رقم المذكرة
146

كلية الطب البشري
السنة الثانية
الفصل الدراسي الثاني
1430 -1429 هـ

عدد الصفحات
29

2nd year

PATH

GENITAL SYSTEM

Now with
Breast lecture For Dr. Sophia
- 13- Jun -

GIRLS

UTERINE CORPUS

ACUTE ENDOMETRITIS

- Is most often related to intrauterine trauma from instrumentation, intrauterine contraceptive device or complications of pregnancy such as post partum retention of placental fragments.
- Is most often caused by staph aureus and streptococcus.

CHRONIC ENDOMETRITIS

- Granulomatous endometritis is seen in TB.

ENDOMETRIOSIS

- Is charcterized by the presence and proliferation of ectopic endometrial tissue.
- is non-neoplastic, not associated with carcinoma. May cause infertility.
- There is menstrual bleeding in the ectopic endometrium, resulting in blood filled spaces (chocolate cyst).
- Sites: commonly in the pelvic area eg. ovary, pelvic ligaments etc.

Adenomyosis

- Is characterized by islands of endometrium in the myometrium of uterus.

ENDOMETRIAL POLYP

- Is a benign lesion
- Usually in females > 40yrs
- May result in uterine bleeding.

ENDOMETRIUM

Endometrial Hyperplasia

- Induced by Prolonged or marked excess of estrogen relative to progestin .
- Hyperplasia ranging from simple hyperplasia to complex hyperplasia .
- Both are classified as with or without atypia.
- Appears to be a continuum based on the level and duration of the estrogen excess.

Endometrial Hyperplasia

- The endometrial hyperplasia may progress to endometrial carcinoma.
- The development of cancer is based on the level and duration of the estrogen excess.
- The risk is depending on the severity of the hyperplastic changes and associated cellular atypia.
- Other potential factors include :

-failure of ovulation

-prolonged administration of estrogenic steroids without counter balancing progestins

-Polycystic ovary

-Cortical stromal hyperplasia

-Granulosa-Theca cell tumors.

- Milder forms of hyperplasia tends to occur in younger patients .
- The great majority of mild hyperplasia regress , either spontaneously or after treatment .
- The more severe forms ,occur predominantly in peri- and postmenopausal women .
- The last form has a significant premalignant potential.

Endometrial Hyperplasia ,Clinical Features

- Abnormal uterine bleeding .
- The severity of bleeding is not necessarily proportional to that of the histologic changes.
- Hyperplasia are uncommon in asymptomatic women .

Endometrial Hyperplasia Risk Factors

- Obesity
- Western diet
- Nulliparity
- Diabetes Mellitus
- Hypertension
- Hyperestrinism

Macroscopic ,Endometrial Hyperplasia

- Might be close to normal, or may show considerable thickening of either the entire mucosa or focal regions.
- When it is focal ,the lesion may acquire a polypoid aspect.
- The color is pale pink
- Curettage usually yields increased amount of tissue

Risk for Cancer in Endometrial Hyperplasia

- Hyperplasia with nuclear atypia has
  20-25 % progression to carcinoma
- Hyperplasia without atypia has 3% progression to carcinoma

Endometrial Adenocarcinoma

- In the USA ,Endometrial Carcinoma is the most frequent cancer of the female genital tract.
- Before it was much less common than
  cervical cancer

Endometrial Adenocarcinoma

Epidemiology

- Most frequently between the ages of 55 and 65
- Uncommon under 40 years of age

Endometrial Carcinoma Risk Factors

- Obesity
- Diabetes
- Hypertension
- Infertility ;single and nulliparous, and non ovulatory cycles
- Any factor increases the estrogen stimulation.
- The majority of the cases arise on a background of endometrial hyperplasia
- 20% of endometrial carcinoma there is no association with hyperestrinism or preexisting hyperplasia ,these cancers tend to occur late in life and have a poor prognosis.

Endometrial Adenocarcinoma Morphology

- May closely resemble normal endometrium
- May be exophytic
- May be Infiltrative
- May be polypoid

Endometrial Carcinoma Grading and staging

- Grading is from 1 to 3
- Staging is from 1 to 4
- Stage 1 : Confined to uterus corpus
- Stage 2 : Cervix involvement
- Stage 3 : beyond the uterus ,but within the true pelvis
- Stage 4 : Distant metastasis

Endometrial Adenocarcinoma Clinical Outcome

- First signs are marked leukorrhea and irregular bleeding ,in a postmenopausal woman
- This reflect erosion and ulceration of the endometrial surface
- In end stages the uterus might be palpated ,and in time it becomes fixed to surrounding structures

Endometrial Adenocarcinoma Survival ,5 year

- Stage 1: 95%
- Stage 2 : 30-50 %
- Stage 3 and 4 : less than 20%

MYOMETRIUM

① LEIOMYOMA / FIBROIDS

- Is the most common uterine tumor.
- It is a benign neoplasm. Malignant transformation almost never occurs.
- Can be multiple.
- Is estrogen sensitive. The tumor often increases in pregnancy and decreases following menopause.
- Can be sub-endometrial, intramural or sub-serosal.
- Presents as menorrhagia, can cause infertility.

② LEIOMYOSARCOMA

- Malignant smooth muscle tumor.
- Arises denovo.
- Is uncommon.

CERVIX

Dr. Sufia Husain

EROSION

Is characterized by columnar epithelium replacing squamous epithelium, grossly resulting in an erythematous area.
It is sometimes a manifestation of chronic cervicitis.

CERVICITIS

Can be caused by staphylococci, enterococci, gardenerella vaginalis, trichomonas vaginalis, candida albicans, and chlamydia trachomatis.
Most often involves the endocervix.
It is often asymptomatic but may have vaginal discharge.

CERVICAL POLYPS

Are inflammatory proliferations of cervical mucosa.
They are not true neoplasms.

Cervix Carcinoma

- One of the major causes of cancer-related death in women, specially in developing world.
- Most common cervical cancer is squamous cell carcinoma. Other types are adenocarcinoma, neuroendocrine carcinoma etc.
- Nowadays there is dramatic improvement because of early diagnosis and treatment.
- The wide use of PAP screening lowered the incidence of invasive cancer .

Precancerous lesion

- Squamous Intraepithelial Lesion (SIL) is the pre-cancerous(non invasive) lesion and detection of these lesions made curative treatment is possible.
- All invasive squamous cell carcinomas arise from pre-cancer epithelial changes referred as Cervical Intraepithelial Neoplasia (CIN) or Squamous intraepithelial lesions.
- Not all cases of CIN progress to invasive cancer.

The majority of cancers are preceded by a precancerous lesion. This lesion may exist in the noninvasive stage for as long as 20 years and shed abnormal cells that can be detected on cytologic examination.

These precancerous changes
- (1) they do not invariably progress to cancer and may spontaneously regress,
- the risk of persistence or progression to cancer increases in the high grade precancerous lesions;
- (2) they are associated with papillomaviruses, and high-risk HPV types are found in increasing frequency in the higher-grade precursors

CIN

- Cytologic examination can detect CIN (SIL) long before any abnormality can be seen grossly .
- Pre-cancer changes can precede the development of an overt cancer by many years.
- CIN lesions may begin as Low Grade CIN and progress to High Grade CIN, or they might start as HG lesion.

CIN histology.

- On the basis of histology ,pre-cancer lesions are graded as follows:

-CIN I = Mild Dysplasia: Lower 1/3rd of the epithelium is replaced by pleomorphic cells

-CIN II = Moderate Dysplasia: Lower 2/3rd of the epithelium is replaced by pleomorphic cells

-CIN III = Severe Dysplasia and Carcinoma in situ. All levels of the epithelium is replaced by pleomorphic cells, (full thickness)

- Cancer is invasive once the basement membrane is ruptured and tumor cells extend into the underlying tissue.
- On gross examination the cervix looks relatively normal. There is no tumor mass.

Cytology screening for precancerous lesions

- The cervix is examined and the cells lining the cervical wall at the transformation zone are scrapped/ sampled with a spatula and then spread on a slide. They are then fixed, stained (Papanicolaou stain/pap stain) and examined under a light microscope.

Cytological cervical Screening with pap stain

- In cytology smears we separate pre-cancer lesions into two groups :
- Low Grade SIL
- High Grade SIL
- Of Low Grade SIL 1-5 % become invasive
- Of High Grade SIL incidence is 6-74%

- CIN I = Low grade SIL
- CIN II = High grade SIL
- CIN III = High grade SIL

Risk Factors for CIN and invasive cervical carcinoma

- Early age at first intercourse
- Multiple sexual partners
- A male partner with multiple previous sexual partners
- Persistent infection by high risk papillomaviruses
- Some other risky factors; low socioeconomic groups
- rare among virgins, multiple pregnancies.

Human papilloma virus

- HPV is the number one reason for abnormal cells of the cervix.
- HPV is a skin virus, which results in warts, common warts ,flat warts, genital warts (condylomas), and planter warts.and precancerous lesions
- HPV can be detected in 85 -90 % of pre-cancer lesions
- High risk types HPV : 16, 18, 31, 33, 35, 39, 45, 52, 56, 58, and 59 .
- Low risk types HPV :6, 11, 42, 44 . These types result in condylomas.

NOTE: There are no visible symptoms that you have dysplasia of the cervix ,without a Pap smear or Pap exam .This is why we have annual pap exams ,as to detect any abnormal cells . The Pap smear detects early HPV infection.

- The common testing procedure for HPV infection is an annual pap exam .
- There is the HPV DNA ISH test ,the Diegene Hyprid Capture test . This test will determine whether you carry high or low risk strains of the virus.

Cervical Carcinoma ,Invasive

- 75 -90% of invasive cancers are Squamous cell carcinomas ,which generally evolves from pre-cancer CIN.
- The remainder are Adenocarcinoma.
- Squamous cell cancers are appearing in increasingly younger women ,now with a peak incidence at about 45 years, about 10-15 years after detection of their precursors.

Cervical Carcinoma .Morphology

- Mainly in the region of the transformation zone ,and range from microscopic foci of early stromal invasion to grossly frank tumors encircling the Os .
- The tumors may be invisible or exophytic .
- Cervical carcinomas are graded from 1 to 3 based on cellular differentiation and staged from 1 to 4 depending on clinical spread.

Cervical Carcinoma, Staging

0 Carcinoma in Situ
1 Confined to the cervix
2 Extension beyond the cervix without extension to the lower third of Vagina or Pelvic Wall
3 Extension to the pelvic wall and / or lower third of the vagina
4 Extends to adjacent organs

Cervical Carcinoma ,Clinical Course

- Many of cervical cancers are diagnosed in early stages , and the vast majority are diagnosed in the pre-invasive phase.
- More advanced cases are seen in women who either have never had a Pap smear or have waited many years since the prior smear.

Cervical Carcinoma ,Survival

- laser or cone biopsy is the most effective method of managing patients with High grade SIL in cancer prevention .

Ovarian Cysts and Tumors

Dr. Sufia Husain

- The most important medical problems in ovaries are the neoplasms
- Silent growth of ovarian tumors is the rule ,which make them so dangerous
- Non neoplastic cysts are common but they are not serious problems
- Primary inflammation of ovaries is rare
- Frequently ,the ovaries affected by endometriosis.

Non-Neoplastic and Functional Cysts of ovary

- Non Neoplastic Cyst are more common than the neoplastic ones
- Follicular and Luteal cysts are most probably physiologic
- cystic follicles:Innocent lesions originate from unruptured follicles or in follicles that have ruptured and sealed. Usually they are small 1 – 1.5 cm ,and filled by clear fluid

Follicular Cyst

- Is due to distention of unruptured graafian follicle
- It is sometimes associated with hyperestrinism and endometrial hyperplasia.

Corpus luteum cyst

- It results from hemorrhage into a persistent mature corpus luteum.

Theca lutein cyst

- Results from gonadotropin stimulation.
- Often multiple and bilateral.

Chocolate cyst

- Is a blood containing cyst resulting from ovarian endometriosis with hemorrhage.
- The ovary is the most common site for endometriosis.

Polycystic Ovaries/ Stein-Leventhal Syndrome

- Young women ,and usually in girls after menarche.

-Oligomenorrhea
-hirsutism
-infertility
-Obesity

- Secondary to excessive production of estrogens and androgens, mainly androgens
- The ovaries are usually twice normal in size ,gray-white with smooth outer surface
- Studded with sub cortical cysts 0.5 to 1.5 cm in diameter.
- Histologically ,thickened fibrosed outer tunica
- Multiple cysts lined by granulosa cells
- Absence of corpora lutea
- High level of LH and low FSH

Ovarian Tumors

- Fifth most common cancer in the USA
- Fifth leading cause of cancer death in women
- Diversity of pathologic entities because of the three cell types make up the normal ovary

Ovarian Tumors classification

- Three cell types :
- 1- the surface epithelium tumors
- 2- Germ cells tumors
- 3- Stromal /sex cord cells tumors

Classification of Ovarian Tumors, Surface Epithelial Tumors

1- Serous Tumors : Benign ,Borderline,And malignant
2- Mucinous Tumors. : Benign ,Borderline , and malignant
3- Endometrioid Tumors. : Benign, Borderline, and malignant
4- Transitional cell Tumors. : Brenner tumors, Benign ,Borderline ,and malignant
5- Undifferentiated Carcinoma

Classification of Ovarian Tumors, Sex Cord-Stromal tumors

1-Granulosa Cell tuomr
2-Thecoma –Fibroma
3-Sertoli-Leydig cell tumor
4-Gynandroblastoma
5-Unclassified

Classification of Ovarian Tumors, Germ Cell Tumors

1 -Dysgerminoma
2-Yolk Sac Tumor
3-Embryonal Carcinoma
4-Choriocarcinoma
5-Teratoma : Mature, Immature
6-Polyembryoma

Ovarian Tumors Surface Epithelium Origin

- Neoplasms of surface epithelium account for the great majority of all primary ovarian tumors.
- 65 – 70 % of overall tumors
- 90 % of malignant tumors
- Age 20+
- Traditionally divided into Benign ,Malignant ,and Borderline in malignancy
- Can be strictly epithelial (serous ,Mucinous)
- Can have stromal component (Cystadenofibroma , Brenner tumor)
- The intermediate ,or the borderline tumors are referred as tumors of low malignant potential. These appear to be low grade cancers with limited invasive potential.They have better prognosis

Serous Tumors

- The most frequent ovarian tumor
- Age is 30 -40
- May be solid ,usually cystic
- Cystadenoma or Cystadenofibroma
- 65% benign ,15% low malignant potential , and 25% malignant
- 65 % of all ovarian cancers
- Most are large ,spherical to ovoid ,cystic structures
- 5 – 10 cm and might be 30-40 cm
- 25% of benign tumors are bilateral
- The surface of the benign is smooth and glistening .In contrast to the malignant forms ,the surface is nodular and irregular
- Cystic spaces are filled by serous fluide
- Papillary formation is very important and need to be sampled well
- Histologically the benign tumors are lined by a single layer of tall columnar epithelium
- Papillary formation can be seen in both the benign and the malignant ones
- Psammoma bodies could be seen
- Between the clearly benign and the solid malignant tumors we can see the tumors of low malignant potential
- LMP tumors may seed the peritoneum, the implants of tumors are non invasive. Sometimes may behave as invasive peritoneal implants.
- The prognosis of LMP tumors is determined mainly by the nature of the peritoneal implants
- Prognosis of invasive Serous cystadenocarcinoma after surgery ,chemotherapy ,and radiation is poor and depend on stage
- 70% 5 –year survival for the tumors confined to the ovary

Serous Tumors

- 5 year survival f0r LMP is 100% ,
- Malignant Tumors with capsular invasion ,survival for 10 years is 13%
- LMP with capsular invasion the 10 year survival is 80%.

Mucinous Tumors
- Epithelium is consists of mucin-producing cells
- Less likely to be malignant
- 10% of ovarian cancers
- 80% of them benign
- 10% LMP
- 10% malignant

Brenner Tumor
- Transitional cell epithelium
- Most are benign

Sex Cord Tumors

Granulosa Cell Tumors
- Most postmenopausal ,could be any age
- Unilateral
- Solid and cystic
- Tiny to large in size
- Produce estrogen
- Malignant behaviour in 5-25%

Thecoma-Fibroma
- Any age
- Unilateral
- Solid gray to yellow
- Rarely malignant

Sertoli – Leydig cell Tumors
- All ages
- Unilateral Gray to yellow
- Produce androgens
- Uncommonly malignant

Germ Cell Tumors

Dysgerminoma
- 2^{nd} and 3^{rd} decades
- Unilateral
- Counterpart to Seminoma
- Solid ,gray to yellow
- All malignant
- PLAP positive

Embryonal Carcinoma
-2nd and 3rd decades
- aggressive tumor
- solid
-CD 30 positive

Teratoma
- 15-20 % of Ovarian tumors
- Majority in the first 2 decades
- The younger the patient ,the greater the likelihood of malignancy
- Over 90% are benign cystic ,mature teratomas
- Immature teratomas are malignant and are rare.

Endodermal Sinus (Yolk Sac) Tumor
- the tumor is rich in α-fetoprotein and α1-antitrypsin.
- Its characteristic histologic feature is a glomerulus-like structure composed of a central blood vessel enveloped by germ cells within a space lined by germ cells (Schiller-Duval body)
- stained for α-fetoprotein by immunoperoxidase techniques
- Most patients are children or young women presenting with abdominal pain and a rapidly developing pelvic mass. The tumors usually appear to involve a single ovary but grow rapidly and aggressively.

Choriocarcinoma
- More commonly of placental origin, ~~the choriocarcinoma, similar to the~~
- Most ovarian choriocarcinomas exist in combination with other germ cell tumors, and pure choriocarcinomas are extremely rare.
- are aggressive tumors that generally have metastasized widely through the bloodstream to the lungs, liver, bone, and other viscera by the time of diagnosis.
- high levels of chorionic gonadotropins that are sometimes helpful in establishing the diagnosis or detecting recurrences.

Metastatic Carcinoma
- Older ages
- Mostly Bilateral
- Primaries are Breast ,lung, and G.I.T. (Krukenberg Tumors)

Q: What are ! common pediatric brain tumer ?

Q: ~ ≤ ⇒ ⇒ adult ∴ ⇒ ?

Q: What is ! CSF finding in Acute Aseptic & acute pyogenic meningitis ?

⇒ ↑ lymphocyte

⇒ ↑ neutrophil

Q: What is the possible etiology of pyogenic meningitis in 3 month old infant & in 15 years old boy?

Q: What is the diagnosis ?

- 60 old man supraclavicular Lymphadenopathy & cough metastatic Lung cancer.

- 7 years with cervical Lymphadenopathy & cough. pharyngitis.

- 45 years with axillary lymphadenitis breast cancer.

- Florid reactive follicular Hyperplasia, clusters of epithelioid histocytes (Micro granulomas). (Toxoplasmosis)

- Kapposi Sarcoma (HIV)

- Bartonella henselae (Cat scratch disease)

- paul Bunnell test = Monospot test. (infectious mononucleosis).

- well-circ. necrosis with many plasmacytoid monocyte. (Kikuchi).

⇒ HIV encephalopathy hallmark is:-

↳ multinucleatic giant cell

⇒ Tuft of proliferated endothelial cell suggests the brain tumer is:-

↳ angiosarcoma

↳ Epindymoma

answer ↳ glioblastoma ⇝ CB it has hemorrage.

↳ medulloblastoma

↳ metastatic lung tumer.

① lymphoblastic lymphoma.

② mantle cell lymphoma

③ Mycosis Fungoides
, sezary syndrom

④ Anaplastic Large cell lymphoma.

④ - T-cell or NK cell Large anaplastic cell ass. ALK gene, common in children.

③ - indolent CD4 TH involve the skin, 3 stages / Leukemia phase

② - small to medium sized B-cells extranodal submucosal nodules in bowel.

① - children & adolescents T/B cell type.

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① Nodular sclerosis HL

② Mixed cellularity HL

③ lymphocyte depletion HL

④ Nodular lymphocyte predominance HL

② - Most frequent in older people 2nd most frequent.

④ - popcorn cell in contrast to R cell They are CD 20 +ve CD 30 & CD 15 -ve

① - Band fibrosis, lacunar cell most common in.

③ - High grade type majority of the cells are abnormal RS- & RS like cells.

① Hodgkin lymphoma

② Non - Hodgkin lymphoma.

② - mesentric nodes & Waldeyer ring commonly involved

① - localized to a single axial group of nodes.

① - extranodal involvement uncommon.

② - commonly involve extranodal sites :- GI - skin.

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① Burkitt lymphoma.

② Diffuse Large B-cell lymphoma

③ Extranodal Marginal zone mult lymphoma

④ Follicular lymphoma

⑤ small lymphocytic lymphoma SLL
Chronic ⇒ Leukemia CLL

④ - t (14, 18) CE
overexpression of BCL_2

③ - typically arise areas of immune activation
(Hishmoto .. , Sjogren syndrom , H. pylori).

① - starry sky apperance

② - Commonest type of lymphoma effect elderly & childhood population.

⑤ - small well-differentiated mature B-lymphocyte with

Ependymoma ⇒ There are tubules or rosettes.

meningiomas ⇒ benign & slow grad

pilocytic astrocytoma ⇒ common in children & it is in the cerebellum / 3rd ventricle / optic N.

medulloblastoma ⇒ composed of sheets of undifferentiated small round blue cell tumer

Hemangioblastoma ⇒ Von - Hippel - Lindau.

Jakob disease ⇒ abnormal patient which is congored +ve & PAS +ve

multiple foci ⇒ metastasis.

لاتنسوني من دعواتكم

وسامحوني إذا أخطأت

Breast Pathology

Sufia Husain

Normal Breast

- Specialized epithelium and stroma that gives rise to both benign and malignant lesions
- Six to ten major ductal systems originate at the nipple.
- Branching of the large ducts leads to the terminal duct lobular units.
- The TDU branches into grapelike clusters of small acini to form the lobule.

Clinical Presentation

1) Pain (mastalgia): is the most common breast symptom and may be cyclical with menses or noncyclical. Diffuse cyclical pain has no pathologic significance. Noncyclical pain is usually associated with a focal site in the breast. Causes include ruptured cysts or areas of prior injury or infections,or sometime no specific cause.

Although the great majority of painful masses are benign, about 10% of breast cancers present with pain, and all masses need to be investigated.

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2)Palpable mass

3)Nipple discharge:

Milky discharge has not been associated with malignancy.

Bloody or serous discharges are most commonly associated with benign lesions but, rarely, can be due to a malignancy.

Characteristics of Breast Carcinomas by Clinical Presentation

- Palpable mass
- Mammographic density
- Mammographic calcifications

Mammographic screening was introduced in the 1980s as a means to detect small, nonpalpable breast carcinomas not associated with breast symptoms. Screening is generally recommended to start at age 40. Younger women usually undergo mammography only if they are at high risk for developing carcinoma. *The principal mammographic signs of breast carcinoma are densities and calcifications.*

Benign Epithelial Lesions of breast

1- Non proliferative breast changes
2- Proliferative breast disease
3- Atypical hyperplasia

Non proliferative Breast Changes (Fibrocystic Changes)

- Should be distinguished from the proliferative changes associated with increased incidence of breast cancer ,
- No increased risk for cancer
- Could produce palpable breast mass, mammographic densities, calcifications ,or nipple discharge.
- Cysts are the most common cause of a palpable mass and they are alarming when they are solitary, firm .
- Three patterns of morphologic changes :

1- Cyst formation
2- Fibrosis
3- Adenosis

- Cysts :small to big in size ,lined by benign epithelium with apocrine metaplasia
- Semi-translucent or turbid fluid
- Fibrosis : contribute to the palpable firmness of the breast
- Adenosis : Increase in the number of acini per lobule.
- Normal adenosis could be seen during pregnancy
- ~~In a study of normal breasts in unselected forensic postmortem cases ,Grossly evident cysts and fibrosis were found in 20% and histologic changes in 59% of women~~

Proliferative Disease without Atypia

- Rarely form palpable masses
- Detected as mammographic densities.
- Incidental finding
- Large duct papilloma present in 80% as nipple discharge.
- Risk for cancer is 1.5 – 2 times normal
- ~~Proliferation of ductal epithelium and/or stroma without cellular abnormalities suggestive of cancer~~
- Many entities are included here :

1- Epithelial hyperplasia
2- Sclerosing adenosis
3- complex sclerosing lesions/radial scar
3- Papillomas

Epithelial Hyperplasia.

In the normal breast, only myoepithelial cells and a single layer of luminal cells. Epithelial hyperplasia is defined by the presence of more than two cell layers. Hyperplasia is moderate to florid when there are more than four cell layers. The proliferating epithelium, often including both luminal and myoepithelial cells, fills and distends the ducts and lobules.

Sclerosing Adenosis.
-number of acini per terminal duct is increased.
-normal lobular arrangement is maintained.
-The acini are compressed and distorted in the. Myoepithelial cells are usually prominent.

Papillomas
- are composed of multiple branching fibrovascular cores, each having a connective tissue axis lined by luminal and myoepithelial cells.
- It occurs within a dilated duct. Epithelial hyperplasia and apocrine metaplasia are frequently present.

Proliferative Breast Disease with Atpyia

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

Breast cancer

Breast Carcinoma

- The most common malignancy of breast is carcinoma
- Carcinoma of the breast is the most common cancer in women
- Women who lives to age 90 has a one in eight chance to have breast cancer
- Mammographic screening increased dramatically the detection of small invasive cancers
- DCIS is almost exclusively detected by mammography ,so the incidence of DCIS is increased
- The number of women with an advanced cancer is markedly decreased

Because of mammograph

~~Breast Cancer:~~
- ~~During 1980s the number of women dying of breast cancer remained steady ?~~
- ~~May be the screening is detecting clinically insignificant cancers~~
- ~~In 1994,the mortality rate started to decline.~~
- Currently only 20% of the women with breast cancer are expected to die of the disease

Breast Cancer
Risk Factors

- Age : breast cancer is rare before 25 yrs, except familial forms ,77% of cases occur in women >50 yrs of age. The average age at diagnosis is 64 years
- Age at Menarche: Menarche younger than age 11 have a 20% increased risk to that who have their menarch at 14yrs.
- First Live birth: Full term pregnancy before age 20 years has half the risk of nulliparous ,or women who have first birth after age 35. i.e. 1st Live birth at younger age reduces the risk.
- First Degree relative with Breast Cancer . The risk increases with the number of affected first degree relatives. The majority of cancers occur in women without such history
- Breast Biopsy :Atypical hyperplasia increases the risk for breast cancer
- Race :Overall incidence of breast cancer is lower in African American women
- Estrogen Exposure: postmenopausal hormone replacement slightly increase the risk
- Radiation exposure: Higher rate of breast cancer
- Carcinoma of the contralateral breast or Endometrium
- Geographic influence :Four to seven times in USA and Europe higher than those in other countries
- Diet: Fat might increase the risk
- Obesity : may play a role
- Exercise :some studies showed degreased risk
- Breast–Feeding :The longer the women breast –feed ,the lower the risk
- Environmental toxins: 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, be divided into sporadic cases, possibly related to hormonal exposure, and hereditary cases, associated with family history or germ-line mutations

<u>Hereditary Breast Cancer</u>

- A family history of breast cancer in a first-degree relative is reported in 13% of women with the disease
- *About 25% of familial cancers (or around 3% of all breast cancers) can be attributed to two highly penetrant autosomal-dominant genes: BRCA1 and BRCA2*

<u>Sporadic Breast Cancer</u>

- *The major risk factors for sporadic breast cancer are related to 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 ER

Breast Carcinoma
Classification

- Almost all are Adenocarcinoma
- Divided into In situ Carcinoma and Invasive carcinoma

Breast Carcinoma

Classification of Carcinoma in situ

1- DCIS In Situ Carcinoma 80%
2- LCIS 20%

DCIS(Ductal Carcinoma In Situ)

- Rapidly increased in the past two decades
- Half of mammographically detected cancers
- Most frequently as a calcifications
- Less frequently as a density or a vaquely palpable mass or nipple discharge
- Many subtypes

-Comedocarcinoma,
-solid ,
-Papillary,
-and micropapillary.

Paget's Disease

- Rare manifestation of breast cancer(1 to 2 %)
- Pruritus is common ,might be mistaken for Eczema, presents as a unilateral erythematous eruption with a scale crust.
- Malignant cells, referred to as Paget cells and are fopund scattered ion 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.
- past, all women were treated with mastectomy, and the current practice of surgical excision usually followed by radiation is largely curative
- The consensus seems to be that many cases of small, low-grade DCIS, and probably most cases of high-grade and extensive DCIS, progress to invasive carcinoma, emphasizing the importance of proper diagnosis and appropriate therapy for this condition.

- Breast conservation is appropriate for most women with DCIS but results in a slightly higher risk of recurrence and therefore death from breast cancer. The major risk factors for recurrence are (1) grade, (2) size, and (3) margins. of the tumor .

LCIS -Lobular Carcinoma in Situ

- Always an incidental finding in a biopsy performed for another reason
- Infrequent (1% to 6%)of all carcinomas
- Bilateral in 20% to 40% of women when both breasts are biopsied
- LCIS is frequently multicentric and bilateral and subsequent carcinomas occur at equal frequency in both breasts

Invasive Breast Carcinoma Classification

- Invasive Carcinoma :

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

- In young women or in older women not undergoing mammographic screening, invasive carcinoma almost always presents as a 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
- Grossly ,firm ,hard, and have an irregular border
- In the center ,there are small foci of chalky white stroma and occasionally calcifications

Invasive Carcinoma

- Characteristic grating sound when cut or scraped
- Could be soft and well demarcated
- Accompanied by varying amounts of DCIS
- Carcinomas associated with a large amount of DCIS require large excisions with wide margins to reduce local recurrences
- Most are firm to hard with irregular margins
- Single infiltrating cells ,often one cell width
- No tubules or papillary formation

Medullary Carcinoma

- Well circumscribed mass
- May mistaken clinically and radiologically for fibroadenoma
- No desmoplasia
- Soft fleshy consistency

Colloid Carcinoma

- Commonly as a circumscribed mass
- Older women
- grow slowly
- Extremely soft
- The consistency and appearance of gray-Blue gelatin

Breast Carcinoma , Major Prognostic Factors

- 1- Invasive or In situ disease: By definition, in situ carcinoma is confined to the ductal system and cannot metastasize. Breast cancer deaths associated with DCIS are due to the subsequent development of invasive carcinoma or areas of invasion undetected at the time of diagnosis. 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.

Sentinel lymph nodes: Most breast carcinomas drain to one or two *sentinel nodes* that can be identified by radiotracer colored dye, or both. The sentinel node is highly predictive of the status of the remaining nodes. Sentinel node biopsy can spare women the increased morbidity of a complete axillary dissection.

- 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.

- 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, such cases have fortunately decreased in frequency and are 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: tubular, mucinous, medullary, lobular, and papillary have better prognosis.

- 2- Tumor Grade: The most commonly used grading system to assess the degree of tumor differentiation (*Bloom Richardson*) combines nuclear grade, tubule formation, and mitotic rate. There are there grades and grade 1 has better prognosis then grade2.

- 3- Estrogen and progesteron 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 chemotherapuetic 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

STROMAL TUMORS

- 2 basic stromal tumors are
  - fibroadenoma
  - Phylloids tumor

Fibroadenoma

- The most common benign tumor of the female breast
- Any age ,most common before age 30
- Usually present with a palpable mass
- Regression usually occurs after menopause
- Spherical nodules
- Sharply demarcated
- Freely movable
- Size vary
- Proliferation in both glands and stroma
- Treatment: lumpectomy (only the lump is removed)

Phylloides tumor

- Phyllodes tumors, like fibroadenomas, arise from intralobular stroma. Although they can occur at any age, most present in the sixth decade, 10 to 20 years later than the average presentation of a fibroadenoma
- Most present as palpable masses
- Phyllodes tumors must be excised with wide margins to avoid the high risk of local recurrences.
- The majority are low-grade tumors that may recur locally but only rarely metastasize. Rare high-grade lesions behave aggressively, with frequent local recurrences and distant hematogenous metastases in about one third of cases.