

Pathology of female genital system

Dr. \ Hani Ahmed Alanqar

Consultant of pathology

El shifa medical hospital

M.B.,B.CH.,

Egyptian board of pathology (Cairo university)

Palestinian board of pathology

INFECTIONS

A large variety of organisms can infect the female genital tract. Some infections with microorganisms such as *Candida*, *Trichomonas*, and *Gardnerella* are very common and may cause significant discomfort, but are without serious sequelae. Others, such as *Neisseria gonorrhoeae* and *Chlamydia* infections, are major causes of infertility, while organisms such as Group B *Streptococcus* infections are implicated in preterm deliveries, stillbirths, and neonatal infections. Viruses, especially herpes simplex viruses (HSVs) and human papillomaviruses (HPVs), also account for considerable morbidity; HSVs cause painful genital ulcerations, whereas HPVs are involved in the pathogenesis of cervical, vaginal, and vulvar cancers

Many of these infections are sexually transmitted, including trichomoniasis, gonorrhea, Mycoplasma, Chlamydia, HSV, and HPV as well as less common infections such as syphilis and chancroid.

Infections of the Lower Genital Tract

Herpes Simplex Virus

Genital herpes simplex virus (HSV) infection is common and may involve the vulva, vagina, or cervix. HSVs are DNA viruses that include two serotypes, HSV-1 and HSV-2. HSV-1 typically results in perioral infection, whereas HSV-2 usually involves genital mucosa and skin. HSV-1 may be detected in the genital region and HSV-2 may cause oral infections as well. By 40 years of age, approximately 30% of women are seropositive for antibodies against HSV-2.

About one-third of newly infected individuals are symptomatic. Lesions typically develop 3 to 7 days after transmission and are often associated with systemic symptoms such as fever, malaise, and tender inguinal lymph nodes. The earliest lesions usually consist of red papules that progress to vesicles and then to painful coalescent ulcers.

The lesions are easily visible on vulvar skin and mucosa, while cervical and vaginal lesions present with purulent discharge and pelvic pain. Lesions around the urethra may cause painful urination and urine retention.



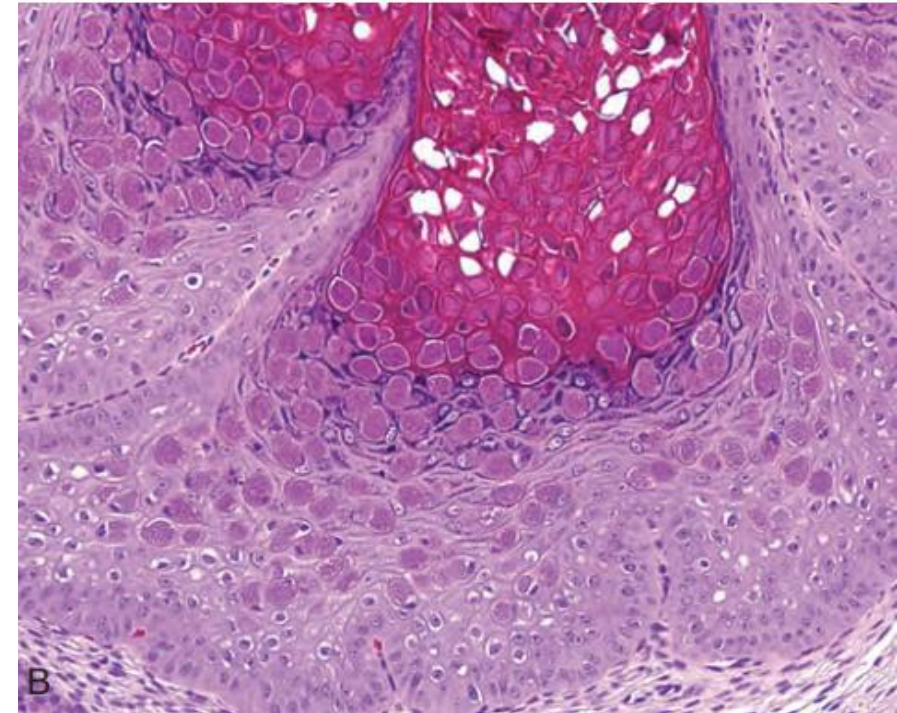
MORPHOLOGY

By the time an HSV lesion is biopsied, it typically has ulcerated. The epithelium is desquamated, and marked acute inflammation is present in the ulcer bed. Smears of the inflammatory exudate from active lesions show characteristic cytopathic changes consisting of multinucleated squamous cells containing eosinophilic to basophilic viral inclusions with a “ground-glass” appearance

Other Lower Female Genital Tract Infections

As mentioned earlier, a variety of other viruses, fungi, and bacteria can also cause symptomatic infections of the lower genital tract. Those that are most common include the following:

- Molluscum contagiosum is a cutaneous or mucosal lesion caused by poxvirus. There are four types of molluscum contagiosum viruses (MCVs), MCV-1 to MCV-4, with MCV-1 being the most prevalent and MCV-2 being most often sexually transmitted.



- Fungal infections, especially those caused by yeast (Candida), are extremely common; in fact, yeast are part of many women's normal vaginal microflora, and the development of symptomatic candidiasis is typically a result of a disturbance in the patient's vaginal microbial ecosystem.

Diabetes mellitus, antibiotics, and pregnancy, which manifests by marked vulvovaginal pruritus, erythema, swelling, and curdlike vaginal discharge. Severe infection may result in mucosal ulcerations.

- *Trichomonas vaginalis* is a large, flagellated ovoid protozoan that is usually transmitted by sexual contact. Infected patients may be asymptomatic or may complain of yellow, frothy vaginal discharge, vulvovaginal discomfort, dysuria (painful urination), and dyspareunia (painful intercourse).
- *Gardnerella vaginalis* is a gram-negative coccobacillus that is implicated as the main cause of bacterial vaginosis (vaginitis). Patients typically present with thin, green-gray, malodorous (fishy) vaginal discharge.
- *Chlamydia trachomatis* infections mainly take the form of cervicitis. However, in some patients the infection may ascend to the uterus and fallopian tubes, resulting in endometritis and salpingitis; thus *Chlamydia* is one of the causes of pelvic inflammatory disease.

Infections Involving the Lower and Upper Genital Tract

Pelvic Inflammatory Disease (PID)

PID is an infection that begins in the vulva or vagina and spreads upward to involve most of the structures in the female genital system, resulting in pelvic pain, adnexal tenderness, fever, and vaginal discharge. *Neisseria gonorrhoeae* continues to be a common cause of PID, the most serious complication of gonorrhea in women. Chlamydia infection is another well recognized cause of PID. Infections after spontaneous or induced abortions and normal or abnormal deliveries (called puerperal infections) are also important causes of PID. In these situations, the infections are typically polymicrobial and may be caused by staphylococci, and streptococci

With gonococcus, inflammatory changes start to appear approximately 2 to 7 days after inoculation. The initial infection most commonly involves the endocervical mucosa, but it may also begin in the Bartholin gland and other vestibular, or periurethral, glands. From these sites, the organisms may spread upward to involve the fallopian tubes and tuboovarian region. The non-gonococcal bacterial infections that follow induced abortion, dilation and curettage of the uterus, and other surgical procedures are thought to spread upward from the uterus through the lymphatics or venous channels rather than on the mucosal surfaces

The acute complications of PID include peritonitis and bacteremia, which in turn may result in endocarditis, meningitis, and suppurative arthritis. The chronic sequelae of PID include infertility and tubal obstruction, ectopic pregnancy, pelvic pain, and intestinal obstruction due to adhesions between the bowel and pelvic organs. In the early stages, gonococcal infections are usually readily controlled with antibiotics, although penicillin-resistant strains have emerged. Infections that become walled off in tubo-ovarian abscesses are difficult to eradicate with antibiotics, and it sometimes becomes necessary to remove the organs surgically. Postabortion and postpartum PIDs may also be amenable to treatment with antibiotics, but are far more difficult to control because of the broad spectrum of pathogens that may be involved.

MORPHOLOGY

Gonococcal infection is characterized by marked acute inflammation of involved mucosal surfaces. Smears of the inflammatory exudate disclose phagocytosed gram-negative diplococci within neutrophils. . If infection spreads, the endometrium is usually spared (for unclear reasons), but within the fallopian tubes, an acute suppurative salpingitis ensues . The tubal mucosa becomes congested and diffusely infiltrated by neutrophils, plasma cells, and lymphocytes,

Vulva

Diseases of the vulva in the aggregate constitute only a small fraction of gynecologic practice. Many inflammatory diseases that affect skin elsewhere on the body also occur on the vulva, such as psoriasis, eczema, and allergic dermatitis. Because it is constantly exposed to secretions and moisture, the vulva is more prone to superficial infections than skin elsewhere on the body. Nonspecific vulvitis is particularly likely to occur in the setting of immunosuppression. Most skin cysts (epidermal inclusion cysts) and skin tumors such as squamous cell carcinoma, basal cell carcinoma, and melanoma can also occur in the vulva. Here we discuss vulvar disorders that are relatively specific and common, including Bartholin cyst, non-neoplastic epithelial disorders, benign exophytic lesions, and tumors of the vulva.

BARTHOLIN CYST

Infection of the Bartholin gland produces an acute inflammation (adenitis) and may result in an abscess. Bartholin duct cysts are relatively common, occur at all ages, and result from obstruction of the duct by an inflammatory process. These cysts are usually lined by transitional or squamous epithelium. They may become large, up to 3 to 5 cm in diameter, and produce pain and local discomfort. Bartholin duct cysts are either excised or opened permanently

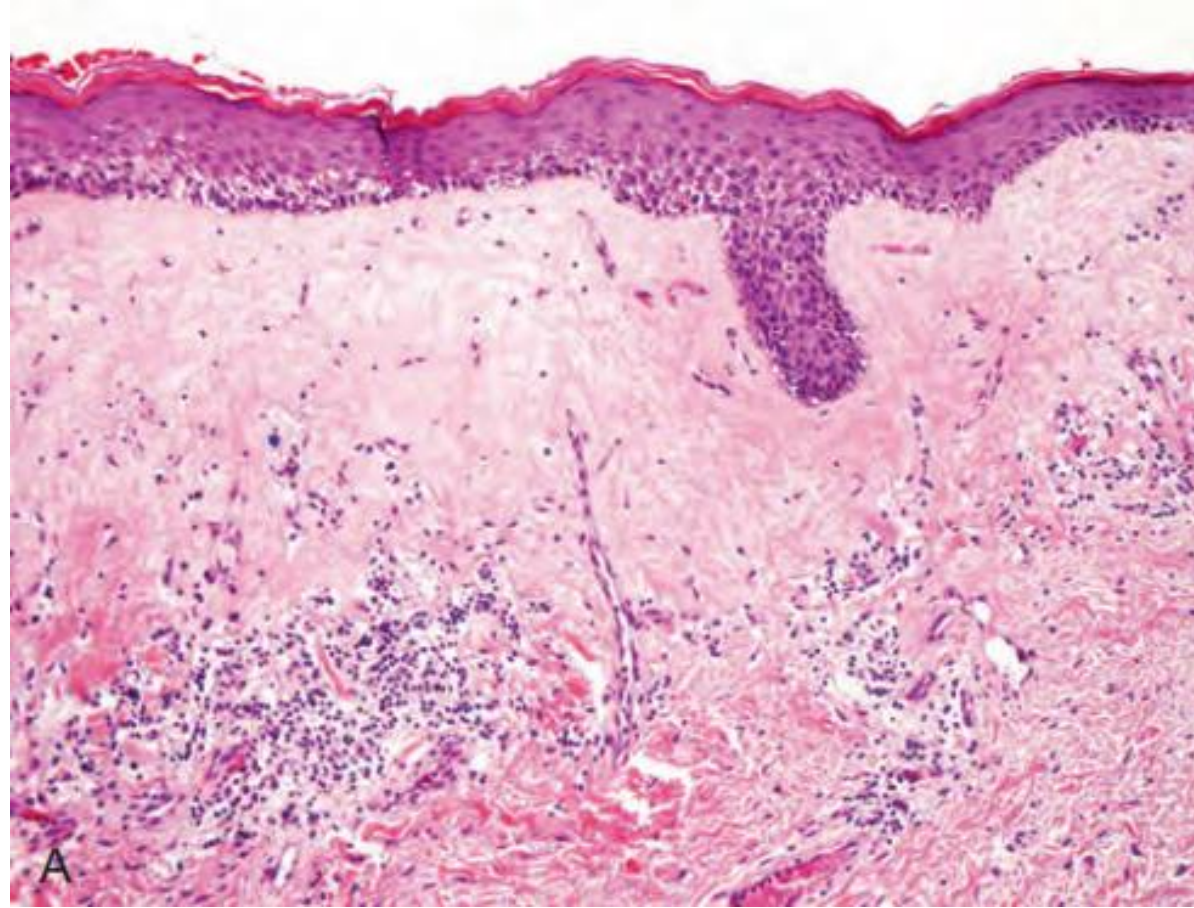
NON-NEOPLASTIC EPITHELIAL DISORDERS

Leukoplakia is a descriptive clinical term for opaque, white, plaquelike epithelial thickening that may produce pruritus and scaling. Leukoplakia (literally, white plaques) may be caused by a variety of benign, premalignant, or malignant disorders, including the following:

- Inflammatory dermatoses (e.g., psoriasis, chronic dermatitis)
- Lichen sclerosus and squamous cell hyperplasia
- Neoplasias, such as vulvar intraepithelial neoplasia (VIN), Paget disease, and invasive carcinoma

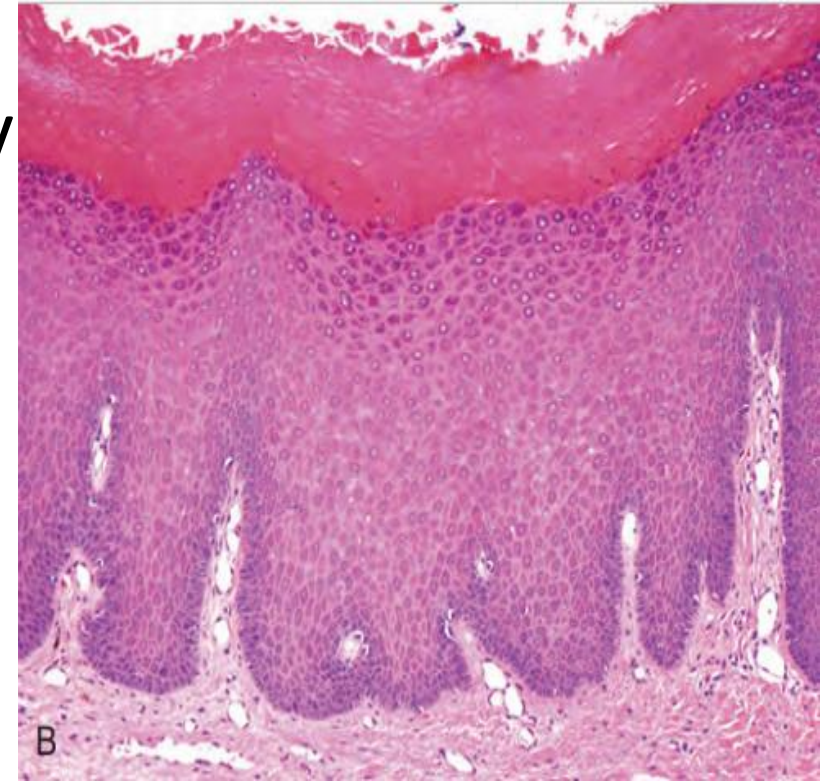
Lichen Sclerosus

Presents as smooth, white plaques or macules that in time may enlarge. When the entire vulva is affected, the labia become atrophic. Histologically, the lesion is characterized by marked thinning of the epidermis, degeneration of the basal epithelial cells, excessive keratinization (hyperkeratosis), sclerotic changes of the superficial dermis, and a bandlike lymphocytic infiltrate in the underlying dermis. The disease occurs in all age groups but is most common in postmenopausal women. It may also be encountered elsewhere on the skin. Its pathogenesis is uncertain, but the presence of activated T cells in the subepithelial inflammatory infiltrate and the increased frequency of autoimmune disorders in affected women suggest that an autoimmune reaction is involved.



Squamous Cell Hyperplasia

Previously called hyperplastic dystrophy or lichen simplex chronicus, squamous cell hyperplasia is a nonspecific condition resulting from rubbing or scratching of the skin to relieve pruritus. Clinically it presents as leukoplakia, and histologic examination reveals thickening of the epidermis (acanthosis) and hyperkeratosis. Lymphocytic infiltration of the dermis is sometimes present. The hyperplastic epithelium may show mitotic activity but lacks cellular atypia. While squamous cell hyperplasia is not considered premalignant, it is sometimes present at the margins of vulvar cancers.



BENIGN EXOPHYTIC LESIONS

Benign raised (exophytic) or wartlike lesions of the vulva may be caused by infection or may be reactive conditions of unknown etiology.

Condyloma acuminatum, a papilloma virus induced lesion, also called a genital wart, and syphilitic condyloma latum are consequences of sexually transmitted infections. Vulvar fibroepithelial polyps, or skin tags, are similar to skin tags occurring elsewhere on the skin. Vulvar squamous papillomas are benign exophytic proliferations covered by nonkeratinized squamous epithelium that develop on vulvar surfaces; they may be single or numerous (vulvar papillomatosis). The etiology of fibroepithelial polyps and squamous papillomas is unknown.

Condyloma Acuminatum

Condylomata acuminata are benign genital warts caused by low-risk HPV, mainly types 6 and 11. They may be solitary, but are more frequently multifocal, and they may involve vulvar, perineal, and perianal regions as well as the vagina and, less commonly, the cervix. The lesions are identical to those found on the penis and around the anus in males . On histologic examination, they consist of papillary, exophytic, treelike cores of stroma covered by thickened squamous epithelium . The surface epithelium shows characteristic viral cytopathic changes referred to as koilocytic atypia , which manifest as nuclear enlargement, hyperchromasia, and a cytoplasmic perinuclear halo . Condylomata acuminata are not precancerous lesions. HPV vaccines provide excellent protection against infection by low-risk HPV and genital warts.

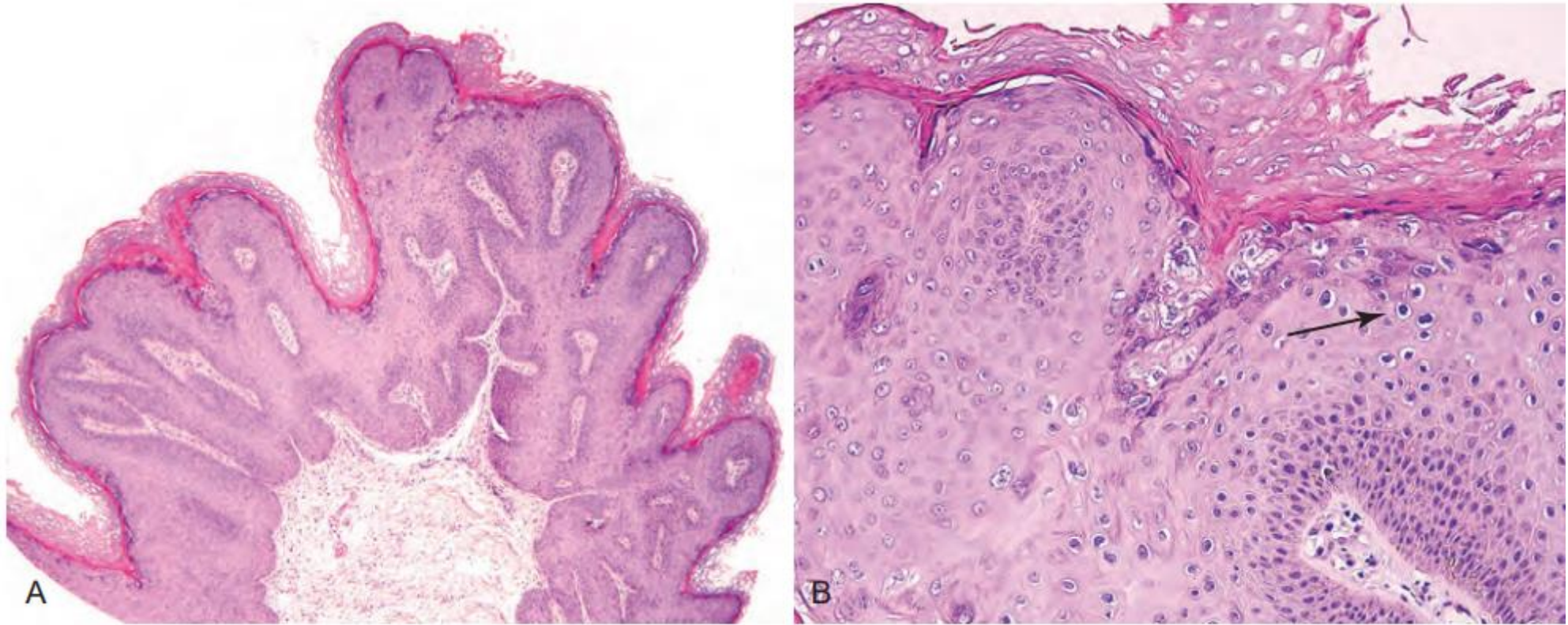


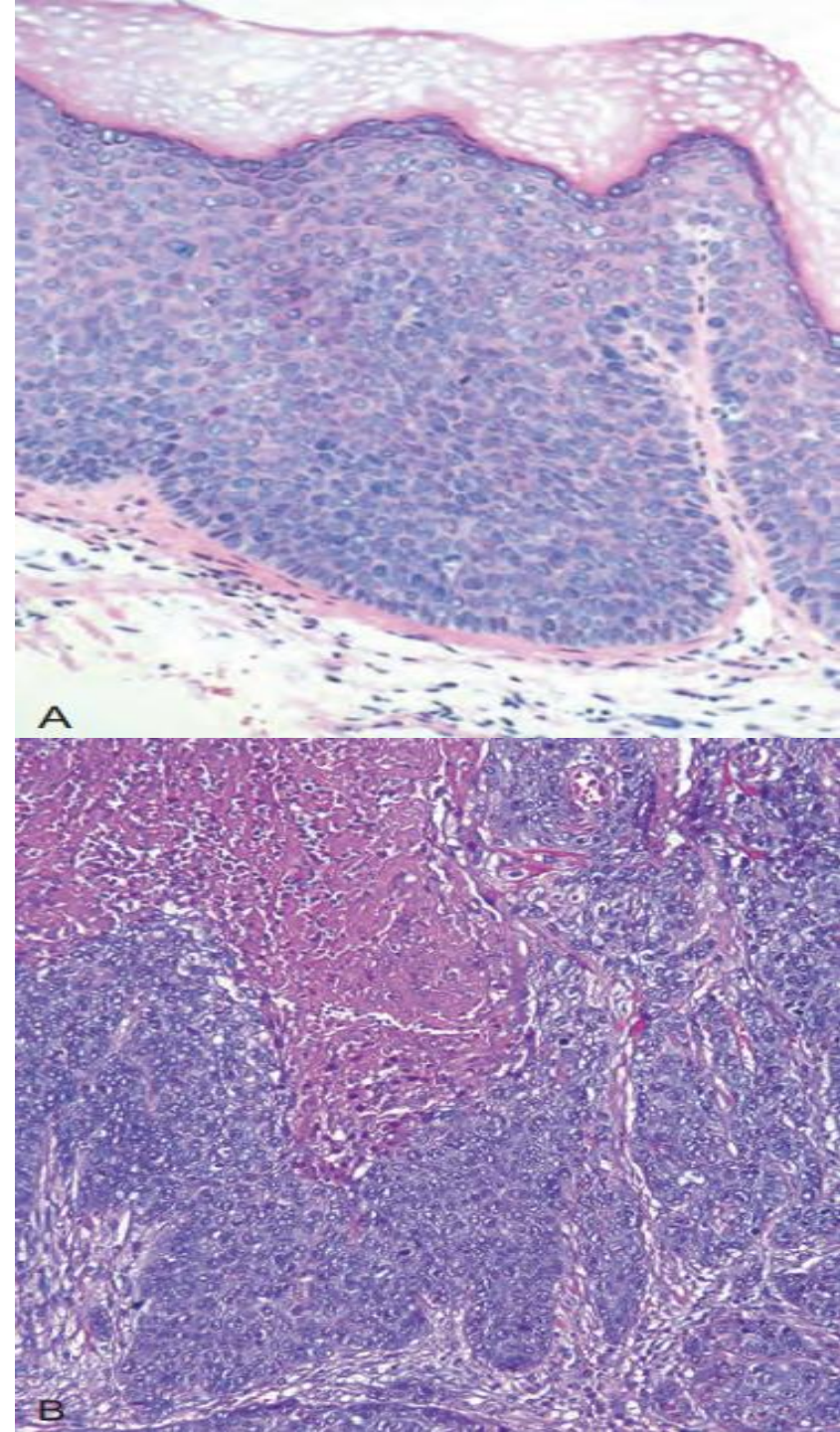
Figure 22.6 Condyloma acuminatum. (A) Low-power view showing exophytic, papillary architecture. (B) High-power view reveals human papillomavirus cytopathic effect (koilocytic atypia) characterized by atypical, enlarged, hyperchromatic nuclei with perinuclear halos (arrow).

SQUAMOUS NEOPLASTIC LESIONS

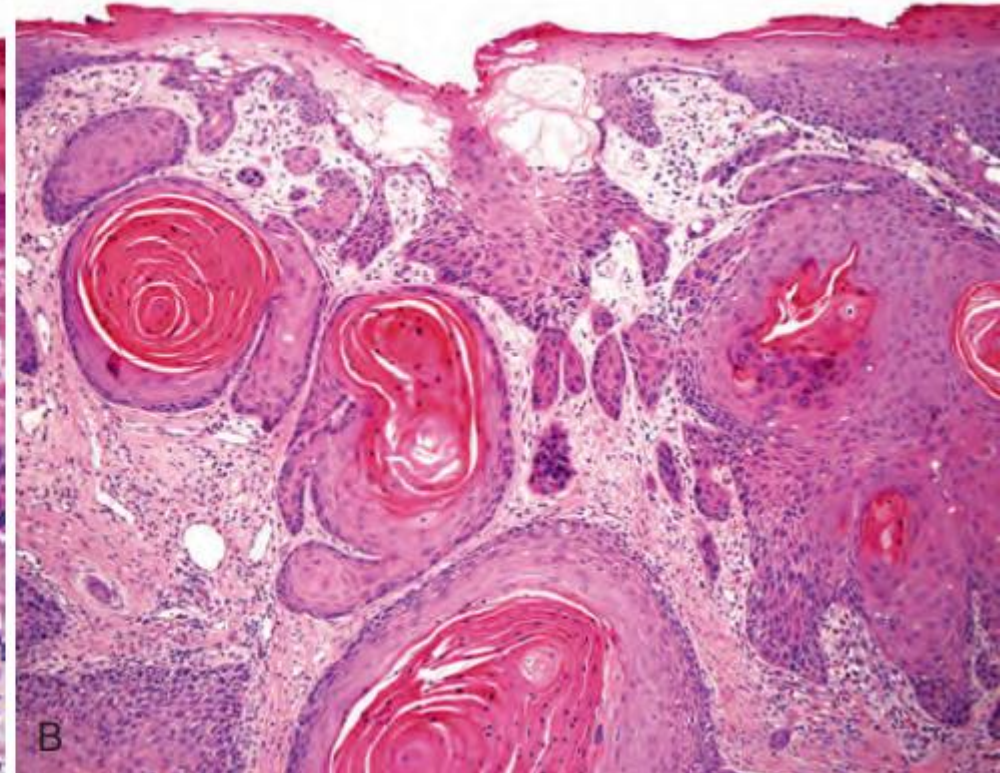
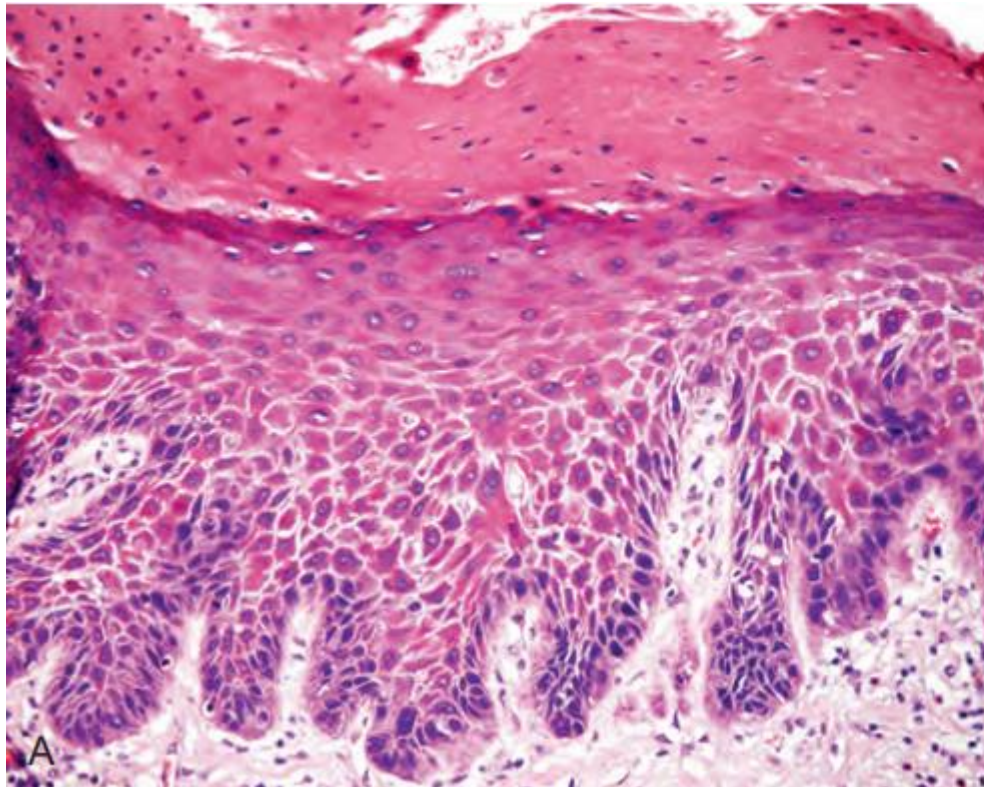
Vulvar Intraepithelial Neoplasia and Vulvar Carcinoma

Carcinoma of the vulva is an uncommon malignant neoplasm (approximately one-eighth as frequent as cervical cancer) representing about 3% of all genital cancers in the female; approximately two-thirds occur in women older than 60 years of age. Squamous cell carcinoma is the most common histologic type of vulvar cancer. In terms of etiology, pathogenesis, and histologic features, vulvar squamous cell carcinomas are divided into two groups:

- **Basaloid and warty carcinomas** are related to infection with high-risk HPVs, most commonly HPV-16. These are less common (30% of cases) and occur in younger women (average 60 years of age). develop from an in situ precursor lesion called classic vulvar intraepithelial neoplasia (classicVIN). This form of VIN occurs mainly in reproductive age women and includes lesions formerly designated as carcinoma in situ or Bowen disease. The risk factors for VIN are the same as those associated with cervical squamous intraepithelial lesions (e.g., young age at first intercourse, multiple sexual partners, male partner with multiple sexual partners),



- **Keratinizing squamous cell carcinomas** are unrelated to HPV infection. These are more common (70% of cases) and occur in older women (average 75 years of age). most often in individuals with long-standing lichen sclerosus or squamous cell hyperplasia and is not related to HPV. It arises from a precursor lesion referred to as **differentiated vulvar intraepithelial neoplasia (differentiated VIN)**.

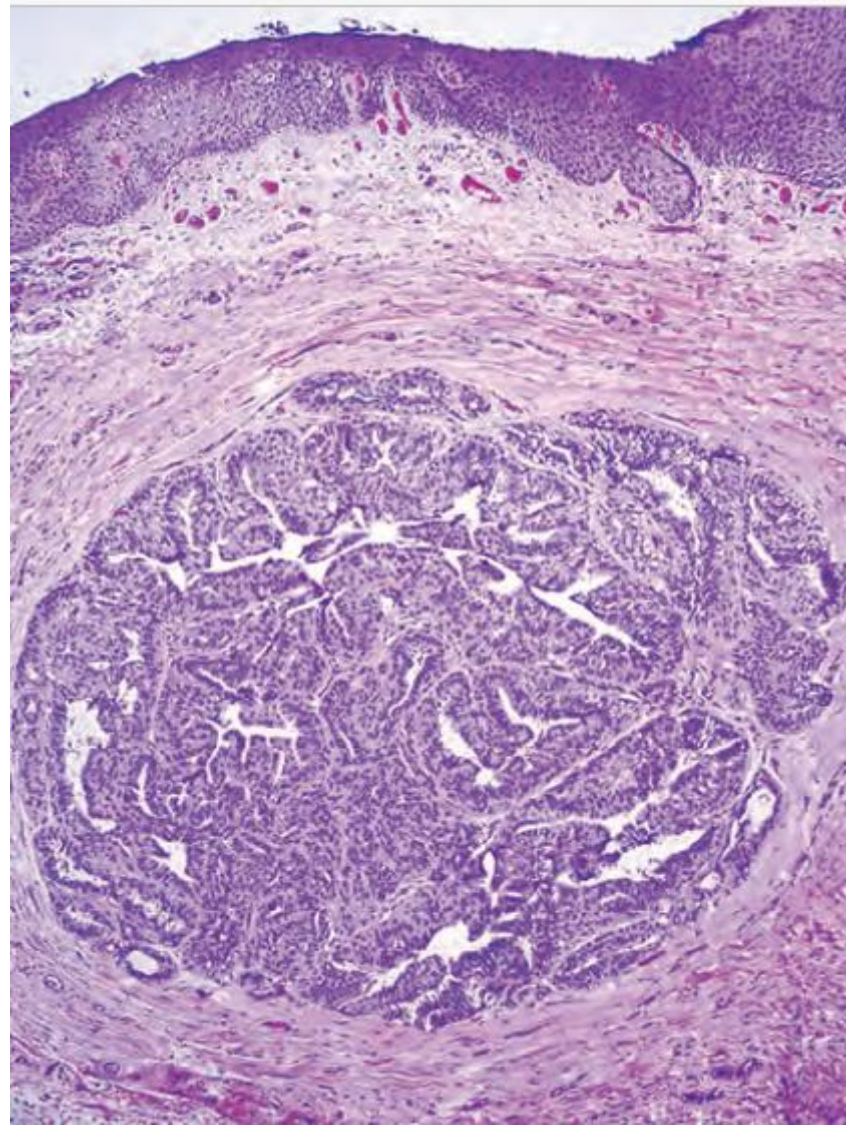


GLANDULAR NEOPLASTIC LESIONS

Like the breast, the vulva contains modified apocrine sweat glands. Presumably because of these “breastlike” features, the vulva may be involved by two tumors with counterparts in the breast, papillary hidradenoma and extramammary Paget disease.

Papillary Hidradenoma

Papillary hidradenoma presents as a sharply circumscribed nodule, most commonly on the labia majora or interlabial folds, and may be confused clinically with carcinoma because of its tendency to ulcerate. Its histologic appearance is identical to that of intraductal papilloma of the breast and consists of papillary projections covered by two cell layers, an upper layer of columnar secretory cells and a deeper layer of flattened myoepithelial cells. These myoepithelial elements are characteristic of sweat glands and sweat gland tumors



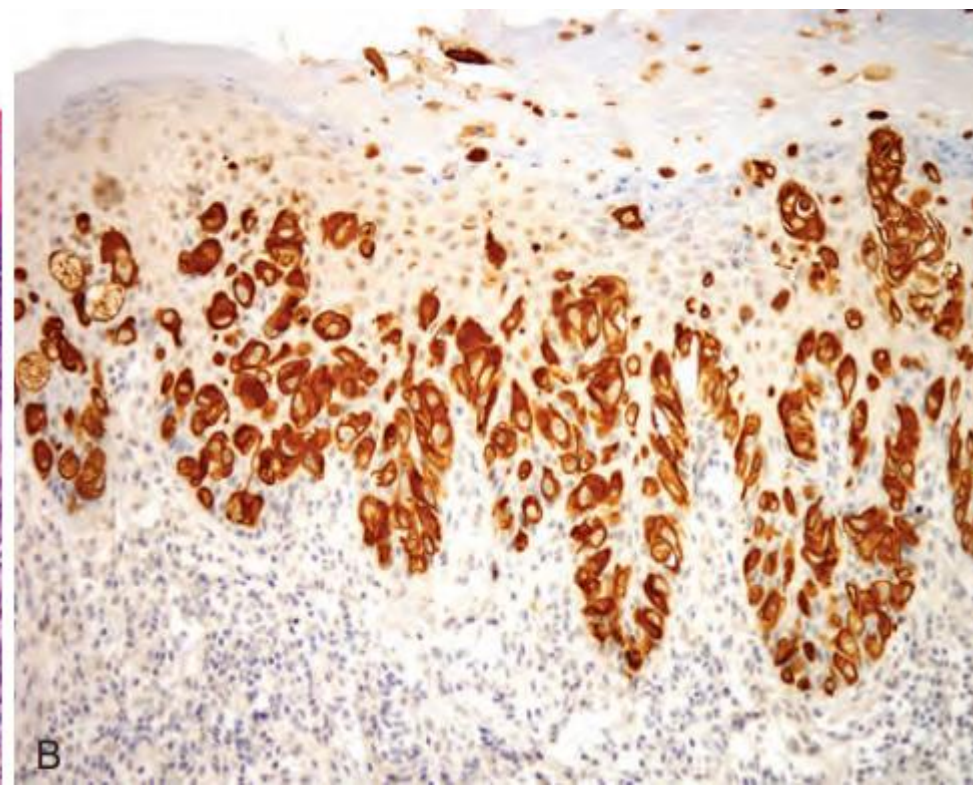
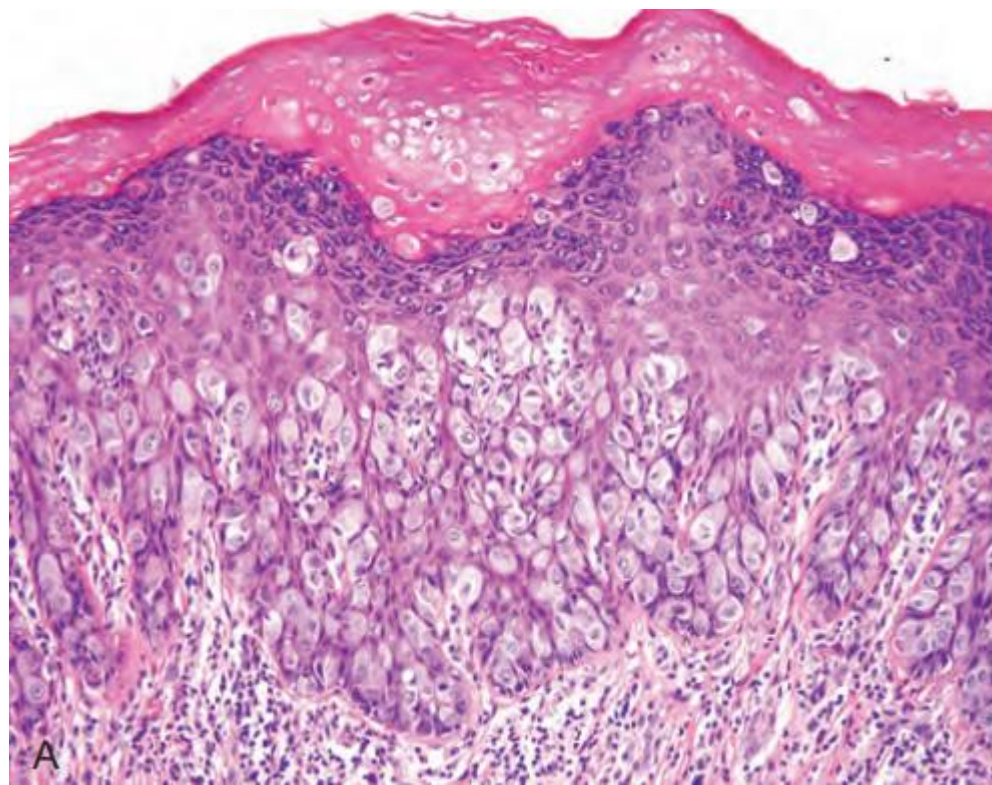
Extramammary Paget Disease

This curious and rare lesion of the vulva is similar in its manifestations to Paget disease of the breast .

In the vulva, it presents as a pruritic, red, crusted, maplike area, usually on the labia majora. In contrast to Paget disease of the nipple, in which 100% of patients have an underlying ductal breast carcinoma, vulvar Paget is typically not associated with underlying cancer and is confined to the vulvar epidermis. Treatment consists of wide local excision, which is necessary because Paget cells spread laterally within the epidermis and may be present beyond the confines of the grossly visible lesion. Intra-epidermal Paget disease may persist for many years or even decades without invasion or metastases. In the rare instances when invasion develops, the prognosis is poor.

MORPHOLOGY

Paget disease is a distinctive intraepithelial proliferation of malignant cells. Paget cells are larger than surrounding keratinocytes and are seen singly or in small clusters within the epidermis . The cells have pale cytoplasm containing mucopolysaccharide that stains with periodic acid–Schiff (PAS), Alcian blue, or mucicarmine stains. In addition, unlike squamous epithelium, the cells express cytokeratin 7 . Ultrastructurally, Paget cells display apocrine, eccrine, and keratinocyte differentiation and presumably arise from multipotent cells found within the mammary gland–like ducts of the vulvar skin.



vagina

The vagina is a portion of the female genital tract that is remarkably resistant to diseases that affect nearby structures. For example, in the adult, inflammation that begins in the vulva and perivulvar structures often spreads to the cervix without significant involvement of the vagina. Primary lesions of the vagina are rare, the most serious being vaginal squamous cell carcinoma.

DEVELOPMENTAL ANOMALIES Septate, or double, vagina is an uncommon anomaly that arises from a failure of müllerian duct fusion and is accompanied by a double uterus

PREMALIGNANT AND MALIGNANT NEOPLASMS OF THE VAGINA

Most benign tumors of the vagina occur in reproductive-age women and include stromal tumors (stromal polyps), leiomyomas, and hemangiomas. The most common malignant tumor to involve the vagina is carcinoma spreading from the cervix, followed by primary squamous cell carcinoma of the vagina. Infants may develop a unique, rare malignancy— embryonal rhabdomyosarcoma (sarcoma botryoides).

Vaginal Intraepithelial Neoplasia and Squamous Cell Carcinoma

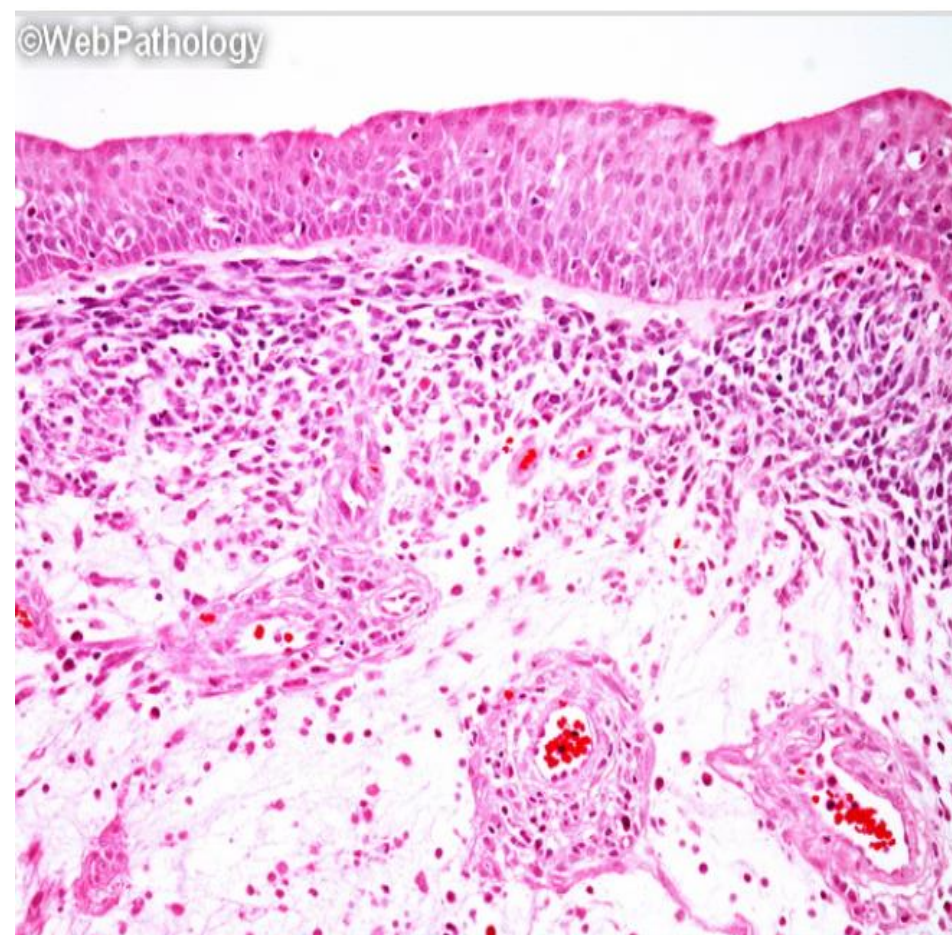
Virtually all primary carcinomas of the vagina are squamous cell carcinomas associated with high-risk HPV infection.

Vaginal carcinoma is extremely uncommon (about 0.6 per 100,000 women yearly) and accounts for about 1% of malignant neoplasms in the female genital tract. The greatest risk factor is a previous carcinoma of the cervix or vulva; 1% to 2% of women with an invasive cervical carcinoma eventually develop a vaginal squamous cell carcinoma. Squamous cell carcinoma of the vagina arises from a premalignant lesion, vaginal intraepithelial neoplasia, analogous to cervical squamous intraepithelial lesion .

Most often the invasive tumor affects the upper vagina, particularly the posterior wall at the junction with the ectocervix. The lesions in the lower two-thirds of the vagina metastasize to the inguinal nodes, whereas lesions in the upper vagina tend to spread to regional iliac nodes.

Embryonal Rhabdomyosarcoma

Also called sarcoma botryoides, this uncommon vaginal tumor composed of malignant embryonal rhabdomyoblasts is most frequently found in infants and children younger than 5 years of age. These tumors tend to grow as polypoid, rounded, bulky masses that have the appearance and consistency of grapelike clusters. The tumor cells are small and have oval nuclei, with small protrusions of cytoplasm from one end, resembling a tennis racket. Rarely, striations (indicative of muscle differentiation) can be seen within the cytoplasm. Beneath the vaginal epithelium, the tumor cells are crowded in a so-called cambium layer, but in the deep regions they lie within a loose edematous fibromyxomatous stroma that may contain many inflammatory cells. Such lesions can be mistaken for benign inflammatory polyps. The tumors tend to invade locally and cause death by penetration into the peritoneal cavity or by obstruction of the urinary tract. Conservative surgery coupled with chemotherapy offer the best hope, particularly in cases diagnosed sufficiently early.



CERVIX

Anatomically the cervix consists of the external vaginal portion (ectocervix) and the endocervical canal. The ectocervix is visible on vaginal examination and is covered by a mature squamous epithelium that is continuous with the vaginal wall.

INFLAMMATIONS

Acute and Chronic Cervicitis

At the onset of menarche, the production of estrogens by the ovary stimulates maturation of the cervical and vaginal squamous mucosa and formation of intracellular glycogen vacuoles in the squamous cells. As these cells are shed, the glycogen provides a substrate for various endogenous vaginal aerobes and anaerobes, but particularly lactobacilli, which are the dominant microbial species in the normal vagina

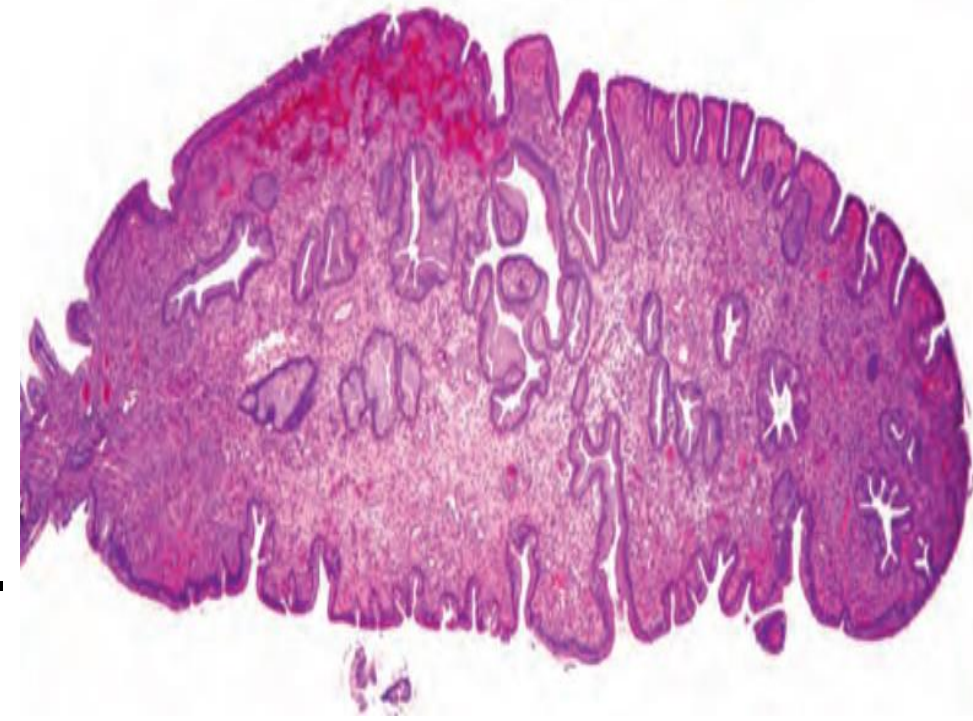
Lactobacilli produce lactic acid, which maintains the vaginal pH below 4.5, suppressing the growth of other saprophytic and pathogenic organisms. In addition, at low pH, lactobacilli produce bacteriotoxic hydrogen peroxide (H_2O_2). If the pH becomes alkaline due to bleeding, sexual intercourse, or vaginal douching, H_2O_2 production by lactobacilli decreases.

Antibiotic therapy that suppresses lactobacilli can also cause the pH to rise of other microorganisms, which may result in cervicitis or vaginitis. Some degree of cervical inflammation may be found in virtually all women, and it is usually of little clinical consequence.

However, infections by gonococci, chlamydiae, mycoplasmas, and HSV may produce significant acute or chronic cervicitis and are important to identify due to their association with upper genital tract disease, complications during pregnancy, and sexual transmission. Marked cervical inflammation produces reparative and reactive changes of the epithelium and shedding of atypical-appearing squamous cells, and therefore may cause an abnormal Pap test result.

ENDOCERVICAL POLYPS

Endocervical polyps are common benign exophytic growths that arise within the endocervical canal. They vary from small, sessile “bumps” to large polypoid masses that may protrude through the cervical os. Histologically, they are composed of a fibrous stroma covered by mucus-secreting endocervical glands, often accompanied by inflammation. Their main significance is that they may be the source of irregular vaginal “spotting” . Simple curettage or surgical excision is curative.



PREMALIGNANT AND MALIGNANT NEOPLASMS OF THE CERVIX

Worldwide, cervical carcinoma is the fourth most common cancer in women, with an estimated 570,000 new cases in 2018, of which more than one-half will prove fatal. In the United States, it was estimated in 2019 that 13,179 women would be diagnosed with cervical cancer and that 4250 women would die of the disease.

Pathogenesis

High-risk HPVs are by far the most important factor in the development of cervical cancer. HPVs are DNA viruses that are grouped into those of high and low oncogenic risk based on their genotypes. There are 15 high-risk HPVs that are currently identified, but HPV-16 alone accounts for almost 60% of cervical cancer cases, and HPV-18 accounts for another 10% of cases; other HPV types contribute to less than 5% of cases, individually. High-risk HPVs are also implicated in squamous cell carcinomas arising at many other sites, including the vagina, vulva, penis, anus, tonsil, and other oropharyngeal locations. As noted earlier, low oncogenic risk HPVs are the cause of sexually transmitted vulvar, perineal, and perianal warts (condyloma acuminatum).

The ability of HPV to act as a carcinogen depends on the viral E6 and E7 proteins, which interfere with the activity of the key tumor suppressor proteins, p53 and RB, respectively.

Cervical Intraepithelial Neoplasia (Squamous Intraepithelial Lesions)

The oldest classification system grouped lesions as having mild dysplasia on one end and severe dysplasia/carcinoma in situ on the other.

This was followed by the cervical intraepithelial neoplasia (CIN) classification, with mild dysplasia termed CIN I, moderate dysplasia termed CIN II, and severe dysplasia termed CIN III. Because the decision with regard to patient management is two-tiered (observation vs. surgical treatment), the three-tier classification system has been recently simplified to a two-tiered system, with CIN I renamed low-grade squamous intraepithelial lesion (LSIL) and CIN II and CIN III combined into one category referred to as high-grade squamous intraepithelial lesion (HSIL)

LSIL does not progress directly to invasive carcinoma, and, in fact, most cases regress spontaneously; only a small percentage progress to HSIL. LSIL represents a productive HPV infection in which there is a high level of viral replication, but only mild alterations in the growth of host cells. For these reasons, LSIL is not treated like a premalignant lesion. LSIL is approximately ten times more common than HSIL. By contrast to LSIL, HSIL is considered to be at high risk for progression to carcinoma. In HSIL, there is a progressive deregulation of the cell cycle by HPV, which results in increased cellular proliferation, decreased or arrested epithelial maturation, and a lower rate of viral replication as compared with LSIL. Derangement of the cell cycle in HSIL may become irreversible and lead to a fully transformed malignant phenotype. More than 80% of LSILs and 100% of HSILs are associated with high-risk HPVs, with HPV-16 being the most common HPV type in both lesions.

Classification Systems for Squamous Cervical Precursor Lesions

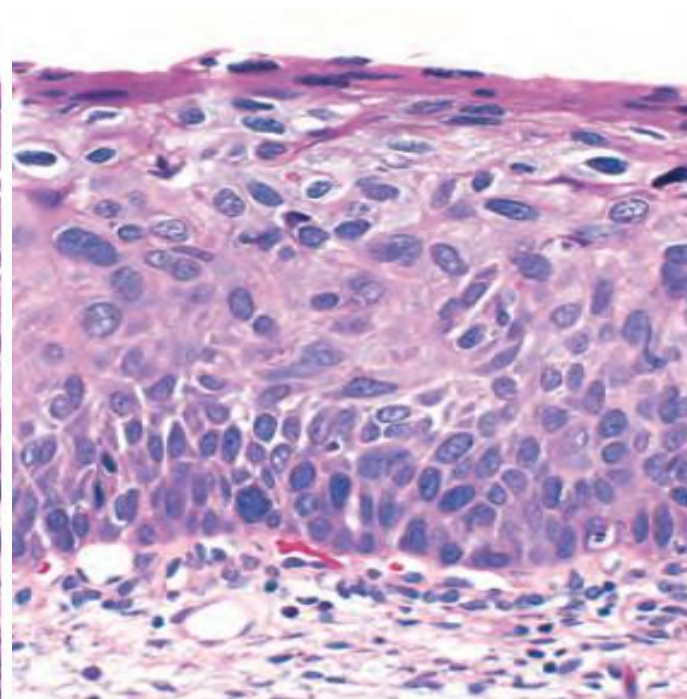
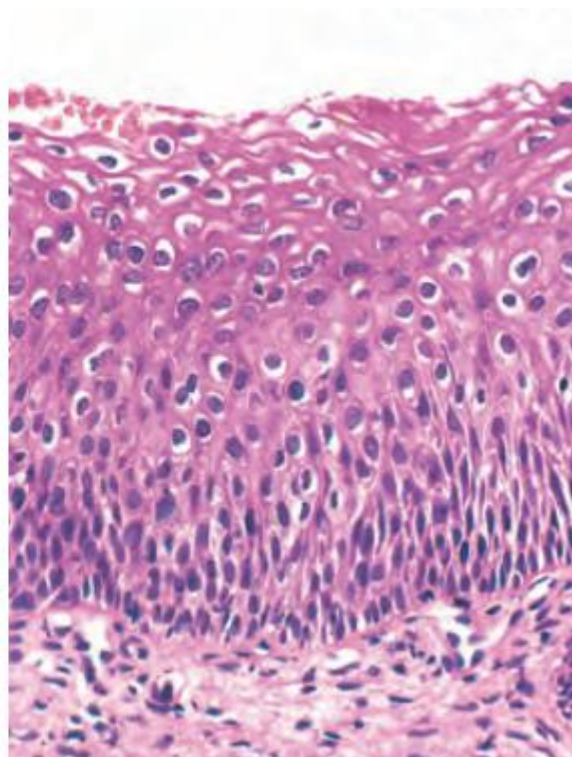
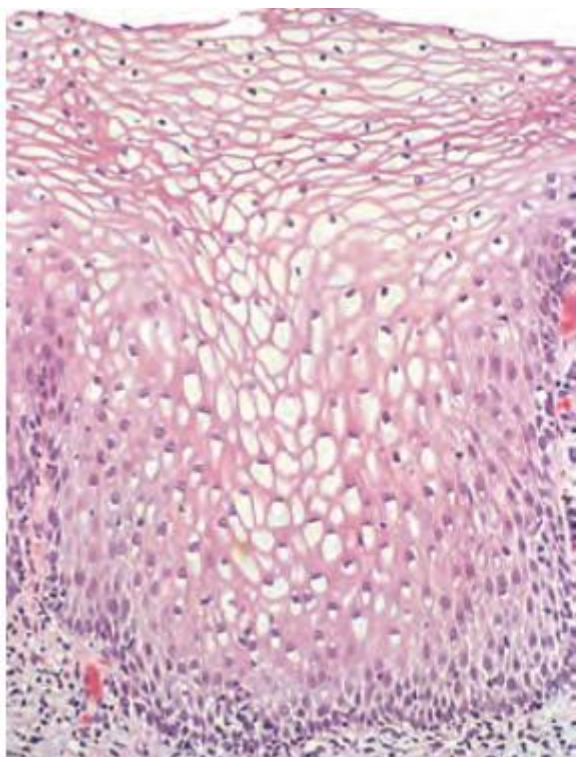
▪ Mild dysplasia	CIN I	Low-grade SIL (LSIL).
▪ Moderate dysplasia	CIN II	High-grade SIL (HSIL).
▪ Severe dysplasia	CIN III	High-grade SIL (HSIL).
▪ Carcinoma in situ	CIN III	High-grade SIL (HSIL).

MORPHOLOGY

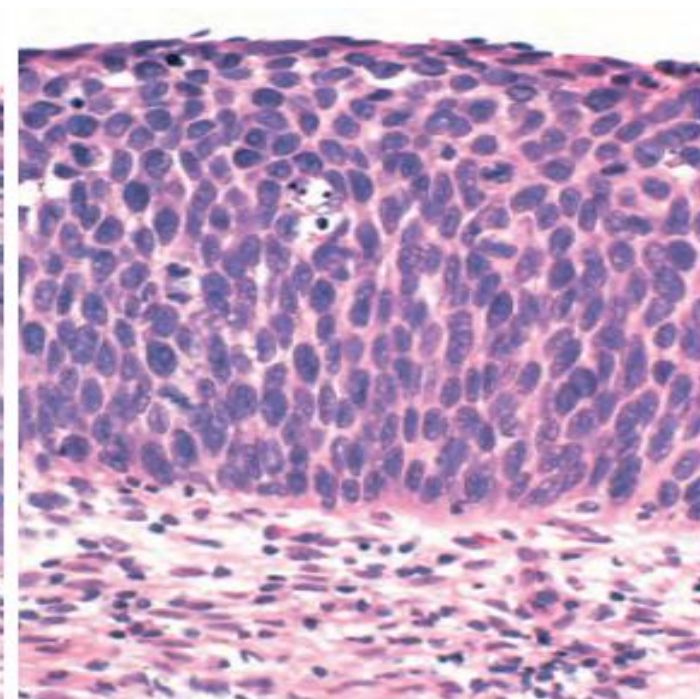
The diagnosis of SIL is based on identification of nuclear atypia characterized by nuclear enlargement, hyperchromasia (dark staining), coarse chromatin granules, and variation in nuclear size and shape . The nuclear changes are often accompanied by cytoplasmic “halos.” At an ultrastructural level, these “halos” consist of perinuclear vacuoles, a cytopathic change created in part by an HPV-encoded protein E5 that localizes to the membranes of the endoplasmic reticulum. Nuclear alterations associated with perinuclear halos are termed koilocytic atypia. The grading of SIL into low or high grade is based on expansion of the immature cell layer from its normal, basal location. If the immature squamous cells are confined to the lower one-third of the epithelium, the lesion is called LSIL; if they expand to the upper two-thirds of the epithelial thickness, it is called HSIL.

The histologic features of LSIL correlate with HPV replication and changes in host cell growth and gene expression . The highest viral loads (assessed by in situ hybridization for HPV DNA; are found in maturing keratinocytes in the upper half of the epithelium. HPV E6 and E7 proteins prevent cell cycle arrest. As a result, cells in the upper portion of the epithelium express markers of actively dividing cells, such as Ki-67

, that are normally confined to the basal layer of the epithelium. Disturbed growth regulation also leads to overexpression of p16, a cyclin-dependent kinase inhibitor . Both Ki-67 and p16 staining are highly correlated with HPV infection and are useful for confirmation of the diagnosis in equivocal cases of SIL. More than 80% of LSILs and 100% of HSIL



CIN II



CIN III

Cervical Carcinoma

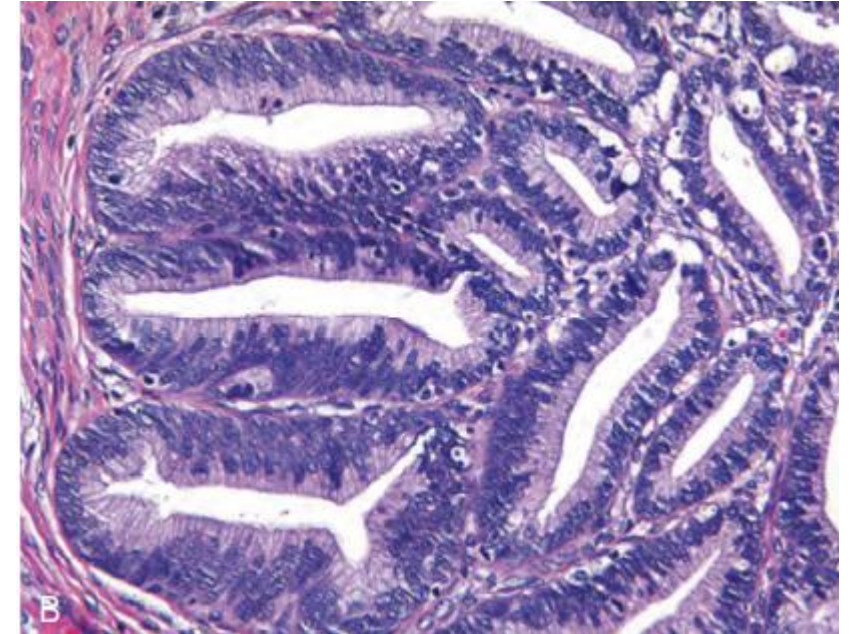
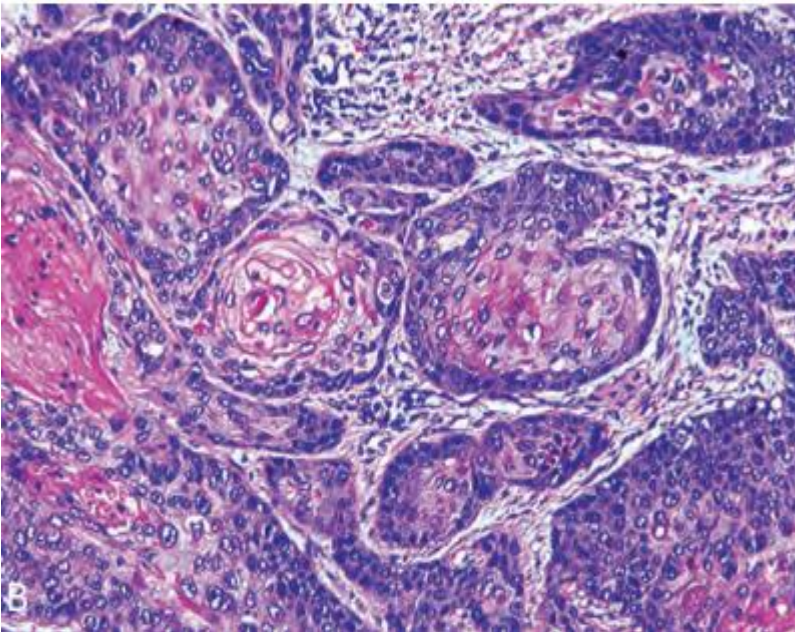
The average age of patients with invasive cervical carcinoma is between 45 and 50 years. Squamous cell carcinoma is the most common histologic subtype, accounting for approximately 80% of cases. The second most common tumor type is adenocarcinoma, which constitutes about 15% of cervical cancer cases and develops from a precursor lesion called adenocarcinoma in situ. Adenosquamous and neuroendocrine carcinomas are rare cervical tumors that account for the remaining 5% of cases. All of the aforementioned tumor types are caused by high-risk HPVs. The progression time from in situ to invasive adenosquamous and neuroendocrine carcinomas is shorter than in squamous cell carcinoma, and patients with these tumors often present with advanced disease and have a less favorable prognosis.

MORPHOLOGY

Invasive cervical carcinoma may manifest as fungating (exophytic) or infiltrative masses. Squamous cell carcinoma is composed of nests and tongues of malignant squamous epithelium, either keratinizing or nonkeratinizing, which invade the underlying cervical stroma . Adenocarcinoma is characterized by proliferation of glandular epithelium composed of malignant endocervical cells with large, hyperchromatic nuclei and relatively mucin-depleted cytoplasm, resulting in a dark appearance of the glands, as compared with the normal endocervical epithelium

Adenosquamous carcinoma is composed of intermixed malignant glandular and squamous epithelium. Neuroendocrine cervical carcinoma has an appearance similar to small cell carcinoma of the lung but differs in being positive for high-risk HPVs.

Advanced cervical carcinoma spreads by direct extension to contiguous tissues, including paracervical soft tissue, urinary bladder, ureters (resulting in hydronephrosis), rectum, and vagina. Lymphovascular invasion results in local and distant lymph nodes metastases. Distant metastases may also be found in the liver, lungs, bone marrow, and other organs.



Cervical cancer is staged as follows:

Stage 0—Carcinoma in situ (CIN III, HSIL)

Stage I—Carcinoma confined to the cervix

Ia—Preclinical carcinoma, that is, diagnosed only by microscopy

Ia1—Stromal invasion no deeper than 3 mm and no wider than 7 mm (so-called superficially invasive squamous cell carcinoma)

Ia2—Maximum depth of invasion of stroma deeper than 3 mm and no deeper than 5 mm taken from base of epithelium; horizontal invasion no more than 7 mm

Ib—Histologically invasive carcinoma confined to the cervix and greater than stage Ia2

Stage II—Carcinoma extends beyond the cervix but not to the pelvic wall. Carcinoma involves the vagina but not the lower third.

Stage III—Carcinoma has extended to the pelvic wall. On rectal examination, there is no cancer-free space between the tumor and the pelvic wall. The tumor involves the lower third of the vagina.

Stage IV—Carcinoma has extended beyond the true pelvis or has involved the mucosa of the bladder or rectum. This stage also includes cancers with metastatic dissemination.

Clinical Features

More than one-half of invasive cervical cancers are detected in women who did not participate in regular screening.

While superficially invasive squamous cell carcinomas may be treated by cervical cone excision alone, most invasive cancers are managed by hysterectomy with lymph node dissection and, for advanced lesions, radiation and chemotherapy. The prognosis for invasive carcinomas depends on the stage of the cancer at diagnosis and to some degree on histologic subtype, with small-cell neuroendocrine tumors having a very poor prognosis.

With current treatments, the 5-year survival rate is 100% for superficially invasive squamous cell carcinomas and less than 20% for tumors extending beyond the pelvis. Most patients with advanced cervical cancer die of the consequences of local tumor invasion (e.g., ureteral obstruction, pyelonephritis, and uremia) rather than distant metastases.

CERVICAL CANCER SCREENING AND PREVENTION

As is well known, cytologic cancer screening has significantly reduced mortality from cervical cancer. In countries where such screening is not widely practiced, cervical cancer continues to exact a high toll. The reason that cytologic screening is so effective in preventing cervical cancer is that most cancers arise from precursor lesions over the course of years. These lesions shed abnormal cells that can be detected on cytologic examination.

Body of Uterus and Endometrium

The uterus has two major components: the myometrium and the endometrium. The myometrium is composed of tightly interwoven bundles of smooth muscle that form the wall of the uterus. The internal cavity of the uterus is lined by the endometrium, which is composed of glands embedded in a cellular stroma. The uterus is affected by a variety of disorders, the most common of which results from endocrine imbalances, complications of pregnancy, and neoplastic proliferation.

FUNCTIONAL ENDOMETRIAL DISORDERS (DYSFUNCTIONAL UTERINE BLEEDING)

Although abnormal uterine bleeding can be caused by well-defined pathologic conditions, such as chronic endometritis, endometrial polyps , submucosal leiomyomas , or endometrial neoplasms, it most commonly stems from hormonal disturbances that produce dysfunctional uterine bleeding . This is a clinical term for uterine bleeding that lacks an underlying structural abnormality. the normal cyclical proliferation, differentiation, and shedding of the endometrium requires that all the involved pituitary and ovarian hormones be released at the proper time in the right amounts. Any disturbance of this finely tuned system may result in dysfunctional uterine bleeding.

Causes of Abnormal Uterine Bleeding by Age Group

Prepuberty Precocious puberty (hypothalamic, pituitary, or ovarian origin)

Adolescence Anovulatory cycle, coagulation disorders

Reproductive age Complications of pregnancy (abortion, trophoblastic disease, ectopic pregnancy)

Anatomic lesions (leiomyoma, adenomyosis, polyps, endometrial hyperplasia, carcinoma)

Dysfunctional uterine bleeding (Anovulatory cycle, Ovulatory dysfunctional bleeding (e.g., inadequate luteal phase))

Perimenopausal Dysfunctional uterine bleeding (Anovulatory cycle)

Anatomic lesions (carcinoma, hyperplasia, polyps)

Postmenopausal Endometrial atrophy

Anatomic lesions (carcinoma, hyperplasia, polyps)

Anovulatory Cycle

The most frequent cause of dysfunctional bleeding is anovulation (failure to ovulate). Anovulatory cycles result from hormonal imbalances and are most common at menarche and in the perimenopausal period. Less commonly, anovulation is the result of the following:

- Endocrine disorders, such as thyroid disease, adrenal disease, or pituitary tumors
- Ovarian lesions, such as a functioning ovarian tumor (granulosa cell tumors) or polycystic ovaries .
- Generalized metabolic disturbances, such as obesity, malnutrition, or other chronic systemic diseases

Failure of ovulation results in excessive endometrial stimulation by estrogens that is unopposed by progesterone.

Under these circumstances, the endometrial glands undergo mild architectural changes, including cystic dilation, that usually resolve due to a subsequent ovulatory cycle. However, repeated anovulation may result in bleeding

INFLAMMATORY DISORDERS

The endometrium and myometrium are relatively resistant to infections, primarily because the endocervix forms a barrier to ascending infection. Thus, although chronic inflammation in the cervix is common and usually insignificant, it is of concern in the endometrium.

Acute Endometritis

Acute endometritis is uncommon and limited to bacterial infections that arise after delivery or miscarriage. Retained products of conception are the usual predisposing factors; the causative agents include group A hemolytic streptococci, staphylococci, and other bacteria. The inflammatory response is chiefly limited to the stroma and is entirely nonspecific.

Removal of the retained gestational products by curettage and antibiotic therapy promptly clears these infections.

Chronic Endometritis

Chronic endometritis occurs in association with the following disorders:

- Chronic pelvic inflammatory disease
- Retained gestational tissue, postpartum or postabortion
- Intrauterine contraceptive devices
- Tuberculosis, either from miliary spread or, more often, from drainage of tuberculous salpingitis. Endometrial tuberculosis is rare in high income countries.

The diagnosis of chronic endometritis rests on the identification of plasma cells in the stroma , which are not seen in normal endometrium.

ENDOMETRIOSIS AND ADENOMYOSIS

Endometriosis is defined by the presence of “ectopic” endometrial tissue at a site outside of the uterus. The abnormal tissue most commonly includes both endometrial glands and stroma, but may consist only of stroma in some cases. It occurs in the following sites, in descending order of frequency:

- (1) ovaries,
- (2) uterine ligaments,
- (3) rectovaginal septum,
- (4) pelvic peritoneum,
- (5) serosa of the large and small bowel and appendix,
- (6) mucosa of the cervix, vagina, and fallopian tubes, and
- (7) laparotomy scars.

Endometriosis can have significant clinical consequences; it often causes infertility, dysmenorrhea (painful menstruation), pelvic pain, and other problems. The disorder is principally a disease of women in active reproductive life, most often in the third and fourth decades, and affects approximately 10% of women. There are three types of endometriosis: superficial peritoneal endometriosis, ovarian endometriosis, and deep infiltrating endometriosis . The superficial and ovarian forms of endometriosis are uncommonly associated with the development of malignancy, whereas it is extremely rare for the deep infiltrating form to undergo malignant transformation.

Pathogenesis

The pathogenesis of endometriosis remains elusive. Proposed origins of endometriotic lesions fall into two main categories: (1) those that propose an origin from the uterine endometrium and (2) those that propose an origin from cells outside the uterus that have the capacity to give rise to endometrial tissue. The leading theories are as follows:

- The regurgitation theory proposes that endometrial tissue implants at ectopic sites via retrograde flow of menstrual endometrium.
- The benign metastasis theory holds that endometrial tissue from the uterus can “spread” to distant sites (e.g., bone, lung, and brain) via blood vessels and lymphatic channels.
- The metaplastic theory suggests that endometrium arises directly from coelomic epithelium (mesothelium of pelvis or abdomen), from which the müllerian ducts and ultimately the endometrium itself originate during embryonic development. In addition, mesonephric remnants may undergo endometrial differentiation and give rise to ectopic endometrial tissue.
- The extrauterine stem/progenitor cell theory proposes that stem/progenitor cells from the bone marrow differentiate into endometrial tissue.

Clinical Features

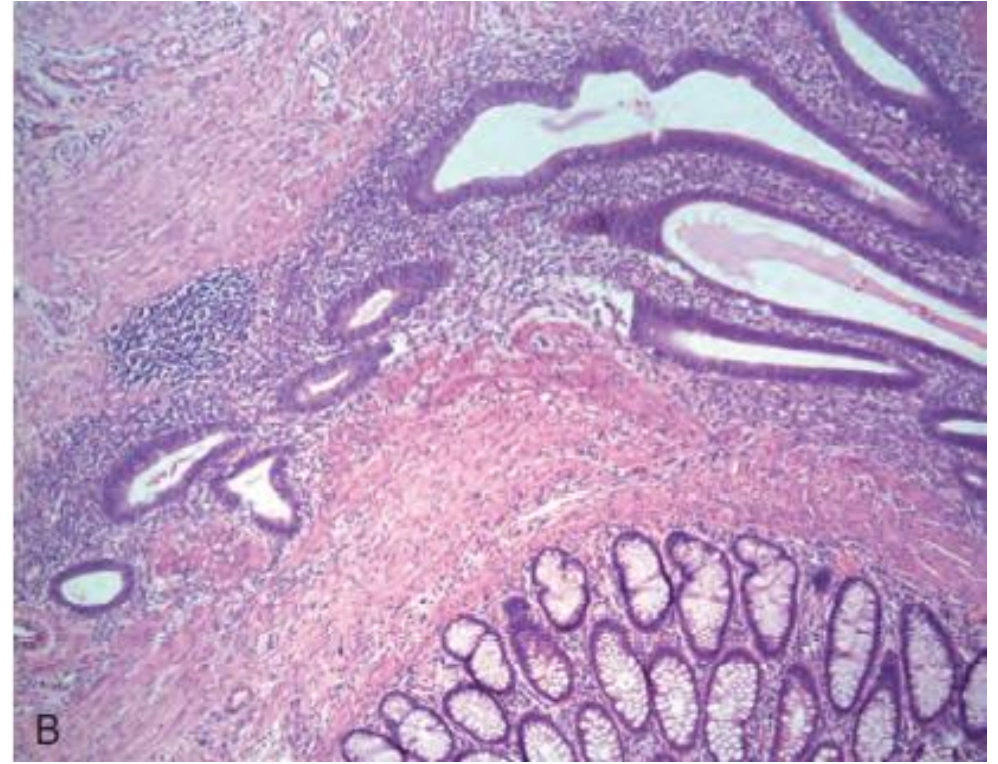
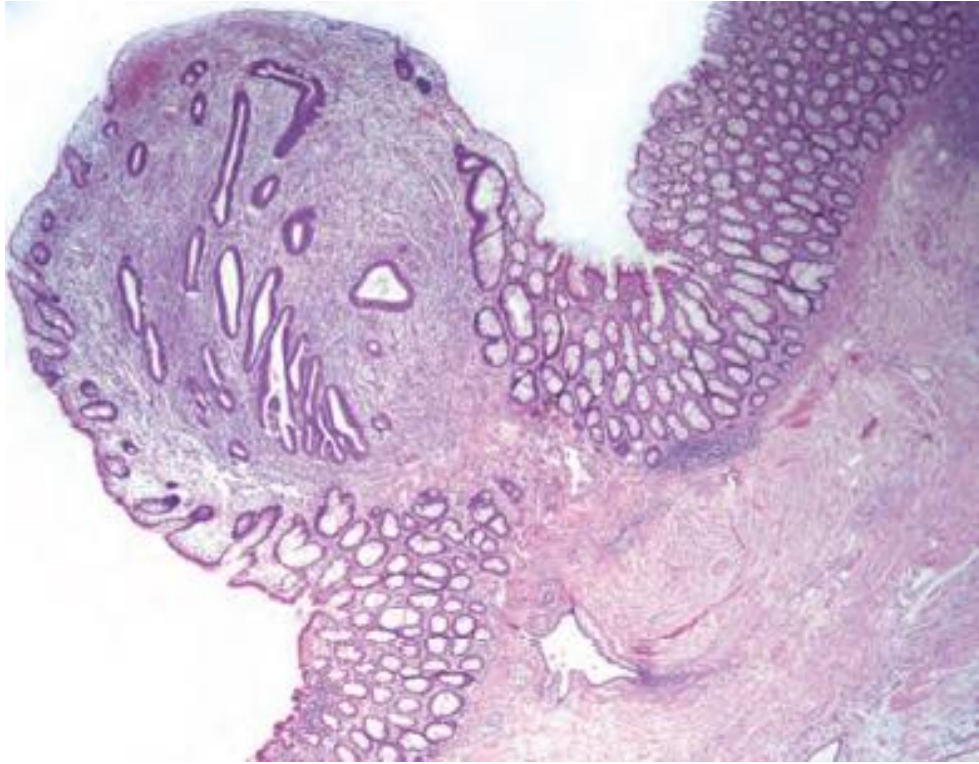
Clinical signs and symptoms usually include severe dysmenorrhea, dyspareunia (pain with intercourse), and pelvic pain due to the intrapelvic bleeding and periuterine adhesions. Menstrual irregularities are common, and infertility is the presenting complaint in 30% to 40% of women. In addition, although uncommon, malignancies can develop within endometriomas, suggesting that these lesions contain “at-risk” epithelium.

A related disorder, **adenomyosis**, is defined as the presence of endometrial tissue within the uterine wall (myometrium). Adenomyosis remains in continuity with the endometrium, presumably signifying down-growth of endometrial tissue into and between the smooth muscle fascicles of the myometrium. Adenomyosis occurs in up to 20% of uteri. **On microscopic examination**, irregular nests of endometrial stroma, with or without glands, are arranged within the myometrium. Like endometriosis, the clinical symptoms of adenomyosis include menometrorrhagia (irregular and heavy menses), colicky dysmenorrhea, dyspareunia, and pelvic pain, particularly during the premenstrual period. It can coexist with endometriosis.

MORPHOLOGY

Endometriotic lesions bleed periodically in response to both extrinsic cyclic (ovarian) and intrinsic hormonal stimulation. This bleeding produces nodules with a red-blue to yellow-brown appearance on or just beneath the mucosal and/or serosal surfaces at sites of involvement. When lesions are widespread, organizing hemorrhage causes extensive fibrous adhesions between tubes, ovaries, and other structures and obliterates the pouch of Douglas. The ovaries may become markedly distorted by large cystic masses (3 to 5 cm in diameter) filled with brown fluid resulting from previous hemorrhage; these are referred to clinically as chocolate cysts or endometriomas. Deeply infiltrating endometriosis can invade tissues and also cause fibrosis and adhesions.

Atypical endometriosis, the likely precursor to endometriosis-related ovarian carcinoma, has two morphologic appearances. One shows cytologic atypia of the epithelium lining the endometriotic cyst, without major architectural changes. The second is marked by glandular crowding due to excessive epithelial proliferation, often associated with cytologic atypia, producing an appearance that resembles complex atypical endometrial hyperplasia



Endometrial Polyps

Endometrial polyps are exophytic masses of variable size that project into the endometrial cavity. They may be single or multiple and are usually sessile and relatively small, measuring 0.5 to 3 cm in diameter, but are occasionally large and pedunculated. Polyps may be asymptomatic or may cause abnormal bleeding and infertility.

ENDOMETRIAL HYPERPLASIA

Endometrial hyperplasia is an important cause of abnormal bleeding and a frequent precursor to the most common type of endometrial carcinoma. It is defined as an abnormal proliferation of the endometrial glands relative to the stroma, resulting in an increased gland-to-stroma ratio when compared with normal proliferative endometrium.

Clinicopathologic and epidemiologic studies have pointed to the malignant potential of endometrial hyperplasia, and molecular studies have confirmed this relationship, as endometrial hyperplasia and carcinoma share specific acquired driver mutations in cancer genes

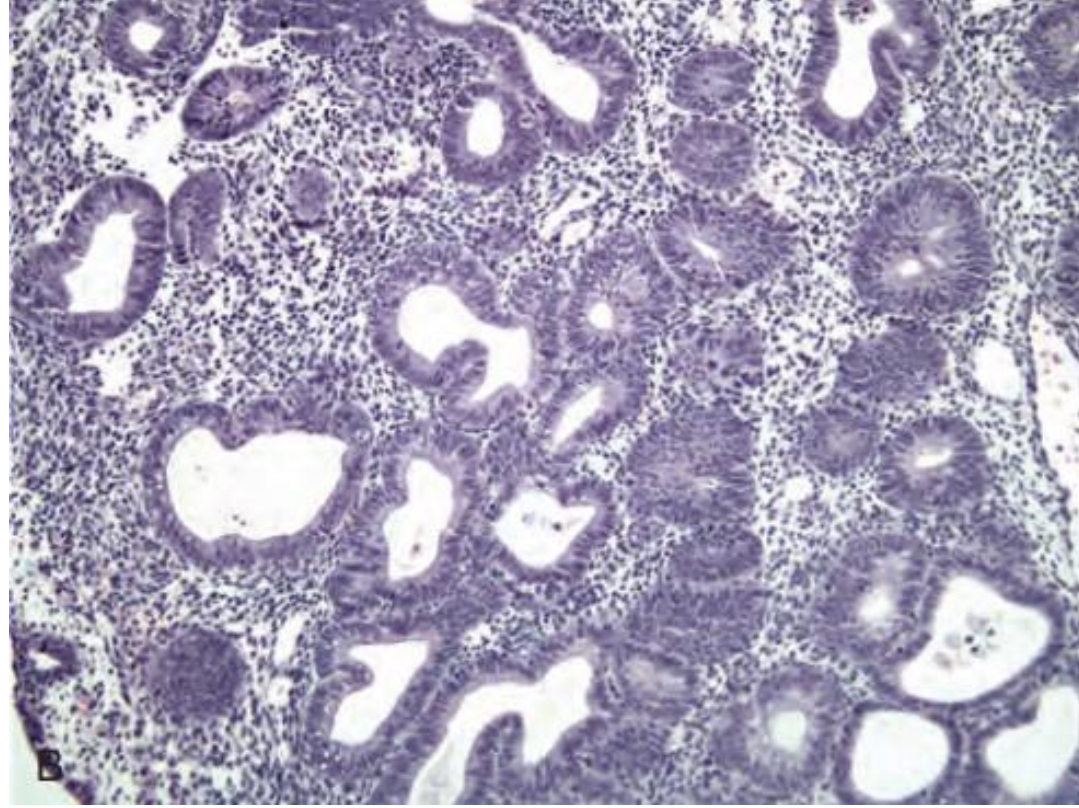
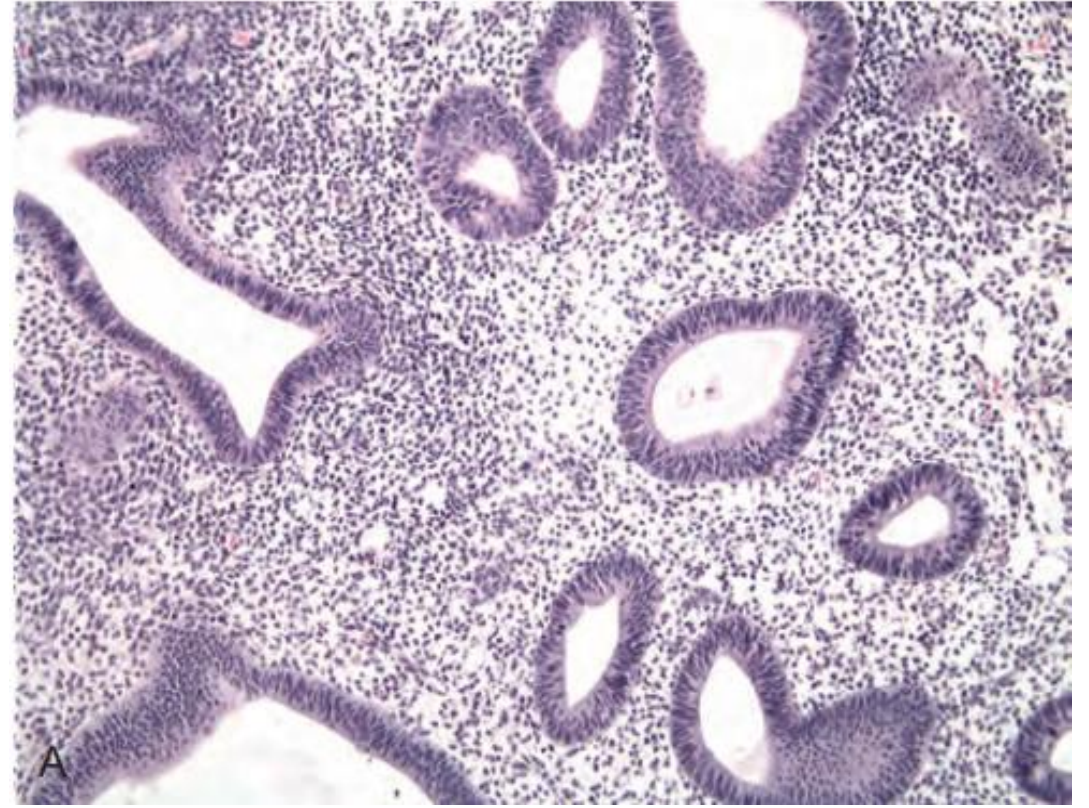
Endometrial hyperplasia is associated with prolonged estrogenic stimulation of the endometrium, which can be due to anovulation, increased estrogen production from endogenous sources, or exogenous estrogen. Associated conditions include the following:

- Obesity (peripheral conversion of androgens to estrogens)
- Menopause
- Polycystic ovarian syndrome
- Functioning granulosa cell tumors of the ovary
- Excessive ovarian cortical function (cortical stromal hyperplasia)
- Prolonged administration of estrogenic substances (estrogen replacement therapy)

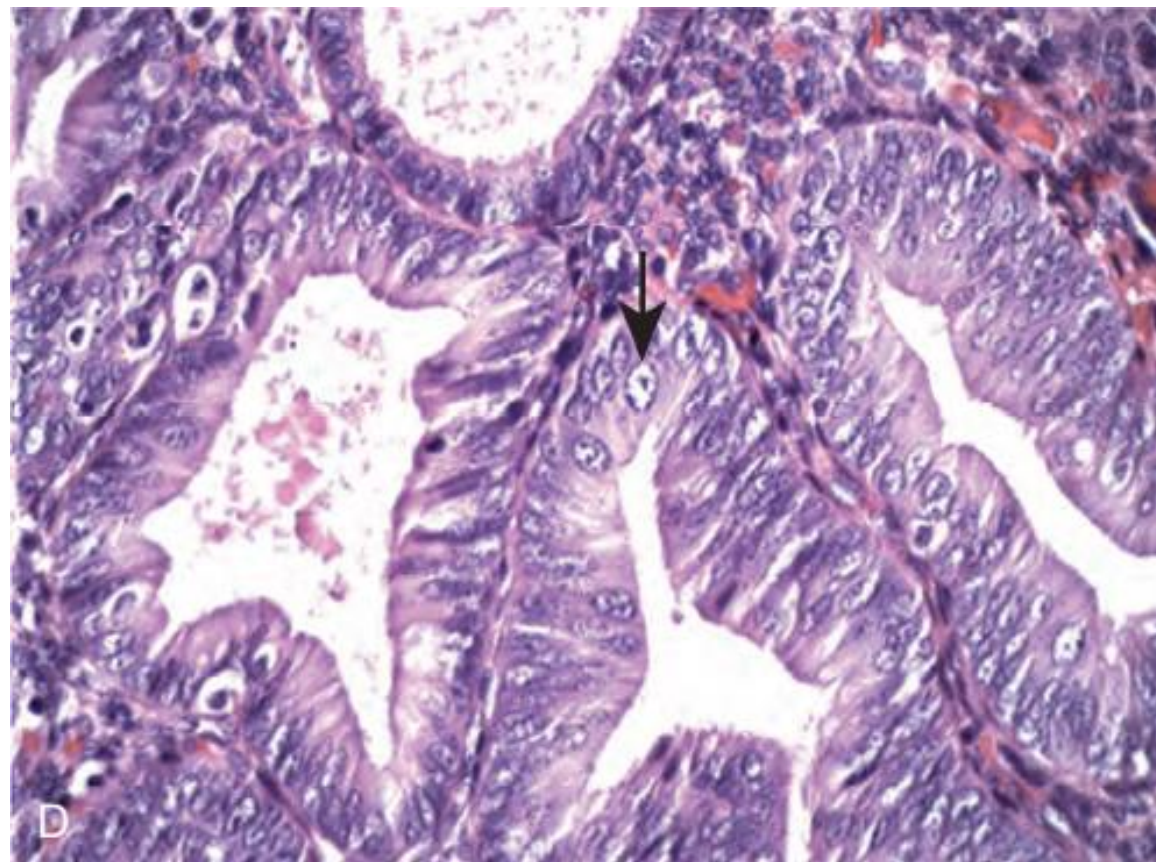
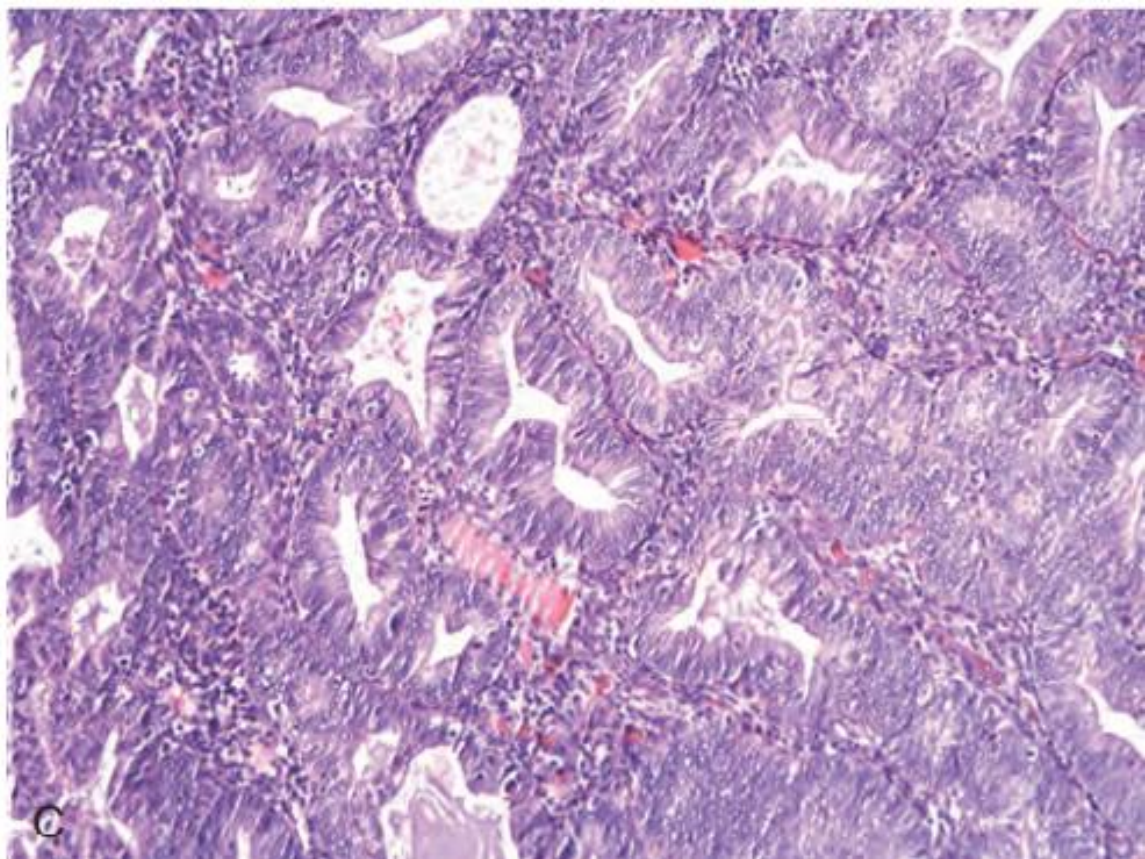
Inactivation of the PTEN tumor suppressor gene is a common genetic alteration in both endometrial hyperplasias and endometrioid endometrial carcinoma.

MORPHOLOGY

The classification of endometrial hyperplasia according to the World Health Organization (WHO) includes two major categories, hyperplasia and atypical hyperplasia (also referred to as endometrial intraepithelial neoplasia), which differ in appearance and propensity to progress to carcinoma. Typical hyperplasia has a wide-range of appearances, but the cardinal feature is an increased gland-to stroma ratio. The glands show variation in size and shape and may be dilated . Although there may be back-to-back glands focally, some intervening stroma is usually retained . These lesions are caused by persistent estrogen stimulation and rarely progress to adenocarcinoma (approximately 1% to 3%). Hyperplasia may evolve into cystic atrophy when estrogen is withdrawn.



Atypical hyperplasia (endometrial intraepithelial neoplasia) is composed of complex patterns of proliferating glands displaying nuclear atypia. The glands are commonly back to-back and often have complex outlines due to branching structures. Individual cells are rounded and lose the normal perpendicular orientation to the basement membrane. In addition, the nuclei have open (vesicular) chromatin and conspicuous nucleoli. The features of atypical hyperplasia have considerable overlap with those of well-differentiated endometrioid adenocarcinoma and accurate distinction from cancer may not be possible without hysterectomy . Indeed, up to 50% of women with a diagnosis of atypical hyperplasia are found to have carcinoma when a hysterectomy is performed.



MALIGNANT TUMORS OF THE ENDOMETRIUM

Carcinoma of the Endometrium

Endometrial carcinoma is the most common invasive cancer of the female genital tract. It accounts for 7% of all invasive cancer in women, excluding skin cancer.

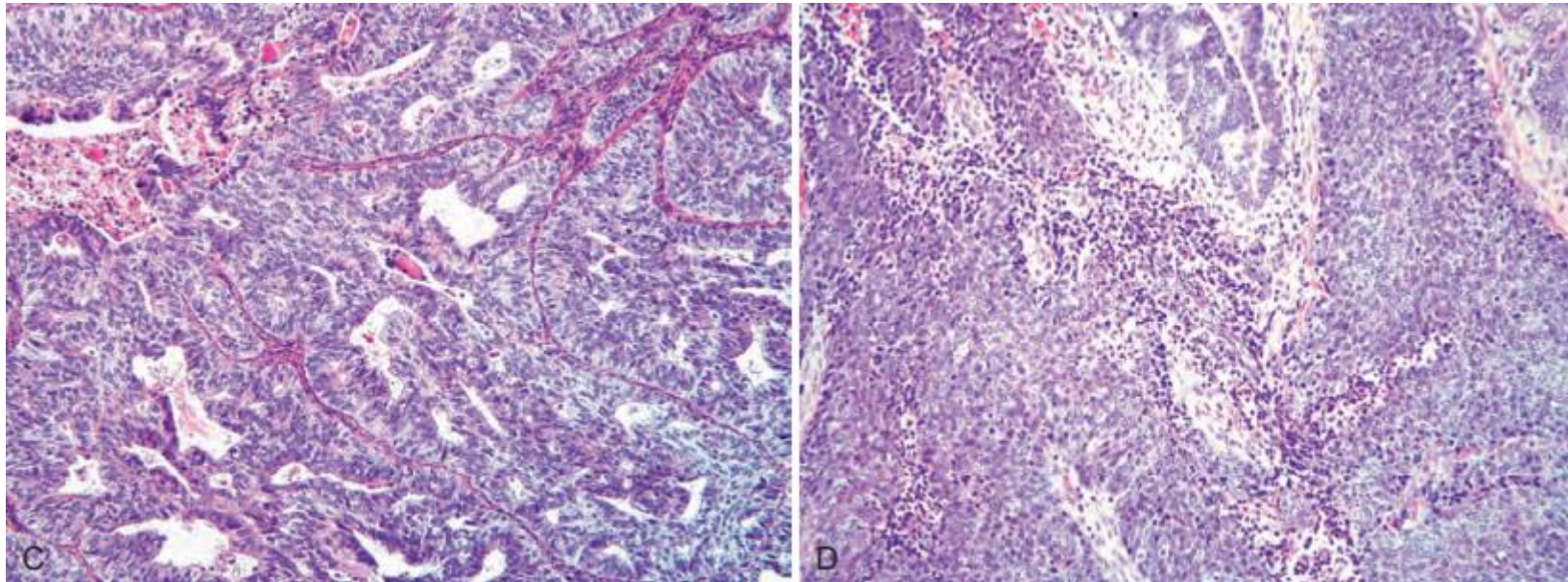
Pathogenesis:

Clinicopathologic studies and molecular analyses support the existence of two broad categories of endometrial carcinoma referred to as type I and type II, each with distinct risk factors, precursor lesions, molecular genetics, and clinical behaviors

Characteristics	Type I	Type II
Age	55–65 years	65–75 years
Clinical setting	Unopposed estrogen Obesity Hypertension Diabetes	Atrophy Thin physique
Morphology	Endometrioid	Serous Clear cell Mixed müllerian tumor
Precursor	Hyperplasia	Serous endometrial intraepithelial carcinoma
Mutated genes/ genetic abnormalities	<i>PTEN</i> <i>ARID1A</i> (regulator of chromatin) <i>PIK3CA</i> (PI3K) <i>KRAS</i> <i>FGF2</i> (growth factor) MSI ^a <i>CTNNB1</i> (Wnt signaling) <i>POLE</i> <i>TP53</i> (progressed tumors)	<i>TP53</i> Aneuploidy <i>PIK3CA</i> (PI3K) <i>FBXW7</i> (regulator of MYC, cyclin E) <i>CCNE1</i> <i>PPP2R1A</i> (PP2A)
Behavior	Indolent Spreads via lymphatics	Aggressive Intraperitoneal and lymphatic spread

Endometrioid Endometrial Carcinoma:

This is the most common type of endometrial carcinoma, accounting for approximately 80% to 85% of cases. The majority of these tumors fall in to the type I category. Most are well differentiated and mimic proliferative endometrial glands



MORPHOLOGY Endometrioid carcinoma can take the form of a localized polypoid mass or diffusely involve the endometrial lining . Spread generally occurs by myometrial invasion followed by direct extension to adjacent structures/organs.

Histology:

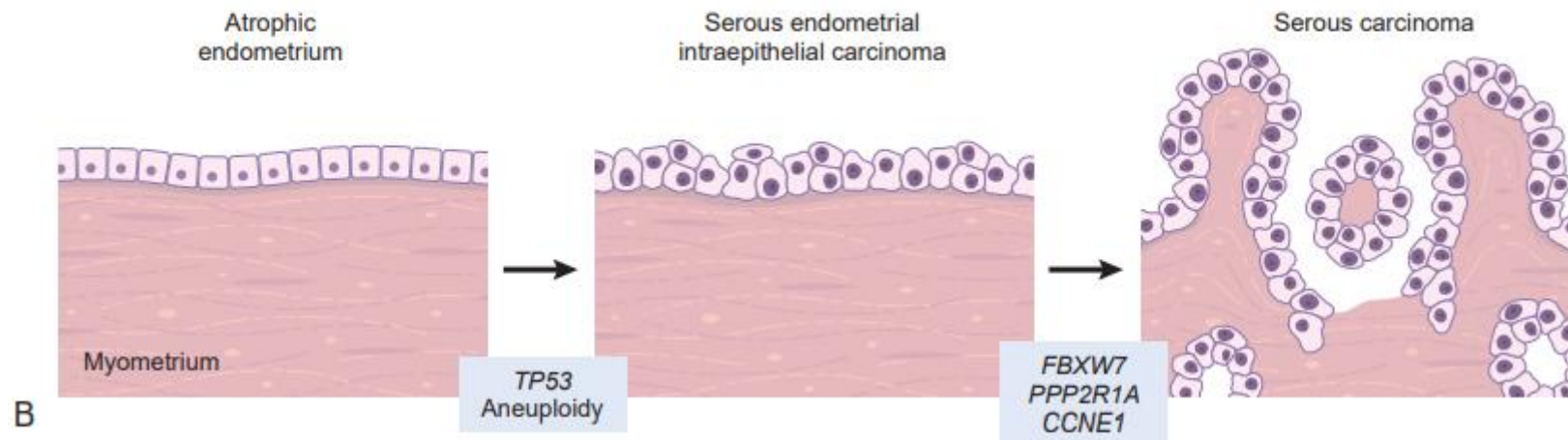
- Crowded, complex branching glands with cribriform architecture and back-to back glands without intervening stroma
- Loss of polarity and cytologic atypia: large, round nuclei with prominent nucleoli, nuclear membrane condensation
- Glands may infiltrate into the myometrium, inducing a desmoplastic response
- Grading is based on the degree of glandular differentiation versus solid areas
 - Grade 1: less than 5% of the tumor is composed of solid areas
 - Grade 2: 5% to 50% of the tumor is composed of solid areas
 - Grade 3: greater than 50% of the tumor is composed of solid areas

Serous Endometrial Carcinoma

Serous endometrial carcinoma generally occurs in women who are about 10 years older than those with endometrioid carcinomas, and in contrast with endometrioid carcinoma, they usually arise in the setting of endometrial atrophy . Serous tumors are considered type II tumors and are by definition poorly differentiated (grade 3). They account for approximately 15% of cases of endometrial carcinoma. This subtype shows significant morphologic and biologic overlap with ovarian serous carcinoma.

Pathogenesis :

Serous endometrial carcinoma is highly associated with disruptive mutations in the TP53 tumor suppressor gene.



MORPHOLOGY:

- Thick and thin papillae with marked nuclear pleomorphism
- Cellular stratification, apoptotic bodies, and tumor necrosis
- Psammoma bodies may be present (>30% of cases)
- By definition, a high-grade tumor with poor prognosis (grade 2 or 3)

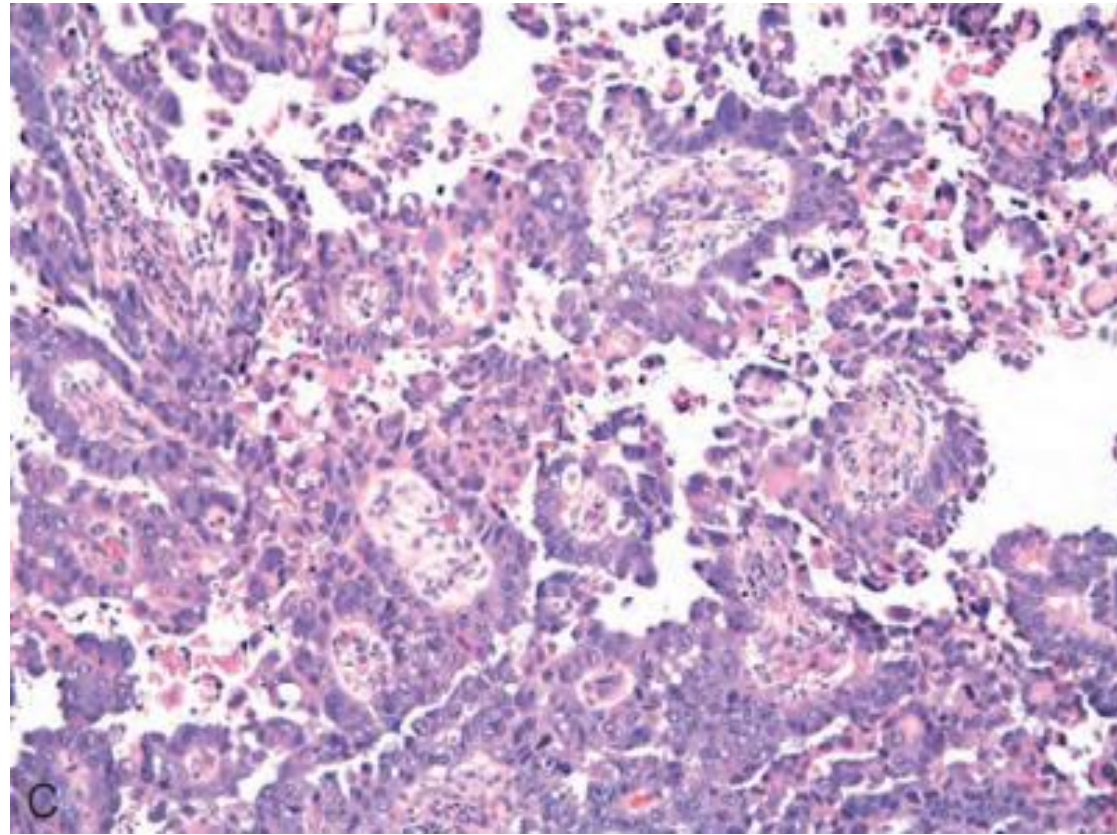
The staging system for endometrial adenocarcinoma is as follows:

Stage I—Carcinoma is confined to the corpus uteri itself.

Stage II—Carcinoma involves the corpus and the cervix.

Stage III—Carcinoma extends outside the uterus but not outside the true pelvis.

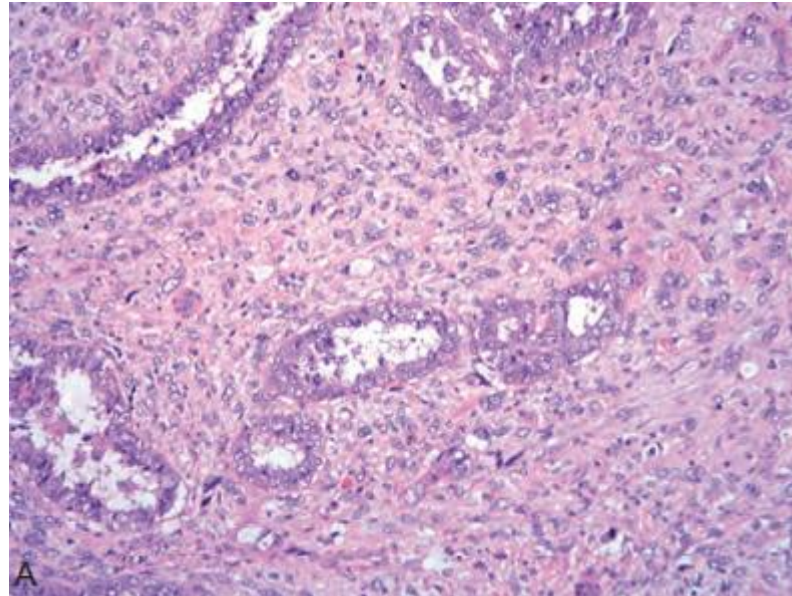
Stage IV—Carcinoma extends outside the true pelvis or involves the mucosa of the bladder or the rectum.



Carcinosarcoma (Malignant Mixed Müllerian Tumors)

Carcinosarcomas (also referred to as malignant mixed müllerian tumors) are mixed epithelial and mesenchymal tumors. The epithelial component most often resembles poorly differentiated endometrioid or serous carcinoma, while the mesenchymal component can take a number of forms. Some contain uterine mesenchymal elements (stromal sarcoma, leiomyosarcoma), while others contain heterologous malignant cell types (rhabdomyosarcoma, chondrosarcoma).

Carcinosarcomas occur in postmenopausal women and present with bleeding. Outcome is determined primarily by depth of invasion and stage. The only other known prognostic factor is the differentiation of the mesenchymal component; patients with tumors that have heterologous mesenchymal components have a poorer prognosis than those whose tumors do not. Overall 5-year survival rates are 25% to 30% for patients with high-stage disease.



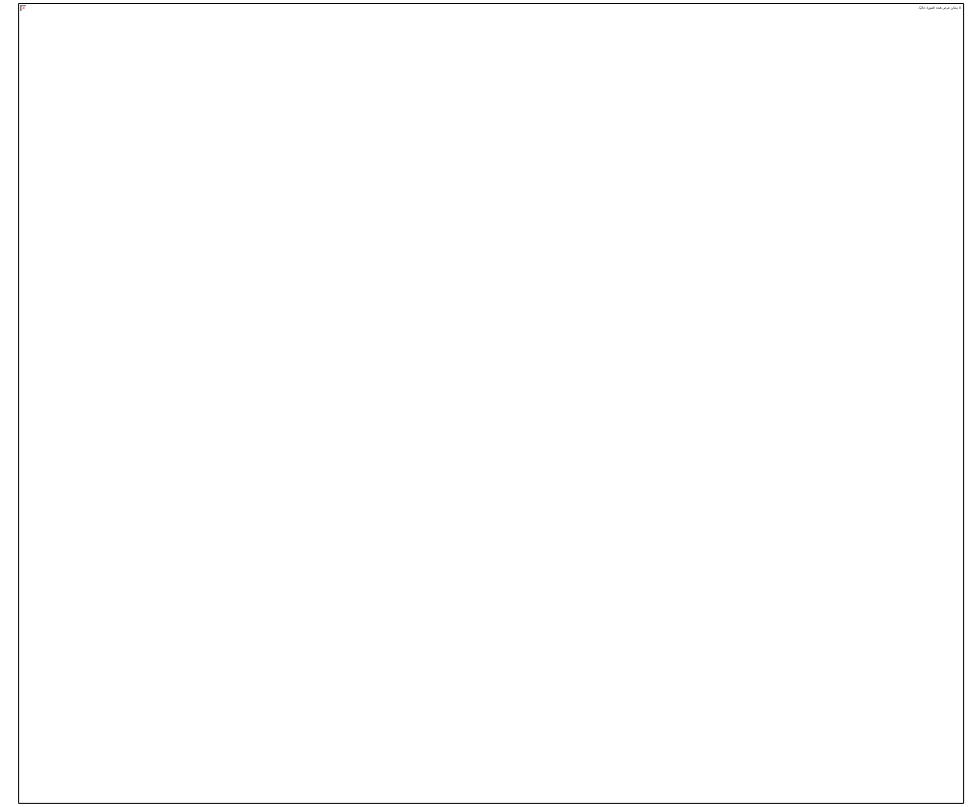
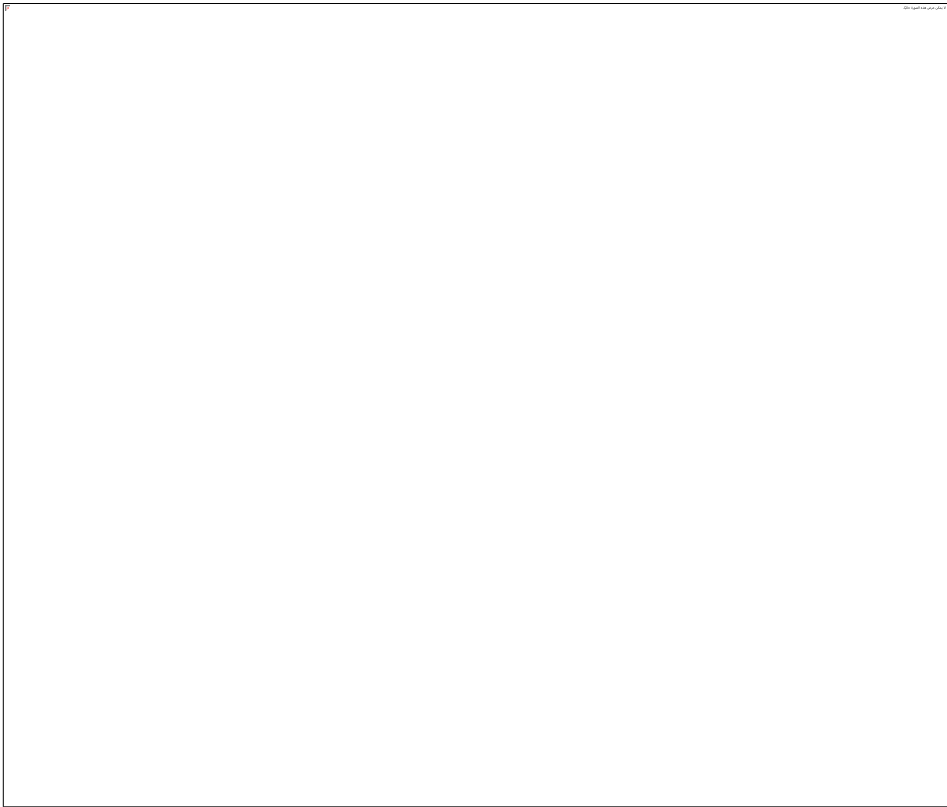
TUMORS OF ENDOMETRIAL STROMA

These relatively uncommon tumors comprise less than 5% of endometrial cancers and include stromal neoplasms admixed with benign glands (adenosarcomas) and pure stromal neoplasms.

Adenosarcoma:

Adenosarcoma presents most commonly as large broad-based endometrial polypoid growths that may prolapse through the cervical os. The diagnosis is based on the presence of malignant-appearing stroma, which coexists with benign but abnormally shaped endometrial glands. These tumors predominate in women between the fourth and fifth decades and are generally considered to be a low-grade malignancy.

Stromal Tumors The endometrium occasionally gives rise to neoplasms that resemble normal stromal cells. Endometrial stromal neoplasms are divided into two categories: (1) benign stromal nodules and (2) endometrial stromal sarcoma. Stromal sarcoma may be further divided into low-grade and high grade types depending on their differentiation.



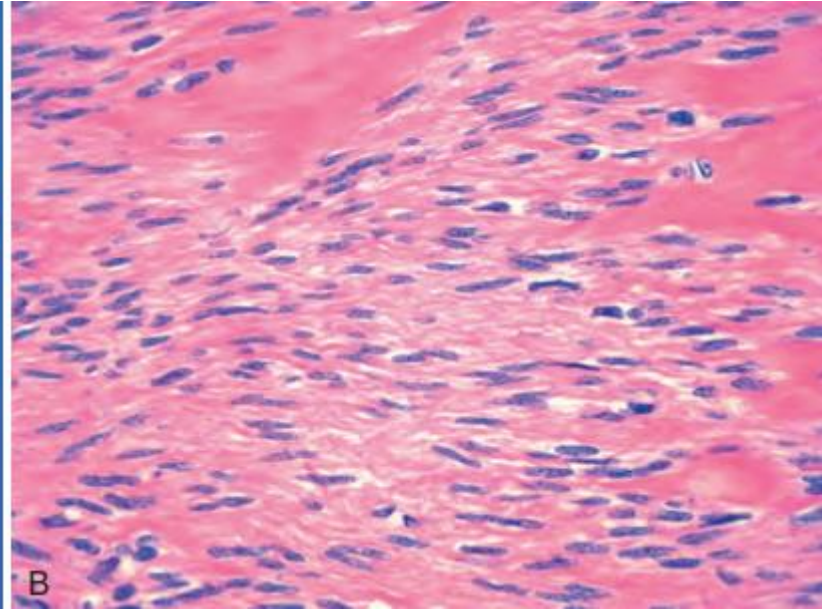
TUMORS OF THE MYOMETRIUM

Leiomyoma

Uterine leiomyoma (commonly called fibroid) is perhaps the most common tumor in women. They are benign smooth muscle neoplasms that may occur singly, but more often are multiple.

MORPHOLOGY Leiomyomas are sharply circumscribed, discrete, round, firm, gray-white tumors varying in size from small, barely visible nodules to massive tumors that fill the pelvis. They can occur within the myometrium (intramural), just beneath the endometrium (submucosal) or beneath the serosa (subserosal) . The characteristic whorled pattern of smooth muscle bundles on cut section usually makes these lesions readily identifiable.

Leiomyomas are composed of bundles of smooth muscle cells that resemble the uninvolved myometrium . Usually, the individual muscle cells are uniform in size and shape and have a characteristic oval nucleus and long, slender bipolar cytoplasmic processes. Mitotic figures are rare. Morphologic variants include leiomyoma with bizarre nuclei, which has nuclear atypia and giant cells, and cellular leiomyomas. Both have a low mitotic index, helping to distinguish these benign tumors from leiomyosarcoma. An extremely rare variant, intravenous leiomyomatosis, is a uterine leiomyoma that extends into vessels and spreads hematogenously to other sites, most commonly the vena cava and the right atrium. Another variant, disseminated peritoneal leiomyomatosis, presents as multiple small peritoneal nodules. Both are considered benign despite their unusual behavior.



Leiomyosarcoma

Clinical Features

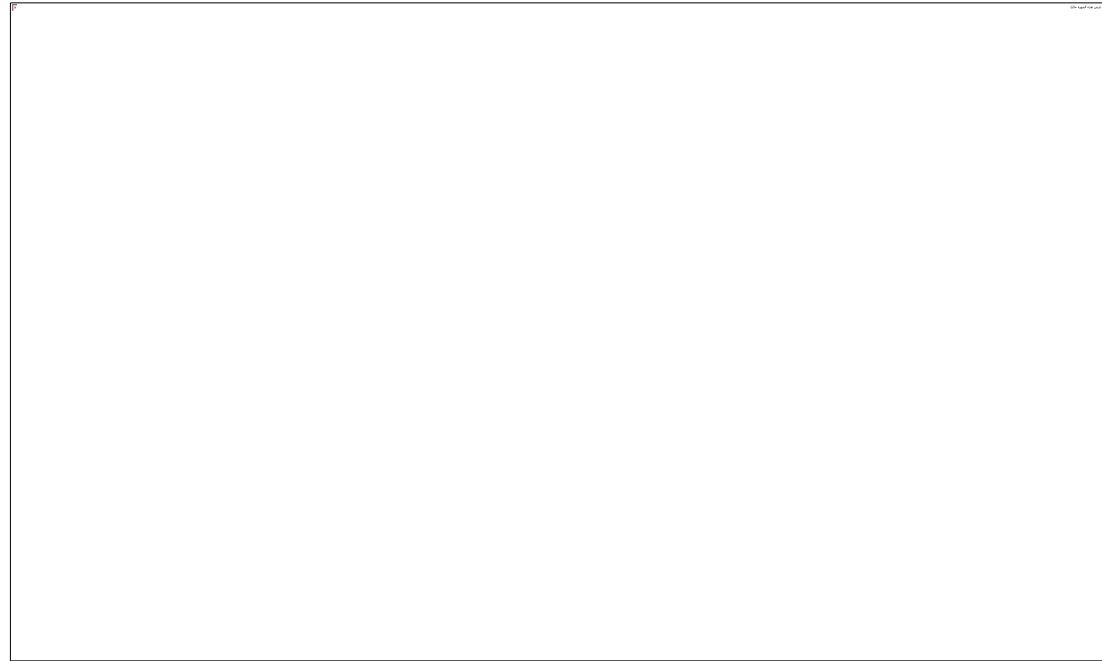
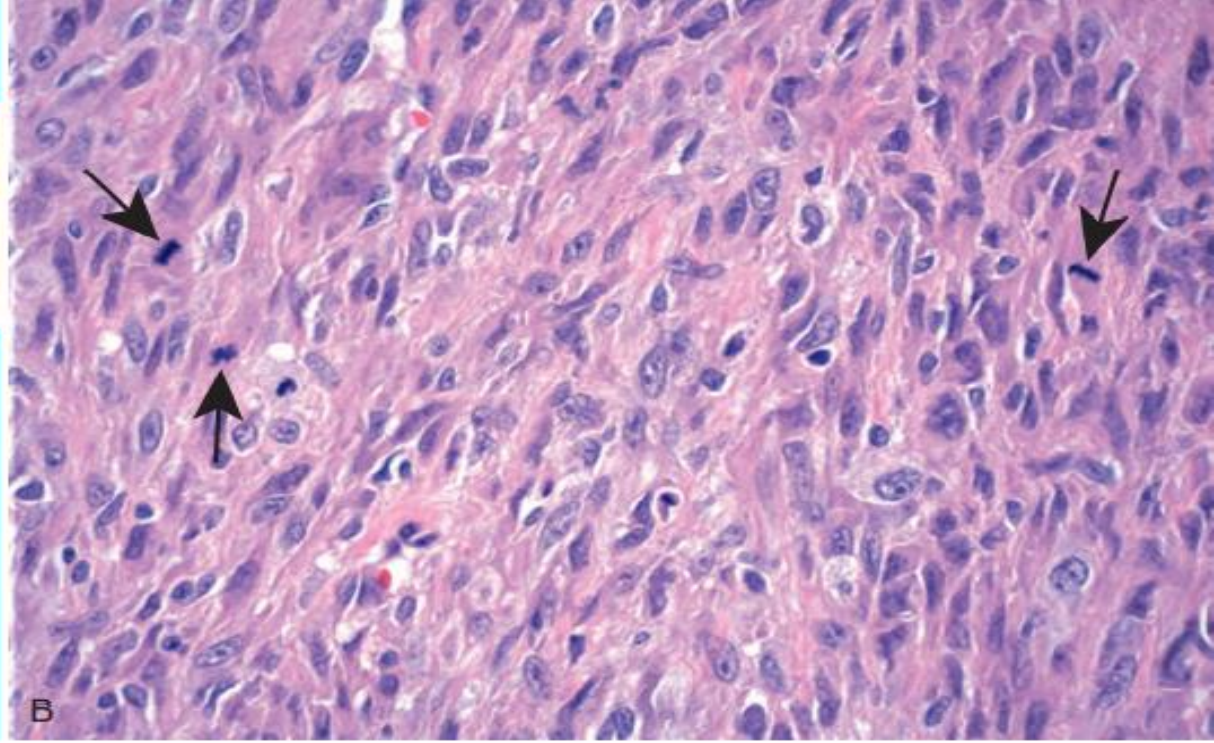
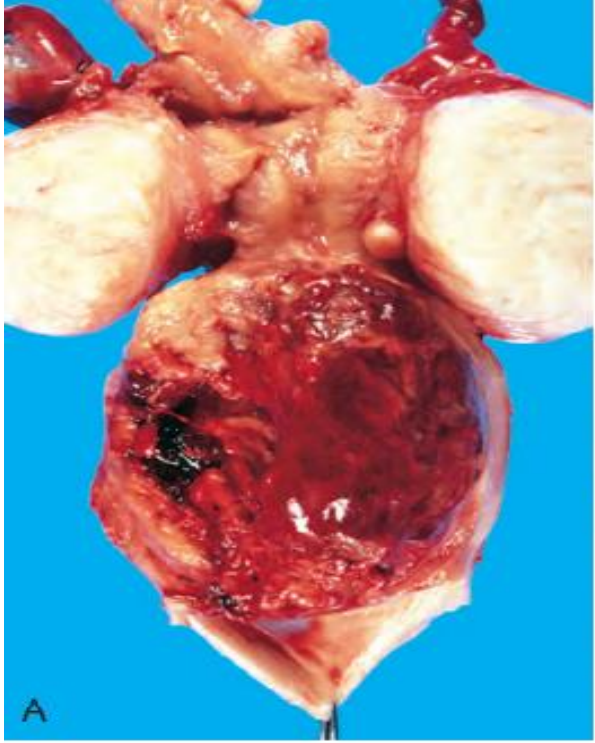
- Rapidly growing tumor that usually arises in postmenopausal women
- Large tumor that may cause pain, dysmenorrhea, urinary difficulties, changes in bowel habits, and, in extreme cases, infertility
- Often diagnosed on pelvic examination and specifically localized by ultrasound
- Commonly has spread into the pelvic cavity by the time of presentation
- Often detected as an incidental finding in hysterectomy specimen
- Distant metastases may occur months or years later, often in the lungs
- Prognosis is variable depending on stage and grade

Gross Pathology

- Usually solitary
- Large, poorly circumscribed mass, often extending beyond the uterine serosa
- Soft, fleshy, variegated cut surface showing hemorrhage and necrosis

Histopathology

- Densely cellular tumor composed of interlacing fascicles of pleomorphic spindled cells
- Coagulative necrosis is often present
- Mitoses are generally greater than 10 to 20 mitotic figures/hpf in areas with highest mitotic activity (viewed with a 40× objective)
- Infiltrative margins with occasional vascular invasion
- Variants
 - Epithelioid
 - ◆ Rounded, highly atypical polygonal cells with necrosis and increased mitosis
 - Myxoid
 - ◆ Myxoid matrix that makes tumor appear less cellular and mitotically active
 - ◆ Infiltrates myometrium and vessels



FALLOPIAN TUBES

The most common disorders affecting the fallopian tube are infections and associated inflammatory conditions, followed in frequency by ectopic (tubal) pregnancy and endometriosis.

Inflammations

Suppurative salpingitis may be caused by any pyogenic organism; in some cases more than one organism is involved. Gonococcus is the causative organism in more than 60% of cases, with Chlamydiae being responsible for many of the remaining cases. These tubal infections are a part of pelvic inflammatory disease. Tuberculous salpingitis accounting for not more than 1% to 2% of all forms of salpingitis. It is more common, however, in parts of the world where tuberculosis is prevalent and is an important cause of infertility in these areas.

TUMORS AND CYSTS

The most common primary lesions of the fallopian tube (excluding endometriosis) are minute, 0.1- to 2-cm translucent cysts filled with clear serous fluid, called paratubal cysts.

Benign tumors of the fallopian tube are rare and include adenomatoid tumor

fallopian tube carcinoma was considered to be a rare entity



Ovaries

The most common lesions encountered in the ovary are functional or benign cysts and tumors. Neoplastic disorders can be grouped according to their origin from each of the three main ovarian cell types:

(1) müllerian epithelium.

(2) germ cells.

(3) sex cord–stromal cells.

Primary inflammations of the ovary (oophoritis) are uncommon, and on rare occasions may have an autoimmune basis (autoimmune oophoritis); the autoimmune reactions affect the ovarian follicles and may lead to infertility.

NON-NEOPLASTIC AND FUNCTIONAL CYSTS

Follicle and Luteal Cysts Cystic follicles are very common in the ovary. They originate from unruptured graafian follicles or in follicles that have ruptured and immediately sealed.

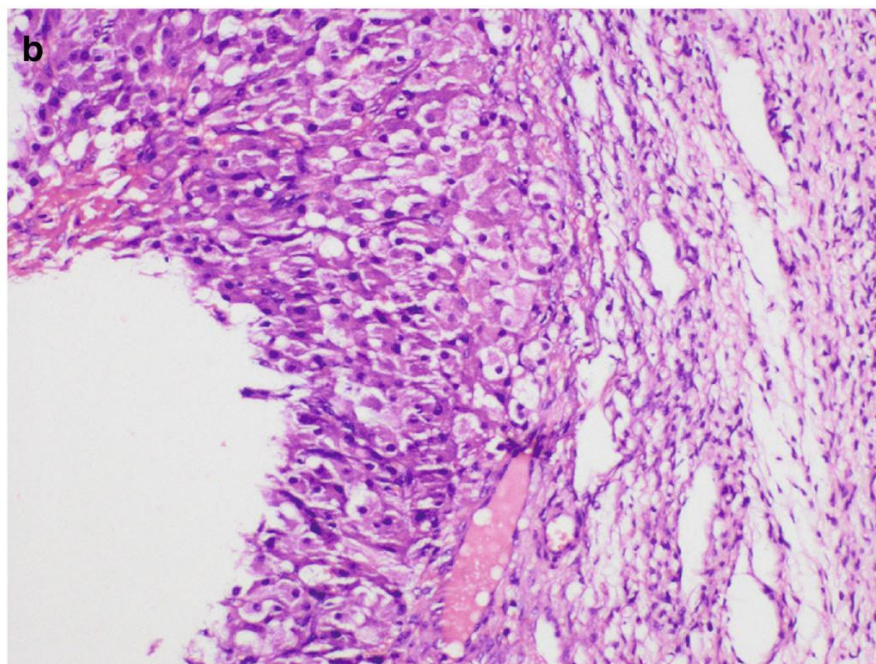
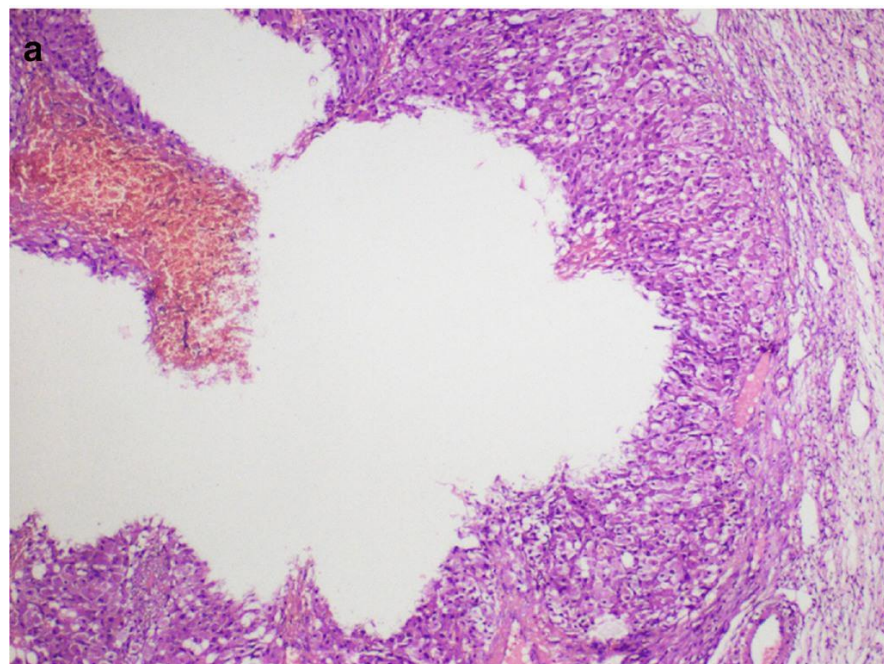
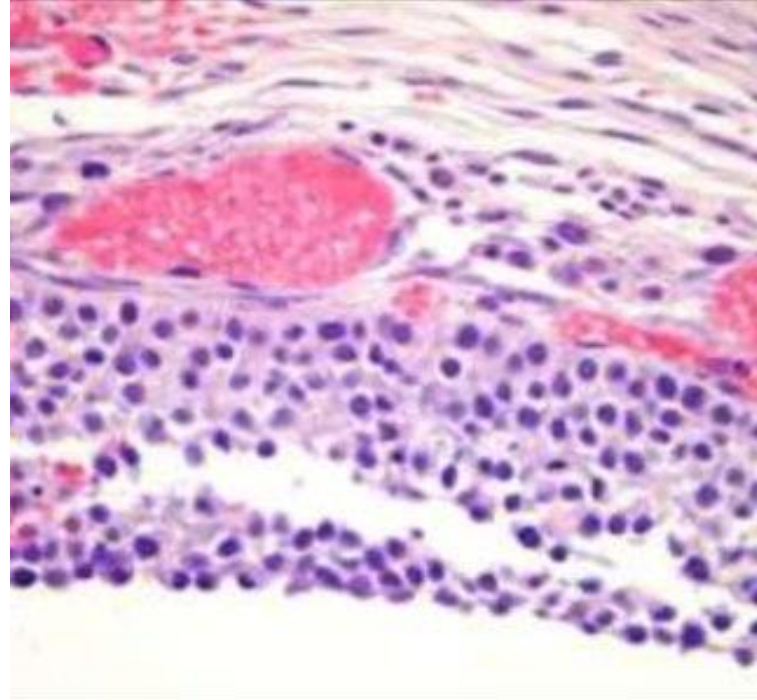
MORPHOLOGY

These cysts are usually multiple. They range in size up to 2 cm in diameter, are filled with a clear serous fluid, and are lined by a gray membrane. The cyst lining by granulosa cells.

Luteal cysts (corpora lutea) are present in the normal ovaries of women of reproductive age. They are lined by a rim of bright yellow tissue containing luteinized granulosa cells.

Polycystic Ovaries

Polycystic ovarian syndrome (PCOS) is a complex endocrine disorder characterized by hyperandrogenism, menstrual abnormalities, polycystic ovaries, chronic anovulation, and decreased fertility.

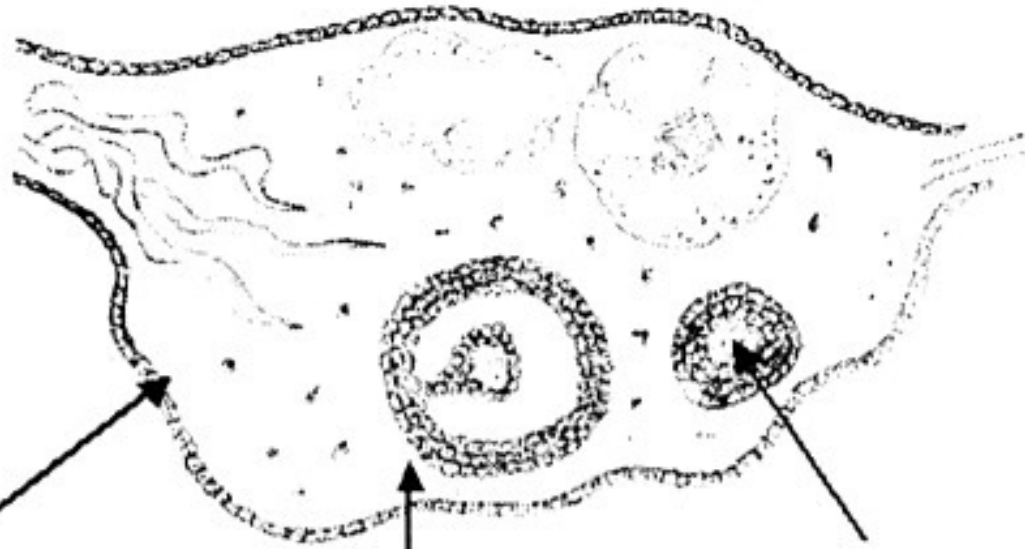


OVARIAN TUMORS

There are numerous types of ovarian tumors. About 80% are benign, and these occur mostly in young women between 20 and 45 years of age. So-called borderline tumors (tumors of indeterminate malignancy) occur at slightly older ages. Malignant tumors are more common in women between 45 and 65 years of age.

Classification:

The classification of ovarian tumors given in a simplified version of the World Health Organization Histological Classification, which separates ovarian neoplasms according to the most probable tissue of origin. It is now believed that most tumors of the ovary arise ultimately from one of three ovarian components:



Surface epithelium-stroma

- Serous
- Mucinous
- Endometrioid
- Clear cell
- Transitional cell

Sex cord-stroma

- Granulosa cell
- Thecoma
- Fibroma
- Sertoli cell
- Sertoli-Leydig
- Steroid

Germ cells

- Dysgerminoma
- Yolk sac
- Embryonal carcinoma
- Choriocarcinoma
- Teratoma

WHO Classification of Ovarian Neoplasms

Surface Epithelial-Stromal Tumors

Serous tumors

Benign (cystadenoma, cystadenofibroma)

Borderline (serous borderline tumor)

Malignant (low- and high-grade serous adenocarcinoma)

Mucinous tumors, endocervical-like and intestinal type

Benign (cystadenoma, cystadenofibroma)

Borderline (mucinous borderline tumor)

Malignant (mucinous adenocarcinoma)

Endometrioid tumors

Benign (cystadenoma, cystadenofibroma)

Borderline (endometrioid borderline tumor)

Malignant (endometrioid adenocarcinoma)

Clear cell tumors

Benign

Borderline

Malignant (clear cell adenocarcinoma)

Transitional cell tumors

Benign Brenner tumor

Brenner tumor of borderline malignancy

Malignant Brenner tumor

Epithelial-stromal

Adenosarcoma

Malignant mixed müllerian tumor

Sex Cord–Stromal Tumors

Granulosa tumors

Fibromas

Fibrothecomas

Thecomas

Sertoli-Leydig cell tumors

Steroid (lipid) cell tumors

Germ Cell Tumors

Teratoma: Immature

Mature

Solid

Cystic (dermoid cyst)

Monodermal (e.g., struma ovarii, carcinoid)

Dysgerminoma

Yolk sac tumor

Mixed germ cell tumors

Metastatic Cancer From Non-Ovarian Primary

Colonic, appendiceal

Gastric

Pancreaticobiliary

Breast

Surface Epithelial-Stromal Tumors

Serous tumors

MORPHOLOGY

Serous tumors may present as a multicystic lesion in which papillary epithelium is contained within fibrous walled cysts (intracystic) (or as a mass projecting from the ovarian surface. Benign tumors typically have a smooth glistening cyst wall with no epithelial thickening or with small papillary projections. Borderline tumors contain an increased number of papillary projections . Larger areas of solid or papillary tumor growth, tumor irregularity, and fixation or nodularity of the capsule are features associated with malignancy

Microscopically, the cysts are lined by columnar epithelium. In benign tumors, the epithelial cells retain abundant cilia, and microscopic papillae may be found. Serous borderline tumors exhibit increased complexity of the stromal papillae, stratification of the epithelium, and mild nuclear atypia, but invasion of the stroma is not seen. The epithelial cells often grow in a delicate, papillary pattern referred to as “micropapillary carcinoma,” which is thought to be the precursor to low-grade serous carcinoma. High-grade serous carcinoma is distinguished by having more complex growth patterns and widespread infiltration or frank effacement of the underlying stroma. The individual tumor cells display marked nuclear atypia, including pleomorphism, atypical mitotic figures.

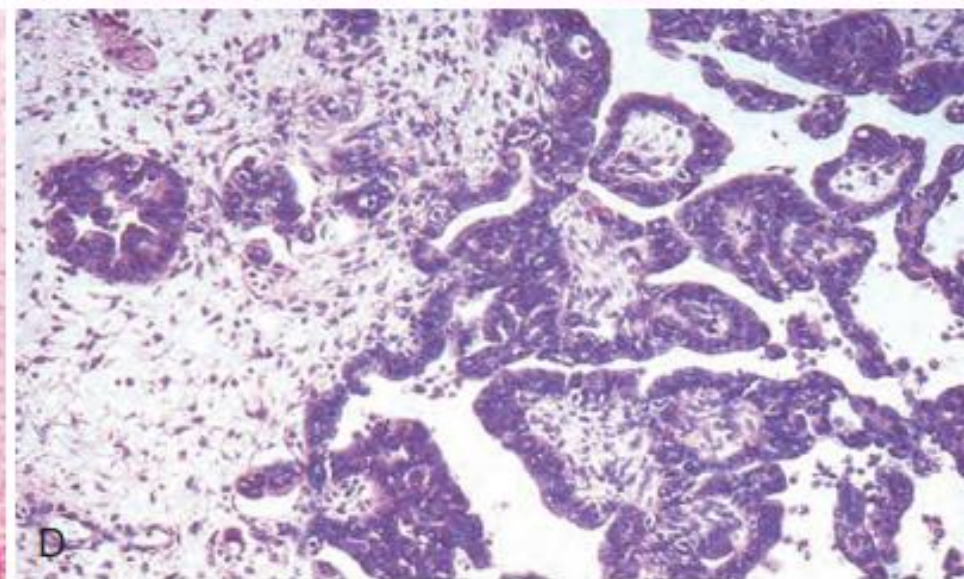
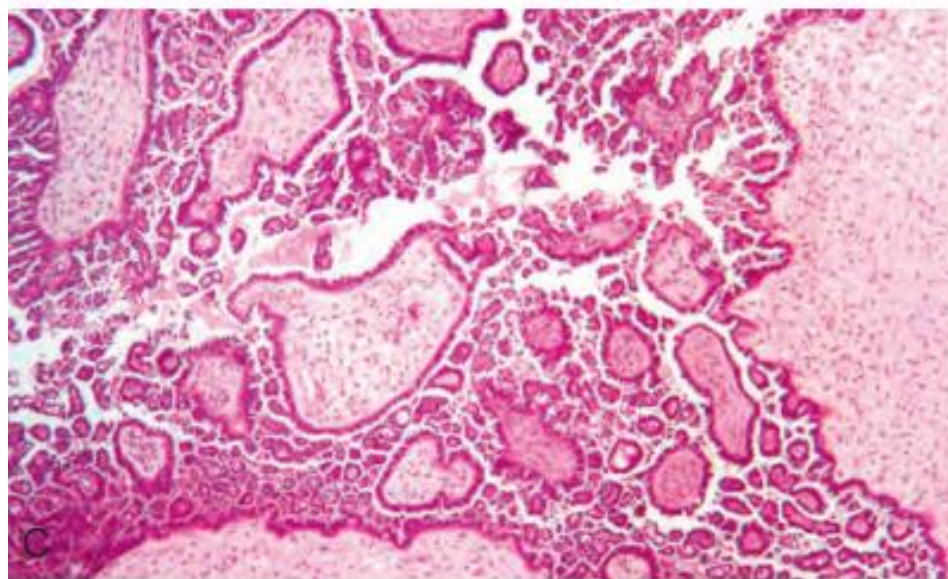
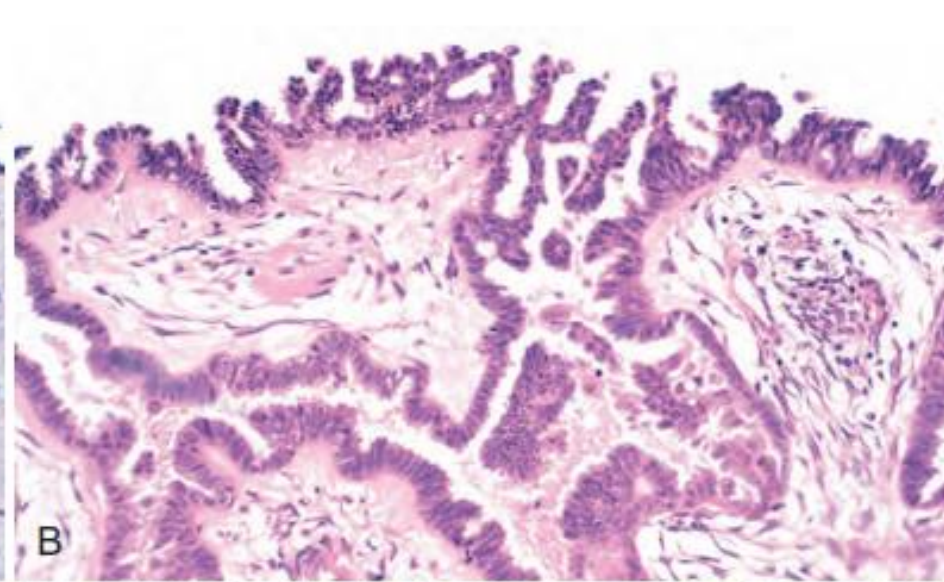
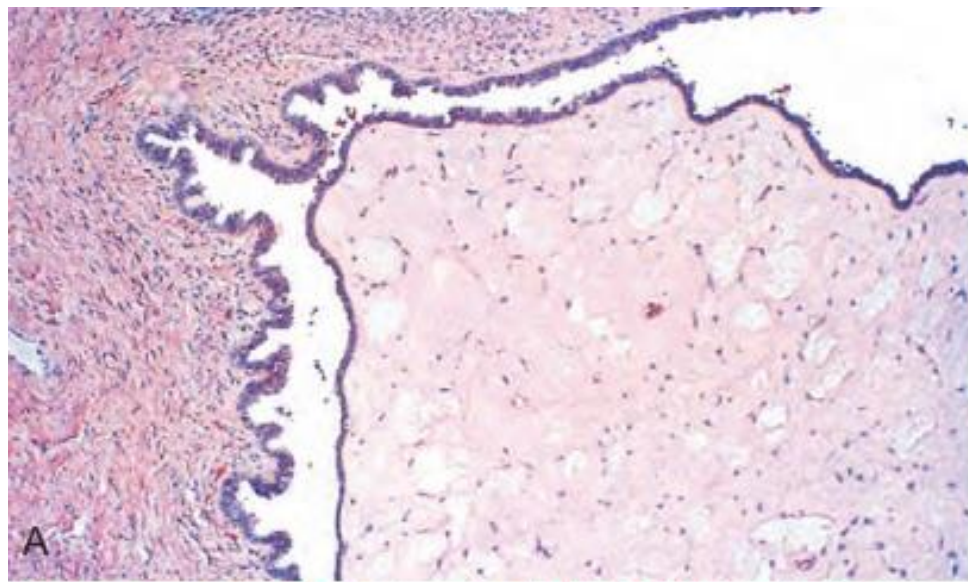
Pathogenesis

The origin of ovarian tumors is still under investigation, but it appears that BRCA1- and BRCA2-related tumors as well as the majority of sporadic ovarian serous tumors likely arise from fallopian tube epithelium rather than ovarian epithelium.

studies have shown that low and high-grade serous carcinoma have distinct mutational profiles, as follows:

- Low-grade tumors arising in serous borderline tumors have mutations in the KRAS, BRAF, or ERBB2 oncogenes, and usually have wild-type TP53 genes.

- High-grade tumors have a high frequency of TP53 mutations and lack mutations in either KRAS or BRAF. Genomic imbalances are very common and include amplifications of a number of oncogenes (e.g., PIK3CA, the gene encoding the catalytic subunit of PI3K) and deletions of tumor suppressor genes (e.g., RB). Almost all ovarian carcinomas arising in women with BRCA1 or BRCA2 mutations are high-grade serous carcinomas with TP53 mutations



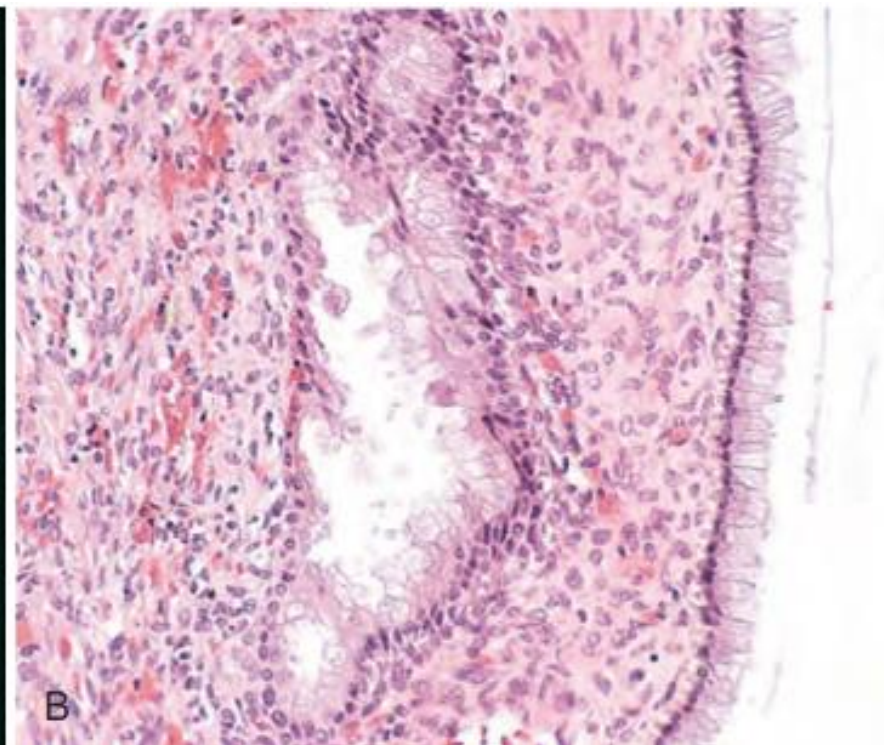
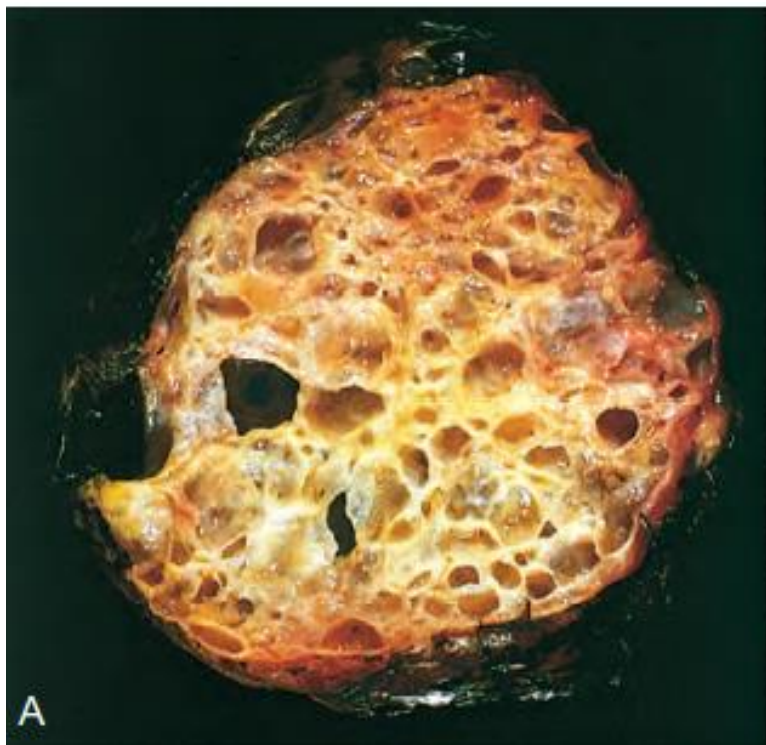
Mucinous Tumors

Mucinous tumors account for about 20% to 25% of all ovarian neoplasms. They occur principally in middle adult life and are rare before puberty and after menopause. The vast majority are benign or borderline tumors. Primary ovarian mucinous carcinomas are uncommon and account for approximately 3% of all ovarian cancers.

Pathogenesis

Mutation of the KRAS proto-oncogene is a consistent genetic alteration in mucinous tumors of the ovary, including the majority of benign mucinous cystadenomas (58%), mucinous borderline tumors (75% to 86%), and ovarian mucinous carcinomas (85%).

MORPHOLOGY Mucinous tumors also tend to produce larger cystic masses; some have been recorded with weights of more than 25 kg. They are multiloculated tumors filled with sticky, gelatinous fluid rich in glycoproteins . Microscopically, benign mucinous tumors are characterized by a lining of tall, columnar epithelial cells with apical mucin that lack cilia. The vast majority demonstrate gastric or intestinal type differentiation; uncommonly, tumors may show endocervical type mucinous differentiation instead. Mucinous borderline tumors are distinguished from cystadenomas by epithelial stratification, tufting, and/or papillary intraglandular growth, often producing an appearance strikingly similar to tubular adenomas or villous adenomas of the intestine. Mucinous carcinoma characteristically demonstrates confluent glandular growth that is now recognized as a form of “expansile” invasion.



Endometrioid Ovarian Tumors

Accounts for approximately 10% to 15% of all ovarian cancers. Benign endometrioid tumors, called endometrioid adenofibroma, and borderline endometrioid tumors also occur, but are uncommon. Approximately 15% to 30% of ovarian endometrioid carcinomas are accompanied by carcinoma of the endometrium

Pathogenesis

In about 15% to 20% of cases, endometrioid carcinoma coexists with endometriosis. The peak incidence of tumors associated with endometriosis is a decade earlier than that of endometrioid carcinomas that are not associated, suggesting that ovarian endometriosis serves as a precursor to ovarian endometrioid carcinoma in some instances

Molecular studies have found striking similarities to endometrial endometrioid carcinoma

MORPHOLOGY

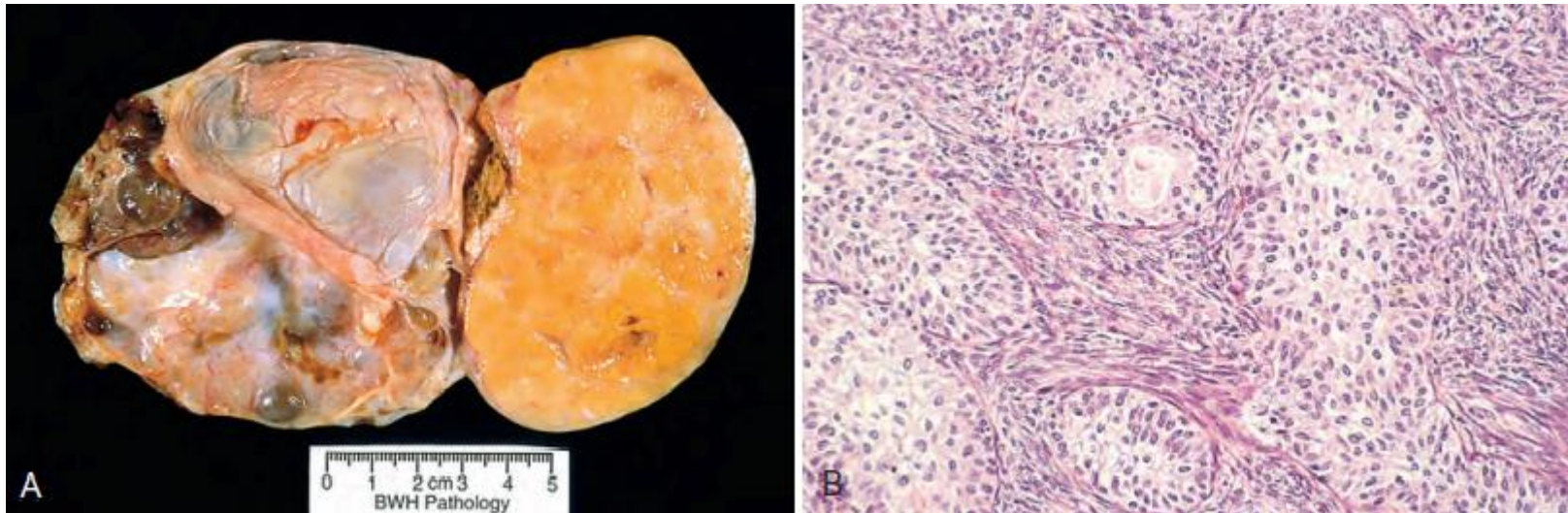
Endometrioid tumors are distinguished from serous and mucinous tumors by the presence of tubular glands resembling benign or malignant endometrium. Endometrioid carcinomas typically present with solid and cystic areas of growth. Forty percent involve both ovaries, and such bilaterality usually implies extension of the neoplasm beyond the genital tract. These are low-grade tumors that reveal glandular patterns bearing a strong resemblance to those of endometrial origin. The 5-year survival rate for patients with stage I tumors is approximately 75%.

Clear Cell Carcinoma

Benign and borderline clear cell tumors are exceedingly rare, and clear cell carcinomas are uncommon. They are composed of large epithelial cells with abundant clear cytoplasm

Transitional Cell Tumors

Transitional cell tumors contain neoplastic epithelial cells resembling urothelium and are usually benign. They comprise roughly 10% of ovarian epithelial tumors and are also referred to as Brenner tumors. Uncommon transitional cell carcinomas also occur in the ovary



Germ Cell Tumors

constitute 15% to 20% of all ovarian tumors and include multiple subtypes. Most are benign cystic teratomas, but others, found principally in children and young adults, may show malignant behavior

Teratoma

divided into three categories: (1) mature (benign), (2) immature (malignant), and (3) monodermal or highly specialized.

Mature (Benign) Teratomas

Most benign teratomas are cystic and are often referred to as dermoid cysts because they are almost always lined by skinlike structures. Cystic teratomas are usually found in young women.

MORPHOLOGY

Benign teratoma is bilateral in 10% to 15% of cases.

Characteristically it consists of a unilocular cyst containing hair and sebaceous material . Sectioning reveals a thin wall lined by opaque, gray-white, wrinkled epidermis, frequently with protruding hair shafts. Within the wall, it is common to find grossly evident tooth structures and areas of calcification. Microscopically, the cyst wall is composed of stratified squamous epithelium with underlying sebaceous glands, hair shafts, and other skin adnexal structures . In most cases, tissues from other germ layers can be identified, such as cartilage, bone, thyroid, and neural tissue.

Monodermal or Specialized Teratomas

Specialized teratomas are a rare but remarkable group of tumors, the most common of which are struma ovarii and carcinoid.

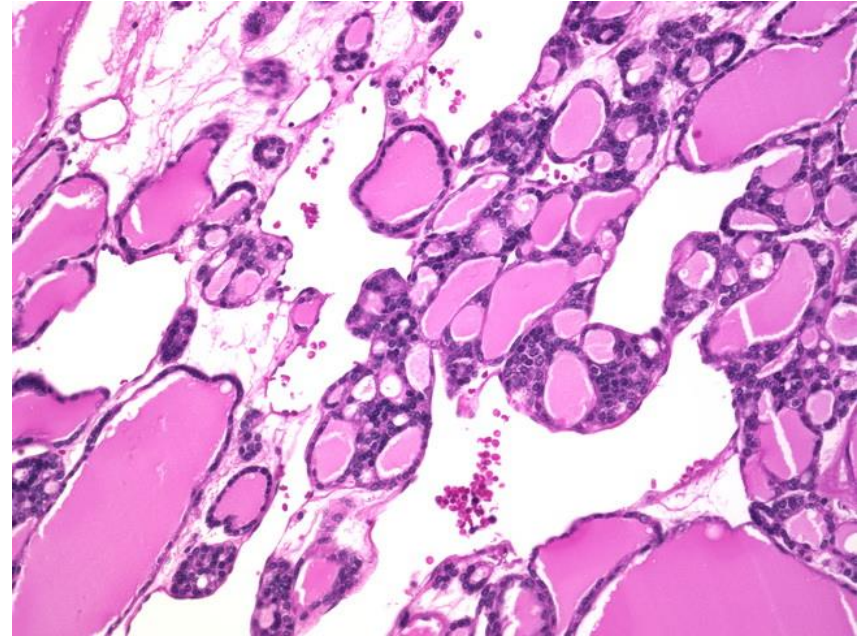
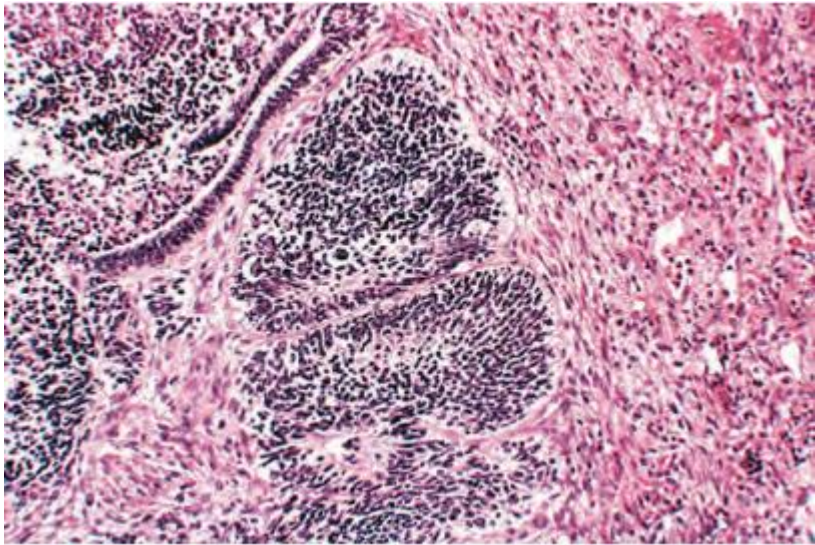
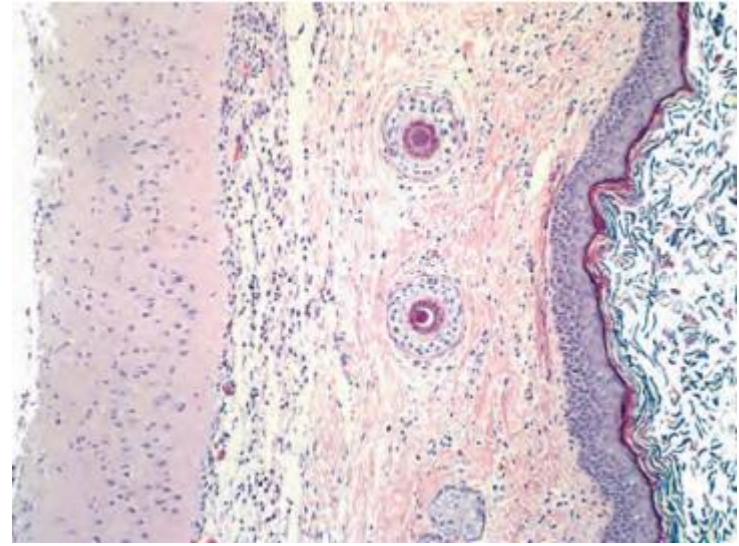
Immature Malignant Teratomas

These are rare tumors that differ from benign teratomas in that the component tissues resemble embryonal and immature fetal tissue. The tumor is found chiefly in prepubertal adolescents and young women, the mean age being 18 years.

Immature teratomas grow rapidly, frequently penetrate the capsule, and spread either locally or distantly. Stage I tumors, particularly those with low-grade (grade 1) histology, have an excellent prognosis. Higher-grade tumors confined to the ovary are generally treated with adjuvant chemotherapy

MORPHOLOGY

Immature malignant teratomas are bulky, have a smooth external surface, and tend to be solid on sectioning. Hair, sebaceous material, cartilage, bone, and calcification may be present, along with areas of necrosis and hemorrhage. On microscopic examination, there are varying amounts of immature neuroepithelium, cartilage, bone, muscle, and other elements. An important risk for subsequent extraovarian spread is the histologic grade (I to III) of the tumor. Grading is based on the proportion of the tumor that is comprised of immature neuroepithelium

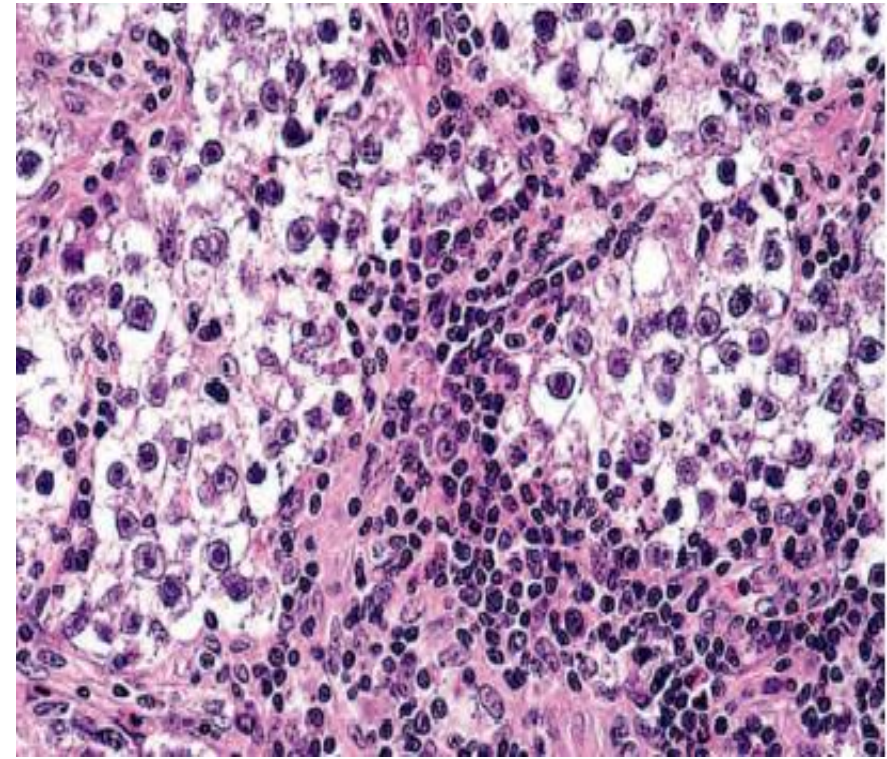


Dysgerminoma

Dysgerminoma is the ovarian counterpart of testicular seminoma. Dysgerminoma accounts for about 2% of ovarian cancers and roughly 50% of malignant ovarian germ cell tumors. They may occur in childhood, but 75% occur in the second and third decades of life. All dysgerminomas are malignant, but the degree of histologic atypia is variable, and only about one-third are aggressive.

MORPHOLOGY

Most dysgerminomas (80% to 90%) are unilateral tumors ranging in size from barely visible nodules to masses that virtually fill the abdomen. On cut surface they have a solid yellow-white to gray pink appearance and are often soft and fleshy. Like seminoma, it is composed of large vesicular cells with clear cytoplasm, well defined cell boundaries, and centrally placed regular nuclei. The tumor cells grow in sheets or cords separated by scant fibrous stroma, which is infiltrated by lymphocytes and may contain noncaseating granulomas



Yolk Sac Tumors

Though rare, yolk sac tumor (also known as endodermal sinus tumor) still ranks as the second most common malignant ovarian tumor of germ cell origin. It is thought to be derived from malignant germ cells that are differentiating along the extraembryonic yolk sac lineage . Similar to the normal yolk sac, the tumor cells elaborate α -fetoprotein.

Its characteristic histologic feature is a glomerulus-like structure composed of a central blood vessel enveloped by tumor cells within a space that is also lined by tumor cells (Schiller-Duval body). Conspicuous intracellular and extracellular hyaline droplets are typically present, some of which stain for α -fetoprotein by immunoperoxidase .

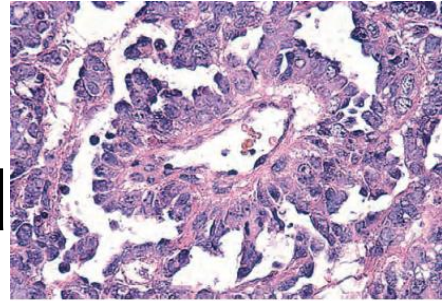


Figure 22.42 A Schiller-Duval body in a yolk sac carcinoma.

Choriocarcinoma

More commonly of placental origin, ovarian choriocarcinoma, like yolk sac tumor, is an example of a malignant germ cell that exhibits extraembryonic differentiation. Most ovarian choriocarcinomas exist in combination with other germ cell tumors, and pure choriocarcinoma is extremely rare. They are histologically identical to the more common placental lesions . The ovarian tumors are aggressive and have usually metastasized hematogenously to the lungs, liver, bone, and other sites by the time of diagnosis. Like all choriocarcinomas, they elaborate high levels of chorionic gonadotropins, which may be helpful in establishing the diagnosis or detecting recurrences. In contrast to choriocarcinoma arising in placental tissue, those arising in the ovary are generally unresponsive to chemotherapy and are often fatal.

Other Germ Cell Tumors These include

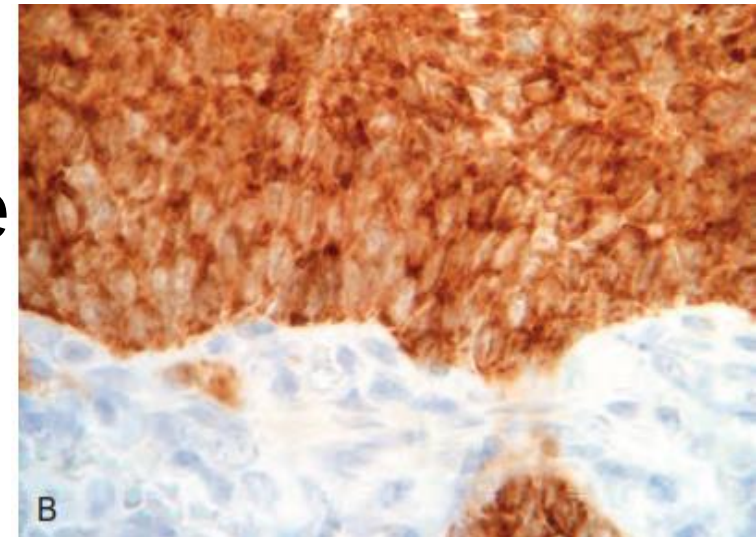
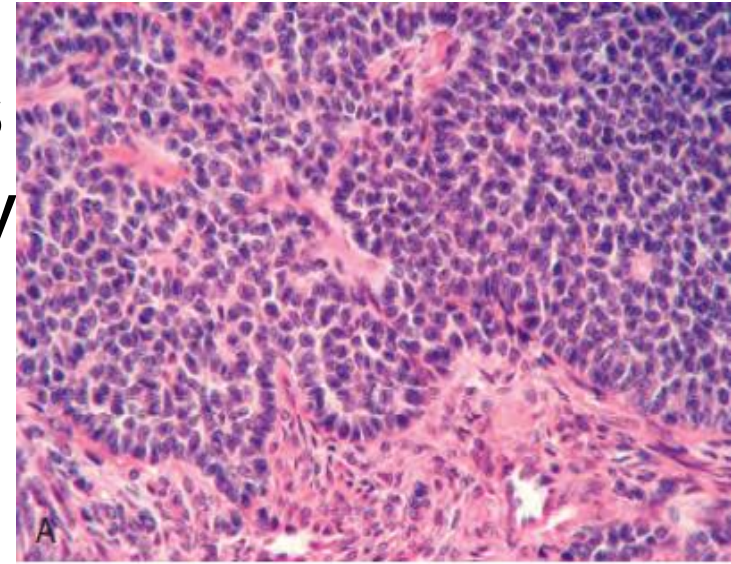
- (1) embryonal carcinoma, a highly malignant tumor of primitive embryonal elements that is histologically similar to embryonal carcinoma arising in the testes
- (2) polyembryoma, a malignant tumor containing so-called embryoid bodies; and
- (3) mixed germ cell tumors containing various combinations of dysgerminoma, teratoma, yolk sac tumor, and choriocarcinoma.

Sex Cord–Stromal Tumors

These ovarian neoplasms arise from the ovarian stroma, which is derived from the sex cords of the embryonic gonad. The undifferentiated gonadal mesenchyme eventually produces specific types of cells in male (Sertoli and Leydig) and female (granulosa and theca) gonads, and tumors resembling all of these cell types can be identified in the ovary. Moreover, because some of these cells normally secrete estrogens (granulosa and theca cells) or androgens (Leydig cells), their corresponding tumors may be either feminizing (granulosa/theca cell tumors) or masculinizing (Leydig cell tumors).

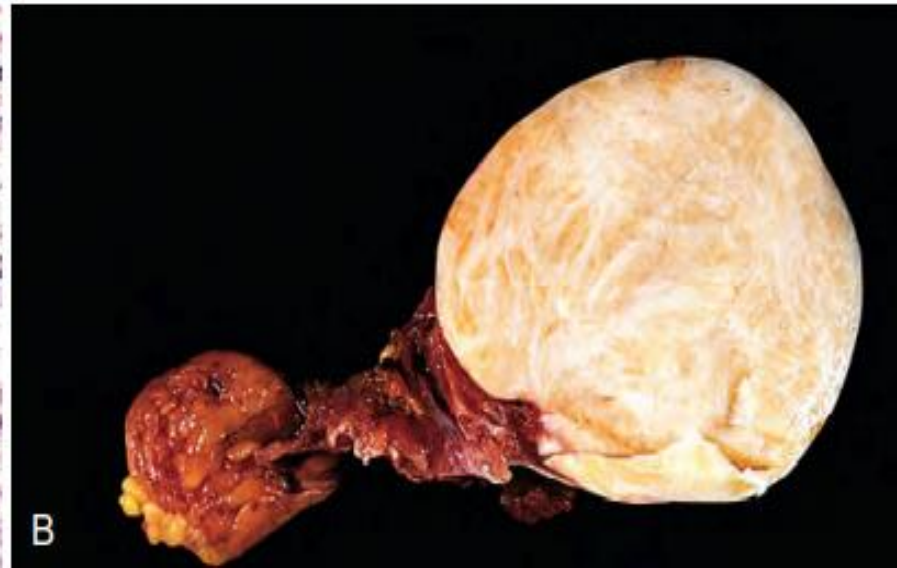
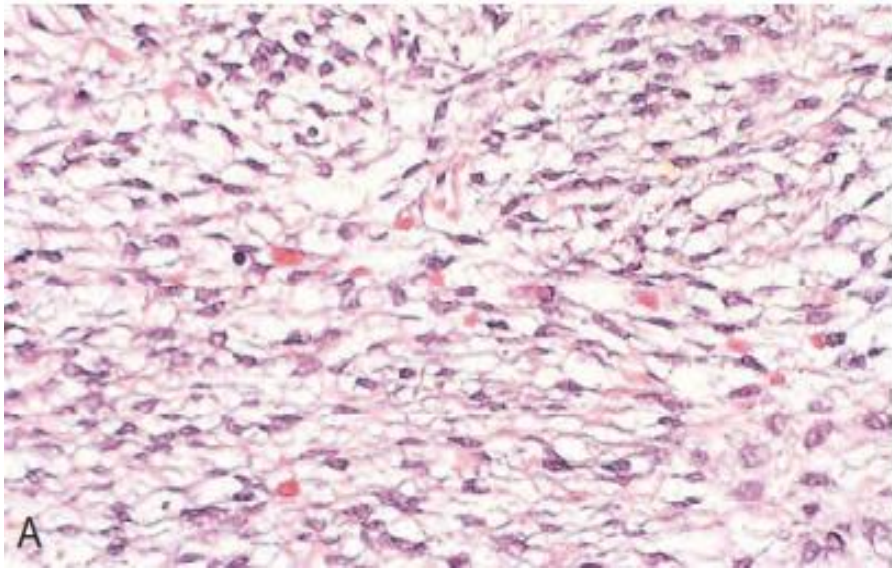
Granulosa Cell Tumors

composed of cells that resemble granulosa cells of a developing ovarian follicle. They are broadly divided into adult and juvenile granulosa cell tumors, based largely on the age of the patient. Collectively, these neoplasms account for about 5% of all ovarian tumors, and 95% of granulosa cell tumors are of the adult type. Although they may be discovered at any age, approximately two-thirds occur in postmenopausal women. Granulosa cell tumors are of clinical importance for two reasons: (1) they sometimes elaborate large amounts of estrogen, and (2) they may behave like low-grade malignancies.



Fibromas, Thecomas, and Fibromathecomas

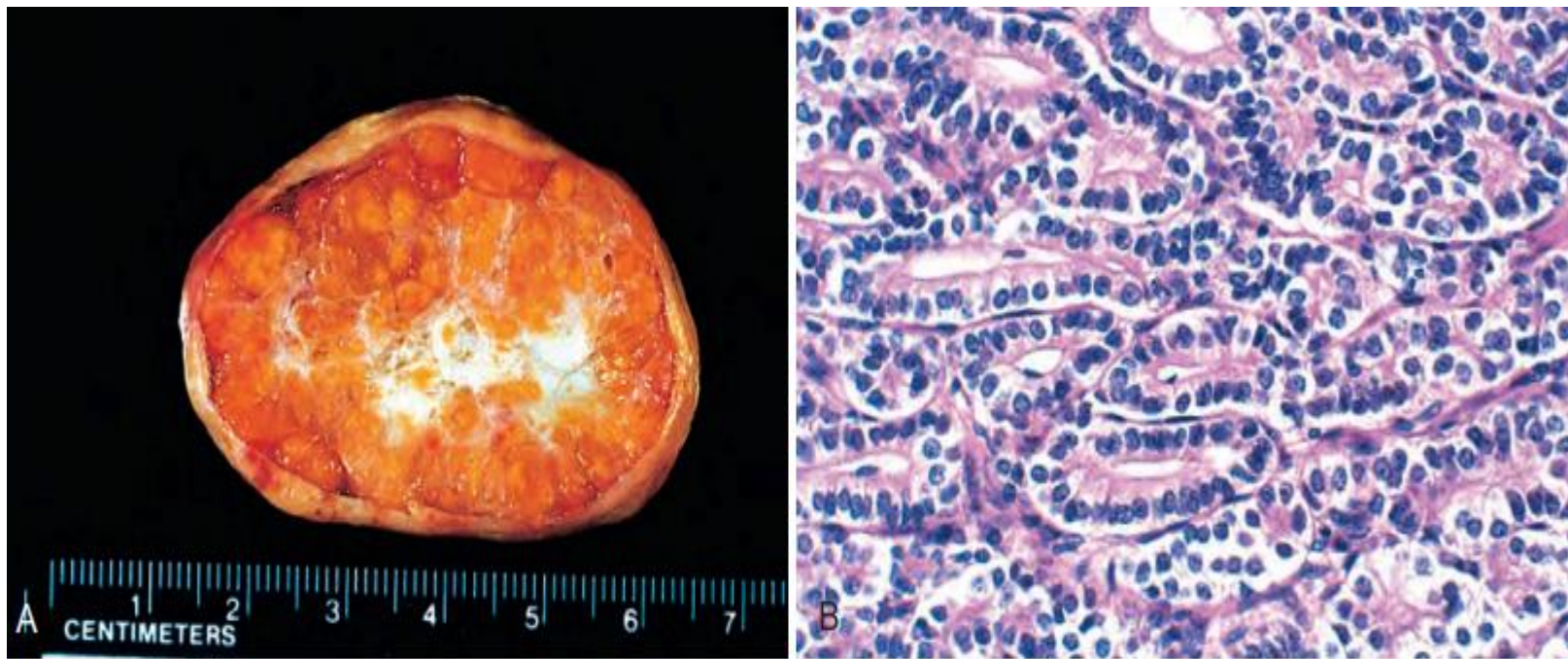
Tumors arising in the ovarian stroma that are composed of either fibroblasts (fibromas) or plump spindle cells with lipid droplets (thecomas) are relatively common, accounting for about 4% of all ovarian tumors. Many tumors contain a mixture of these cells and are termed fibrothecomas. Fibrothecomas and pure thecomas (a rare subtype) may be hormonally active. By contrast, pure fibromas as a rule are hormonally inactive.



Sertoli-Leydig Cell Tumors :These tumors are often functional; they most commonly produce masculinization or defeminization, but a few have estrogenic effects.

Other Sex Cord–Stromal Tumors

- Hilus cell tumors (pure Leydig cell tumors) are rare, unilateral tumors comprised of large lipid-laden Leydig cells with distinct borders and characteristic cytoplasmic structures called Reinke crystalloids. Women with hilus cell tumors usually present with evidence of masculinization (hirsutism, voice changes, and clitoral enlargement), but these changes are milder than those seen in association with Sertoli–Leydig cell tumors. The tumors produce predominantly testosterone. Treatment consists of surgical excision. True hilus cell tumors are almost always benign.



- Pregnancy luteoma refers to a rare tumor that closely resembles the corpus luteum of pregnancy. These tumors may produce virilization in pregnant patients and their female infants.
- Gonadoblastoma is an uncommon tumor composed of germ cells and sex cord–stroma derivatives

Gestational and Placental Disorders

Diseases of pregnancy and pathologic conditions of the placenta are important causes of fetal intrauterine or perinatal death, congenital malformations, intrauterine growth restriction, maternal death, and morbidity for both the mother and child.

DISORDERS OF EARLY PREGNANCY

Spontaneous Abortion

Spontaneous abortion, or “miscarriage,” is defined as pregnancy loss before 20 weeks of gestation. Most of these occur before 12 weeks. In most individual instances, the mechanisms leading to early loss of pregnancy are unknown. However, multiple fetal and maternal causes of spontaneous abortion have been identified. Among the most important are the following:

- Fetal chromosomal anomalies.
- Maternal endocrine factors, including luteal-phase defect, poorly controlled diabetes, and other endocrine disorders
- Physical defects of the uterus, such as submucosal leiomyomas, uterine polyps, or uterine malformations, may prevent or disrupt implantation.
- Systemic disorders affecting the maternal vasculature, such as antiphospholipid antibody syndrome, coagulopathies, and hypertension
- Infections

Ectopic Pregnancy

Ectopic pregnancy refers to implantation of the fetus in a site other than the normal intrauterine location; the most common site is the extrauterine fallopian tube (approximately 90% of cases). Other sites include the ovary, the abdominal cavity, and the intrauterine portion of the fallopian tube (cornual pregnancy). Ectopic pregnancies account for 2% of confirmed pregnancies.

The most important predisposing condition, present in 35% to 50% of patients, is prior pelvic inflammatory disease resulting in intraluminal fallopian tube scarring (chronic salpingitis). The risk of ectopic pregnancy is also increased with peritubal scarring and adhesions, which may be caused by appendicitis, endometriosis, and previous surgery.

Clinical Features

Rupture of a tubal pregnancy is a medical emergency. The clinical course of ectopic tubal pregnancy is characterized by the onset of moderate to severe abdominal pain and vaginal bleeding 6 to 8 weeks after the last menstrual period,

DISORDERS OF LATE PREGNANCY

Disorders that occur in the third trimester of pregnancy are related to the complex anatomy of the maturing placenta. Complete interruption of blood flow through the umbilical cord from any cause (e.g., constricting knots or compression) can be lethal to the fetus

Abnormalities of Placental Implantation Several types of abnormal placental implantations are associated with significant complications. Placenta previa is a condition in which the placenta implants in the lower uterine segment or cervix, often leading to serious third trimester bleeding. A complete placenta previa covers the internal cervical os and thus requires cesarean delivery to avert placental rupture and fatal maternal hemorrhage during vaginal delivery. Placenta accreta is caused by partial or complete absence of the decidua, such that the placental villous tissue adheres directly to the myometrium, which leads to a failure of placental separation at birth. It is an important cause of severe, potentially life-threatening postpartum bleeding. Common predisposing factors are placenta previa (in up to 60% of cases) and history of previous cesarean delivery.

Placental Infections

Infections in the placenta develop by two pathways:

- (1) ascending infection through the birth canal and
- (2) hematogenous (transplacental) infection.

GESTATIONAL TROPHOBLASTIC DISEASE

Gestational trophoblastic disease encompasses a spectrum of tumors and tumorlike conditions characterized by proliferation of placental tissue, either villous or trophoblastic. The major disorders of this type are hydatidiform mole (complete and partial), invasive mole, choriocarcinoma, and placental site trophoblastic tumor (PSTT).

Hydatidiform Mole

are important to recognize because they are associated with an increased risk of persistent trophoblastic disease (invasive mole) or choriocarcinoma. Moles are characterized histologically by cystic swelling of the chorionic villi and variable trophoblastic proliferation. They are usually diagnosed during early pregnancy (average 9 weeks) by pelvic sonography. Molar pregnancy can develop at any age, but the risk is higher at the two ends of reproductive life, in teenagers and between 40 and 50 years of age.

Complete Mole

results from fertilization of an egg that has lost its female chromosomes, and as a result the genetic material is completely paternally derived. Ninety percent have a 46,XX karyotype stemming from the duplication of the genetic material of one sperm (a phenomenon called androgenesis). The remaining 10% result from the fertilization of an empty egg by two sperm; these may have a 46,XX or 46,XY karyotype. In complete moles, the embryo dies very early in development and therefore is usually not identified. Patients have 2.5% risk of subsequent choriocarcinoma and a 15% risk of persistent or invasive mole.

Partial Mole

result from fertilization of an egg with two sperm. In these moles, the karyotype is triploid (e.g., 69,XXY) or occasionally tetraploid (92,XXXXY). Fetal tissues are typically present. Partial moles have an increased risk of persistent molar disease but are not associated with choriocarcinoma.

MORPHOLOGY

Grossly, hydatidiform mole appears as a delicate, friable mass of thin-walled, translucent, cystic, grapelike structures consisting of swollen edematous (hydropic) villi. In complete mole, the microscopic abnormalities involve all or most of the villous tissue. The chorionic villi are enlarged, scalloped in shape with central cavitation (cisterns), and covered by extensive trophoblast proliferation that involves the entire circumference of the villi.

In contrast, in partial moles, only a fraction of the villi are enlarged and edematous, and the trophoblastic hyperplasia is focal and less marked than in complete moles.

Clinical Features

Most women with partial or early complete mole present with spontaneous miscarriage or undergo curettage because of ultrasound findings of abnormal villous enlargement. In cases of complete mole, human chorionic gonadotropin (hCG) levels greatly exceed those of a normal pregnancy of similar gestational age.

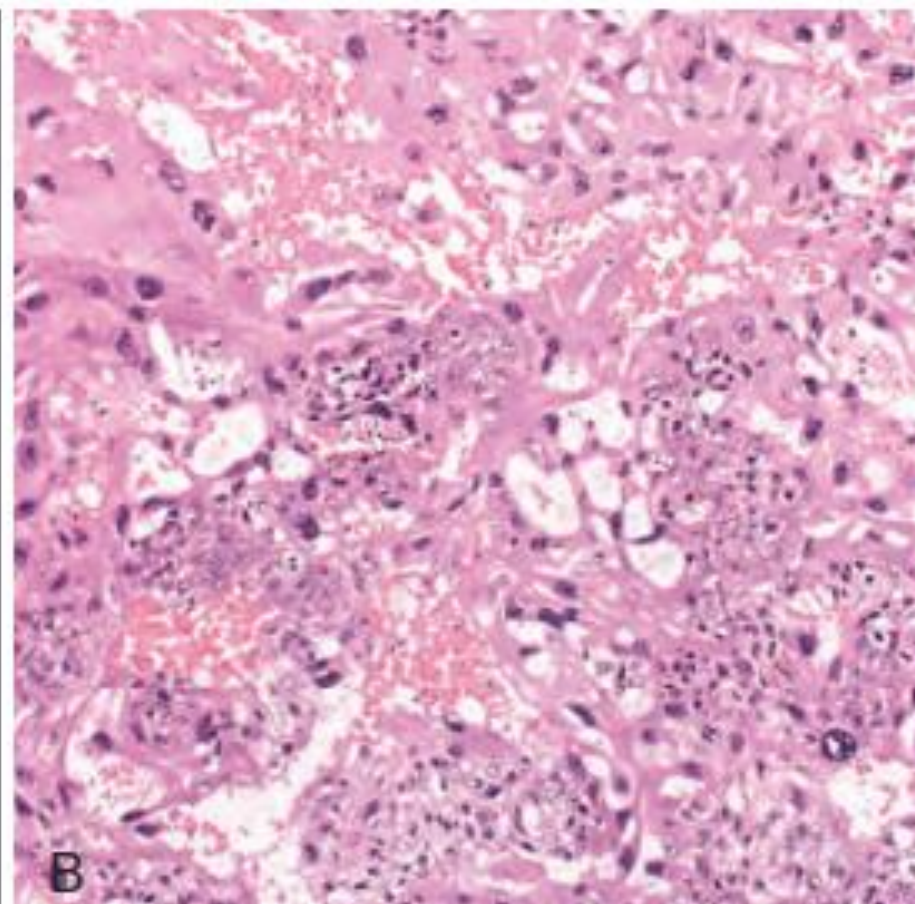
Invasive Mole

is an infiltrative lesion that penetrates or even perforates the uterine wall. There is invasion of the myometrium by hydropic chorionic villi, accompanied by proliferation of both cytotrophoblasts and syncytiotrophoblasts. In some instances, the villi invade parametrial tissue and blood vessels and may even embolize to distant sites, such as the lungs and brain. However, these emboli do not grow, as do true metastases, and even without chemotherapy they eventually regress. The tumor manifests clinically with vaginal bleeding and irregular uterine enlargement. It is always associated with a persistently elevated serum hCG. Invasive mole responds well to chemotherapy but may result in uterine rupture, necessitating hysterectomy.

Choriocarcinoma Gestational choriocarcinoma is a malignant neoplasm of trophoblastic cells derived from a previously normal or abnormal pregnancy, such as an extrauterine ectopic pregnancy. Gestational choriocarcinoma is an uncommon condition that arises in 1 in 20,000 to 30,000 pregnancies in the USA.

MORPHOLOGY Choriocarcinoma is a soft, fleshy, yellow-white tumor that usually has large pale areas of necrosis and extensive hemorrhage .

Histologically, it consists entirely of proliferating syncytiotrophoblasts and cytotrophoblasts ; chorionic villi are absent. Mitoses are abundant and sometimes abnormal. The tumor invades the underlying myometrium, frequently penetrates blood vessels, and in some cases extends out onto the uterine serosa and into adjacent structures.



Placental Site Trophoblastic Tumors

PSTTs comprise less than 2% of gestational trophoblastic neoplasms. They are neoplastic proliferations of extravillous trophoblasts, also called intermediate trophoblasts. Normal extravillous trophoblasts are polygonal mononuclear cells that have abundant cytoplasm and produce human placental lactogen. In normal pregnancy, extravillous trophoblasts are found in the implantation site, as clusters of cells within the placental parenchyma, and in the placental membranes. PSTT presents as a uterine mass, accompanied by either abnormal uterine bleeding or amenorrhea and moderately elevated hCG. The malignant trophoblastic cells typically diffusely infiltrate the endomyometrium. PSTT may follow a normal pregnancy (one-half of the cases), spontaneous abortion, or hydatidiform mole. Patients with localized disease have an excellent prognosis, but 10% to 15% of women die of disseminated disease