Triple Negative Breast Carcinoma in Magnetic Resonance Imaging: Characteristic Findings for Morphological and Dynamic Criteria

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Learning objectives

• The purpose of this exhibit
  • To demonstrate the **pathological features** of **triple negative (TN) breast cancer**
  • To review **imaging features** of triple negative breast cancer focusing on morphological characteristics
  • To identify **typical imaging features** to suggest the criteria that might predict triple negative breast cancer
Background

[Introduction]

- Breast cancer: highly heterogeneous, need for individualized therapy
- Clinical parameters
  - Tumor size and grade, lymph node involvement and patient demographics, several molecular markers: employed in routine patient care
  - Most important molecular markers
    - Estrogen receptor (ER), the progesterone receptor (PR) and the human epidermal growth factor receptor 2 (HER2)

[Immunohistochemistry subtypes]

- Immunohistochemistry (IHC)
  - Most standardized way of assessing the status of biomarkers
  - Number of positively staining cells can be estimated by the pathologist
  - Determination of HER2 protein expression status based on IHC: have a false-positive rate around 10%
    - Highly reliable analyses are essential
- ER positive tumors
  - Have characteristics of the luminal cell type, frequently responsive to endocrine treatment (such as tamoxifen or aromatase inhibitors)
- ER negative tumors
  - More similar to the basal cell type and do not respond to endocrine treatment
- Tumors with a HER2 gene amplification
  - Respond to targeted therapy, such as trastuzumab or lapatinib
- Targeted therapy for breast cancer
  - Guided in large part by the status of ER, PR and HER2
  - ER or PR for endocrine therapy
  - HER2 for anti-HER2 therapy
- Three major breast cancer subtypes
  - Triple-negative type (ER-, PR-, HER2-)
    - Aggressive clinical behavior and a poor clinical outcome
    - Associated with mutations in p53 and BRCA1
  - HER2-positive type (HER2+; ER and PR may be positive or negative)
  - ER-positive type (ER-positive, HER2-negative, PR may be positive or negative)

[Gene expression subtypes]
Analyses of gene expression profiles with cDNA microarray technology

Several subtypes with common molecular features

• Luminal A and B (both ER-positive)
• HER2-positive
• Basal-like tumors
• Luminal C and normal breast-like groups
  • Less well characterized

Luminal A>

• Most like the cells of breast cancers that start in the inner (luminal) cells lining the mammary ducts
• Estrogen receptor-positive (ER+) and/or progesterone receptor-positive (PR +)
• HER2-negative (HER2-)
• Low or moderate tumor grade
• 12-15% have p53 mutations, linked with a poorer prognosis
• The best prognosis, with fairly high survival rates and fairly low recurrence rates
• Tx.: often includes hormone therapy

Luminal B>

• Highly positive for Ki67 (have a high number of cancer cells actively dividing) and/or HER2-positive (HER2+)
• Diagnosed at a younger age than luminal A
• Tend to have poorer prognosis factors
  • Poorer tumor grade
  • Larger tumor size
  • Lymph node-positive
  • p53 gene mutations (about 30%)
• Fairly high survival rates, not as high as luminal A tumors

HER2 type>

• HER2-positive status
  • Estrogen and progesterone receptor-negative (ER-/PR-)
• 10-15% of breast cancers
• Lymph node-positive
• Poorer tumor grade
• About 75 percent of HER2 type tumors contain p53 mutations
  • Fairly poor prognosis, early and frequent recurrence and metastases
• Diagnosed at a younger age than luminal A and luminal B tumors
• Tx.: trastuzumab (Herceptin)

Basal-like tumors>
• Similar to those of the outer (basal) cells lining the mammary ducts
  • Expression of basal cytokeratins, epidermal growth factor receptor, and other basal-related genes
• Estrogen receptor-negative (ER-)
• Progesterone receptor-negative (PR-)
• HER2-negative (HER2-)
• Approximately 70% of triple negative (TN) breast cancers are basal-like (BL) tumors
• 15-20% breast cancers are TN or BL type
• More often in younger women and African American women
• Most BRCA1 breast cancers are both TN and BN type
• Often aggressive and have a poorer prognosis compared to the ER-positive subtypes
• Higher local and distant recurrence rates and early recurrence rates
• Predilection for the development of brain metastases (5 year cumulative incidence of 1.9%)

Normal breast-like>

• A less common molecular subtype of tumor
• 6-10% of all breast cancers
• Usually small and have a good prognosis
• Some researchers question whether these tumors are a distinct molecular subtype
• Unable to be classified into another subtype because the sample tested did not contain enough cancer cells

[Correlated subtypes]

• Immunohistochemical subtypes correspond roughly to the molecular subtypes

<table>
<thead>
<tr>
<th>Molecular subtype</th>
<th>Biomarker profile</th>
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<tbody>
<tr>
<td>Luminal A</td>
<td>ER+ and/or PR+, HER2-, and low Ki67 (&lt;14%)</td>
</tr>
<tr>
<td>Luminal B</td>
<td>ER+ and/or PR+ and HER2+ (luminal-HER2 group)</td>
</tr>
<tr>
<td>HER2</td>
<td>ER-, PR-, and HER2+</td>
</tr>
<tr>
<td>Basal-like</td>
<td>ER-, PR-, HER2-, and CK5/6 and/or EGFR +</td>
</tr>
<tr>
<td>Triple-negative type</td>
<td>ER-, PR-, HER2-</td>
</tr>
</tbody>
</table>
  • Correlation with basal-like breast cancer
• **HER2** (HER2+; ER and PR may be positive or negative)
  • Correlation with **HER2-positive type** breast cancer
• **Luminal A and B** (ER+, HER2-, PR may be positive or negative)
  • Correlation with **ER-positive type**
Findings and procedure details

[Mammography findings]

- Triple negative breast cancer more likely to be identified as masses
  - Round, oval, or lobular masses with indistinct margins
  - Less frequently irregular in shape
  - Less likely to have spiculated margins
  - Less frequently associated with calcifications
    - Relatively low prevalence of DCIS in the TN tumors
- Most common features
  - Circumscribed masses with no associated microcalcifications
- Mammographic features of triple negative (TN) breast cancer
  - ER-negative, HER2-negative tumors
  - Margins may be circumscribed on mammograms
  - More likely to be dismissed as benign lesions
  - Often mammographically occult
    - 18% than 9% of ER-negative HER2-positive cancers
  - Require additional imaging modalities
    - Sonography, magnetic resonance imaging (MRI) for early diagnosis
- HER2 breast cancer
  - ER-negative, HER2-positive tumors
  - More likely to be spiculated
  - Associated pleomorphic microcalcifications
- Luminal A and B breast cancer
  - ER-positive breast cancers
  - Manifest as spiculated masses
  - Speculated tumor margin may reflect such biologic features

<table>
<thead>
<tr>
<th>Characteristic Mammography findings</th>
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<tr>
<td>Luminal A and B</td>
<td>Spiculated masses with speculated tumor margin</td>
</tr>
<tr>
<td>HER2</td>
<td>More likely to be spiculated, associated pleomorphic microcalcifications</td>
</tr>
<tr>
<td>Triple negative</td>
<td>May be <strong>circumscribed margins</strong>, likely to be dismissed as <strong>benign lesions</strong></td>
</tr>
</tbody>
</table>

[Sonographic findings]

- Triple negative (TN) breast cancer
  - More likely to have circumscribed margins
• Less likely to show posterior shadowing
• Complex echoic (11%), hypoechoic (41%), and markedly hypoechoic (48%)
• May simulate benign masses
• Findings in studies
  • In the study by Dogan et al, 86% of the 44 cancers appeared as masses
    • Eight (21.1%) of the 38 masses had circumscribed margins
• Should evaluate the axillary, infraclavicular, supraclavicular, and internal mammary lymph nodes
• Macrometastatic findings
  • Cortical thickening
  • Hilar displacement
  • Hilar compression
  • Loss of the normal echogenic hilum
• Ultrasound-guided fine needle aspiration or core biopsy of suspicious lymph nodes
• Pretreatment imaging
  • Stage the regional (axillary, infraclavicular, supraclavicular, and internal mammary) nodes
  • Critical for surgical and radiation therapy planning

[MRI findings]

• Dynamic contrast-enhanced MR imaging
  • Malignant features more evident than on conventional imaging, can be used for diagnosing
• Associated findings of TN breast cancer
  • A unifocal lesion
  • Mass lesion type: round or oval mass shape
  • Smooth margin
  • Rim of heterogeneous enhancement
  • Very high signal intensity on T2-WI
    • Associated with intratumoral necrosis
• Enhancement kinetics
  • Persistent or washout enhancement patterns
  • 95 % of TN breast cancer showed a washout enhancement pattern
• DWI: reflecting the biological character of tissue
  • Characterization of breast mass
  • Treatment monitoring after chemotherapy
  • Independent of magnetic field strength
  • Does not require contrast medium
  • Performed in less than 2 min
• DWI findings
Malignant tumors usually show higher signal intensity on high b value image, resulting in lower ADC values. Detectability at DWI was not significantly different among tumor subtypes. ADC value as a quantitative assessment, significantly different among tumor subtypes. TN breast cancer showed higher ADC values. Possible explanation:

- High or very high intratumoral T2 signal intensity in TN significantly associated with intratumoral necrosis.
- Areas of tumor necrosis show a decrease in tumor cellularity: higher ADC value on DWI.

[Diagnostic clues for diagnosis]

Mammography findings:
- Margins may be circumscribed on mammograms.
- More likely to be dismissed as benign lesions.
- Often mammographically occult.

Sonography findings:
- More likely to have circumscribed margins.
- Less likely to show posterior shadowing.
- May simulate benign masses.

-> Need further evaluation: MRI

MRI findings:
- Malignant features more evident than on conventional imaging.
- Associated findings of TN breast cancer.

1. A unifocal lesion
2. Mass lesion type: round or oval mass shape
3. Smooth margin
4. Rim of heterogeneous enhancement
5. Very high signal intensity on T2-WI
6. Persistent or washout enhancement patterns
7. 95 % showed a washout enhancement pattern

[TN breast cancer management]

- Lack of a dominant oncogenic factor driving proliferation activity.
  - Hormone therapy is ineffective.
  - Treated with chemotherapy in addition to surgery and radiation therapy.
- Pathologic complete response (pCR) rate.
• 22% to anthracycline and/or taxane based-therapy with TN breast cancer
• 11% with non-TN breast cancer
• Patients who experienced a pCR
  • Excellent survival regardless of breast cancer subtype
• Patients with residual disease after CTx. with TN breast cancer
  • Significantly shorter overall and recurrence free-survival periods
• Risk of relapse and death
  • Significantly higher for patients with TN breast cancer
Images for this section:

**Fig. 1:** Patient with palpable mass in right breast and right axilla. Right mediolateral oblique view mammograms revealed oval shape, circumscribed margin mass opacities in right breast upper portion and right axilla. Benign looking center lucent calcification in right breast upper outer portion. No evidence of abnormal calcification or mass like opacity in left breast. Biopsy revealed TN breast carcinoma in right breast and metastatic mass in right axilla.

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Fig. 2: Patient with palpable nodule in right breast. About 0.8 x 1.0 cm-sized hypoechoic mass (arrow) with circumscribed margins in right breast 1 O’clock at ultrasound. Right craniocaudal mammograms revealed about 1.0 cm oval shape asymmetry with indistinct margins, corresponding to the palpable abnormality (marker). Ultrasound-guided core biopsy revealed TN breast carcinoma.

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Fig. 3: Patient with several palpable masses in right breast and axilla. About 4.7 cm-sized hypoechoic mass (arrow) with indistinct margins in right breast 9 O’clock region at ultrasound. About 3.0 cm-sized enlarged lymph node in right axilla with eccentric wall thickening, represents metastatic lymph node. Biopsy revealed triple negative breast carcinoma.

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Fig. 4: Patient with huge mass in right breast (biopsy revealed triple negative breast carcinoma). Axial contrast-enhanced T1-weighted subtraction 3-T MRI shows a 5.8 cm-sized lobular shape mass with smooth margin and rim enhancement. Fat-suppressed T2-weighted MRI shows the mass with an area of high intratumoral SI. Axial DWI MRI (b-value of 800 s/mm²) shows high intensity mass with central low signal intensity. ADC map shows the mass with peripheral low and central high signal intensity.

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Fig. 5: Dynamic phase contrast-enhanced T1-weighted subtraction 3-T MRI and CAD analysis was done. CAD analysis on dynamic image shows rim enhancement of the mass (arrow). Corresponding time-intensity curve indicates rapid initial rise and washout kinetics highly suspicious for malignancy.
**Fig. 6:** Patient with palpable mass in the right breast (biopsy revealed triple negative breast carcinoma). Axial contrast-enhanced T1-weighted subtraction 3-T MRI shows a 1.2 cm-sized lobular shape mass with smooth margin. Fat-suppressed T2-weighted MRI shows the mass with an rim area of high SI. CAD analysis on dynamic phase contrast-enhanced image shows rim enhancement of the mass. Corresponding time-intensity curve indicates type III rapid initial rise and washout kinetics.
Conclusion

[Summary]

- Three major breast cancer subtypes by immunohistochemistry
  - Triple-negative type (ER-, PR-, HER2-)
    - Correlated with basal-like breast cancer among the molecular subtypes
  - HER2 type (HER2+; ER and PR may be positive or negative)
    - Correlated with HER2 positive type
  - luminal A and B type (ER+, HER2-, PR may be positive or negative)
    - Correlated with ER-positive type
- Image findings: different findings in TN type

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MRI findings

- A unifocal lesion
- Round or oval mass shape, smooth margin
- Rim of heterogeneous enhancement
- Very high signal intensity on T2WI
- Washout or persistent enhancement patterns

[CONCLUSION]

- Nature of triple negative breast cancers among the other subtypes
  - Aggressive biology and late presentation, poor prognosis
- Can mimic lesions with a benign morphology in mammography and sonography
- Imaging recognition of TN breast cancer and other subtypes could assist in both pretreatment planning and prognosis
References


• Stuart J Schnitt. Classification and prognosis of invasive breast cancer: from morphology to molecular taxonomy. Modern Pathology. 2010;23:S60-S64.