Inflammatory Breast Cancer: What You Should Know

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Conflict of Interest

- I, or my immediate family member including spouse/partner, have at present and/or have had within the last 12 months, or anticipate NO financial interest/arrangement or affiliation with one or more organizations that could perceived as a real or apparent conflict of interest in context to the design, implementation, presentation, evaluation etc. of this presentation.
Objectives:

At the end of the presentation the participant will be able to:

1. Describe the epidemiology and statistics of inflammatory breast cancer (IBC).
2. Describe the current prevention, diagnosis, treatment and survival guidelines as they apply to IBC.
3. Discuss future targets to improve survival of IBC patients.
We will talk about

- Statistics
- Clinical presentation
- Differential Diagnosis
- Diagnosis
- Treatment
- Clinical trials
What is Inflammatory Breast Cancer?

- An aggressive subset of breast cancer diagnosed clinically (no current molecular definition!)
- 2-5% of total BC incidence, but ~10% of mortality
- 2 types of IBC
  - **Primary IBC** - IBC developing in a previously normal breast (MOST CASES)
  - **Secondary IBC** - IBC features (and biopsy-proven invasive cancer) on the chest wall post mastectomy for non-IBC or a recurrence with inflammatory features in a breast that already had cancer
- A palpable lump is present in only a third of IBC patients at diagnosis
- Hence the IBC Network’s slogan - “No lump still cancer” slogan

The IBC Network Foundation
IBC has been described for 200 years

- First described in 1814 by Sir Charles Bell as “a purple color on the skin over the tumor, accompanied by shooting pain”
- The term “IBC” was proposed by Lee and Tannenbaum in 1924, after this disease had many previous names
- lactation cancer, carcinoma mastitoides, mastitis carcinomatosa, acute encephaloid cancer, acute mammary carcinoma, acute brawny cancer, acute scirrhous carcinoma, and carcinoma telangiectaticum
Statistics
Demographics of IBC patients (vs non-IBC)

Information from SEER national database

- Younger median age at diagnosis
  - IBC - 58 yrs old
  - nIBC - 63-68 yrs old
- Black and Asian women are diagnosed younger
- 15-20% of IBC occurs in women with a family history of breast cancer
• IBC is different because:
  1. It presents & behaves differently - must be aware of symptoms and rapidly changing breast appearance
  2. It is more difficult to detect by routine imaging (mammograms), and...
  3. Often presents in young women prior to the recommended age for beginning screening mammography.
  4. Requires **multidisciplinary specialty care** by expert team - several critical differences in management (see later section).
Clinical Presentation
Not all symptoms need to be present for a diagnosis of IBC

Table 1. Potential Symptoms of IBC

<table>
<thead>
<tr>
<th>Symptom</th>
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<tr>
<td>Unusual, rapid enlargement of breast</td>
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<tr>
<td>Increased warmth (feverishness) of breast</td>
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<tr>
<td>Rash, redness, or blotchiness of breast skin</td>
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<tr>
<td>Swelling of lymph nodes above collarbone or under arm</td>
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<tr>
<td>“Bug bite” or “bruise” on breast that doesn’t heal</td>
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<tr>
<td>Ridging or dimpling of breast</td>
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<tr>
<td>Thickening or lump in breast tissue</td>
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<tr>
<td>Nipple retraction or flattening</td>
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<tr>
<td>Nipple discharge or change in areola</td>
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<tr>
<td>Stabbing pain, heaviness, aching, or soreness of breast</td>
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*IBC: inflammatory breast cancer.
Source: Reference 7.*
Inflammatory Breast Cancer (IBC)

- Inflammatory breast cancer is a rare and very aggressive type of breast cancer that causes the lymph vessels in the skin of the breast to become blocked. This type of breast cancer is called "inflammatory" because the breast often looks swollen and red, or "inflamed." IBC accounts for 1% to 5% of all breast cancer cases in the United States.
Peau d’orange
Lymphatic infiltration of Tumor Cells
Differential Diagnosis (Erythema)

- Inflammatory breast cancer
- Mastitis
- Abscess
- Cellulitis
- Allergic reaction
- Granulomatous mastitis
- Radiation burn
Breast Abscess
Breast Mastitis
Diagnosis: History/Physical Examination

- Inflammatory breast cancer
- Mastitis
- Abscess
- Cellulitis
- Allergic reaction
- Granulomatous mastitis
- Radiation burn
Imaging Use in IBC

- Breast
  - Diagnostic mammogram (may not observe a lump) - only 43% of IBC detected on a mammogram (Dushkin & Cristofanilli, JNCCN, 2011)
  - Most common finding = skin thickening
  - Ultrasound of breast and nodes
  - MRI

- Metastatic Workup - done because of substantial risk of regional and distant metastatic disease
  - PET/CT highly recommended if not possible then CT of chest, abdomen, pelvis
  - Bone scan
IBC has particular imaging differences

- No palpable lump in 2/3rds of women - frequent ‘webby’ appearance
- Mammograms miss >50% of IBC cases - but key observations include skin thickening, stromal coarsening, diffusely increased breast density (vs calcifications or a discrete lump in most breast cancers)
- High rate of abnormal/enlarged lymph nodes in axilla or superclavicular region - most easily detected by ultrasound
Mammogram: Skin Thickening
Mammogram: Inflammatory Breast Cancer
Mammogram/Ultrasound: Inflammatory Breast Cancer

A

B

C

D
Diagnostic Alternatives
Diagnostic Biopsies

- Skin Punch Biopsy
  - Lesion
  - Skin
  - Fat
  - Area to be removed
  - Skin sample is removed
  - Epidermis
  - Dermis
  - Subcutis
Incisional Biopsy
Diagnostic Biopsies

- US–guided Core biopsy
US–guided FNA biopsy of Suspicious Axillary Nodes
**IBC: Pathology**

- **IBC must be confirmed by a core biopsy so that enough tissue is obtained for biomarker analysis (ER, PR, HER2)**
- **Recommend at least 2 skin punch biopsies to determine presence of lymphovascular emboli (see later slides). Try to sample the areas that are most discolored.**
- **ER, PR, and HER2**
  - Testing must be done to determine potential treatment
  - ER and PR tested via immunohistochemistry (IHC)
  - HER2 tests either by IHC or FISH (fluorescence in situ hybridization). If results fall inside of a ‘grey’ zone, then the other test is performed by reflex.
Examples of ER staining patterns

Estrogen receptor staining = brown, in the nucleus

- Negative
- Negative
- Borderline/equivocal (should test by FISH to confirm)
- Positive - may benefit from Herceptin

HER2 staining is brown and on cell surface
IBC molecular subtypes

- Similar to breast cancer as a whole, IBC can be ER, PR and/or HER2+.
- Difference in proportions:

<table>
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<tr>
<th>IBC</th>
<th>nonIBC</th>
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<tr>
<td>ER/PR+ - ~ 50%</td>
<td>ER/PR+ - ~ 60-70%</td>
</tr>
<tr>
<td>HER2+ - ~ 40%</td>
<td>HER2+ - ~ 15-20%</td>
</tr>
<tr>
<td>TNBC - ~ 30%</td>
<td>TNBC - 15-20%</td>
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IBC Pathology Concepts

- IBC is not a histologic subtype of breast cancer!
- Pathology report may not state “inflammatory breast cancer” since pathologically it is not possible to differentiate IBC from other invasive breast cancers
- Potential histologies include invasive ductal carcinoma (~75%), lobular, mixed ductal + lobular, medullary, small cell, large cell
- So: IBC = invasive breast cancer in the setting of the clinical symptoms described previously
Dermal Lymphovascular Emboli

- Dermal lymphovascular emboli frequently seen in IBC (50-75%) and larger than LABC, but NOT REQUIRED for diagnosis, and the presence of emboli is not SUFFICIENT for an IBC diagnosis either.
IBC Staging per AJCC guidelines: TNM

- IBC staging uses the established AJCC criteria for breast cancer
- TNM system
  - T = tumor size. IBC is always T4d regardless of size of redness
  - N = nodal status. N1-N3 depending on the number and location of clinically positive nodes.
  - M = distant metastatic sites (eg lung, liver, bone, brain etc)
IBC Staging

• By definition, T4 tumors (including IBC) are stage III.

• Non-metastatic IBC (ie breast and lymph nodes only) is always stage IIIB or IIIC (IIIB = T4N0M0, T4N1M0, or T4N2M0, IIIC = T4N3M0)

• De novo metastatic IBC is stage IV

• Stage IIIB/C patients who later develop distant metastases are not technically stage IV in cancer statistics.

• However, many clinicians tell patients they are now stage IV when discussing the goals and duration of treatment (palliative/controlling disease vs “curative intent”)

The IBC Network Foundation
IBC Staging

The IBC Network Foundation
IBC Staging

- Data from MD Anderson registry, patients given optimal treatment based on what was known at the time (ie Trastuzumab when it became available, taxanes added to chemotherapy once data showed superiority)
- TN-IBC has significantly worse outcome in IBC!
- Note that unlike non-IBC, ER/PR+ patients still do quite poorly (~compared to 90+% alive at 5 yrs)
IBC Metastasis

- IBC is characterized by a high rate of recurrence - ~50-60% by 5 years.
- Early spread of tumor cells via lymphatics and secondarily via the blood
- 2 types of recurrences
  - Local - including skin (higher than LABC)
  - Distant - many organs (bone, lung, liver, brain are most common)
- IBC vs LABC
  - More bone and soft tissue (skin and lymph nodes) locations of metastasis in IBC
  - Other visceral (i.e. organ) metastasis similar to non-IBC, and follow similar patterns by histology.
Treatment: NCCN Guidelines

Inflammatory Breast Cancer

**CLINICAL PRESENTATION**

- Clinical pathologic diagnosis of inflammatory breast cancer (IBC)
- Stage T4d, N0-N3, M0

**WORKUP**

- History and physical exam by multidisciplinary team
- CBC
- Liver function tests
- Pathology review
- Determination of tumor ER/PR status and HER2 status
- Bilateral diagnostic mammogram, ultrasound as necessary
- Breast MRI (optional)
- Fertility counseling if premenopausal
- Bone scan or sodium fluoride PET/CT (category 2B)
- Chest/abdominal/pelvic diagnostic CT (category 2B)
- Chest diagnostic CT (if pulmonary symptoms are present)
- Genetic counseling if patient is high risk for hereditary breast cancer
- FDG PET/CT scan (category 2B)

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**Response**

- Preoperative systemic therapy: anthracycline + taxane (preferred)
  - If tumor HER2 positive, HER2-targeted therapy

- No response
Treatment: NCCN Guidelines

Inflammatory Breast Cancer

**TREATMENT**

- *Response*
  - Total mastectomy + level I/II axillary dissection + radiation therapy to chest wall and supraclavicular area (plus internal mammary nodes if involved, consider internal mammary nodes if not clinically involved [category 3]) ± delayed breast reconstruction

- *Complete planned chemotherapy regimen course if not completed preoperatively plus endocrine treatment if ER-positive and/or PR-positive (sequential chemotherapy followed by endocrine therapy).*

- *Complete up to one year of HER2-targeted therapy if HER2 positive (category 1). May be administered concurrently with radiation therapy and with endocrine therapy if indicated.*

- *No response*
  - Consider additional systemic chemotherapy and/or preoperative radiation

  - *Response*
    - See above pathway

  - *No response*
    - Individualized treatment
**Myth 1: If there’s no lump, there’s no cancer**

Unlike other types of breast cancer, IBC may be present without a lump.

Symptoms can include:

- Pain or itchiness of the breast
- Redness of the breast
- Swelling or enlargement of the breast
- Swelling of the lymph nodes in the armpit or above/below the collarbone
- Thickening of the skin of the breast or ridged or dimpled skin texture
Myth 2: IBC is often properly diagnosed at its onset

- IBC symptoms are often misdiagnosed as an infection known as mastitis.
- Mastitis is treated with antibiotics.
- If symptoms don’t improve after a few days on antibiotics, you should talk to a breast surgeon about undergoing breast imaging (mammogram, ultrasound, MRI) and a breast biopsy.
Myth 3: There are no effective treatments for IBC

- There are successful treatments for IBC. It is important to identify the symptoms that could be IBC so that treatment can start quickly.
- Initial treatment includes chemotherapy, followed by surgery.
- Because IBC involves the entire breast, patients undergo chemotherapy and a mastectomy.
- Radiation treatment is used after surgery to take care of any residual cancer that may be in the chest wall or in the lymph nodes.
Myth 4: If I have a mastectomy as part of my treatment for IBC, I can’t have breast reconstruction

- Women who have had IBC can still have breast reconstruction.
- Delaying reconstruction provides the best chance for the radiation to eradicate any residual IBC in the skin and lymph nodes.
- We recommend patients wait six to 12 months before reconstruction to ensure the body heals properly and the reconstruction is successful.
Myth 5: Because IBC is rare, there is not a lot of focus on research

Dana-Farber is working hard to understand IBC and improve treatment:

- Basic scientists are investigating molecular pathways that stimulate the growth of IBC.
- Clinical trials are designed for newly diagnosed patients with IBC and patients with advanced disease.
- Clinical trials specifically target IBC and some of the important molecular pathways that stimulates the cancer's growth.
Clinical Trials

- S1207 Hormone Therapy With or Without Everolimus in Treating Patients With Breast Cancer
- This study is currently recruiting participants. (San Juan City Hospital)
- Sponsor: Southwest Oncology Group
- Collaborator: National Cancer Institute (NCI)
- Phase 3
- ER+ PR+ Her-2 neg. No metastatic disease
Frequently Asked Questions (FAQ)

- Is there a link to BRCA1/2 mutation? Should IBC patients be tested for one of these mutations?
  - Answer: Yes, BRCA1/2 mutations are found in IBC, at a similar rate as non-IBC. Genetic counseling is highly recommended to make testing decisions, using similar criteria as non-IBC (info → https://www.healthpartners.com/public/coverage-criteria/brca-testing/).

- Can men get IBC?
  - Answer: Yes. There is not a large literature, but ~0.5% of male breast cancer is IBC.
Frequently Asked Questions (FAQ)

- Can you look at my biopsy and tell me if I have IBC?
  - Answer: Unfortunately not. Your doctor should use the clinical criteria discussed in the consensus paper mentioned, and confirm the presence of invasive breast cancer to make a diagnosis of IBC.

- Can you get IBC on both breasts at once?
  - Answer: Yes, there have been some cases of bilateral IBC at the same time.
Frequently Asked Questions (FAQ)

- Can recurrences of IBC change hormone receptor status? Why?
  - Answer: Yes, it does happen perhaps 20-40% of the time in breast cancer. There are a few potential reasons including testing inaccuracy and underlying biology. Biological reasons include initial tumor heterogeneity (i.e., ER+ just means ≥1% of cells are positive) and differential response to chemotherapy/targeted therapy of different clones.

- Is IBC caused by a virus?
  - Answer: The role of viruses is unclear. There have been reports of viral DNA found in various breast cancers, but causality is difficult to prove. Some of the viruses (e.g., EBV) are highly prevalent in the US population, and yet only 1-5% of breast cancers are IBC. IBC development is likely multi-factorial, so viral infection is unlikely to be a major driver.
There is Strength in Knowledge

Inflammatory Breast Cancer

Lo que el Cáncer no Puede Hacer

Anónimo

El Cáncer es muy limitado...
No puede incapacitar al amor
No puede romper la esperanza
No puede destruir la fe
No puede destruir la paz
No puede matar a la amistad
No puede suprimir los recuerdos
No puede silenciar el valor
No puede invadir el alma
No puede robar la vida eterna
No puede conquistar el espíritu.