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Breast cancer

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8th Lecture

Breast Cancer

- ✓ The most common malignancy of breast is carcinoma and most common cancer in women
- ✓ Women who live to age 90 has a 1/8 chance to have breast cancer
- ✓ Mammographic screening increased dramatically the early diagnosis of small invasive cancers
- ✓ DCIS (Ductal Carcinoma InSitu) by itself is almost exclusively detected by mammography
- ✓ Currently only 20% of the women with breast cancer are expected to die of the disease

Breast Cancer Risk Factors:

Age :

1. There is a steady increase in the incidence, as women grow older
2. Breast cancer is rare before 25 years(except familial forms)
3. 77% of cases Occur in women >50 years (Post-Menopausal). The average age is 64 years

For each 2 years delay in onset of menstrual activity, the risk is reduced by about 10%.

Early Menarche: Girls who get their Menarche at age < 11 have a 20% increased risk to that who have their menarche at 14years.(because of the Onset of Estrogen Secretion)

Late first Live birth: The earlier a woman has her first birth, the lower her lifetime risk for breast cancer. This is independent of parity.

First Degree relative with Breast Cancer: (mother, sister, or daughter) A woman would automatically be at risk of breast cancer

Breast Biopsy : Atypical hyperplasia increases the risk for breast cancer

Race : incidence of breast cancer is lower in African American women

Estrogen Exposure: late menopause and early menarche

Radiation exposure
Personal history: Women who have had a breast cancer have a 10-fold increased risk of developing a second primary breast cancer.

Geographic influence: industrialized countries than in developing countries
Diet and Obesity : Fat might increase the risk
Exercise :some studies showed degreased risk

Breast–Feeding : The longer the women breast –feed the lower the risk (↓ Estrogen)

Environmental toxins: all kinds of chemicals (e.g. pesticides).

Tobacco: **Not** associated with breast cancer, but associated with the development of peri-ductal mastitis, or sub-areolar abscess.

✓ The major risk factors for the development of breast cancer are hormonal and genetic (family history). Breast carcinomas can, therefore its divided into

Hereditary Breast Cancer

A family history of breast cancer in a first-degree relative is reported in 13% of women

About 25% of familial cancers can be attributed to two highly penetrant autosomal-dominant genes: BRCA1 and BRCA2

Sporadic Breast Cancer (Mostly Associated with hormones)

Hormone exposure: gender, age at menarche and menopause, reproductive history, breast-feeding, and exogenous estrogens. (The majority of these cancers occur in postmenopausal women and overexpress Estrogen)

Breast Carcinoma Classification

- Almost all are Adenocarcinoma

1- Divided into In situ Carcinoma(non-invasive)

2- Invasive carcinoma

Noninvasive carcinoma (Carcinoma in situ): This is epithelial proliferation that is still confined to the Basement membrane of the ducts "Myoepitheluim", has not invaded the surrounding tissue and therefore it is incapable of metastasis

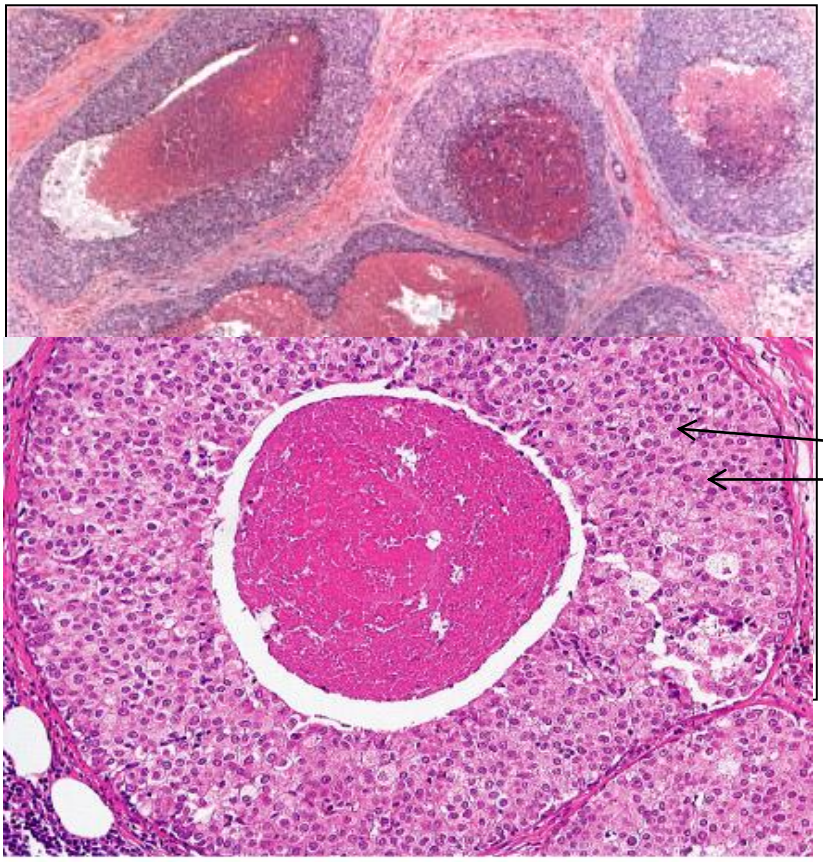
Breast Classification of Carcinoma in situ:

There are two subtypes:

1) **Ductal carcinoma in situ (DCIS)** or intraductal carcinoma 80% (percentage is very important)
2) **Lobular carcinoma in situ**. The incidence in autopsy studies is about 20%.

1. Ductal Carcinoma InSitu (DCIS)

- DCIS comprises a noninvasive neoplastic proliferation with risk of development of subsequent invasive carcinoma. (Very high chance of rupturing the Basement membrane and becoming invasive)
- The tumor distends and distorts the ducts in the TDLU (terminal duct lobular unit)
- Terminal ducts enlarge and resemble large ducts.
- Occurrence: usually seen in 50 to 59 years old (similar to the mean age of women with invasive ductal carcinoma).
- Mammography is a very sensitive diagnostic procedure for detecting DCIS as a substantial proportion **(Micro calcifications are found in 72 to 98% of DCIS).**
- It is **not** palpable.
- Rapidly increased in the past two decades (More people are getting mammograms, and the quality of the mammograms has improved)
- Appears most frequently as a calcifications & less frequently as a density or a vaguely palpable mass or nipple discharge



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Histopathology:

i. Dilated Ducts are infiltered by malignant cells
ii. Intact basement membrane
iii. Necrosis
iv. Calcification

✓ Subtypes of Ductal Carcinoma inSitu

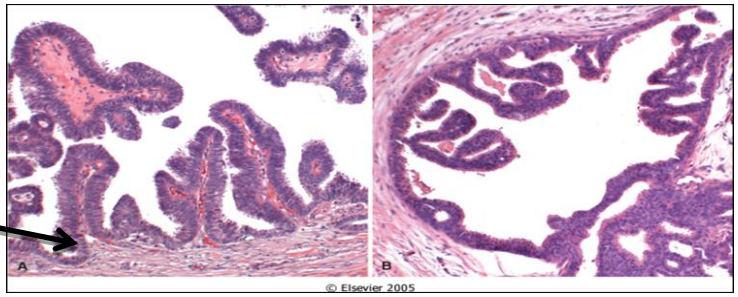
(Dr. Sofia: you're only required to know the names of subtypes)

Different histological patterns often coexist in the same lesion

a. **Comedocarcinoma**

b. **solid**

c. **Papillary, micropapillary.**



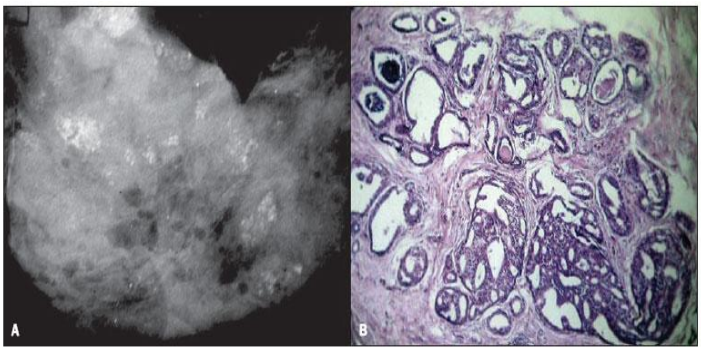
Papillae lined by malignant cells are found inside he ducts

✓ Clinical behavior

- **Comedocarcinoma** has essentially a 100% chance of becoming invasive if untreated (important).

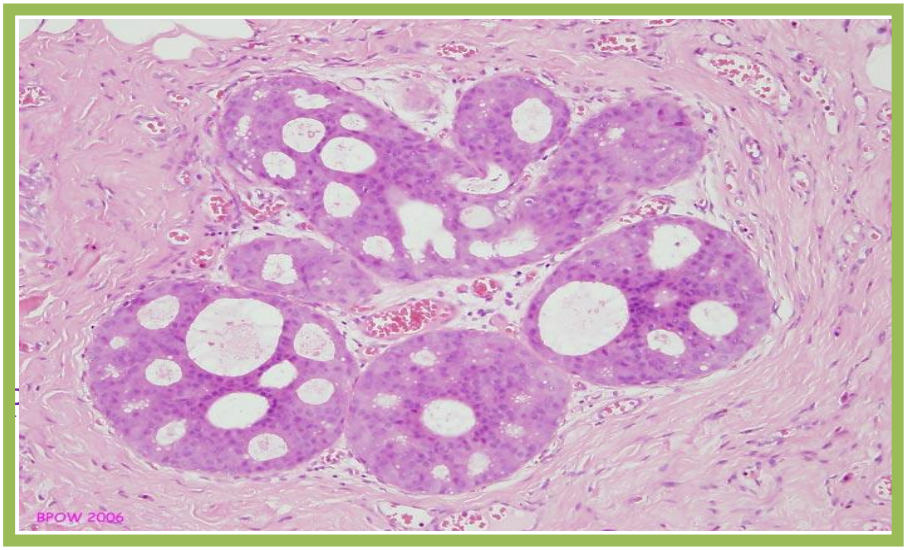
Comedocarcinoma demonstrates central necrosis. It is a type of ductal carcinoma in situ.

The duct will have characteristic necrotic tissue with calcification. Squeezing the duct will secret cheesy-like material similar to toothpaste.



NOT IMPORTANT

- Pure cribriform/micropapillary carries 30% chance of invasive carcinoma.



NOT IMPORTANT

Paget's disease

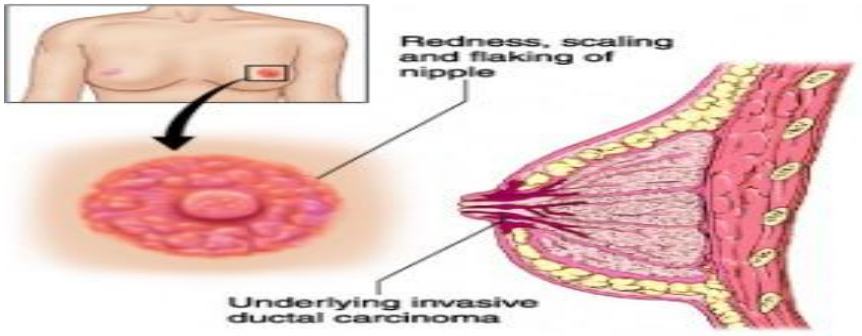
- Rare skin manifestation of breast cancer (1 to 2 %) (travelled from Ductal carcinoma inSitu through the Ductal system of the breast and to the skin)

- Paget's disease of the nipple presents as:

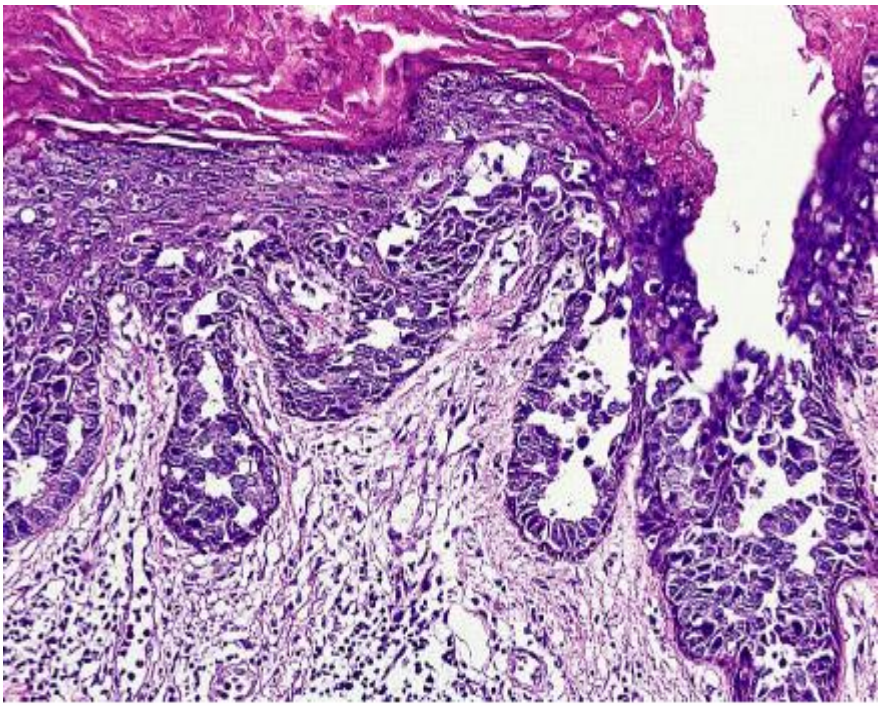
  - ✓ Pruritus (common)
  - ✓ Eczematous area of the nipple, might be mistaken for Eczema
  - ✓ Subtle (delicate) or form eroded weeping lesion (fluid coming out of the nipple)
  - ✓ Unilateral erythematous eruption with a scale crust.

- Malignant cells, referred to as "Paget cells" are found scattered in the epidermis

- Paget cells extend from DCIS within the ductal system into nipple skin **without crossing the basement membrane**



- Palpable mass is present in 50 to 60% of women with Paget disease indicating an underlying invasive carcinoma.



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The histologic hallmark of Paget's disease:

i. the nipple is the infiltration of the epidermis **by large malignant ductal cells**

ii. **Intact basement membrane**

iii. The malignant cells have abundant clear or pale cytoplasm and nuclei with prominent nucleoli.

iv. The cells usually **stain positively for mucin.**

v. Lymphocytes and inflammatory cells

vi. **(+ve)** Estrogen Receptor stain (IHC test that makes the hormone receptor show in a sample of breast cancer tissue)

2. Lobular Carcinoma in Situ (LCIS) less common

- Always an incidental finding in a biopsy performed for another reason
- Infrequent (1% to 6%) of all carcinomas
- **Bilateral And multifocal** in 20% to 40% of women when both breasts are biopsied (thus treatment of LCIS is hard) (very important)
- Not a palpable mass and cannot be detected clinically, felt at operation or seen grossly on pathological examination.
- May have microcalcifications infrequently(so mammography has not been useful for detecting it) .
- LCIS shows a proliferation of cells that fill and distend the TDLU.

Clinical behavior

- If LCIS is left untreated, about 30% of women develop an invasive cancer within 20 years of diagnosis therefore it is a marker of increased cancer in both breasts.

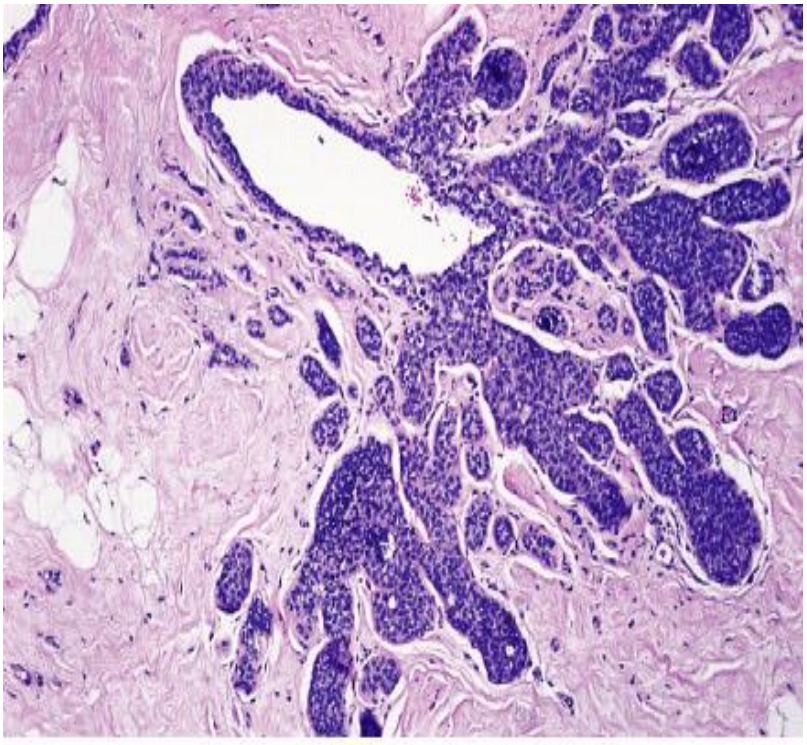
Histopathology:

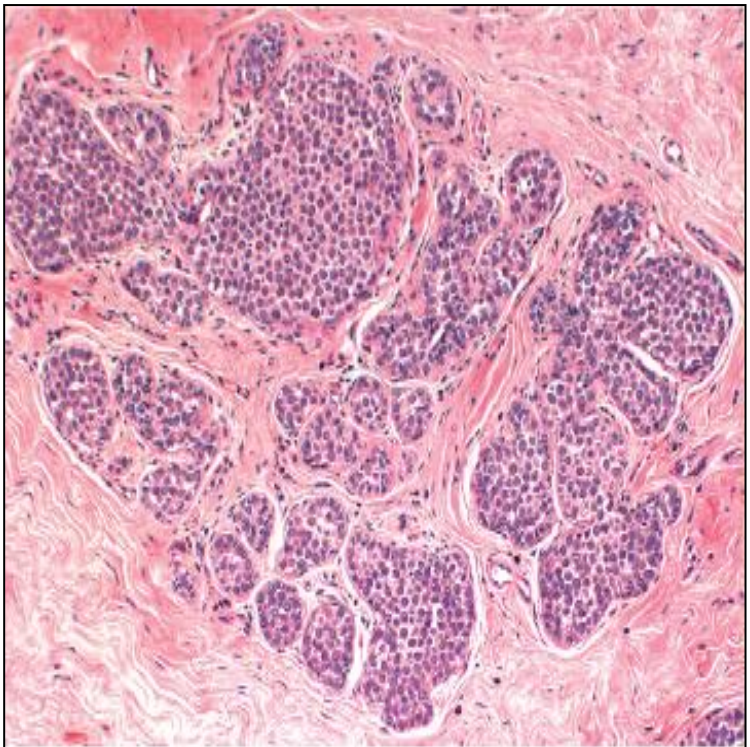
Proliferation of cells

Lobular Acini dilated with malignant material

Atypical glands

Basement membrane is intact → **Insitu**





Invasive Breast Carcinoma

CLASSIFICATION

- Invasive breast carcinoma is tumor that has extended across the basement membrane. This permits access to lymphatics and vessels and the potential distant metastases and thereby a lethal outcome. There are several different types of invasive carcinoma. Invasive breast carcinoma is subdivided into:

1- NOS Ductal 80%

2- Lobular 10%

3- tubular 6%

4-Mucinous(Colloid) 2%

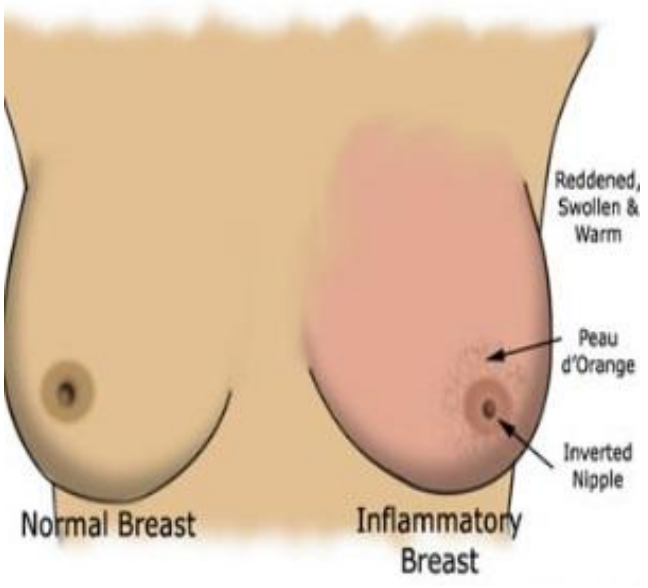
5- Medullary 2%

6- Papillary 1%

7- Metaplastic Carcinoma 1%

CLINICAL FEATURES OF BREAST CANCER

- ***Palpable mass***
- By the time a cancer becomes palpable, over half the patients will have axillary lymph node metastases
- Larger carcinomas may be fixed to the chest wall or cause ***dimpling of the skin*.**
- Lymphatics may become so involved as to block the local area of skin drainage and cause lymphedema and thickening of the skin, a change referred to as ***peau d'orange***.
- When the tumor involves the central portion of the breast, ***retraction of the nipple may develop***.
- In older women undergoing mammography, invasive carcinomas most commonly present as a density and are, on average, half the size of a palpable cancer, Fewer than 20% will have nodal metastases.



- Invasive carcinomas presenting as mammographic calcifications without an associated density are very small in size, and metastases are unusual.

- The term "**inflammatory carcinoma**" refers to the clinical presentation of a ***carcinoma extensively involving dermal lymphatics, resulting in an enlarged erythematous breast.*** The diagnosis is made on clinical grounds and does not correlate with a specific histologic type of carcinoma

Invasive Ductal Carcinoma ,NOS

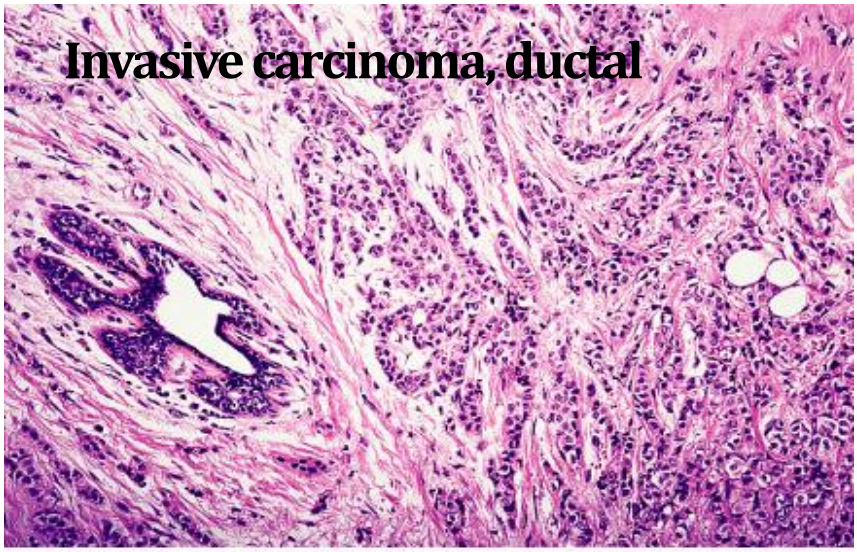
- **It is the commonest type of breast cancer, forming up to 80% of these cancers.**
- Most of these tumors excite a pronounced **fibroblastic stromal reaction to the invading tumor cells producing a palpable mass with hard consistency (hence scirrhous carcinoma)**, which is the most common presentation.
- The tumor shows an infiltrative attachment to the surrounding structures and may cause dimpling of the skin (due to traction on suspensory ligaments) or nipple retraction.

Gross morphology

- Grossly ,firm ,hard, and have an irregular border
- Cut surface is gritty and shows irregular margins with stellate infiltration and in the center there are small foci of chalky white stroma and occasionally **calcifications**
- **Characteristic grating sound when cut or scraped**
- Could be soft and well demarcated
- **Accompanied by varying amounts of DCIS**

Histologically

- the tumor cells are larger than normal epithelium, and can assume a variety of patterns such as glandular formation, cords of cells, broad sheets of cells or a mixture of all these, usually within a dense stroma.
- **The tumors range from well differentiated, in which there is glandular formation, to poorly differentiated, containing solid sheets of pleomorphic neoplastic cells.**



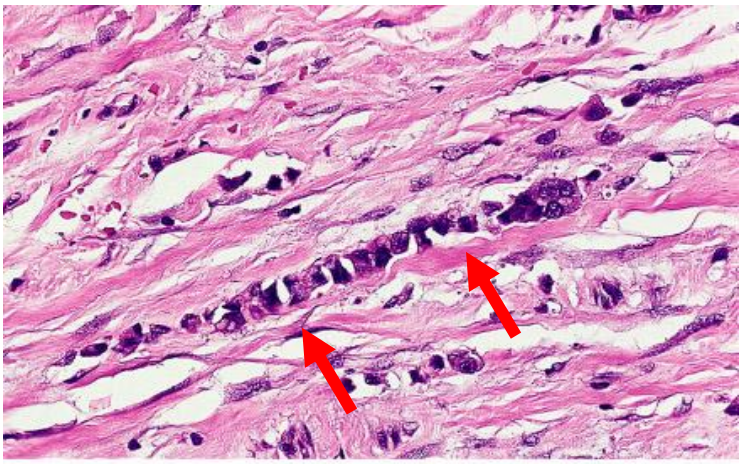
- Carcinomas associated with a large amount of DCIS require large excisions with wide margins to reduce local recurrences.

Invasive Lobular Carcinoma

- It is the **second most common type of invasive breast cancer forming up to 10%** of breast cancers.
- **The tumor may occur alone or in combination with ductal carcinoma**.
- It tends to be **bilateral** more often than ductal carcinoma and **multicentric**.
- The amount of stromal reaction to the tumor varies from dense desmoplasia to little reaction and therefore the presentation varies from a discrete mass to a subtle, diffuse indurated area.

morphology

- Most are firm to hard with irregular margins
- Single infiltrating cells ,often one cell width
- No tubules or papillary formation
- In about 10% of cases, tumors have mixed features of invasive ductal and lobular carcinomas.
- **Characteristic of Invasive Lobular Carcinoma is the " (Indian file) pattern" one row of malignant cells following each other.**



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Medullary Carcinoma

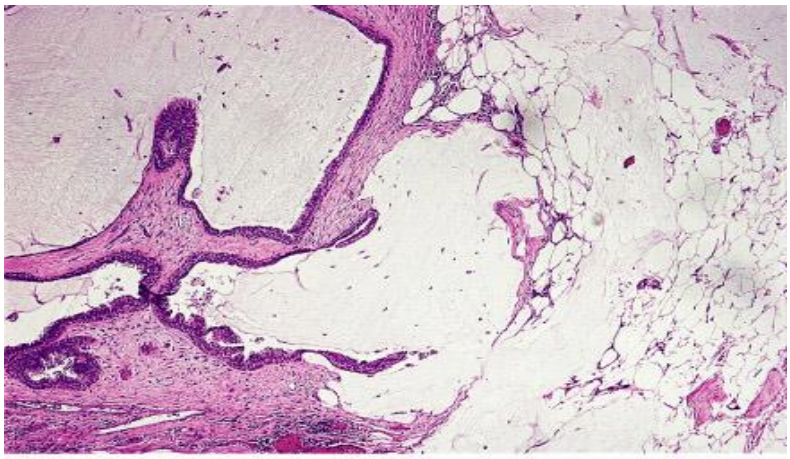
- This subtype of breast cancer presents as a **circumscribed mass**.
- **May mistaken clinically and radiologically fibroadenoma.**
- It does not produce any fibroblastic (desmoplastic) therefore is soft and fleshy (encephaloid).

Medullary carcinoma , imp. points :

- **Well circumscribed**
- **Commonly mistaken for benign lesion**
- **Shows lymphoid inflammatory reaction**
- **Better prognosis than ductal or lobular**

- On section foci of necrosis and hemorrhage are evident.
- Microscopically, the tumor is composed of solid sheets of malignant cells and frequent mitoses. There is scant fibrous stroma**. Lymphocytes and plasma cells surround the tumor cells.**

Colloid Carcinoma/ Mucinous carcinoma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- **Tends to occur in older women.**
- It is sharply circumscribed, lacks fibrous stroma and is slow growing.
- Is soft and gelatinous and has a glistening cut surface.
- It may be in pure mucinous or mixed in which it is associated with other types of invasive breast carcinoma.
- The mucinous tumor is composed of small islands, occasionally forming glands, and isolated tumor cells floating in pools of extracellular mucin.

Breast Carcinoma , Major Prognostic Factors

1- Invasive or In situ disease:

The great majority of women with adequately treated DCIS will be cured. In contrast, at least half of invasive carcinomas will have metastasized locally or distantly at the time of diagnosis.

2- Distant metastasis:

Once distant metastases are present, cure is unlikely, although long-term remissions and palliation can be achieved. Favored sites for dissemination are the lungs, bones, liver, adrenals, brain, and meninges.

3- Lymph node metastasis:

Axillary lymph node status is **the most important prognostic factor** for invasive carcinoma **in the absence of distant metastases.** The clinical assessment of nodal involvement is very inaccurate, therefore, biopsy is necessary for accurate assessment.

With no involvement, the 10-year disease-free survival rate is close to **70% to 80%;** the rate falls to **35% to 40%** with one to three positive nodes and **10% to 15%** in the presence of more than 10 positive nodes.

4- Tumor Size:

The size of the carcinoma is the second most important prognostic factor. The risk of axillary lymph node metastases does increase with the size of the carcinoma.

Tumor size less than 2 cm is associated with a favorable prognosis.

Note : all the above parameters are used to stage the tumor.Stage is a combination of size and lymph node status.

The single most important prognostic indicator is the lymph node status. Negative lymph nodes have the best prognosis. Involvement of 1 to 3 lymph nodes has an intermediate prognosis and 4 or more positive nodes have the worse prognosis.

5- Locally advanced disease:

Tumors invading into skin or skeletal muscle are frequently associated with concurrent or subsequent distant disease. (With increased awareness of breast cancer detection, it is now rare at initial presentation).

6- Inflammatory Carcinoma:

Women presenting with the clinical appearance of breast swelling and skin thickening have a particularly poor prognosis with a 3-year survival rate of only 3% to 10%.

Breast Carcinoma , Minor Prognostic Factors

1- Histologic Subtype:

Infiltrating ductal and lobular carcinomas have the worse prognosis, medullary and mucinous have intermediate and tubular and cribriform have the most favorable prognoses

2- Tumor Grade:

This is calculated by the pathologist. Grading separates tumors into three categories according to the amount of well formed tubules, the degree of nuclear pleomorphism, and the mitotic rate. The most commonly used grading system to assess the degree of tumor differentiation (*Bloom Richardson*).

There are three grades with grade 1 having better prognosis and grade3 having poorer prognosis.

3- Estrogen and progesterone receptors:

50% to 85% of carcinomas express estrogen receptors, such tumors are more common in postmenopausal women, **hormone positive cancers have better prognosis. They respond well to specific chemotherapeutic drugs eg. Tamoxifen.**

Therefore reporting of ER/PR positivity is important when reporting breast cancer.

4- HER2/neu.

(human epidermal growth factor receptor 2 or c-*erb B2* or *neu*) is a glycoprotein overexpressed in 20% to 30% of breast carcinomas.

Many studie shave shown that overexpression of *HER2*/*neu* is associated with a poor prognosis.

In addition, ongoing studies have shown that *HER2*/*neu*-overexpressing tumors respond very well to hormonal or anthracycline chemotherapy regimens eg. Trastuzumab (Herceptin).

Therfore evaluation of HER2/neu is most important when reporting breast cancer.

5- Lymphovascular invasion:

- Tumor cells may be seen within vascular spaces (either lymphatics or small capillaries) surrounding tumors.
- This finding is strongly associated with the presence of lymph node metastases and is a poor prognostic factor in women without lymph node metastases.

6- Proliferative rates

Metastasis to vertebra

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SUMMARY

Breast Carcinoma

The lifetime risk of developing breast cancer for an American woman is 1 in 8.The majority (75%) of breast cancer occurs after the age of 50.Risk factors include delayed child bearing, long duration between menarche and menopause, atypical proliferative lesions, and family history of breast cancer in a first-degree relative, particularly if the disease was multifocal or premenopausal.Only 5% to 10% of all breast cancers are related to inherited mutations; the majority are in the *BRCA1* and *BRCA2* genes, less commonly in *p53, PTEN* or *ATM* genes.Ductal carcinoma in situ (DCIS) is a precursor to invasive ductal carcinoma and is typically found on mammographic examination as calcifications or as a mass. When carcinoma develops in a woman with a previous diagnosis of DCIS, it is usually in the same breast and of ductal histology.Lobular carcinoma in situ (LCIS) is frequently an incidental finding and does not tend to produce a mass lesion. When carcinoma develops in a woman with a previous diagnosis of LCIS, it occurs in the affected or unaffected breast with the same frequency and may be lobular or ductal carcinoma.The natural history of breast carcinoma is long, with metastases sometimes appearing decades after the initial diagnosis.Prognosis is dependent on tumor size, lymph node involvement, distant metastasis at presentation, tumor grade and histologic type, proliferation rate, estrogen receptor status, aneuploidy, and overexpression of *HER2/NEU.*

Questions

1) A female presents with complaints of her breast “looking like an orange.” Examination reveals a tumor. Biopsy shows pinpoint streaks of chalky white elastotic stroma. The pathologist mentions a distinct grinding sound while cutting the tumor with a scalpel. Which of the following is most likely?

a) Invasive ductal carcinoma
b) Comedocarcinoma
c) Papillary-cribriform carcinoma
d) Invasive lobular carcinoma
e) Medullary carcinoma

2) Single filed chords of cells infiltration stroma, Indian files, is the hallmark of:

a) Invasive ductal carcinoma
b) Comedocarcinoma
c) Papillary-cribriform carcinoma
d) Invasive lobular carcinoma
e) Medullary carcinoma

3) A woman is found to have unilateral erythematous eruption with scale crust. After the patient describes pruritus, the clinician believes she has Paget disease. What would this patient also likely have?

a) Gynecomastia
b) Papillary-cribriform carcinoma
c) Invasive carcinoma
d) Comedocarcinoma
e) Angiosarcoma

4) The most important factor related to the prognosis of breast cancer is

a. The presence of activated oncogenes
b. The histologic type and grade
c. The size of the tumor
d. The status of axillary lymph nodes
e. The presence of estrogen receptors

1) A 2) D 3) C 4) D