THE PATHOLOGY OF BREAST CANCER

Ali Fouad El Hindawi
Cairo University. Kasr El Ainy Hospital. Egypt.

Keywords: breast cancer, breast lumps, mammary carcinoma, immunohistochemistry

Contents

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:

Phylloides tumor
Vascular tumors
Sarcomas

- **Lymphoid tumors** (lymphoma) and tumor-like conditions
- **Other primary tumor**s 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 $\leq$ 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-Infraclavicular (subclavicular) LNs
3-Internal mammary LNs: Nodes in the interpectoral 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 $\leq$ 2 cm in greatest dimension.
pT1mic: Microinvasion, $\leq$ 0.1 cm in greatest dimension.
pT1a: > 0.1 cm - $\leq$ 0.5 cm in greatest dimension.
pT1b: > 0.5 cm - $\leq$ 1 cm in greatest dimension.
pT1c: > 1 cm - $\leq$ 2 cm in greatest dimension.
pT2: > 2 cm - $\leq$ 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 $\leq$ 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 ≥ 10 ipsilateral axillary LNs or in infraclavicular LNs or in clinically apparent ipsilateral internal mammary LNs in the presence of ≥ 1 positive axillary LN or in > 3 axillary LNs with clinically negative ,microscopic metastases in internal mammary LNs or in ipsilateral supraclavicular LNs.

pN3a:Metastases in ≥ 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

Stage 0	Tis	N0	M0
Stage 1	T1	N0	M0
Stage IIA	Tis	N1	M0
	T1	N1	M0
	T2	N0	M0
Stage IIB	T2	N1	M0
	T3	N0	M0
Stage IIIA	T0	N2	M0
	T1	N2	M0
	T2	N2	M0
	T3	N1,N2	M0
Stage IIIB	T4	N0,N1,N2	M0
Stage IIIC	Any T	N3	M0
Stage IV	Any T	Any N	M1

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. 2-Expression of ERBB2 (Her 2 neu) & P 53 protein is extremely rare in classical LN
  3. 3-Generally negative for E –cadherin & CK 5,6, positive for HMWCK34BE12

-
-
-

Bibliography

1. Hull MT, Warfel KA (1986): Glycogen-rich clear cell carcinomas of the breast. A clinicopathologic and ultrastructural study. Am J Surg Pathol, 10: 553-559.[article dealing with a special type of breast cancer]

2. Hunter CE Jr., Sawyers JL (1980): Intracystic papillary carcinoma of the breast. South Med J, 73: 1484-1486. .[article dealing with a special type of breast cancer]

3. Jensen ML, Kiaer H, Melsen F (1996): Medullary breast carcinoma vs. poorly differentiated ductal carcinoma: an immunohistochemical study with keratin 19 and oestrogen receptor staining. Histopathology, 29: 241-245. .[article dealing with a special type of breast cancer and its immunohistochemical profile]

4. Jones PA, Laird PW (1999): Cancer epigenetics comes of age. Nat Genet, 21: 163-167. [This article deals with the subject of epigenetics and cancer]

5. Kader HA, Jackson J, Mates D, Andersen S, Hayes M, Olivotto IA (2001): Tubular carcinoma of the breast: a population-based study of nodal metastases at presentation and of patterns of relapse. Breast J, 7: 8-13. [A study dealing with the patterns of relapse and nodal metastasis in a special type of breast cancer]

6. Kuukasjarvi T, Tanner M, Pennanen S, Karhu R, Kallioniem OP, Isola J (1997): Genetic changes in intraductal breast cancer detected by comparative genomic hybridization. Am J Pathol, 150: 1465-1471.[A genomics article about genetic changes in intraductal breast cancer]

7. Kwiatkowska E, Teresiak M, Lamperska KM, Karczewska A, Breborowicz D, Stawicka M, Godlewski D, Krzyzosiak WJ, Mackiewicz A (2001): BRCA2 germline mutations in male breast cancer patients in the Polish population. Hum Mutat, 17: 73.(An article dealing with a certain mutation in Polish males with breast cancer]

8. La Vecchia C, Levi F, Lucchini F (1992): Descriptive epidemiology of male breast cancer in Europe. Int J Cancer, 51: 62-66. [Epidemiologic study of European male breast cancer]

9. La Vecchia C, Parazzini F, Franceschi S, Decarli A (1985): Risk factors for benign breast disease and their relation with breast cancer risk. Pooled information from epidemiologic studies. Tumori, 71: 167-178. [A cancer breast risk factor study]

10. Laake K, Odegard A, Andersen TI, Bukholm IK, Karesen R, Nesland JM, Ottestad L, Shiloh Y, Borresen-Dale AL (1997): Loss of heterozygosity at 11q23.1 in breast carcinomas: indication for involvement of a gene distal and close to ATM. Genes Chromosomes Cancer, 18: 175-180. [This study sheds light on certain genetic abnormalities associated with breast cancer]

11. Lenfant-Pejovic MH, Mlika-Cabanne N, Bouchardy C, Auquier A (1990): Risk factors for male breast cancer: A Franco-Swiss case-control study. Int J Cancer, 45: 661-665. [A case control study of risk factors in male breast cancer]

12. Leong AS, Williams JA (1985): Mucoepidermoid carcinoma of the breast: High grade variant. Pathology, 17: 516-521.[article dealing with a special type of breast cancer]

13. Lesser ML, Rosen PP, Kinne DW (1982): Multicentricity and bilaterality in invasive breast carcinoma. Surgery, 91: 234-240.[A study dealing with multiple tumours and tumours in both breasts]

14. Lesueur GC, Brown RW, Bhathal PS (1983): Incidence of perilobular hemangioma in the female breast. Arch Pathol Lab Med, 107: 308-310.[article dealing with the incidence of a special type of breast

cancer]

15. Levi F, Randimbison L, Te VC, La Vecchia C (1994): Incidence of breast cancer in women with fibroadenoma. Int J Cancer, 57: 681-683.[article dealing with a the incidence of breast cancer in women with benign tumours]

16. Levine PH, steinhorn SC, Ries LG, Aron JL (1985): Inflammatory breast cancer: The experience of the surveillance, epidemiology, and end results (SEER) program. J Natl Cancer Inst, 74: 291-297. [end results of (SEER) program]

17. Li CI, Anderson BO, Porter P, Holt SK, Daling JR, Moe RE (2000): Changing incidence rate of invasive lobular breast carcinoma among older women. Cancer, 88: 2561-2569 .[article dealing with the incidence of a special type of breast cancer]

18. Li CI, Weiss NS, Stanford JL, Daling JR (2000): Hormone replacement therapy in relation to risk of lobular and ductal breast carcinoma in middle-aged women. Cancer, 88: 2570-2577. Article dealing with the relationship of hormone replacement therapy and risk of breast cancer development]

19. Liberman L (2000): Pathologic analysis of sentinel lymph nodes in breast carcinoma. Cancer, 88: 971-977. [article shedding light on the importance of sentinel lymph node evaluation]

20. Liberman L, Giess CS, Dershaw DD, Louie DC, Deutch BM (1994): Non-Hodgkin lymphoma of the breast: Imaging characteristics and correlation with histopathologic findings. Radiology, 192: 157-160. [article dealing with the imaging characteristics of a special type of lymphoma of the breast]

21. Lininger RA, Fujii H, Man YG. Gabrieison E, Tavassoli FA (1998): Comparison of loss heterozygosity in primal and recurrent ductal carcinoma in situ of the breast. Mod Pathol, 11: 1151-1159. [A genetic study of recurrent ductal carcinoma]

22. Lininger RA, Park WS, Man YG, Pham T, MacGrogan G, Zhuang Z, Tavassoli FA (1998): LOH at 16p 13 is a novel chromosomal alteration detected in benign and malignant microdissected papillary neoplasms of the breast. Hum Pathol, 29: 1113-1118. [An article dealing with a genetic aberration in benign and malignant neoplasms of a special type]

23. Lipell F, Ljungberg O, Andersson I (1980): Breast carcinoma. Aspects of early stages, progression and related problems. Acta Pathol Microbiol Scand Suppl, 1-233.[A discussion on the clinical aspects of early breast cancer]

24. Loman N, Johannsson O, Kristoffersson U, Olsson H, Borg A (2001): Family history of breast and ovaraian cancers and BRCA1 and BRCA2 mutations in a population-based series of early-onset breast cancer. J Natl Cancer Inst, 93: 1215-1223.

25. London SJ, Connolly JL, Schnitt SJ, Colditz GA (1992): A prospective study of benign breast disease and the risk of breast cancer. JAMA, 267: 941-944. [A cancer breast risk factor study]

26. Loose JH, Patchefsky AS, Hollander IJ, Lavin LS, Cooper HS, Katz SM (1992): Adenomyoepithelioma of the breast. A spectrum of biologic behavior. Am J Surg Pathol, 16: 868-876. [article dealing with the behaviour of a special type of breast cancer]

27. Losi L, Lorenzini R, Eusebi V, Bussolati G (1995): Apocrine differentiation in invasive carcinoma of the breast. Appl Immunohistochem, 3: 91-98. [article dealing with a special type of breast cancer]

28. Luna-More S, Gonzalez B, Acedo C, Rodrigo I, Luna C (1994): Invasive micropapillary carcinoma of the breast. A new special type of invasive mammary carcinoma. Pathol Res Pract, 190: 668-674. [article dealing with a special type of breast cancer]

29. McDivitt RW, Stevens JA, Lee NC, Wingo PA, Rubin GL, Gersell D (1992): Histologic types of benign breast disease and the risk for breast cancer. The Cancer and Steroid Hormone Study Group. Cancer, 60: 1408-1414.[A study of breast cancer risk in different types of benign breast disorders]

30. McDivitt RW, Stewart FW (1966): Breast carcinoma in children. JAMA, 195: 388-390.[A study on breast cancer in childhood]