THE PATHOLOGY OF BREAST CANCER

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Summary

Breast cancer is the most common cancer in females. It may have strong family history (genetically related). It most commonly arises from breast ducts and less frequently from lobules. Since mammary carcinoma is the most common form of breast malignancy and one of the most common human cancers, most of this chapter is concentrated on the differential diagnosis of breast carcinoma

1. Introduction

In clinical practice, a breast lump is very common. It may be accompanied in some cases by other patient’s complaints such as pain and/or nipple discharge, which may be bloody. Sometimes more than one lump is detected in the same breast, or in both breasts. Cutaneous manifestations as nipple retraction, nipple and/or skin erosion, skin dimpling, erythema and peau d’orange may also be noted; both by the patient and her physician. A lump may not be palpable in spite of breast symptoms such as pain and or nipple discharge. Cytological examination, mammography and ultrasonography in these cases may help to detect small clinically impalpable lesions such as duct papilloma, a small intraduct carcinoma, duct ectasia and others.

The pathological specimens in common practice include cytology of nipple discharge and aspirated breast cystic lesions, fine needle aspiration cytology (FNAC) of a breast lump, random or guided core biopsies, excisional or incisional biopsy, frozen section
examination, conservative, radical and simple mastectomy specimens. The pathologist should be aware that any given specimen may be further utilized for other purposes, such as immunohistochemical and genetic studies as well as research work, therefore, preservation of paraffin blocks, a representative frozen part of the specimen or unstained cytology smears has to be always considered.

Although breast lumps are far more common in females, similar non-neoplastic, benign and malignant neoplastic lumps can occur in males. However, the single most common male breast lump is gynecomastia. Breast lumps are most commonly specific to the mammary gland, but many other lumps can arise from structures nonspecific to the breast such as skin, cutaneous adenexa, adipose tissue, connective tissue, pectoral fascia and muscle.

2. Types of breast lumps

- **Ectopic mammary tissue** (within the axillary tail or within axillary lymph nodes).
- **Inflammatory and related lesions**
  - Duct ectasia
  - Fat necrosis
  - Abscess
  - Granulomatous mastitis
  - Others
- **Benign proliferative breast disease**
  - **Fibroadenoma**
  - Adenoma
  - Nipple adenoma
  - Intraductal papilloma
  - Adenosis
    - Blunt duct adenosis
    - Sclerosing adenosis
    - Nodular adenosis
    - Microglandular adenosis
  - Fibrocystic disease
  - Fibrocystic disease with atypical ductal and/or lobular hyperplasia
- **Carcinoma**
  - **In situ carcinoma**
    - Lobular carcinoma in situ (LCIS): Usually an incidental finding
    - Duct carcinoma in situ (DCIS): Low and high grades.
    - Special variants as comedo & papillary
  - Invasive carcinoma:
    - Invasive ductal carcinoma (IDC): Not otherwise specified (NOS)
      - Special variants.
    - Invasive lobular carcinoma (ILC): Classical
      - Special variants
    - Mixed ductal and lobular carcinoma
    - Unclassified carcinoma
    - Microinvasive carcinoma
    - Paget’s disease of the breast
• **Salivary, sweat gland and myoepithelial tumors**
• **Stromal tumors** and tumor-like conditions:
  Phyllloides tumor
  Vascular tumors
  Sarcomas
• **Lymphoid tumors** (lymphoma) and tumor-like conditions
• **Other primary tumors** and tumor-like conditions
• **Metastatic tumors.**
• **Male breast lumps**, most common are:
  Gynecomastia
  Carcinoma
  Myofibroblastoma
  Others (more or less similar to those of the female breast)

3. Breast carcinoma

Pathological TNM Classification (PTNM) (who 2003)

Special Considerations in TNM Staging of Breast Cancer:

• pT (primary tumor) assessment is accepted only with no tumor involving the margins.
• pT can be accepted if there is only microscopic tumor at the margin.
• pT is only a measurement of the invasive component of carcinoma. In situ component is excluded. If for example a tumor measures 6 cm composed predominantly of intraduct (in situ) carcinoma with the invasive component measuring 0.5 cm, this would be classified as pT1a.
• Microinvasion is defined as extension of tumor cells beyond the basement membrane, with no focus more than 0.1 cm in greatest dimension. When microinvasion is multifocal, the larger focus and the sum of foci is used in classification.
• Chest wall is defined as ribs, intercostal muscles, serratus anterior muscle, but not pectoral muscle.
• Skin dimpling and nipple retraction do not alter the T category
• Inflammatory carcinoma is diagnosed when there is diffuse, brawny induration of the skin with an erysipeloid edge.
• Paget’s disease is Tis and/or tumor. T classification is based on tumor size as usual.
• Cases with isolated tumor cells (ITC) in regional lymph nodes (LNs) are classified as pN0. ITC is defined as single tumor cells or micrometastases < 0.2 mm in greatest dimension.
• Regional LNs include the following ipsilateral groups:

1-Axillary LNs → Level I (low axilla): LNs lateral to the lateral border of pectoralis minor muscle.
   Intramammary LNs are coded as axillary nodes level I.
   → Level II (mid axilla): LNs between the medial & lateral borders of pectoralis minor muscle and the interpectoral (Rotter) LNs.
   → Level III (apical axilla): Apical LNs & those medial to the medial margin of pectoralis minor muscle ,excluding those designated as subclavicular or infraclavicular
2-Infracavicular (subclavicular) LNs
3-Internal mammary LNs: Nodes in the interpectorals spaces along the edge of the sternum in the endothoracic fascia.
4-Supraclavicular LNs.

- Pathological evaluation of LNs (pN) requires resection and examination of at least level I axillary LNs. Examination of one or more sentinel LNs may be used for pathological classification. If classification is used solely on sentinel LN biopsy without subsequent axillary LN dissection it should be designated (sn) e.g. pN1(sn).

**Primary Tumor (pT):**

- **pTX:** Primary tumor cannot be assessed.
- **pT0:** No evidence of primary tumor.
- **pTis:** Carcinoma in situ.
- pTis (DCIS): Duct carcinoma in situ.
- pTis (LCIS): Lobular carcinoma in situ
- pTis (Paget): Paget disease of the nipple with no tumor.
- **pT1:** Tumor ≤ 2 cm in greatest dimension.
- pT1mic: Microinvasion, ≤ 0.1 cm in greatest dimension.
- pT1a: > 0.1 cm - ≤ 0.5 cm in greatest dimension.
- pT1b: > 0.5 cm - ≤ 1 cm in greatest dimension.
- pT1c: > 1 cm - ≤ 2 cm in greatest dimension.
- **pT2:** > 2 cm - ≤ 5 cm in greatest dimension.
- **pT3:** > 5 cm in greatest dimension.
- **pT4:** Any size + direct extension to chest wall or skin as described below.
  - **pT4a:** Extension to chest wall.
  - **pT4b:** Oedema (including peau d’orange) or breast skin ulceration or satellite skin nodules of same breast.
  - **pT4c:** pT4a + pT4b.
  - **pT4d:** Inflammatory carcinoma.

**Regional Lymph Nodes (pN):**

- **pNX:** Regional lymph nodes (LNs) cannot be assessed(nor t removed or previously removed)
- **pN0:** No regional LN metastases ITC).
- **pN1mi:** Micrometastases > 0.2 mm , but ≤ 2 mm in greatest dimension.
- **pN1:** Metastases in 1-3 ipsilateral axillary LNs and/or internal mammary LNs with microscopic metastases in sentinel LN which is not clinically apparent
  - **pN1a:** Metastases in 1-3 axillary LNs; at least one larger than 0.2 cm
  - **pN1b:** Internal mammary LNs with microscopic metastases detected by sentinel LN dissection which is not clinically apparent
  - **pN1c:** pN1a + pN1b
- **pN2:** Metastases in 4-9 ipsilateral axillary LNs; or in clinically apparent (by clinical examination or imaging studies) ipsilateral internal mammary LNs in the absence of axillary LN metastases
  - **pN2a:** Metastases in 4-9 axillary LNs; at least one larger than 0.2 cm
  - **pN2b:** Metastases in ) apparent internal mammary LNs in the absence of axillary LN
metastases

**pN3:** Metastases in $\geq 10$ ipsilateral axillary LNs or in infraclavicular LNs or in clinically apparent ipsilateral internal mammary LNs in the presence of $\geq 1$ positive axillary LN or in $\geq 3$ axillary LNs with clinically negative, microscopic metastases in internal mammary LNs or in ipsilateral supraclavicular LNs.

**pN3a:** Metastases in $\geq 10$ axillary LNs (at least one larger than 2 mm), or metastases in infraclavicular LNs

**pN3b:** Metastases in clinically apparent internal mammary LNs metastases (in the presence of 1 or more positive axillary LNs), or in more than 3 axillary LNs & in internal mammary LNs with microscopic metastases detected by sentinel LN dissection, but not clinically apparent metastases

**pN3c:** Metastases in ipsilateral supraclavicular LN

**Distant Metastases (pM):**

**pMX:** Distant metastases cannot be assessed

**pM0:** No evidence of distant metastases

**pM1:** Distant metastases

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Table 1. Stage grouping

### 3.1 In Situ Carcinoma of the Mammary Gland

Most in situ and invasive tumors of the breast are believed to arise from the epithelium of the terminal ductal lobular unit (TDLU)

#### 3.1.1 Lobular Neoplasia (LN)

**Definition**

Proliferation of often loosely cohesive small cells filling and distending the acini, with or without pagetoid involvement of the terminal ducts, without basement membrane invasion. It is considered as a precursor for subsequent development of invasive carcinoma of either breast and of either lobular or ductal types.

**Clinical & Radiological Features**
- Multicentricity in 85% of patients and bilaterality in 30% of cases
- No mammographic abnormalities, except in the rare variant of LN showing necrosis and calcification

**Macroscopy**

No gross abnormality. The lesion is usually an incidental microscopic finding in surgically excised specimens.

**Histopathology**

- **Lobular Carcinoma In Situ (LCIS) and Atypical Lobular Hyperplasia (ALH)**
  
  Classification of lobular/acinar proliferation into LCIS and ALH was found to be of no prognostic significance. Haagensen (1978) suggested the designation of LN for these lesions. Bratthauer and Tavassoli (2002) proposed the term lobular intraepithelial neoplasia (LIN) and categorized it into three grades. However, this grading system is not yet endorsed.
  
  - **Cell morphology; two types (may be mixed)**
    1. Type A cells: This is the common classical type. The cells are small uniform with indistinct cell margins, sparse cytoplasm & round regular nuclei showing uniform chromatin, inconspicuous nucleoli and rare mitoses.
    2. Type B cells: Larger more atypical cells with less uniform chromatin & conspicuous nucleoli. The cells may be obviously pleomorphic (pleomorphic LN) or signet ring.
  
  - **Architectural features**
    1. Involvement of one or more lobules, with architectural preservation.
    2. Variable grades of acinar distension with type A and or type B cells
    3. Preserved basal myoepithelial component or admixture of myoepithelial cells with the proliferating neoplastic cells.
    4. Intact basement membrane (may need special stains).
    5. Frequent pagetoid involvement of adjacent ducts by neoplastic cells sandwiched between intact flattened epithelium and the underlying basement membrane; sometimes in a cloverleaf or necklace pattern.
    6. Massive acinar distension may be accompanied by central necrosis and possible calcification.
    7. Differentiation from the solid variant of duct carcinoma in situ (DCIS) may be morphologically difficult. However; DCIS may show secondary lumina or a rosette-like arrangement of cells and typically positive for E-cadherin & negative for HMWCK34BE12

- **Immunoprofile**
  1. 1-60-90% of cases are positive for estrogen receptor (ER).
  2. Expression of ERBB2 (Her 2 neu) & P 53 protein is extremely rare in classical LN
  3. Generally negative for E–cadherin & CK 5,6, positive for HMWCK34BE12
Bibliography


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