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Summary file
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Pathology
Breast Pathology

439

Revised & Approved

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اللهم لا سهل الا ماجعلته سهلا وانت
تجعل الحزن إذا شئت سهلا

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Lecture content

1- Inflammatory lesions

- Acute mastitis
- Periductal mastitis
- Mammary duct ectasia: dilated ducts disease
- Fat necrosis: due to mechanical trauma, surgical or otherwise
- Lymphocytic mastopathy (sclerosing lymphocytic lobulitis) seen in diabetics
- Granulomatous mastitis

2- Benign epithelial lesions

- Non proliferative breast changes
- Proliferative breast disease without atypia.
- Proliferative breast disease with atypia

3- Stromal tumors

- Fibroadenoma
- Phyllodes tumors

5- Invasive carcinoma

- Ductal carcinoma
- Lobular carcinoma

4- Carcinoma in situ

- Ductal carcinoma in situ
- Lobular carcinoma in situ

Breast Inflammatory diseases

Introduction

❖ The functional unit of the breast is the lobule, which is supported by intralobular stroma.

❖ Lined by myoepithelial and luminal cells.

❖ The inner luminal epithelial cells produce milk during lactation.

❖ The basally located myoepithelial cells have contractile function to aid in milk ejection and also help support the basement membrane

❖ The ducts are conduits for milk to reach the nipple.

❖ The size of the breast is determined primarily by interlobular stroma, which increases during puberty and involutes with age.

❖ Each normal constituent is a source of Inflammatory, benign and malignant lesions.
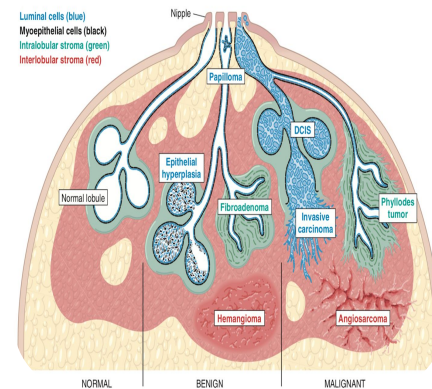
Benign Breast lesions

Inflammatory lesions	Benign epithelial lesions	Benign stromal lesions
- Acute mastitis: Staphylococcus aureus infection is the most common organism. **– Periductal mastitis** **– Mammary duct ectasia** → dilated ducts disease **– Fat necrosis**: It is usually due to a mechanical or surgical trauma. **– Lymphocytic mastopathy** (sclerosing lymphocytic lobulitis): It is seen in diabetic women. **– Granulomatous mastitis**: It can be idiopathic, due to sarcoidosis or TB.	**– Non proliferative breast changes (fibrocystic changes)** **– Proliferative breast disease without atypia** **– Proliferative breast disease with atypia / Atypical hyperplasia**	**– Fibroadenoma** **– Benign phyllodes tumors**

Mastitis

1) Acute mastitis[1]:

❖ **Rare** and may be caused by autoimmune disease, or foreign body–type reactions.

❖ **Or Infections:**
➢ The only agent is **Staphylococcus aureus.**
➢ Cause breast disease with any frequency.

Gains entry via fissures in nipple skin during the first weeks of **breastfeeding**.	→	Forms **lactational abscesses:** collections of neutrophils and associated bacteria in fibroadipose tissue.	→	If untreated, tissue necrosis may lead to the appearance of **fistula tracks opening onto the skin.**

❖ **Symptoms include:**
➢ Erythema and edema, often accompanied by pain and focal tenderness.
➢ Because it is rare, the possibility that the symptoms are caused by inflammatory carcinoma should always be considered.

❖ Most cases are treated adequately with antibiotics and continued expression of milk. Rarely, surgical incision and drainage is required.

2) Periductal mastitis: strongly associated with **smoking**, not lactation.

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1. Most cases are treated with antibiotics and continued expression of milk.

Intro to Breast tumors

Clinical presentation

Pain (mastalgia or mastodynia)

- Common symptom often related to menses, possibly due to cyclic edema and swelling.
- **Pain localized** is usually caused by a ruptured cyst or trauma to adipose tissue (fat necrosis).
- Almost **all painful masses are benign**, but for unknown reasons about 10% of cancers cause pain.

Inflammation

- Causes an edematous and erythematous breast.
- It is **rare** and is most often caused by infections, which only occur with any frequency during lactation and breastfeeding.
- **An important mimic of inflammation is "inflammatory" breast carcinoma.**

Nipple discharge

- May be normal when small in quantity and bilateral.
- **The most common benign lesion producing a nipple discharge is a large duct papilloma.**
- Discharges that are **spontaneous, unilateral**, **and bloody** are of greatest concern for **malignancy**.

Lumpiness, or a diffuse nodularity

- Throughout the breast, is usually a result of normal glandular tissue.
- When pronounced, imaging studies may help to determine whether a discrete mass is present.

Palpable masses[1]

- Can arise from proliferations of stromal or epithelial cells.
- Detected when they are 2-3 cm size.
- **Most (95%) are benign**; these tend to be round to oval and to have well circumscribed borders.
- In contrast, malignant tumors usually invade across tissue planes and have irregular borders.

Gynecomastia

- The only common breast symptom in **males**.
- There is an increase in both stroma and epithelial cells resulting from an imbalance between estrogens, which stimulate breast tissue, and androgens, which counteract these effects.
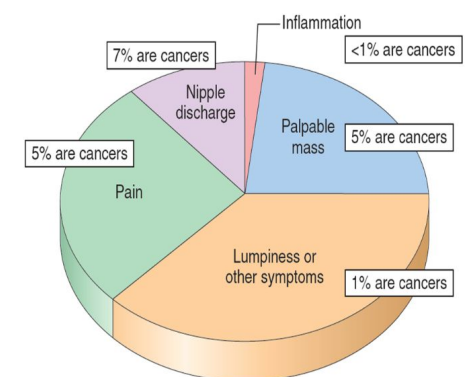
Mammographic screening

❖ Detect early, nonpalpable asymptomatic breast carcinomas before metastatic spread has occurred.

❖ The average size of invasive carcinomas detected by mammography is significantly smaller than cancers identified by palpation, and only 15% will have metastasized to regional lymph nodes at the time of diagnosis.

❖ Generally recommended to start after age 40.

❖ **Densities (mass):**
  ➤ Most tumors appear radiologically **denser** than the normal breast.
  ➤ Fibroadenomas, cysts etc. can also present as densities.

❖ **Calcifications**:
  ➤ Calcium gets deposited in secretions, necrotic debris, or hyalinized stroma.
  ➤ It can be seen in **benign** and **malignancy** (small, irregular, numerous, & clustered).
  ➤ Ductal carcinoma in situ (**DCIS**) is **most commonly detected as mammographic calcifications**. it has increased the diagnosis of DCIS. So whenever there is classification we should evaluated by biopsy to exclude DCIS and invasive carcinoma

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1. because some cancers grow deceptively as circumscribed masses, all palpable masses require evaluation.

Benign epithelial lesions

1- Non proliferative Breast Changes (Fibrocystic changes)

- ❖ **Most common disorder of the breast.**
- ❖ **No increased risk for cancer.**
- ❖ Produce palpable masses, mammographic densities, nipple discharge. Cyclic pain
- ❖ **Age**: **20-55 years**, decreases progressively after menopause.
- ❖ Thought to be due to caused by hormonal imbalances. (increase estrogen to progesterone ratio)

Histology

- ❖ **Nonproliferative** because the lesions contain 2 layers of cells (Epithelial & myoepithelial
- ❖ Three morphological changes:

1- Cysts with apocrine metaplasia	2- Fibrosis (fibrocystic changes)	3- Adenosis
- simple Cysts are lined by luminal benign flattened to columnar epithelium. - With focal apocrine metaplasia: cells become large and have abundant eosinophilic cytoplasm. - Apocrine secretions may **calcify within cyst and be detected by mammography.**	- The cysts can rupture and cause inflammation and fibrosis in response to the spilled debris. - May **produce palpable firmness (nodularity)** of the breast.after cyst rupture	- An increase in the number of acini per lobule. - can also be seen in pregnancy.
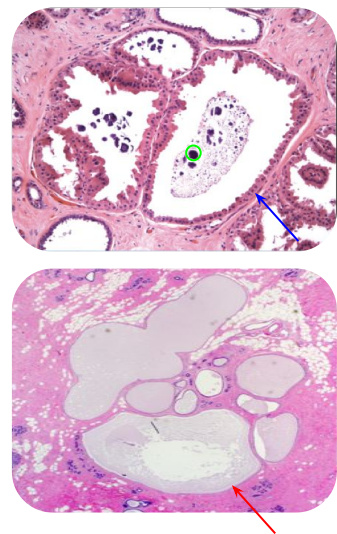
2- Proliferative Disease without Atypia.

- ❖ Rarely form palpable masses.
- ❖ Incidental finding; detected as small mammographic densities.
- ❖ **Risk for cancer is 1.5 – 2 times normal.**so the patient need careful follow up
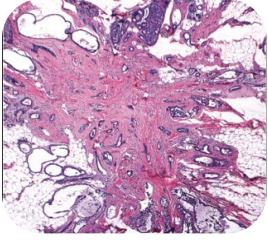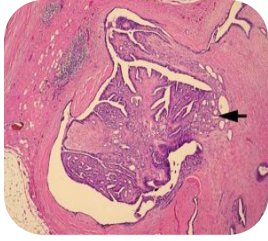- ❖ Include the following entities:

Normal Acinus to compare.
- Dark inner: Epithelium
- Light outer: Myoepithelium

|		Microscopy:
a- Epithelial Hyperplasia (usually epithelial hyperplasia)	- The normal breast has a 2 layers of cells (epithelial and myoepithelial cells). Thus, epithelial hyperplasia is defined as the presence of more than 2 layers. - Hyperplasia can range from mild, moderate and severe/florid. -When it is seen in fibrocystic disease: it is called as proliferative type/variant of fibrocystic disease.	**Microscopy:** - Both epithelial and myoepithelial cells proliferate. - Can be seen in the ducts and lobules.
b- Sclerosing Adenosis	- Mostly as incidental microscopic finding but may occasionally present as a palpable mass that is mistaken clinically for cancer. - <u>Calcification</u> is commonly seen in the lesion, so even on mammography it can mimic cancer. Almost always associated with fibrocystic changes	**Microscopy:** - (<u>Adenosis</u> = increase number of being , acini gland) and stromal <u>fibrosis</u> in the lobule which leads to compression and distortion of the lobule. -if the gland lined by epithelial and myoepithelial that mean it is being

Benign epithelial lesions

c- Complex Sclerosing Lesion (Radial Scar)	- **Radial scars**[1]: are stellate lesions characterized by a **central nidus (fibrous tissue) of entrapped glands in a hyalinized stroma.** - Nidus is surrounded by radiating arms of epithelium w/ cysts & hyperplasia -the word scar refer to morphological appearance, and no prior information , trauma or surgery	- Present as an irregular mammographic density. - Closely **mimic an invasive carcinoma**[2] both mammographically and grossly because they are irregular So we should confirm present of myoepithelial to exclude cancer .

|		
d- Papillomas	- Is a papillary tumor that arises from the ductal epithelium.	
	Large duct papillomas (central papillomas):	**Small duct papillomas:**
	- **More common.** - **Solitary** and situated in the lactiferous duct at the nipple. - Patients present with **bloody nipple discharge.** Sometimes, subareolar mass	- Commonly **multiple** and located deeper within the ductal system. - Increase the risk of subsequent carcinoma.
E-Proliferative variant of Fibrocystic disease	- When epithelial hyperplasia features are seen in fibrocystic disease it is called proliferative variant of fibrocystic disease	

3- Proliferative breast disease with atypia

❖ Atypical hyperplasia is a cellular proliferation resembling ductal carcinoma in situ (DCIS) or lobular carcinoma in situ (LCIS) but lacking sufficient qualitative or quantitative features for a diagnosis of carcinoma in situ.

❖ **Risk for cancer is 4-5 times normal.**

❖ Has some of the architectural and cytologic features of carcinoma in situ but lack the complete criteria for that diagnosis and is categorized as:

1 **Atypical ductal hyperplasia**
Once it get outside the duct it called invasive
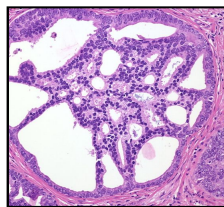
2 **Atypical lobular hyperplasia**
Within lobule
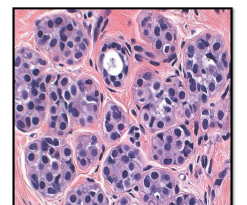
Stromal tumors

Interlobular stroma

❖ **Monophasic:** only comprised of mesenchymal cells.

❖ Include benign soft tissue tumors found elsewhere in the body, such as hemangiomas and lipomas.

❖ The only malignancy derived from this type is **angiosarcoma**, which may arise in the breast after local radiotherapy. As complication after 10 years of radiotherapy

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1- The word "scar" refers to the morphologic appearance, and not a prior inflammation, trauma or surgery.
2- Difficult to differentiate from carcinoma.

Stromal tumors

Intralobular stroma

- ❖ **Biphasic:** comprised of both stromal cells and epithelial cells.
- ❖ As the neoplastic proliferation of specialized lobular fibroblasts also stimulates reactive proliferation of lobular epithelial cells.
- ❖ Two types: fibroadenoma and phyllodes tumors.

Fibroadenoma

- ❖ The **most common benign tumor** of female breast, Almost **never malignant.**
- ❖ Any age, most common before age 30.
- ❖ **Classic presentation:**
  - ➢ <u>Firm</u>, <u>mobile</u> lump "breast mouse".
  - ➢ It may increase in size during pregnancy or stop growing and regress after menopause.
- ❖ usually solitary but may be multiple and involve both breasts.
- ❖ **Treatment:** lumpectomy (only the lump is removed)
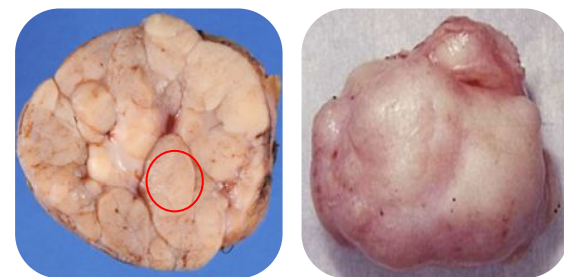
Morphology

- ❖ **Gross:**
  - ➢ Spherical nodules, size vary (1cm to 10cm).
  - ➢ Sharply demarcated and circumscribed
  - ➢ <u>Freely movable</u> and can be shelled out.
  - ➢ **Cut surface:** pearl-white and whorled.
- ❖ **Histology:**
  - ➢ Mixture of ducts and fibrous connective tissue.
  - ➢ The stromal proliferation push and distort the associated epithelium. Sharp borders.
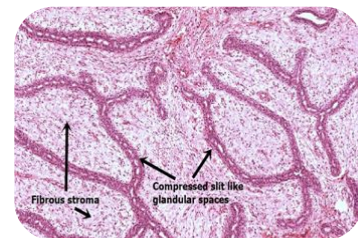
Phyllodes

- ❖ Can occur at any age, but most present in the 40s and 50s.
- ❖ Much less common than fibroadenomas.
- ❖ Most present as large palpable masses (usually 3 to 4 cm in diameter)
- ❖ **Morphology:** fibroepithelial tumors, have a **Phyllodes (leaflike) pattern** and a cellular stroma.
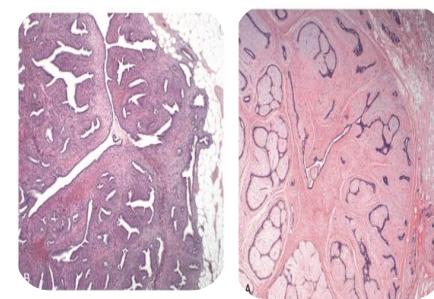
Benign phyllodes	Low-grade phyllodes Borderline	High-grade phyllodes Malignant
- Most (75%) of phyllodes tumors are benign.	- They tend to recur locally and a rarely metastasize.	- Uncommon and they behave aggressively. - Frequent local recurrences. - Can metastasize to lung, bone, CNS.

Introduction to Breast Carcinoma

Introduction

- ❖ The most common malignancy[1] and causes the majority of cancer deaths of women.
- ❖ Women by the age of 90 have a ⅛ chance of developing breast cancer.
- ❖ >95% of breast malignancies are adenocarcinomas.
- ❖ The most common location is in the upper outer quadrant (50%), followed by the central portion (20%). About 4% of women have bilateral primary tumors or sequentia llesions in the same breast.

Classification

First system:

- ❖ Breast cancers are divided based on the expression of:
  1. **Hormone receptors:** estrogen receptor (**ER**) and progesterone receptor (**PR**).
  2. **The human epidermal growth factor receptor 2 (HER2), also known as (ERBB2).**
- ❖ Classified into 3 major groups:
  1. **ER positive** (HER2 negative; 50%–65% of cancers).
  2. **HER2 positive** (ER positive or negative; 10%–20% of cancers).
  3. **Triple negative** (ER, PR, and HER2 negative; 10%–20% of cancers).
- ❖ These three groups show striking differences in patient characteristics,
- ❖ pathologic features, treatment response, metastatic patterns, time to relapse, and outcome.

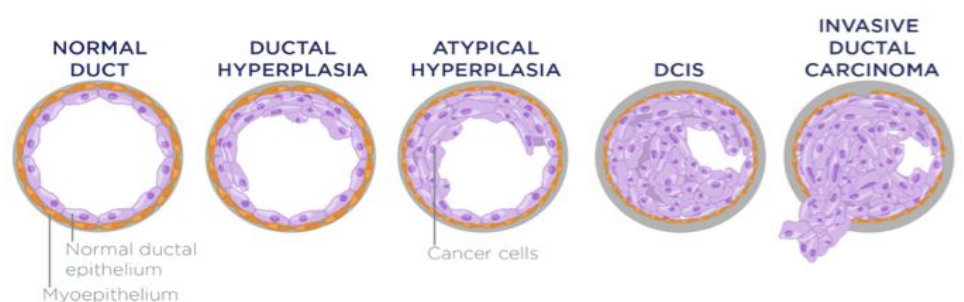Table 19.7 Summary of the Major Biologic Types of Breast Cancer

Second system[2]:

- ❖ An alternative classification system with substantial overlap relies on gene expression profiling.
- ❖ Divides breast cancers into four major types:
  1. **Luminal A:** are lower-grade, ER-positive, HER2 negative.
  2. **Luminal B:** are higher-grade, ER-positive, may be HER2 positive.
  3. **HER2-enriched:** overexpress HER2 and do not express ER.
  4. **Basal-like:** The majority by gene expression profiling resemble basally located myoepithelial cells and are ER-negative, HER2-negative.

Table 19.6 Factors Associated With Development of Invasive Carcinoma

Morphological classification:

- ❖ Classified according to whether they have penetrated the basement membrane.
- ❖ The main forms are as follows:
  - ➢ **Noninvasive** (remains within the basement membrane):
    - ■ **Ductal carcinoma in situ.**
    - ■ **Lobular carcinoma in situ.**
  - ➢ **Invasive:**
    - ■ **Discussed later in the slides..**

NORMAL DUCT — DUCTAL HYPERPLASIA — ATYPICAL HYPERPLASIA — DCIS — INVASIVE DUCTAL CARCINOMA

Normal ductal epithelium
Myoepithelium
Cancer cells

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1. Excluding nonmelanoma skin cancer.
2. This system is currently used mainly in the context of clinical research.

Introduction to Breast Carcinoma

Risk factors

Hereditary breast cancer	Sporadic breast cancer
– A family history of breast cancer in a first-degree relative. – About 25% of familial cancers (or around 3% of all breast cancers) can be attributed to two autosomal-dominant genes: BRCA1 and BRCA2.	– The major risk factors for sporadic breast cancer are related to exposure to hormones, gender, age at menarche and menopause, reproductive history, breast-feeding, and exogenous estrogens. – The majority of these cancers occur in postmenopausal women and in cases of overexpression to estrogen.

Female dr : this is for you to read

Age and gender	Reproductive History
- Rare in women < age 25 - Increases in incidence rapidly after age 30 - 75% of women with breast cancer are > age 50 - 5% are < 40 - Incidence in men is only 1% of that in women.	- Early age of menarche. - nulliparity - **absence of breastfeeding**, - older age at first pregnancy (because each increases the exposure of breast epithelial cells to estrogenic stimulation)
Family history	**Race/Ethnicity**
- Individuals with **multiple affected first-degree relatives** with early-onset breast cancer are at high risk. - In most families, it is thought that various combinations of **low penetrance**, "weak" cancer genes are responsible for increased risk. - However, approximately **5% to 10%** of cases occur in persons who inherit **highly penetrant** germline mutations in tumor suppressor genes which will increase the risk by 90%. - Majority of cancers occur in women without such history	- The highest rate of breast cancer is in women of European descent, largely because of a higher incidence of ER-positive cancers. - Hispanic and African American women tend to develop cancer at a younger age and are more likely to develop aggressive tumors. - Such disparities are thought to result from a combination of differences in genetics, social factors, and access to health care and are an area of intense study.
Geographic factors	Ionizing Radiation
- High risk in the Americas and Europe than in Asia and Africa. - Diet, reproductive patterns, and breastfeeding practices are thought to be involved. - Breast cancer rates appear to be rising in parts of the world that are adopting Western habits.	- Radiation to the chest increases the risk of breast cancer if exposure occurs while the breast is still developing. - For example, breast cancer develops in 25% to 30% of women who underwent irradiation for Hodgkin lymphoma in their teens and 20s, but the risk for women treated later in life is not elevated.

| Other |
|---|
| - Postmenopausal obesity, postmenopausal hormone replacement, mammographic density, and alcohol consumption also have been implicated as risk factors.
- The risk associated with obesity probably is due to exposure of the breast to estrogen produced by adipose tissue. In keeping with this, obesity is only associated with an increased risk of tumors that express ER.
- Environmental toxins: pesticides.
- Tobacco: Not associated with breast cancer, but associated with the development of periductal mastitis or sub-areolar abscesse |

Carcinoma In Situ

Ductal Carcinoma In Situ

❖ This is an epithelial proliferation that is still confined to the TDLU and has not invaded beyond the basement membrane and is therefore incapable of metastasis.

❖ The non-invasive proliferation of malignant cells within the duct system **without breaching the underlying basement membrane.**

❖ Have a very high risk of developing a subsequent invasive carcinoma

❖ Relative risk of development invasive carcinoma **is 8-10 times normal** in both types of carcinoma in situ.

A

B

Morphology

❖ Variety of **histological appearance/subtypes:**

A. **Comedo:** Extensive <u>central necrosis</u>, which produces toothpaste like necrotic tissue with <u>calcified</u> debris. (This type of DCIS is most frequently detected as radiologic calcifications)

■ Most frequently detected as radiologic calcifications.

■ Less commonly, the surrounding desmoplasia results in an ill-defined palpable mass or a mammographic density.

■ If untreated, 100% will become invasive.

B. **Cribriform:**

■ Cells forming round, regular (**cookie cutter**) spaces.

■ The lumens are often filled with calcifying secretory material.

C. **Solid** (cells fill spaces).

D. **Micropapillary and papillary**.

■ 30% of Pure cribriform/micropapillary become invasive.

❖ **Nuclear appearances:**

➢ Bland and monotonous: low nuclear grade.

➢ Pleomorphic: high nuclear grade.

C

D
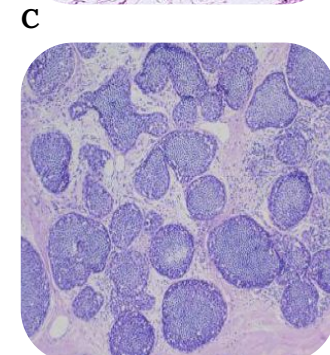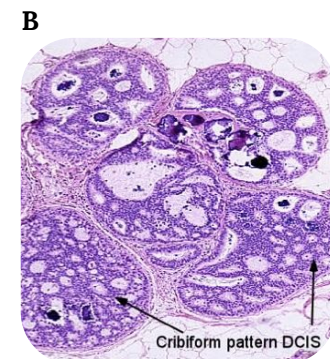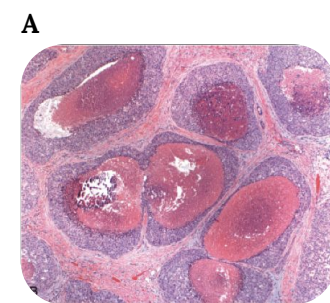
Clinical behavior

❖ Clinical behavior may vary depending on the subtype and the grade

➢ Comedocarcinoma has essentially a 100% chance of becoming invasive if left untreated.

➢ Pure cribriform/micropapillary carries only a 30% chance of becoming invasive carcinoma.

❖ Often multifocal: malignant cells can spread widely through the ductal system without breaching the basement membrane

Mammography

❖ **(E) micro-Calcifications** due to calcification of necrotic debris or secretory material.

❖ Mammography is specifically important here because there may not be a palpable mass, or discharge..
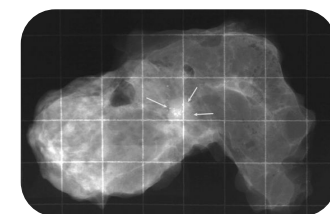
Treatment

❖ **surgery:** Wide local excision or mastectomy.

❖ Treatment with anti-estrogenic agents such as tamoxifen also is used to decrease the risk of recurrence of **ER-positive** DCIS.

Prognosis

❖ The prognosis is excellent, with greater than 97% long-term survival.

❖ If untreated, DCIS progresses to invasive cancer in roughly ⅓ of cases, usually in the same breast and quadrant as the earlier DCIS

❖ Women with DCIS are at risk of recurrent DCIS following treatmen

Fig. 19.28 Carcinoma in situ. (A) Lobular carcinoma in situ (LCIS). (B) Ductal carcinoma in situ (DCIS). DCIS partially involves the lobule in the lower half of this photo and has completely effaced the upper lobules, producing a ductlike appearance. (C) Mammographic detection of calcifications associated with DCIS

Carcinoma In Situ

Paget disease

- ❖ Paget's disease of the breast is a rare type of breast cancer that is characterized by a red, scaly eczematous lesion on the nipple and surrounding areola.
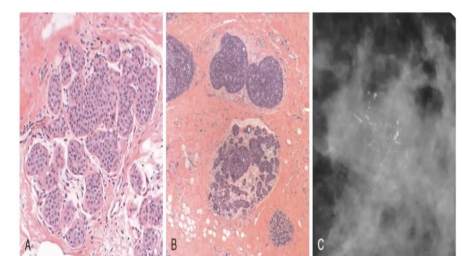- ❖ Paget's disease may be subtle or appear as an eroded and weeping erythematous eruption. Pruritus is common and it might be mistaken for eczema.
- ❖ Paget disease of the nipple is caused by the **extension of DCIS up the lactiferous ducts** and into the contiguous skin of the nipple.
- ❖ Produce a **unilateral** crusting exudate over the nipple and areolar skin.
- ❖ The prognosis of the carcinoma of origin is affected by the presence of paget disease and is determined by other factors.
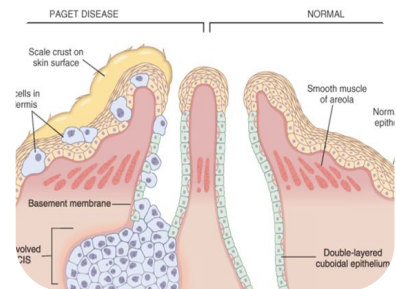
Morphology

- ❖ **Histologic hallmark**: the infiltration of the epidermis by:
  - ➤ Large neoplastic ductal cells with abundant cytoplasm.
  - ➤ Pleomorphic nuclei and prominent nucleoli.
  - ➤ The cells usually stain positively for **mucin**.
  - ➤ **Extension from DCIS within the ductal system without crossing the basement membrane.**
  - ➤ Palpable mass in 50% of patients
  - ➤ Epidermis with hyperkeratosis (thick layer of keratin = scale crust) and possibly ulcer
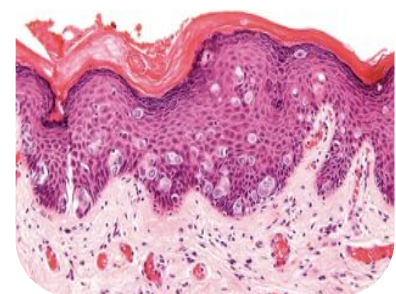
Lobular Carcinoma In Situ

- ❖ Always an incidental finding because, unlike DCIS, it is only **rarely associated with calcifications.**
- ❖ LCIS does not form a palpable mass and cannot be detected clinically on palpation or on gross pathological examination.
- ❖ LCIS is uncommon.
- ❖ LCIS tends to be multicentric and bilateral and therefore subsequent carcinomas can occur both breasts.
- ❖ Microcalcifications in LCIS are infrequent and so mammography is not useful for detection.
- ❖ Approximately ⅓ of untreated women eventually **develop invasive carcinoma** (mostly lobular):
  - ➤ ⅔ may arise in the same breast and ⅓ in the contralateral breast.
  - ➤ LCIS is both a marker of an increased risk of carcinoma in both breasts and a direct precursor of some cancers.

Morphology

- ❖ Has a **uniform appearance**.
- ❖ The cells are **monomorphic**.
- ❖ With bland, round nuclei, and are found in **loosely cohesive** clusters within lobules.
- ❖ The cells fill and expand the acini, but the normal structure can still be recognized.

Treatment (Female only)

- ❖ Current treatment options include close clinical and radiologic follow-up.
- ❖ Chemoprevention with tamoxifen.
- ❖ Less commonly, bilateral prophylactic mastectomy.
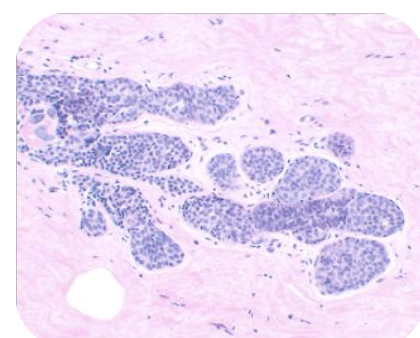
Invasive breast carcinoma

Introduction

- ❖ Invasive breast carcinoma is tumor that has **extended across the basement membrane.**
- ❖ This permits access to lymphatics and vessels and Therefore the potential to metastasize.

Classification First two are the most important

- ❖ **Invasive ductal carcinoma**: 70% to 80%. (NOS; not otherwise specified)
- ❖ **Invasive lobular carcinoma**: ~10% to 15%.
- ❖ Carcinoma with medullary features: ~5% .
- ❖ Mucinous carcinoma (colloid carcinoma): ~5%.
- ❖ Tubular carcinoma: ~5%.
- ❖ Other types

Invasive Ductal Carcinoma

- ❖ Includes all carcinomas that **cannot be subclassified** into one of the specialized types.
- ❖ Most of these tumors induce a marked fibroblastic (desmoplastic) stromal reaction to the invading tumor cells producing a palpable mass with a hard consistency (scirrhous carcinoma). And therefore a palpable mass is the   most common presentation.
- ❖ It is **associated with Ductal Carcinoma In Situ**, require large excisions with wide margins to reduce local recurrences.
- ❖ Gene expression classification:
  - ➢ 50-60% are ER positive
  - ➢ 20% are HER2 positive
  - ➢ 15% are negative for both ER and HER2
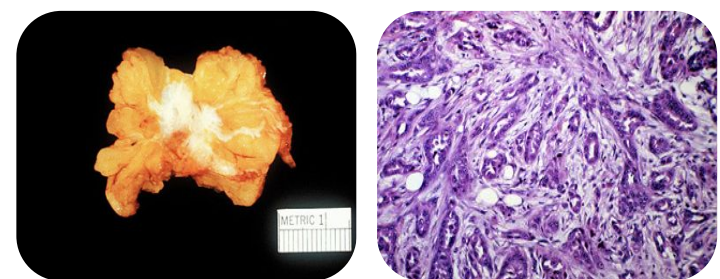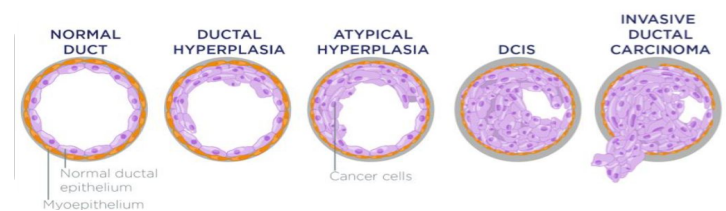
Morphology

- ❖ **Gross:**
  - ➢ Firm, hard, with an irregular border.
- ❖ **Cut surface:**
  - ➢ Gritty and shows irregular margins with stellate infiltration (sometimes it can be soft and well demarcated).
  - ➢ In the center there are small **foci of chalky white stroma** and occasionally calcifications.
- ❖ **Histology**:
  - ➢ Cells are large and pleomorphic usually within a dense stroma. , mitosis , and composed only of one layer
  - ➢ **Adenocarcinomas**: so they show glandular formation but can also be arranged in cords or sheets of cells.
  - ➢ Range from well differentiated → moderately → poorly differentiated.

Invasive breast carcinoma

Invasive Lobular Carcinoma

- ❖ It is the **second most common** invasive breast cancer.
- ❖ It may occur alone or in combination with ductal carcinoma.

### Clinical features

- ❖ Tend to be **bilateral** and multicentric.
- ❖ ⅔ of the cases are associated with LCIS.
- ❖ Almost all express hormone receptors, whereas HER2 overexpression is rare.
- ❖ The **pattern of metastasis is** unique:
  - ➤ they frequently spread to CSF, serosal surfaces, GIT, ovary, uterus, and bone marrow.
- ❖ The amount of stromal reaction to the tumor varies:
  - ➤ Marked fibroblastic **(desmoplastic)** response to **little to no reaction**[1].
  - ➤ therefore the presentation varies from a discrete mass to a subtle, diffuse indurated area.
- ❖ Although most manifest as palpable masses or monographic densities , a significant subgroup invade without producing desmoplastic response such tumors clinically (occult = even in clinical examinations we can not appreciate presence of mass) and difficult to detect by imaging

Morphology

- ❖ Morphologically similar to the tumor cells seen in LCIS.
- ❖ **Gross:** Most are firm to hard with irregular margin.
- ❖ **Microscopic:**
- ➤ **Single infiltrating malignant cells,** forming a **line** often one **cell** width (called as **indian file pattern**).
- ➤ The cell invade stroma individually and often are aligned in (single file)
- ➤ No tubules or papillary formation.
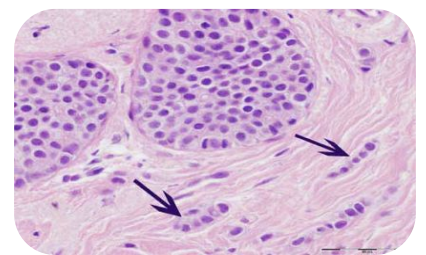
Cell grow in single file , liner patterns with minimal desmoplastic response

Medullary Carcinoma

- ❖ Special type of **triple-negative** cancer, This subtype of breast cancer presents as a well circumscribed mass.
- ❖ Typically grow as rounded well circumscribed masses that can be **difficult to distinguish from benign tumors on imaging**. (May be mistaken clinically and radiologically for a fibroadenoma.)
- ❖ It does **not produce any fibroblastic (desmoplastic)** reaction and therefore it is **soft** and fleshy.
- ❖ Seen frequently in women with germline **BRCA1 mutations**, but most women with these carcinomas are not carriers.

Morphology

- ❖ **Sheets** of large anaplastic cells. surrounded by many lymphocytes and plasma cells. There is scant fibrous stroma.
- ❖ Pronounced **lymphocytic infiltrates** predominantly (T cells).
- ❖ The presence of lymphocytes lead to a better response to chemotherapy compared to poorly differentiated carcinomas without lymphoid infiltrates .
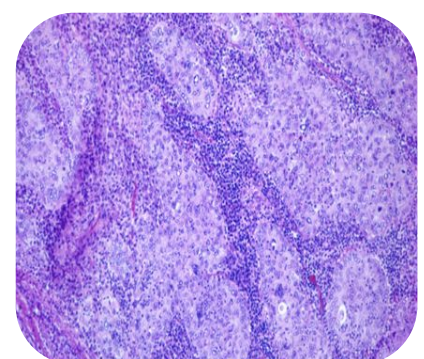
1. Clinically occult and difficult to detect by imaging.

Invasive breast carcinoma

|	Colloid Carcinoma (mucinous)	Tubular Carcinoma
general	- Tends to occur in older women. - ER-positive/HER2 negative - produce extracellular mucin - may be pure, more mixed with other type	- ER-positive/HER2 negative - **mammography**: as a small irregular mas
Gross	- Sharply well circumscribed - Lack fibrous stroma, slow growing - Soft & gelatinous, glistering surface	
Microscopy	Small islands of tumor cells and single cells in a pool of mucin	- Cells are arranged in well formed tubules - low grade nuclei
prognosis	Lumpectomy, mastectomy	Lymph node metastases are rare, and the **prognosis is excellent**
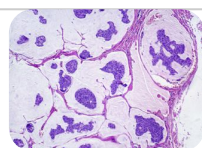
Inflammatory carcinoma

❖ Defined by its **clinical presentation**, rather than a specific morphology.

❖ Patients present with a **swollen erythematous breast without a palpable mass.**

Morphology

❖ The underlying invasive carcinoma is **poorly differentiated** and diffusely infiltrates and <u>**obstructs dermal lymphatic spaces, causing the inflamed[1] appearance.**</u>

Prognosis

❖ Many of these tumors **metastasize** to distant sites.

❖ The overall 5-year survival is less than 50%, and lower in metastasis.

❖ About half express ER.

❖ 40% to 60% overexpress HER2.

Invasive carcinoma Grading

❖ All type of invasive breast carcinoma are assigned a grade from 1 (low grade) to 3 (high grade)
Based on **nuclear pleomorphism, tubule formation and proliferation[2]:**

❖ **Low grade nuclei:**

➢ Similar to normal cells.

➢ Most form well-defined tubules,

➢ Difficult to distinguish from benign lesions.

❖ **High grade nuclei:**

➢ Enlarged with irregular nuclear contours.

➢ Invade as solid sheets or single cells.

❖ Proliferation is evaluated by counting mitotic figures.

---

1. True inflammation is absent.

Invasive breast carcinoma

Clinical presentations

Unscreened population:
- ❖ Most breast cancers are detected as a palpable mass by the affected patient.
- ❖ Such carcinomas are almost all invasive and are typically at least 2 to 3 cm.
- ❖ At least ½ of these cancers will already have **spread to regional lymph nodes.**
- ❖ Tumor may be fixed to the chest wall, causing dimpling of the skin

Older screened populations:
- ❖ 60% of breast cancers are discovered before symptoms are present.
- ❖ About 20% are in situ carcinomas.
- ❖ On mammography, invasive carcinomas commonly present as a density.
- ❖ Invasive carcinomas presenting as mammographic calcifications without an associated density are usually very small in size.
- ❖ Invasive carcinomas detected by screening in older women are 1 to 2 cm.
- ❖ Only 15% will have metastasized to lymph nodes.

Peau d'orange:
- ❖ Lymphatics may become involved and the lymphatic drainage of that area and the overlying skin gets blocked causing **lymphedema and thickening of the skin.**
- ❖ When the tumor involves the central portion of the breast, **retraction** of the nipple may develop.
- ❖ 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
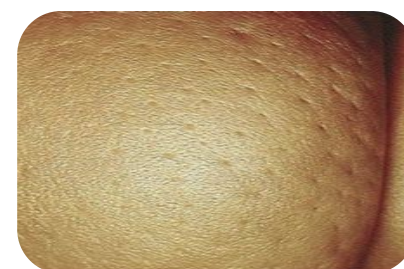
Prognostic factors
- ❖ Prognosis and clinical outcome for women can be predicted based on the molecular and morphological features of the cancer and its stage =size at the time of diagnosis also depend on hormonal marker , present of lymph node ,and distant metastasis ,

Biologic type
- ❖ The biologic type of cancer is evaluated by a combination of histologic appearance, grade (including proliferative rate), expression of hormone receptors, and expression of HER2 not hormonal receptor .

Proliferation	Expression of ER or PR	Overexpression of HER2
- Evaluated by mitotic count. - Tied to responsiveness to cytotoxic chemotherapy.	- **Predicts response to anti-estrogen therapy.** - The growth of hormone receptor positive cancers can be inhibited with therapy and survival with distant metastases is possible. - Resistance often develops in because of mutations in the ER gene. - In contrast, there is no therapy available for triple negative cancers, which are treated with chemotherapy.	- Is seen in about 20% of breast cancers. - HER2 remains one of the best-characterized examples of an effective therapy that is directed against a tumor-specific molecular lesion.

Invasive breast carcinoma

RNA expression

❖ RNA expression profiling is a newer method of sub classifying cancers.

Tumor stage

❖ Stage is a measure of the extent of tumor at the time of diagnosis and is important for all biologic types of carcinoma.

❖ Based on features of (TNM):

➢ **The primary tumor (T):**
   ■ Tumors classified as T1, T2, and T3 based on the tumor size.
   ■ <u>**T4 tumors**</u> have ulceration of the skin, involvement of the deep muscles of the chest wall, or are clinically diagnosed as <u>**inflammatory carcinoma**</u> high stage carcinoma

➢ **Involvement of regional lymph nodes (N):**
   ■ Lymphatic drainage goes to one or two sentinel lymph nodes in the axilla in most patients.
   ■ If these nodes are not involved, the remaining axillary nodes are usually free of carcinoma.
   ■ Sentinel node biopsy has become the standard for assessing nodal involvement, replacing more extensive lymph node dissections, which are associated with significant morbidity.

➢ **The presence of distant metastases (M):**
   ■ Only detected in 5% of newly diagnosed women.

❖ **Stages:**

0
- CIS
- Survival rates >95%.

1
- Includes smaller cancers and either free nodes or with micrometastases.
- Survival is ~86% at 10 years.

2
- Larger tumor size or up to 3 positive nodes.
- Survival declines to ~71% at Stage II.

3
- large size, involvement of skin or chest wall, or by 4 or more positive nodes.
- Only ~54% of patients survive 10 years.

4
- Distant metastases
- survival is very poor (~11%).

Summary

Benign Epithelial Lesions	Risk of Cancer	Histopathology	Comments
Non proliferative	No risk	- Cysts with apocrine metaplasia - Fibrosis & Adenosis	**Most common disorder of the breast.**
Proliferative without atypia			
Epithelial Hyperplasia	1.5 - 2 times normal	Proliferation of both epithelial and myoepithelial cells	Defined as the presence of more than 2 layers.
Sclerosing Adenosis		Adenosis and stromal fibrosis with compression of the lobule.	Incidental microscopic finding
Complex Sclerosing		Central nidus of entrapped glands in a hyalinized stroma.	Mimic an invasive carcinoma
Papiloma		**Large Duct:** - Solitary. - In lactiferous duct.	**Large Duct:** - Bloody nipple discharge. - Subareolar palpable mass.
		Small duct: - Multiple. - Deeper within ductal system.	**Small duct:** - Increase the risk of subsequent carcinoma
Proliferative without atypia	4-5 times normal	Atypical ductal or lobular hyperplasia.	Resembling carcinoma in situ but lack the sufficient features for that diagnosis.
Intralobular stromal tumors			
Fibroadenoma	**Most common benign tumor**		- Cut surface: pearl-white and whorled. - Mixture of ducts and fibrous connective tissue.
Phyllodes	Most present as large palpable masses		- Phyllodes (leaflike) pattern and a cellular stroma.

Summary

Breast cancer	
Noninvasive	
DCIS	- Non-invasive proliferation of malignant cells within the duct system. - Histological Variants: **comedo** (necrotic center), Cribriform (cookie cutter). - Micro-Calcifications is common.
LCIS	- Incidental finding. - ⅓ of women eventually develop invasive carcinoma. - Rarely associated with Calcifications
Invasive	
Invasive Ductal Carcinoma	- Includes all carcinomas that cannot be subclassified into one of the specialized types. - Associated with DCIS. - 50-60% are ER positive.
Invasive Lobular Carcinoma	- Tend to be bilateral and multicentric. - Unique metastatic pattern, to CSF, GIT, ovary, uterus and bone marrow. - Single file invasion of stroma.
Medullary Carcinoma	-Triple negative cancer presenting as a rounded mass. - Associated with BRCA1 germline mutations. - Sheets of large anaplastic cells associated with lymphocytic infiltrates (T cells).
Colloid (Mucinous) Carcinoma	-ER positive, HER2 negative. - Produces abundant amounts of extracellular mucin. - Soft and gelatinous.
Tubular carcinoma	-ER positive, HER2 negative. - Detected on mammography as a small irregular mass. - Cells are arranged in well formed tubules, with low grade nuclei.
Inflammatory carcinomas	-Defined by clinical presentation, swollen erythematous breast without a palpable mass. - Metastasize to distant sites. - 50% are ER positive, 40-60% overexpress HER2. - Cause inflamed appearance.

MCQs

QUIZ!

01 | Which of the following is the most common benign tumor of the female breast?

| A) Phyllodes tumor | B) Papilloma | C) Fibroadenoma | D) LCIS |

02 | A 52-year-old woman presents with a 3 month history of a palpable breast mass. Physical examination confirms a 1-cm nodule in the upper outer quadrant of the right breast. A biopsy shows small cuboidal cells with round nuclei and prominent nucleoli. The cells are arranged in single cell columns between strands of connective tissue. What is the most likely diagnosis?

| A) Acute mastitis with abscess | B) Invasive lobular carcinoma | C) Fibroadenoma | D) Intraductal carcinoma |

03 | A 48-year-old woman has noticed a red, scaly area of skin on her left breast that has grown slightly larger over the past 4 months. On physical examination, there is a 1-cm area of eczematous skin adjacent to the areola. The figure shows the microscopic appearance of the skin biopsy specimen. What is the most likely diagnosis?

| A) Paget disease of the breast | B) Fat necrosis | C) Apocrine metaplasia | D) Lobular carcinoma in situ |

04| A 38-year-old woman feels a lump in her right breast. Examination of the cross-section showed a firm mass with gritty margins and stellate infiltration, and small foci of chalky white stroma. The most likely diagnosis is:

| A) Invasive ductal carcinoma | B) Invasive lobular carcinoma | C) Fibroadenoma | D) Intraductal carcinoma |

05 | A 52-year-old woman was diagnosed with breast cancer. Upon examination of the tumor, it was soft, sharply circumscribed, and lacked fibrous stroma. It also had small islands of tumor cells and single tumor cells floating in pools of extracellular mucin. The most likely diagnosis is:

| A) Invasive ductal carcinoma | B) Medullary carcinoma | C) Colloid carcinoma | D) Intraductal carcinoma |

06 | A 40-year-old woman noticed a red, scaly appearance on her left nipple and surrounding areola. On histological examination of the nipple, there was infiltration of the epidermis by large neoplastic ductal cells with abundant cytoplasm, pleomorphism, and prominent nucleoli. The cells stain positive for mucin? What is the most likely diagnosis?

| A) Ductal carcinoma in-situ | B) Fibroadenoma | C) Paget's disease of the breast | D) Granulomatous mastitis |

MCQs Answer key	01	02	03	04	05	06
	C	B	A	A	C	D

Thank You!

We kept 438 pathology theme in the credits to remind you that this wonderful work was originally done by them

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Edited by : **439 Pathology leaders**

This is our last pathology lecture after 2 whole years. We hope that we achieved our goal and made the lectures much easier and fun to study.

Huge thanks to our great future doctors, to our academic leaders and batch leaders, to the amazing members who made this work the way it look, and to every student who took the time to help 💙

Good luck in your next years !

- Pathology team leaders
(Hamad Almousa & Fatimah Alhilal)