presence of cancer cells. Here's how the diagnostic process typically unfolds (Fig. 4) [27]:

1. **Physical Examination:** During a physical exam, the doctor will look for signs of IBC, such as breast swelling, redness, warmth, and skin changes like the "peau d'orange" (orange peel) appearance.
2. **Imaging Tests:**
   - **Mammogram:** While IBC may not always show up clearly on a mammogram, it can help detect any abnormalities in the breast tissue.

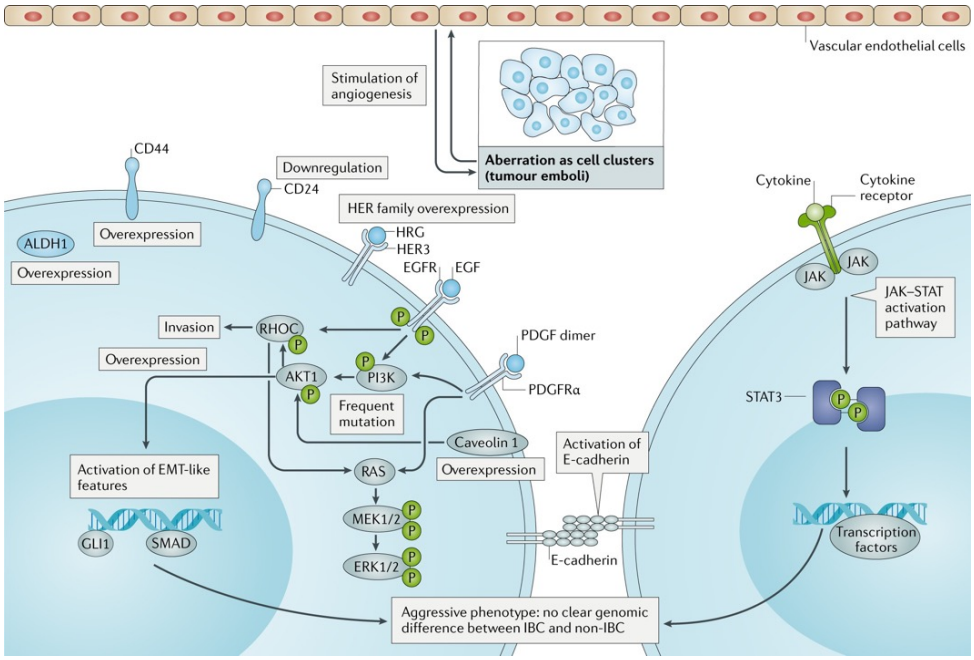

Figure 4. Diagnosis and Staging.

- **Ultrasound:** An ultrasound can help distinguish between solid masses and fluid-filled cysts, and can also guide the biopsy needle to the appropriate area.
- **Magnetic Resonance Imaging (MRI):** An MRI can provide detailed images of the breast and surrounding tissues, helping to determine the extent of the cancer's spread.
- **Positron Emission Tomography (PET)/Computed Tomography (CT) Scan:** A PET/CT scan can help detect if the cancer has spread to other parts of the body, such as the lymph nodes or distant organs.

3. **Biopsy:** A biopsy is essential for confirming the diagnosis of IBC. During a biopsy, a small sample of breast tissue is removed and examined under a microscope for the presence of cancer cells. The biopsy sample is also tested for hormone receptor status (estrogen and progesterone receptors) and HER2 protein expression, which can help guide treatment decisions [28, 29].

Once IBC is confirmed, the next step is staging, which determines the extent of the cancer's spread. All cases of IBC are classified as at least stage III (T4dNXM0) because the cancer has already spread to the skin. If the cancer has metastasized (spread) to distant organs or lymph nodes, it is classified as stage IV [30, 31, 32].

It's important to note that IBC can be challenging to diagnose, as it may not always present with a distinct lump or mass, and about one-third of women with IBC have metastatic disease at the time of diagnosis. Prompt and accurate diagnosis is crucial for initiating appropriate treatment and improving outcomes [33, 34].

5. Treatment Options

The treatment of inflammatory breast cancer (IBC) typically involves a multimodal approach combining various therapies, including chemotherapy, surgery, radiation therapy, targeted therapies,

hormone therapy, and immunotherapy. The specific treatment plan is tailored based on the stage of the cancer and its molecular characteristics [35, 36, 37, 38].

1. **Neoadjuvant Chemotherapy:** This is the standard initial treatment for IBC. Chemotherapy is administered first to shrink the tumor before surgery. The goal is to reduce the tumor size and eliminate any potential micrometastases (spread of cancer cells to other parts of the body).
2. **Surgery:** After chemotherapy, surgery is performed, typically a modified radical mastectomy, which involves removing the entire affected breast and some nearby lymph nodes. The extent of surgery depends on the tumor's response to chemotherapy and the presence of any residual disease.
3. **Radiation Therapy:** Following surgery, radiation therapy is commonly used to target any remaining cancer cells in the breast area and nearby lymph nodes. This helps reduce the risk of local recurrence.
4. **Targeted Therapies:** Depending on the molecular characteristics of the tumor, targeted therapies may be included in the treatment plan. For example:
   - Trastuzumab and pertuzumab are used for HER2-positive IBC, targeting the HER2 protein on cancer cells.
   - PARP inhibitors may be used for patients with BRCA gene mutations or other DNA repair deficiencies.
5. **Hormone Therapy:** If the cancer cells are hormone receptor-positive (estrogen or progesterone receptor-positive), hormone therapy, such as tamoxifen or aromatase inhibitors, may be prescribed to block the effects of hormones on cancer cell growth.
6. **Immunotherapy:** Immunotherapy drugs, like checkpoint inhibitors, may be used to stimulate the body's immune system to recognize and attack cancer cells.

For metastatic IBC (stage IV), where the cancer has spread to distant organs, the primary treatment approach is systemic therapy, such as chemotherapy, targeted therapies, hormone therapy, or immunotherapy. The goal of treatment in these cases is palliative, aiming to prolong survival and improve quality of life [39, 40, 41]. Clinical trials are crucial for advancing IBC treatment, and patients are encouraged to consider participating in trials, especially at the time of diagnosis before starting treatment. Cancer centers like the Moffitt Cancer Center offer comprehensive treatment options, including advanced clinical trials, for IBC patients [42, 43, 44].

6. Breast Cancer Prevention

Unfortunately, there is no known way to completely prevent inflammatory breast cancer (IBC) from developing. However, there are certain measures that can be taken to reduce the risk of developing IBC, which are similar to those recommended for other types of breast cancer [45, 46]:

- **Regular Breast Cancer Screening:**Undergoing regular breast cancer screening, such as mammograms, can help detect any abnormalities early, increasing the chances of successful treatment. However, it's important to note that IBC may not always show up clearly on mammograms, making it challenging to detect in the early stages.
- **Breast Self-Exams:** Becoming familiar with the normal appearance and feel of your breasts can help you identify any changes or abnormalities early on. Report any changes, such as swelling, redness, or skin changes, to your healthcare provider immediately.
- **Limiting Alcohol Intake:** Excessive alcohol consumption has been linked to an increased risk of breast cancer. Limiting alcohol intake or abstaining from alcohol can help reduce this risk.
- **Regular Exercise:** Maintaining a regular exercise routine and staying physically active can help lower the risk of breast cancer, including IBC.

- **Maintaining a Healthy Weight:** Being overweight or obese is a risk factor for IBC. Maintaining a healthy weight through a balanced diet and regular exercise can help mitigate this risk.
- **Limiting Hormone Therapy during Menopause:** Hormone replacement therapy (HRT) during menopause has been associated with an increased risk of breast cancer. Discussing the risks and benefits of HRT with a healthcare provider and considering alternative options can help reduce this risk.

It's important to note that there are no standardized screening tests specifically designed for IBC. The best approach is to be familiar with the symptoms of IBC and report any changes or concerns to a healthcare provider promptly, as early detection is crucial for successful treatment [47, 48, 49].

Researchers continue to investigate the factors that contribute to the development of IBC, including potential preventive measures. If you have concerns about your risk of developing IBC or any form of breast cancer, it's recommended to consult with a healthcare provider or seek a consultation at a specialized cancer center like the Moffitt Cancer Center, where they offer comprehensive care and resources for breast cancer patients [50, 51].

7. Prognosis and Survival Rates

Inflammatory breast cancer (IBC) is an aggressive and rapidly progressing form of breast cancer, and its prognosis is generally poorer compared to other types of breast cancer. However, with advancements in treatment strategies, survival rates have improved, and some individuals live many years after an IBC diagnosis.

- **Overall Survival Rates:**
  - The 5-year relative survival rate for IBC in the United States is approximately 40
  - If the cancer has spread to regional lymph nodes, the 5-year relative survival rate is 54% [16].
  - If the cancer has metastasized to distant parts of the body, the 5-year relative survival rate drops significantly to 19
- **Factors Affecting Prognosis:**
  - **Stage at Diagnosis:** IBC is often diagnosed at an advanced stage, with about one-third of cases already metastatic at the time of diagnosis [52]. Early and accurate diagnosis is crucial for better outcomes.
  - **Receptor Status:** Hormone receptor-positive and HER2-positive IBC cases generally have a better prognosis compared to triple-negative or HER2-negative cases.
  - **Lymph Node Involvement:** Increased lymph node involvement is associated with poorer outcomes.
  - **Response to Neoadjuvant Chemotherapy:** Lack of response to initial chemotherapy before surgery is a poor prognostic factor [53, 54].

While IBC has a relatively poor prognosis compared to other breast cancer types, survival rates have improved in recent years due to advancements in treatment strategies and personalized, multidisciplinary care at specialized cancer centers.

- Recent studies suggest that the 5-year survival rate for stage III IBC patients is now closer to 70%, and for newly diagnosed stage IV IBC patients, it is around 50%.
- Factors contributing to improved outcomes include early and accurate diagnosis by experts, personalized treatment plans, and access to clinical trials at centers with expertise in IBC [55].

It's important to note that survival rates can vary based on individual factors such as age, overall health, and the effectiveness of the chosen treatment approach. Continued research and access to specialized care are crucial for improving the prognosis and survival rates for individuals diagnosed with inflammatory breast cancer [56].

8. Living with Breast Cancer

Living with inflammatory breast cancer (IBC) can be a challenging and emotional journey, but many patients have found strength and resilience through their experiences. One such inspiring story is that of Mary Sheskey, who was diagnosed with stage 3 IBC in 2013 (Fig. 5).

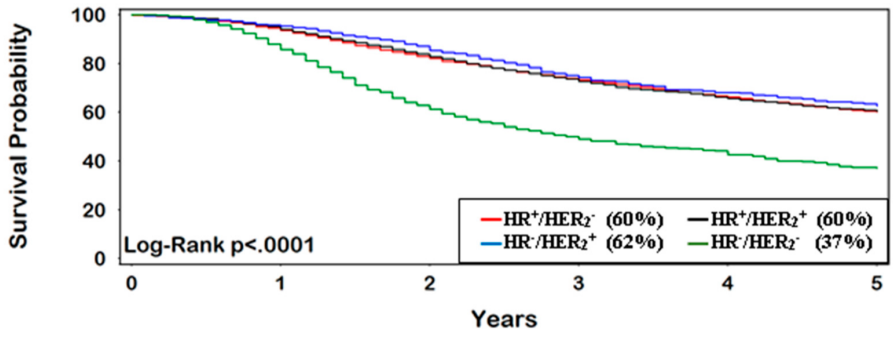

Figure 5. All patients (5-year survival).

When Mary first noticed a red, swollen area on her right breast, she initially thought it might be a sebaceous cyst. However, she knew something was not right and promptly sought medical attention. Her treatment plan was rigorous, involving:

1. 8 rounds of chemotherapy
2. Surgery to remove her right breast and 14 lymph nodes
3. 6 weeks of radiation therapy
4. An oral medication to be taken for 10 years

Despite the challenges, Mary's determination and resilience shone through. At age 61, after completing her treatment, she went back to college and obtained a master's degree in social work, driven by her experiences and a desire to help others going through cancer [57]. Mary's advice to newly diagnosed IBC patients is to find a strong support system, just as she did with a group that helped drive her to appointments and kept her company during chemotherapy. She has also shared her story publicly, speaking at the Ohio Statehouse, in the hopes of making a difference and helping others [58].

For IBC patients seeking specialized care and support, the Dana-Farber Cancer Institute offers an Inflammatory Breast Cancer Program. This program provides:

- Comprehensive care from experts in IBC
- Access to the latest research and treatment approaches
- An annual IBC Patient Forum to share scientific information and patient experiences

The program highlights the stories of IBC patients like Caroline, Nadege, Lynda, Ellen, and Trish, who have undergone various treatments and continue to live full lives [59, 60]. Experts at Dana-Farber emphasize the importance of seeking care from a cancer center that specializes in IBC and

has access to the latest research and treatment options [61]. Additionally, they recommend that patients:

- Learn about IBC to make informed treatment decisions
- Maintain close relationships with friends and family for practical and emotional support
- Consider talking to a counselor, social worker, or joining a support group to cope with the diagnosis and treatment [62].

9. Conclusion

Inflammatory breast cancer is an aggressive and challenging form of breast cancer that requires prompt and specialized care. While its rarity and rapid progression make it a daunting diagnosis, advancements in treatment strategies, including personalized multidisciplinary approaches and access to clinical trials, have improved outcomes for many patients. Seeking care from cancer centers with expertise in IBC and a strong support system can make a significant difference in navigating the journey. Early detection, accurate diagnosis, and understanding the risk factors are crucial steps in managing IBC effectively. Continued research efforts and raising awareness about this rare cancer type will further enhance our ability to prevent, diagnose, and treat it successfully, offering hope to those affected by this formidable disease.

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