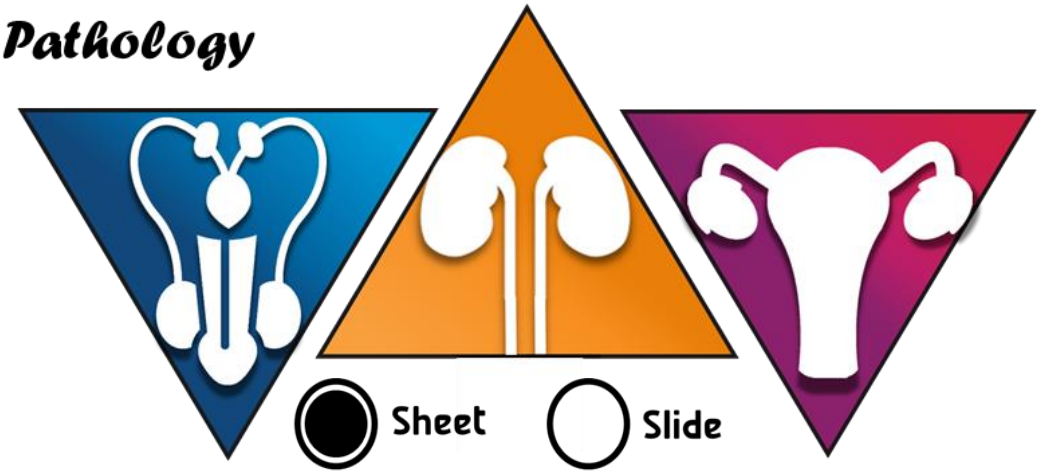
Urogenital system

Pathology



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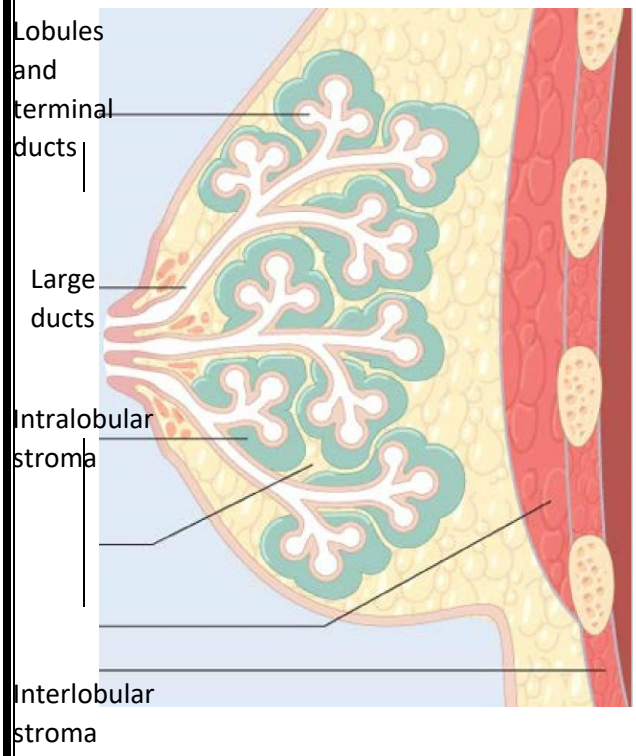
❖Normal breast



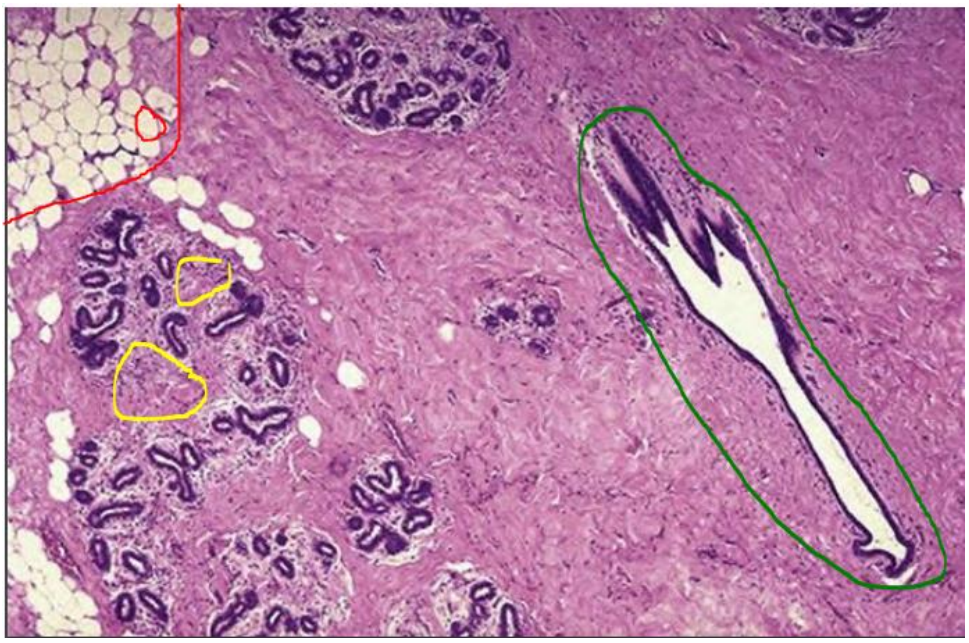
The breast is composed of stromal component and epithelial component. **The epithelial component** is composed of a branching duct~~s~~ system. These ducts are: large sized ducts, intermediate sized ducts and terminal ducts. All ducts are lined by a double cell layer (luminal cell layer and myoepithelial cell layer), and this lining by a double layer is a sign of benignicity. ~~So if we have a duct or a lobule lined by the double cell layer, we can say that the patient is safe.~~

The stromal component is composed of two types of stroma; intralobular stroma and interlobular stroma. The stroma between lobules is called interlobular stroma and the stroma inside lobules is called intralobular stroma.

The intralobular stroma is a specialized type of stroma because it is a hormone responsive. It undergoes changes according to the fluctuations of hormones (like estrogen and progesterone). So it changes according to the time of the menstrual cycle, pregnancy, menopause, etc…

The interlobular stroma is made of dense fibrous tissue, which gives the breast its firm consistency. It also has a fat component that starts to appear around the age of 30 and increases with time. So at the beginning the breast is really dense, and that's why if you do mammographic screening, the entire breast will be dense, so it's difficult to see the contrast between the normal stroma and any mass. On the other hand, with the increase of age, the radiolucent fatty component will increase, so we can identify the abnormal structures or masses. That is why we do the breast cancer screening after the age of 40.

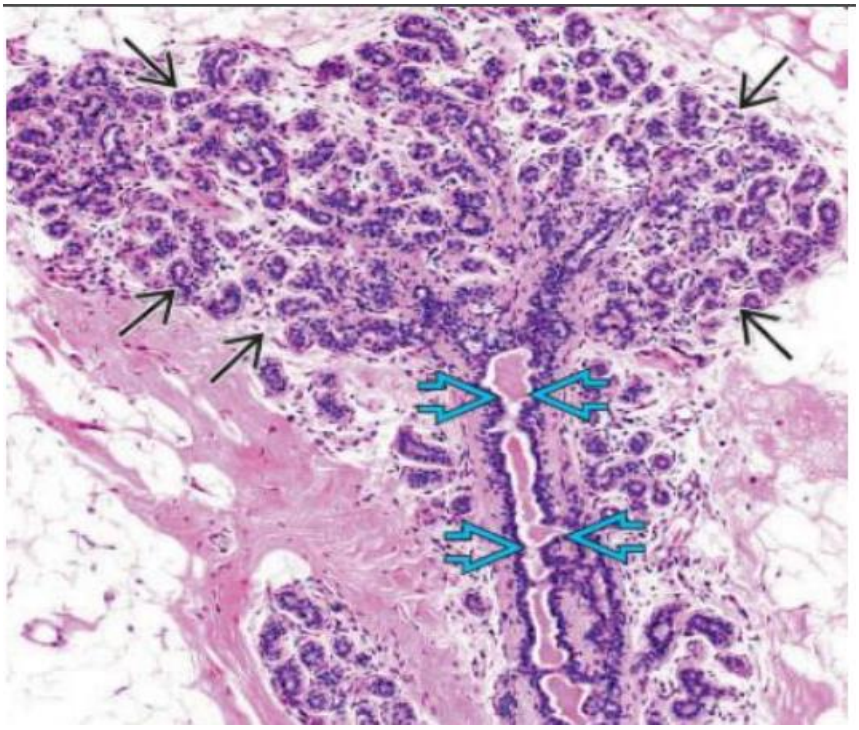
Histological section of the breast:



*The red structure is the interlobular stroma (look at the fat cells)

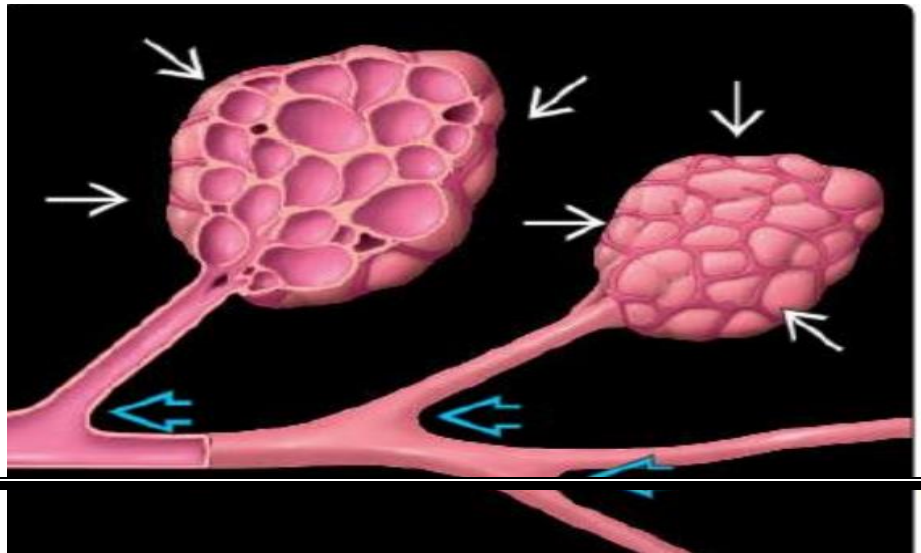
*The yellow structure is the intralobular stroma (surrounded by lobular unit and acini)

*The green structure is an intermediate size duct.



*This section looks like a tree. The stem of the tree is the terminal duct, and the leaves are lobular units with intralobular stroma.

*The fatty component is the interlobular stroma.



*Branching system, composed of large

ducts, intermediate and terminal ducts and the lobules with acini.

Note: You need to remember that the majority of the lesions (90%) are benign regardless of the symptoms (a mass, tenderness, discharge). Some women will come to the clinic scared of the symptoms they are having. You should always remember that 90% of breast lesions are benign.

-The main determinant of malignancy and benignicity is the woman's age. For example: if two women came with the same symptoms, one is 20 years and the other is 60 years. In case of the 20 year old woman, the symptoms are most probably due to a benign cause while In case of the 60 year old woman, the symptoms have more than 40% chance to be caused by a malignancy.

Some statistics:

-The risk of nipple discharge being due to carcinoma in ladies younger than 60 years is only 7%, while the risk in woman older than the age of 60 raises to 30%.

-Palpable mass: in women less than 40, 10% of palpable masses are due to carcinoma. It increases to 60% in women above 50.

Of women diagnosed with cancer:

45% are symptomatic. This means that more than half of the cases are asymptomatic. The most common symptom is **palpable mass**, followed by pain, nipple discharge and inflammatory changes.

The other 55% are diagnosed through screening (mammography, clinical physical examination and ultrasound **DEPENDING ON AGE**)

❖Mammographic screening:

Detects early; nonpalpable; asymptomatic breast carcinomas before metastasis. The average size of invasive carcinomas detected by mammography is about 1 cm; at this stage only 15% will have metastasized to regional lymph nodes.

-Clinical physical examination detects masses with size about 2-3 cm. Masses at this size are at a higher stage. So mammographic screening gives a better outcome.

-All the radiological studies depend on the breast consistency. The fibrotic interlobular stroma in the reproductive age ladies will decrease the productivity of the test since both are radiodense (stroma & masses)

That's why these tests have decreased sensitivity and specificity in younger age. The age of 40-45 is the age to start use the screening, because the fat, which is radiolucent, will be increased by age and it's much easier to differentiate radiodense masses against radiolucent background of fat.

The symptoms of breast disease:

1-Pain, which can be:

Cyclic: refers to the menstrual cycle. Cyclic pain is diffuse and bilateral. It happens due to premenstrual edema and swelling (congestion of the breast).

Noncyclic: noncyclic pain is localized. It happens due to a ruptured cyst, physical trauma or infection.

-Almost all painful masses are benign except for 10% of cases that relates to cancers.

2- Inflammation:

- Causes edematous and erythematous breast, but without masses.

- Most often caused by infections (***staphylococcus aureus*** enter: through fissures in the skin, during lactation and breastfeeding). The infection might cause abscesses or fistulas.

- Inflammation is an important mimic of inflammatory breast cancer. If a woman comes with orange peel breast, this is a red flag for inflammatory carcinoma, especially if she isn't breastfeeding or non-reproductive age lady

3-Nipple discharge:

-Types of nipple discharge

A-Normal: when small in quantity and bilateral.

B-Milky discharges (galactorrhea), which are associated with:

* Elevated prolactin levels (pituitary adenoma or Prolactinoma)

*hypothyroidism, or endocrine anovulatory syndromes

*Patients taking OCPs, tricyclic antidepressants, methyldopa, or phenothiazines.

C-Bloody or serous discharges (yellow red): commonly due to large duct papillomas and cysts (benign). Bloody discharges may also appear during pregnancy, resulting from the rapid growth of the epithelium of the breast and the remodelling of the breast.

BUT spontaneous, unilateral, and bloody discharge increases concern for malignancy

4-Palpable masses:

-95% of the masses are benign
how are palpable masses of benign lesions look like: They look like circumscribed oval rounded masses that are sharply demarcated from the surrounding tissue.

How are palpable masses of malignant lesions look like: Carcinomas usually have infiltrative orders and are hard to differentiate between them and the breast. However, 5% of carcinomas look like they are

benign and are sharply demarcated from the surrounding tissue (deceiving), but on the histology, they turn out to be carcinomas. **That is why every palpable mass must be investigated.**

*The most common causes of palpable lesions are cysts, fibroadenomas and invasive carcinomas

5-Gynecomastia: The only common breast symptom in males. - resulting from an imbalance between estrogens, which stimulate breast tissue, and androgens, which counteract these effects.

Inflammatory processes:

-Rare. They are caused by infections, autoimmune disease, or foreign body–type reactions.

-Clinically: erythema, edema, pain and focal tenderness.

-The only infectious agent is Staphylococcus aureus. It enters via fissures in nipple skin during the first weeks of breastfeeding causing lactational abscess.

-If untreated, leads to tissue necrosis and fistula tracks opening onto the skin.

Treatment: antibiotics and continued expression of milk (not breastfeeding). Rarely, surgical incision and drainage is required.

Note: Because inflammatory diseases are rare, the possibility that the symptoms are caused by inflammatory carcinoma should always be considered.

❖Stromal neoplasms

-Tumors arising from Intralobular stroma are: fibroadenoma and phyllodes tumor.

-These tumors are called biphasic tumors. Biphasic means that the tumor contains epithelial and stromal (mesenchymal) tissues.

-Specialized stroma (intralobular) may elaborate growth factors resulting in proliferation of the non-neoplastic epithelial component of these

tumors, so they are called biphasic (the origin is stromal, but the neoplasm happens in both stroma and epithelium).

-Fibroadenoma is the most common benign neoplasm of the female breast.

Tumors arising from Interlobular stroma:

-They are monophasic tumors (only mesenchymal cells)

-These tumors may be the same as tumors in other sites that appear in tissues that have mesenchymal cells. Examples are lipoma, hemangioma and angiosarcoma. There are types that only appear in the breast. Examples are pseudoangiomatous stromal hyperplasia and myofibroblastoma.

-The only malignancy derived from interlobular stromal cells of note is angiosarcoma (mostly after radiation).

❖Fibroadenoma:

Happens in reproductive age women that are 20 to 30 years old. They have an easily mobile breast lesion or nodule that is not connected to the skin. Its size ranges between 1-10 cm. 10% of cases have multiple and bilateral fibroadenomas.

-It is a hormonally responsive tumor. Lesions might enlarge due to menstrual period or during pregnancy. After menopause, they start to calcify and regress.

-They are well circumscribed, so easily removed surgically.

-Fibroadenomas are the most common benign tumor of the breast.

-In histology: It is sharply demarcated. The pale grey background is the stromal component of the tumor. There are still open ducts but some became slit-like spaces because the stroma proliferates more than the epithelium. (look at the picture in the slides)

❖Phyllodes tumor

-It is a rare tumor. Most present in the sixth decade

-It has an infiltrative lesion, not sharply demarcated from the background breast.

-Arise from the intralobular stroma and not from pre-existing fibroadenomas.

-It has more stromal proliferation, so that the stroma will bulge into the duct and make a leaf like or slit like pattern.

{Phyllodes (Greek for "leaf like")}

Grading of phyllodes:

1- Low-grade (70%): occasionally recurrence locally & do not metastasize.
2- Intermediate grade: often recur locally unless they are treated with wide excision or mastectomy.
3- High-grade: uncommon, give rise to distant hematogenous metastases in 1/3 of cases.

70% are benign and tend to remain localized and cured by excision.

- Grading is according to: cellularity, mitotic rate, nuclear pleomorphism, stromal overgrowth, necrosis and infiltrative borders.
- we use grading to predict the recurrence and metastasis
- The low grade is the most common, and the high grade is the least common.

-In histology: If you look at the stroma of normal breast, there will be low number of nuclei. Here, you may notice too many blue nuclei reflecting the stromal cellularity. The prominent stromal proliferation results in leaf-like or the villous-like pattern. (look at the picture in the slides).

❖Benign epithelial lesions:

-mostly discovered incidentally after mammography. The mammography shows calcification, so we take a biopsy.

Benign changes are divided into three groups according to the prediction of breast carcinoma:

1- **Nonproliferative changes** (fibrocystic): is not associated with an increased risk of breast cancer.
2- **Proliferative changes without atypia**: they are associated with a minimal risk of breast carcinoma (1.5 to 2 folds compared to the general population). They are polyclonal hyperplasias. They can't become malignant, but they are risky because they might be found next to malignant tumors.
3- **Proliferative disease with atypia**: monoclonal "precancers" & associated with 4-5 folds increase risk of breast cancer in both breast.

1-Nonproliferative breast changes (fibrocystic):

- They are the most common.

-There are three principal morphologic changes:

(1) Cystic change, often with apocrine metaplasia (most common)

(2) Fibrosis

(3) Adenosis: it is the increase in the number of ducts in the terminal duct lobular unit. But still all the ducts are lined by the double layers.

- There is neither cytologic atypia nor structural atypia in the Nonproliferative changes. So these changes are completely benign and there is no risk of malignancy.

-In histology: the picture in the slides shows an apocrine cyst. It has a dilated lumen. There is a myoepithelial lining outside (the flattened cells are the myoepithelial cells) and on top of those myoepithelial cells there are epithelial cells. Epithelial cells have basally located nuclei. They also have apically located pink cytoplasm which is called apocrine metaplasia.

2-Proliferative disease without atypia

It has 4 types:

1- Epithelial hyperplasia: we said that every duct and lobule is lined by 2 layers. Here, they are lined by more than 2 layers; but no atypia.
2- sclerosing adenosis

Adenosis: increasing the number of ducts in the terminal unit. Here, adenosis comes with the background of fibrosis. You can also find calcifications.

3- complex sclerosing lesion

Like a rose. In the middle there is a scar or fibrosis, and surrounded by dilated ducts. So it has fibrosis and adenosis.

4- papilloma

Finger like projection with fibrovascular core, lined by 2 layers (myoepithelial layer and the luminal layer).

*They aren't precursors for cancer. They are polyclonal. They can be found adjacent to a malignant tumor.

3-Proliferative disease with atypia

-Here we have a lesion with a cytologic or architectural problem, but still it does not meet the criteria of carcinoma in situ. To be considered carcinoma in situ, it has to have full cytological and architectural abnormalities. Lesions that have atypia but do not have full abnormality are put in these two categories:

1-atypical lobular hyperplasia (ALH): resembles lobular carcinoma in situ (LCIS)

2-atypical ductal hyperplasia (ADH): resembles ductal carcinoma in situ (DCIS)

-They are clonal proliferations having some, but not all, histological features that are required for the diagnosis of carcinoma in situ. (They

can't be classified as carcinoma in situ, or epithelial hyperplasia, so we classify them as proliferative with atypia).

*Associated with a moderately increased risk of carcinoma

-In histology: The ducts are hyperplastic (you can find more than one layer). The difference here is that we have some hyperchromatic cells, you can find mitotic figures and there is also atypia. But this is not enough to be called carcinoma in situ; and you can't downgrade them to epithelial hyperplasia, so we put them in this category.

❖Non invasive (in situ) carcinoma:

Include:

1. Ductal carcinoma in situ, DCIS

2. Lobular carcinoma in situ, LCIS

*Both types arise from cells in the terminal duct that give rise to lobules.

*Both are clonal, both are malignant with no stromal invasion, no lymphatic invasion and no vascular invasion. They have the cytological and morphological changes to be called carcinoma, but none of them has invaded the basement membrane and are still trapped in the duct or the lobule they formed in.

By definition; both are confined by a basement membrane and do not invade into stroma or lymphovascular channels.

1-Lobular carcinoma in situ

-Malignant clonal proliferation of cells within **ducts and lobules**.

-Cells grow in a discohesive fashion because of an acquired loss of the tumor suppressive adhesion protein E-cadherin.

***They are differentiated from Ductal carcinoma in situ by the loss of E-cadherin.**

The term “lobular” was used to describe this lesion because the cells expand but do not distort involved spaces and, thus, the underlying lobular architecture is preserved.

2-Ductal carcinoma in situ

-Malignant clonal proliferation of epithelial cells within **ducts and lobules**.

-The E-cadherin is preserved.

DCIS has a wide variety of histological appearances including:

Solid (fill the duct completely) , comedo (tooth paste like necrosis in the center), cribriform (cookie cutter like), papillary, and micropapillary (no fibrovascular cores)

Frequently associated with Calcifications ◊ detected by mammography

DCIS management:

1- Simple mastectomy:, The prognosis is excellent (97% long-term survival after simple mastectomy (no lymph node dissection))
2- Radiation
3- We might use Tamaxofin (estrogen receptor antagonist)

Significance:

Might be adjacent to invasive CA (we have to make extensive sampling of the breast)

Become invasive if untreated (1/3 of cases)