INFLAMMATORY BREAST CANCER: DEFINITION AND BIOLOGY

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ESMO preceptorship on breast cancer
OUTLINE

• Definition
  • Locally advanced BC
  • Inflammatory BC
• Diagnosis
• Biology
• Take-home message
LOCALLY ADVANCED BREAST CANCER

LABC corresponds either to

- T4a extension to the **chest wall** (beyond the pectoralis muscle)
- T4b ulceration, ipsilateral satellite **skin** nodules or skin edema (including peau d’orange)
- or both (T4c)
CLARIFICATIONS IN THE AJCC 8TH EDITION

• Skin involvement
  – Satellite skin foci must be macroscopically identified and separate from the primary tumor (not contiguous).
  – Direct extension into skin and skin involvement only identified microscopically are NOT categorized as pT4b. Such tumors are categorized based on tumor size.
  – In the absence of clinical findings of inflammatory carcinoma (erythema and edema involving 1/3 of breast skin), dermal lymphatic tumor emboli are NOT categorized as pT4d.
INFLAMMATORY BREAST CANCER
= a rare and aggressive variant of LABC

Clinical presentation
• T4d
• Erythema
• Swelling
• Rare (<5%) and aggressive

Morrow RJ et al Mediators of Inflammation 2017, doi.org/10.1155/2017/4754827
IBC : DIFFERENTIAL DIAGNOSIS

• This swollen and inflammatory aspect is also present in **inflammatory lesions** of the breast
  – Abscess
  – Mastitis
  – Galactophoritis

• **Metastatic carcinoma to the breast** may produce clinical signs mimicking IBC (metastatic from ovarian origin, gastric carcinoma, rarely from squamous cell carcinoma of the tonsil, and lung and pancreatic adenocarcinoma)

→ Ruled out by biopsy and clinical context
PRIMARY VS SECONDARY IBC

- “Primary IBC” = *de novo* development of IBC in a previously normal breast.
- “Secondary IBC” = development of inflammatory skin changes that mimic primary IBC either in a breast that already had cancer or on the chest wall after a mastectomy for non-IBC.
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SKIN BIOPSY

- By punch or scalpel (at least 2)
- Aiming at identifying dermal vascular invasion
HISTOPATHOLOGY

• Presence of numerous dermal tumor emboli in the papillary and reticular dermis of the skin overlying the breast
• But
  – Absent in 25% of IBC (the diagnosis is clinical)
  – In the absence of a clinical presentation of inflammatory carcinoma (i.e. erythema and edema invading 1/3 of breast skin), dermal tumor emboli ARE NOT CLASSIFIED as pT4d
• Lobular histology in only 4.5%

• Histology has no significant effect on survival outcomes in IBC patients, unlike in patients with non-inflammatory breast cancer (n-IBC), indicating the distinct biological behavior of the IBC phenotype.

<table>
<thead>
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<th>ILC 30 (4.6%)</th>
<th>Mixed 37 (5.6%)</th>
<th>IDC 592 (89.8%)</th>
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<tr>
<td>Gr 3</td>
<td>60%</td>
<td>61%</td>
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<td>Stage IV</td>
<td>47%</td>
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<td>57%</td>
<td>62%</td>
<td>76%</td>
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<td>3yrs OS</td>
<td>68%</td>
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ROLE OF NORMAL BREAST PARENCHYMA?

Pattern of broad involvement throughout the breast, but not beyond, despite absence of a clear anatomical barrier

- The unique presentation of IBC might require specific, identifiable changes in the breast parenchyma that occur before the tumour-initiating event (increased breast density, no breast feeding or interrupted BF?)
  ➔ production of CD44+ CD49f+CD133+ stem cells that are found in 100% of IBC with a unique distribution (IBC-promoting tissue) = “Primed parenchyma”?

- Difference between a local skin limitation and the highly metastatic predisposition

Inflammatory breast cancer: unique biological and therapeutic considerations

_Lancet Oncol_ 2015; 16: e568–76
IBC INTRINSIC CLASSIFICATION

- 403 pts extracted from 2010-2013
- HR+/HER2-: 36.5% - BCSM 16.3% - higher prob of bone mets
- HR+/HER2+: 20.5% - BCSM 9.8%
- HR-/HER2+: 17% - BCSM 21.7%
- TNBC: 26% - BCSM 30.5% - higher prob of lung mets

- Multivariate analysis ➔ ER and HER2 positivity associated with better survival ➔ TN subtype: poorer OS and BCSM (p< 0.05).
- 75% of IBCs belonged to aggressive subtypes (basal-like, ERBB2, claudin-low and luminal B), vs 53% of non-IBCs.
- Luminal A subtype: 19% of IBCs vs 42% of non-IBCs
- Differences in gene expression between IBC and non-IBC are dominated by the molecular subtype related differences
A genomically unstable disease with high frequency of genomic abnormalities

**TP53** (62%), **MYC** (32%), **PIK3CA** (28%), **HER2** (26%), **FGFR1** (17%), **BRCA2** (15%), and **PTEN** (15%).
High rates of activating HER3 point mutations

Infiltration by numerous CD8+/PD-L1+ lymphocytes

Immune infiltration correlated with an NGS-based estimate of neoantigen exposure (somatic mutation rate and mutant allele frequency) = iScore.

DNA mismatch repair alterations (43%) correlated with high TILS.
TAKE-HOME MESSAGES

- IBC is a rare and aggressive form of BC that remains poorly understood (role of normal breast? specific genes?)
- **Diagnosis is clinical**, numerous dermal emboli in 75% of IBC
- Under-representation of lobular cancer
- **More aggressive phenotypes** (TNBC 26%, HER2+ 37.5%, 43% HR-)
- Discriminator genes (IBC vs non IBC) are associated with cell motility, adhesion and angiogenesis
- Activated pathways in IBC can provide potential therapeutic targets in HER2/PI3K/mTOR signaling
- Neoadjuvant treatment is the standard/ radiation therapy is important
- Potential candidate for immunotherapy
THANK YOU!

Pierre Auguste RENOIR
Grand nu (« nu sur les coussins »)
1907