SAQs

{ ومن لم يذق مرّ التعلُّمِ **ساعةً**.. تجرع ذلَّ الجهل **طوال** حياتهِ }

References:

Team work, First Aid & Kaplan Lecture Notes.

Uterine Corpus

Endometrial hyperplasia:

Refers to a histological proliferation of endometrial glands with 2 important histopathologic categories:
• Benign endometrial hyperplasia shows uniform remodeling of glands with cyst formation.
• Endometrial intraepithelial neoplasia shows crowded architecture and cytologic alteration on biopsy.
• Patients are at high risk for endometrial adenocarcinoma.

TABLE 9-14. Types of Endometrial Hyperplasia, Cytologic Features, and Progression to Endometrial Carcinoma

Type	Cytologic Features	Progression to Endometrial Cancer (%)
Simple	Cystic hyperplasia without atypia.	1
Complex	Adenomatous hyperplasia without atypia.	3–5
Simple with atypia	Cystic hyperplasia with atypia.	8–10
Complex with atypia	Adenomatous hyperplasia with atypia.	29

Endometrial adenocarcinoma:

Is the most common malignant tumor of the lower female genital tract. It most commonly affects postmenopausal women who present with abnormal uterine bleeding. Risk factors are mostly related to estrogen:

- Early menarche and late menopause • Nulliparity • Hypertension and diabetes • Obesity
- Chronic anovulation • Estrogen-producing ovarian tumors (granulosa cell tumors)
- ERT and tamoxifen • Endometrial hyperplasia (complex atypical hyperplasia)
- Lynch syndrome (colorectal, endometrial, and ovarian cancers)

Endometrial adenocarcinoma typically forms a tan polypoid endometrial mass; invasion of myometrium is prognostically important.

- Endometrioid adenocarcinoma (most common histological type): associated with *PTEN* mutations
- Serous tumors: associated with *TP53* mutations

Leiomyoma (fibroid):

- The most common tumor of the female genital tract, is a benign, smooth muscle tumor of the myometrium. Leiomyomas have a high incidence in African Americans, though they are common across all populations. Their growth is estrogen-dependent.
- Leiomyomas may present with menorrhagia, abdominal mass, pelvic/back pain, suprapubic discomfort, or infertility and spontaneous abortion.
- Grossly, leiomyomas form well-circumscribed, rubbery, white-tan masses with a whorled, trabeculated appearance on cut section. Leiomyomas are commonly multiple, and may have subserosal, intramural, and submucosal location. The malignant variant is leiomyosarcoma.

CHARACTERISTICS OF TYPE I AND TYPE II ENDOMETRIAL CARCINOMAS		
FEATURES	**TYPE I**	**TYPE II**
HISTOLOGIC TYPE	Endometrioid adenocarcinoma	Serous or clear cell carcinoma
AGE	Premenopausal and perimenopausal (50-60 yrs)	Post-menopausal (~ 70 yrs)
UNOPPOSED ESTROGEN	Present	Absent
PRECURSOR LESION	Hyperplasia with atypia	Endometrial intraepithelial carcinoma
GROWTH	Slow growing	Rapidly progressing
GRADE	Low	High
MYOMETRIAL INVASION	Usually superficial	Usually deep
PROGNOSIS	Favorable	Poor
GENETIC ALTERATIONS NOTED	PTEN, microsatellite instability	P53 mutations

Ovaries & PCOS

Table 22-2. Origins of Common Ovarian Neoplasms

	Surface Epithelial Cells	Germ Cell	Sex Cord–Stroma	Metastasis to Ovaries
Age group affected	20+ years	0–25+ years	All ages	Variable
Types	• Serous tumor • Mucinous tumor • Endometrioid tumor • Clear cell tumor • Brenner tumor	• Teratoma • Dysgerminoma • Endodermal sinus tumor • Choriocarcinoma	• Fibroma • Granulosa–theca cell tumor • Sertoli-Leydig cell tumor	
Overall frequency	65–70%	15–20%	5–10%	5%
Percentage of malignant ovarian tumors	90%	3–5%	2–3%	5%

Follicular Cyst: When the LH surge does not occur and the Graafian follicle does not extrude the ovum, it grows and results in a follicular cyst that does not usually require treatment. It goes away on its own after two or three menstrual cycles. Some- times an OCP can be used.

Corpus Luteum Cyst: Hemorrhage into a persistent corpus luteum. Normally after the LH surge, the ovum is extruded. The follicle then turns into a corpus luteum. However, the corpus luteum can sometimes accumulate fluid, thus becoming a corpus luteum cyst. Corpus luteum cysts are also called hemorrhagic cysts. The cysts usually regress spontaneously. There is an association of corpus luteum cysts with the use of ovulation-inducing medication such as clomiphene citrate.

Theca Lutein Cyst Lined with theca interna cells, theca lutein cysts are usually bilateral and often regress spontaneously. They may grow to a large size and rupture. The cysts are associated with molar pregnancy, choriocarcinoma, twin pregnancy, Rh isoimmunization, and ovulation-inducing agents such as clomiphene citrate.

TABLE 9-15. Germ Cell Tumors, Tumor Markers, and Characteristic Features

Germ Cell Tumors	Tumor Markers	Characteristic Features
Dysgerminoma	PLAP, LDH, and hCG	Large round cells with clear cytoplasm.
Endodermal sinus tumor	AFP	Blood vessels with cancer cells resembling primitive glomeruli (Schiller-Duval bodies).
Embryonal carcinoma	hCG and AFP	Large cells, basophilic cytoplasm with indistinct borders.
Choriocarcinoma	hCG	Syncytiotrophoblast and cytotrophoblast.
Teratoma	AFP and hCG	Differentiated somatic cells from endoderm, ectoderm, and mesoderm.

AFP, α-fetoprotein; hCG, human chorionic gonadotropin; LDH, lactate dehydrogenase; PLAP, placental-like alkaline phosphatase.

Epithelial Ovarian Tumors

- Epithelial ovarian tumors are the most common form of ovarian tumor. Risk factors include nulliparity, family history, and germline mutations.
- Previously, epithelial tumors were characterized by histology into the categories cystadenoma (benign), borderline, and cystadenocarcinoma. Now, **serous tumors** are classified as **low grade** and **high grade** for prognostic significance.
- Low grade serous tumors are associated with *KRAS*, *BRAF*, or *ERB 2*mutations.
- Most high grade serous tumors have *TP53* mutations.
- The most common malignant ovarian tumor is **serous cystadenocarcinoma**.
- Hereditary risk factors include *BRCA1* (breast and ovarian cancers) and Lynch syndrome.
- Well-differentiated serous tumors show psammoma bodies and a lining similar to that of the fallopian tube.
- **Mucinous tumors** commonly have goblet cells like intestinal mucosal cells. CA 125 can be used to follow treatment.

Ovarian Germ Cell Tumors

- **Teratoma (dermoid cyst)**
  - Vast majority (>95%) of ovarian (but not testicular) teratomas are benign; commonly occurs in early reproductive years
  - Include elements from all 3 germ cell layers: ectoderm (skin, hair, adnexa, neural tissue), mesoderm (bone, cartilage), and endoderm (thyroid, bronchial tissue)
  - Complications include torsion, rupture, and malignant transformation
  - Can contain hair, teeth, and sebaceous material
  - The term *struma ovarii* is used when there is a preponderance of thyroid tissue
  - Immature teratoma is characterized by histologically immature tissue
- **Dysgerminoma**
  - Malignant; commonly occurs in children and young adults
  - Risk factors include Turner syndrome and disorders of sexual development
  - Gross and microscopic features are like seminomas
  - Are radiosensitive; prognosis is good

Ovarian Sex Cord–Stromal Tumors:

- **Ovarian fibroma:**
  1. Most common stromal tumor; forms a firm, white mass
  2. **Meigs syndrome** refers to the combination of fibroma, ascites, and pleural effusion.
- **Granulosa cell tumor:**
  1. Potentially malignant, **estrogen-producing** tumor
  2. Presentation depends on age:
     - Prepubertal patients with juvenile granulosa cell tumor present with precocious puberty
     - Reproductive age patients present with irregular menses
     - Postmenopausal patients present with vaginal bleeding
  3. Complications include endometrial hyperplasia and cancer
  4. Tumor forms a yellow-white mass that microscopically shows polygonal tumor cells and formation of follicle-like structures (Call-Exner bodies)
- **Sertoli-Leydig cell tumor:**

  An androgen-producing tumor that presents with virilization, usually in young women. Primary sites for metastatic tumor to the ovary include breast cancer, colon cancer, endometrial cancer, and gastric "signet-ring cell" cancer (Krukenberg tumor).

Polycystic ovarian disease (Stein-Leventhal syndrome):

- An endocrine disorder of unknown etiology showing signs of androgen excess (clinical or biochemical), oligoovulation and/or anovulation, and polycystic ovaries.
- Accurate diagnosis requires exclusion of other endocrine disorders that might affect reproduction. Patients are usually young women of reproductive age who present with oligomenorrhea or secondary amenorrhea, hirsutism, infertility, or obesity. Treatment is lifestyle change and hormone therapy.
- Lab studies show elevated luteinizing hormone (LH), low follicle-stimulating hormone (FSH), and elevated testosterone. Gross examination is notable for bilaterally enlarged ovaries with multiple cysts; microscopic examination shows multiple cystic follicles.

Testicular pathology

Infectious Diseases:

ORCHITIS:

- An inflammation of the testes usually caused by the mumps virus and usually affects only one testis.
- If the condition is bilateral (uncommon), it may lead to sterility resulting from atrophy of the seminiferous tubules. In the case of sterility, levels of testosterone are decreased, but levels of FSH and LH are increased.

EPIDIDYMITIS:

- An infection of the epididymis that can be caused by a variety of bacteria.
- < 35 years old: Chlamydia trachomatis and Neisseria gonorrhoeae.
- > 3 5 years old: Escherichia coli and Pseudomonas aeruginosa. A tuberculous infection can start in the epididymis and travel to the seminal vesicles, prostate, and testicles.

Germ Cell Tumors:

SEMINOMA:

Most common germ cell tumor of the testes. Large, so, well-demarcated, gray-white tumor that bulges from the cut surface of the affected testis. Microscopically, large cells with distinct cell borders, pale nuclei, and prominent nucleoli ("fried egg" appearance) as well as a lymphocytic infiltrate are seen. Seminoma is associated with an increase in hCG and placental-like alkaline phosphatase (PLAP) . It mainly affects males between the ages of 1 5 and 3 5 years old. Seminoma metastasizes via the lymphatics and is radiosensitive with an excellent prognosis.

YOLK SAC TUMOR:

Large, may be well demarcated. Microscopically, cells appear as cuboidal to columnar epithelium forming sheets, glands, papillae, and microcysts, and are often associated with hyaline globules. Schiller-Duval bodies, which are structures resembling primitive glomeruli, are a distinctive feature of yolk sac tumors. This is the most common primary testicular neoplasm in children < 3 years. a-Fetoprotein (AFP) can be demonstrated within the cytoplasm of these neoplastic cells.

EMBRYONAL CARCINOMA:

Ill-defined invasive mass containing foci of hemorrhage and necrosis. Metastases are common. Histologically, the cells are large and primitive looking, with basophilic cytoplasm, indistinct cell borders, and large nuclei with prominent nucleoli. The cells may be arranged in undifferentiated, solid sheets or glandular structures. Embryonal carcinoma is associated with an increase in hCG.

CHORIOCARCINOMA:

Grossly, primary tumor is small and nonpalpable. Microscopically, choriocarcinoma is composed of sheets of small cuboidal cells irregularly intermingled with or capped by large, eosinophilic syncytial cells containing multiple dark, pleomorphic nuclei; these represent cytotrophoblastic and syncytiotrophoblastic differentiation, respectively. hCG is elevated. Choriocarcinoma metastasizes hematogenously.

TERATOMAS:

Firm masses that contain cysts and recognizable areas of cartilage and other tissue types. Originating from germ cells, they neoplastically differentiate into ectoderm, endoderm, and mesoderm. Histologically, there are three major variants: mature, immature with or without malignant transformation, and mixed.

- Mature: Fully differentiated tissues from multiple germ cell layers (eg, neural tissue, cartilage, adipose, bone, and epithelium) in a random array.
- Immature: Immature somatic elements reminiscent of those in developing fetal tissue.
- With malignant transformation: Characterized by the development of frank malignancy in preexisting teratomatous elements, usually in the form of a squamous cell carcinoma or adenocarcinoma. Usually occurs in adults.
- Mixed: Combinations of any of the germ cell tumors above may occur in mixed tumors, the most common being a combination of teratoma, embryonal carcinoma, and yolk sac tumors. hCG and AFP are elevated.

Interstitial Cell Tumors:

LEYDIG CELL TUMOR:

Arises from Leydig cells that contain rod-shaped Reinke crystals, and is usually benign in nature. Golden-brown mass consisting of large, uniform cells with indistinct cell borders. It produces androgens or estrogens, leading to gynecomastia in men and precocious puberty in boys. Treatment is orchidectomy.

SERTOLI CELL TUMOR:

Arises from Sertoli cells. Grossly, it is a gray-white to yellow mass. Microscopically, it shows cord-like structures resembling seminiferous tubules. Secretes a small amount of androgens or estrogens that is typically insufficient to induce gynecomastia & loss of libido. It is usually a benign condition, and orchiectomy is curative.

TABLE 9-13. Characteristics, Tumor Markers, and Prognosis of Germ Cell Testicular Tumors

Malignancy	Characteristics	Tumor Markers	Prognosis
Seminoma	Large, well-demarcated mass.	Increased hCG, PLAP	Excellent
Yolk sac tumor	Schiller-Duval bodies.	Increased AFP	Good
Embryonal carcinoma	Ill-defined masses with foci of necrosis and hemorrhage.	Increased hCG	Poor
Choriocarcinoma	Trophoblastic tissue.	Increased hCG	Poor
Teratoma	Derivatives from multiple germ layers (ectoderm, endoderm, mesoderm).	Increased AFP and/or hCG	Good

AFP, α-fetoprotein; hCG, human chorionic gonadotropin; PLAP, placental-like alkaline phosphatase.

Prostate

Benign prostatic hyperplasia (BPH):

- (also called nodular hyperplasia; glandular and stromal hyperplasia) is extremely common.
- Androgens (dihydrotestosterone) play an important role in the pathogenesis, and the lesion is not premalignant.
- The incidence increases with age (age 60 is 70%; age 70 is 80%). BPH typically presents with the following:
  - Decreased caliber and force of stream
  - Trouble starting (hesitancy)/stopping the stream
  - Postvoid dribbling • Urinary retention • Incontinence
  - Nocturia/dysuria • Urgency/frequency
  - Possible elevation in prostate specific antigen (PSA) but usually <10 ng/mL
- Complications include urinary tract infection, urinary bladder trabeculation and diverticula formation, and hydronephrosis and renal failure (rare). Treatment varies, with available modalities including transurethral resection of prostate (TURP); the 5-alpha reductase inhibitor, finasteride; and the selective alpaha-1 receptor blockers, terazosin and prazosin.
- **Grossly**, BPH causes an enlarged prostate with well-demarcated nodules in the transition and central (periurethral) zones, which often results in slit-like compression of the prostatic urethra.
- **Microscopically**, the lesion shows glandular and stromal hyperplasia resulting in the characteristic prostate enlargement.

Prostate adenocarcinoma

- The most common cancer in men in the United States and the second most common cause of cancer death in men.
- Often clinically silent but may present with lower back pain secondary to metastasis
- Advanced localized disease may present with urinary tract obstruction or UTI (rare)
- Metastases most commonly involve obturator and pelvic lymph nodes
- Osteoblastic bone metastasis to lumbar spine can occur, and can be associated with elevated alkaline phosphatase
- Pathologically, an ill-defined, firm, yellow mass commonly arises in the posterior aspect of the peripheral zone.
- Microscopically, adenocarcinoma is graded with the **Gleason system**, which scores glandular differentiation.
- *TMPRSS2-ETS* fusion genes are present in nearly 50% of all prostatic carcinomas.

Cervix

Cervical Dysplasia:

Abnormal organization of cells in cervical epithelium starting from the basal layer. It has a tendency to progress from mild to severe dysplasia, and finally to invasive carcinoma. Ninety percent of cervical intraepithelial neoplasia (CIN) is associated with HPV infection. On biopsy, CIN is histologically classified as:

- CIN I (mild dysplasia): Involves the basal third of the epithelium.
- CIN II (moderate dysplasia): Involves the basal two-thirds of the epithelium. CIN III (severe dysplasia): Involves more than two-thirds of the epithelium.
- Carcinoma in situ: Involves the entire thickness of the epithelium.

According to the Bethesda system for cytologic (Pap) smear examinations, atypical squamous cells are classified into those of undetermined significance (ASCUS), low-grade squamous intraepithelial lesion (LGSIL), and high-grade squamous intraepithelial lesion (HGSIL).

Invasive Carcinoma

Early cervical cancer is often asymptomatic. Risk factors for development are related to infection with oncogenic HPV, including early age at first intercourse, multiple partners, cigarette smoking, and high-risk HPV infection (most important risk factor). Progression from CIN III to invasive carcinoma requires approximately 10 years (Figure 9-47). Cervical cancer can invade directly into the uterus, vagina, peritoneal cavity, bladder, or rectum, and by lymphatic or hematogenous dissemination.

PRESENTATION: Postcoital vaginal bleeding, abnormal vaginal bleeding, or a mucinous dis- charge. In late-stage disease, the patient may present with foul-smelling vagi- nal discharge, weight loss, or obstructive uropathy.

High-Risk HPV (Types 16, 18, 31, 33, 35, and 39)

HPV infections can be detected in 85-90% of cases, with the most com- mon types being 16 and 18. High-risk HPVs integrate into the host's DNA and express the proteins E6 and E7, which inactivate p53 and Rb respectively, allowing uncontrolled cellular proliferation.

DIAGNOSIS:

Pap smear is a screening test that looks for abnormal cervical cells while the patient is asymptomatic. Increased detection of abnormal cells with Pap smears has reduced the number of cervical cancer cases in developed countries. Women with abnormal cytology should undergo colposcopy. Rectal examination may reveal nodularity when carcinoma invades into the parametrium. Biopsy alone is sufficient for diagnosis.

PREVENION:

Vaccination against HPV-16 and -18 reduces the risk of developing cervical neoplasia and cervical cancer.

Trophoblastic Diseases

Hydatidiform mole (molar pregnancy): is a tumor of placental trophoblastic tissue. Incidence in the United States is 1 per 1,000 pregnancies, with an even higher incidence in Asia. Women ages <15 and >40 are at increased risk.

Complete mole:

- Results from fertilization of an ovum that *lost* allof its chromosomal material, so that all chromosomal material is derived from sperm.
- 90% of the time, the molar karyotype is 46, XX
- 10% of the time, the molar karyotype includes a Y chromosome
- The embryo does not develop

Partial mole:

- Results from fertilization of an ovum (that has not lost its chromosomal material) by 2 sperms, one 23, X and one 23,.
- Results in a triploid cell 69, XXY (23, X [maternal] + 23,X [one sperm] + 23,Y [the other sperm])
- The embryo may develop for a few weeks

Patients with hydatidiform mole typically present with the following:

- Excessive uterine enlargement ("size greater than dates") • Vaginal bleeding
- Passage of edematous, grape-like soft tissue
- Elevated beta-human chorionic gonadotropin (β-hCG)

Microscopically, molar tissue will show edematous chorionic villi, trophoblast proliferation, and fetal tissue (only in partial mole). Diagnosis is by U/S. Treatment is endometrial curettage and following of β-hCG levels.

Invasive mole is a mole that invades the myometrium of the uterine wall.

Choriocarcinoma:

- A malignant germ cell tumor derived from the trophoblast that forms a necrotic and hemorrhagic mass.
- Almost 50% arise from complete moles. The most common presentation is a rising or plateaued titer of hCG after a molar pregnancy, abortion, or ectopic pregnancy.
- **Microscopically**, choriocarcinoma shows proliferation of cytotrophoblasts, intermediate trophoblasts, and syncytiotrophoblasts. Hematogenous spread can occur, with seeding of tumor to lungs, brain, liver, etc. Treatment is chemotherapy.

Table 22-3. Partial Mole Versus a Complete Mole

	Partial Mole	Complete Mole
Ploidy	Triploid	Diploid
Number of chromosomes	69	46 (All paternal)
β-hCG	Elevated (+)	Elevated (+++)
Chorionic villi	Some are hydropic	All are hydropic
Trophoblast proliferation	Focal	Marked
Fetal tissue	Present	Absent
Invasive mole	2%	10%
Choriocarcinoma	Rare	2%

Breast

MASTITIS:

- Mastitis is an infection of the breast tissue.
- **Acute mastitis** causes an area of erythema and firmness in the breast, commonly during lactation. The most common infecting organism is *S. aureus*. The breast is often biopsied to differentiate the condition from inflammatory carcinoma, another painful breast condition. Microscopically there is acute and chronic inflammation with abscess formation in some cases.
- **Fat necrosis** is often related to trauma or prior surgery, and it may produce a palpable mass or a discrete lesion with calcifications on mammography. Microscopic changes include fat necrosis, chronic inflammation, hemosiderin deposits and fibrosis with calcification.

FIBROCYSTIC CHANGES

Fibrocystic changes (formerly called *fibrocystic disease*) are a group of very com- mon, benign changes that can be classified as **proliferative** (having an increase in the glandular elements or epithelial cells) or **nonproliferative**. Because they carry varying degrees of risk for breast cancer, it is important to identify each type histologically.

Fibrocystic changes primarily affect women in their reproductive years. The changes most often involve the upper outer quadrant and may produce a palpable mass or nodularity.

- Fibrosis may mimic a tumor on clinical exam and U/S.
- Cysts can usually be diagnosed by U/S.
- Apocrine metaplasia is often seen in cyst walls.
- Microcalcifications occur in benign and malignant processes.
- Ductal hyperplasia is classified as usual or atypical on the basis of cytology and microlumen architecture; atypical ductal hyperplasia is differentiated from DCIS on the basis of microscopic extent.
- Atypical lobular hyperplasia is differentiated from LCIS histologically on the basis of the percentage of acini involved.
- Sclerosing adenosis is distinguished from carcinoma histologically by the preservation of the myoepithelial layer.

BENIGN NEOPLASMS:

- **Fibroadenoma** is the most common benign breast tumor in women age <35.
    - It causes a palpable, round, movable, rubbery mass, which on cross-section shows small, cleft-like spaces.
    - Microscopically, the mass shows proliferation of benign stroma, ducts, and lobules.
- **Phyllodes** tumor (cystosarcoma phyllodes) usually involves an older patient population (age 50s) and can be benign or malignant.
    - Local recurrence is common but the incidence of metastasis is low.
    - Microscopically, the mass shows increased stromal cellularity, clefts lined by epithelium, stromal overgrowth, and irregular margins.

Table 23-1. Nonproliferative Versus Proliferative Fibrocystic Changes

Nonproliferative	Proliferative Changes
Fibrosis Cysts (blue-domed) Apocrine metaplasia Microcalcifications	Ductal hyperplasia ± atypia Sclerosing adenosis Atypical lobular hyperplasia

Table 23-2. Relative Risk of Developing Breast Cancer with Fibrocystic Change

Relative Risk	Fibrocystic Change
No increase	Fibrosis, cysts, apocrine metaplasia, adenosis
1.5–2×	Sclerosing ductal hyperplasia, papillomas
4–5×	Atypical ductal or lobular hyperplasia

Table 23-3. Features That Distinguish Fibrocystic Change from Breast Cancer

Fibrocystic Change	Breast Cancer
Often bilateral	Often unilateral
May have multiple nodules	Usually single
Menstrual variation	No menstrual variation
May regress during pregnancy	Does not regress during pregnancy

MALIGNANT NEOPLASMS:

Carcinoma of the breast is the most common cancer in women and affects 1 in 9 women in the United States. It is also the second most common cause of cancer death. The incidence is increasing and is higher in the United States than in Japan. Many risk factors have been identified.

The incidence increases with the following factors:

- Age.
- Unusually long/ intense exposure to estrogens.
- Presence of proliferative fibrocystic changes, especially **atypical hyperplasia.**
- First-degree relative with breast cancer.
- Hereditary influences are thought to be involved in 5–10% of breast cancers, with important genes as follows:
    - ***BRCA1*** (error-free repair of DNA double-strand breaks) chromosome 17q21.
    - ***BRCA2***(error-free repair of DNA double-strand breaks)chromosome13q12.3.
    - ***TP53*** germline mutation (Li-Fraumeni syndrome).

Carcinoma in situ and risk of invasive carcinoma. About 35% of women with untreated DCIS will develop invasive cancer, usually in the same quadrant of the breast. About 35% of women with LCIS will develop invasive lobular or ductal carcinoma, in either breast.

Breast cancer is most common in the upper outer quadrant. Gross examination of a breast cancer typically shows a stellate, white-tan, gritty mass. Clinically, it can cause:

- Mammographic calcifications or architectural distortion
- Palpable solitary painless mass • Nipple retraction or skin dimpling
- Fixation of breast tissue to the chest wall

Paget disease of the nipple:

An intra-epidermal spread of tumor cells from an underlying ductal carcinoma in situ or invasive ductal carcinoma. The tumor cells often lie in lacunae, and there can be a dermal lymphocytic infiltrate.

Mammary Paget disease (Paget disease of the nipple) is commonly associated with an underlying invasive or in situ ductal carcinoma. It may present with ulceration, oozing, crusting, and fissuring of the nipple and areola. Microscopic examination shows intraepidermal spread of tumor cells (Paget cells), with the cells occurring singly or in groups within the epidermis; there is often a clear halo surrounding the nucleus.

Histologic variants of breast cancer are as follows:

- **(DCIS) and (LCIS).** Preservation of the myoepithelial cell layer distinguishes them from their invasive counterparts.
- **Invasive (infiltrating) ductal carcinoma** is the most common form (>80% of cases). Microscopically, it shows tumor cells forming ducts within a desmoplastic stroma. About 70% of cases are ER/PR positive and 30% overexpress HER2.
- **Invasive (infiltrating) lobular carcinoma** (5–10% of cases) is characterized by small, bland tumor cells forming a single-file pattern.
- **Multifocal and bilateral disease** occurs commonly.
- **Mucinous (colloid) carcinoma** is characterized microscopically by clusters of bland tumor cells floating within pools of mucin. It has a better prognosis.
- **Tubular carcinoma** rarely metastasizes and has an excellent prognosis.
- **Medullary carcinoma** is characterized microscopically by pleomorphic tumor cells forming syncytial groups surrounded by a dense lymphocytic host response. It has a better prognosis.

HIV

ACQUIRED IMMUNODEFICIENCY SYNDROME (AIDS)

AIDS can be diagnosed when a person is HIV-positive and has CD4 count <200 cells/mL, **or** when a person is HIV-positive and has an AIDS-defining disease. Males are affected more frequently than females.

The ***human immunodeficiency virus*** (HIV) is an enveloped RNA retrovirus that contains reverse transcriptase. HIV infects CD4-positive cells, including CD4+ T lymphocytes, all macrophages, lymph node follicular dendritic cells, and Langerhans cells. The mechanism of infection is by binding of CD4 by the viral gp120, followed by entry into cell by fusion, which requires gp41 and CCR5 (β-chemokine receptor 5) and CXCR4 (α-chemokine receptor).

Transmission of HIV can occur by many mechanisms, including sexual contact (most common mode, including both homosexual transmission and an increasing rate of heterosexual transmission, with important cofactors including herpes and syphilis infection); parenteral transmission; IV drug use; blood transfusions (including those done in hemophiliacs); accidental needle sticks in hospital workers; and vertical transmission.