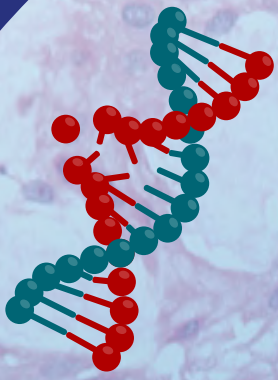
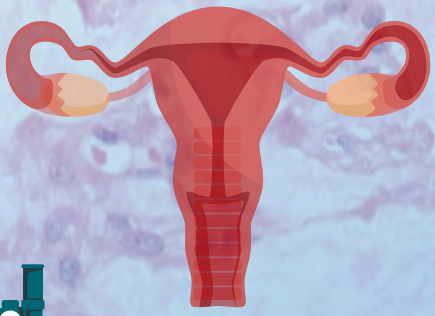
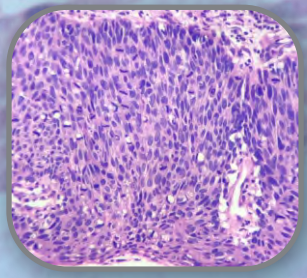
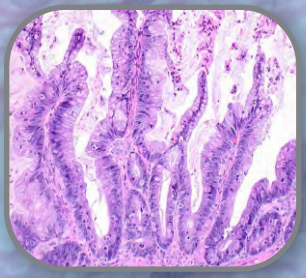
Handbook of Gynaecpathology

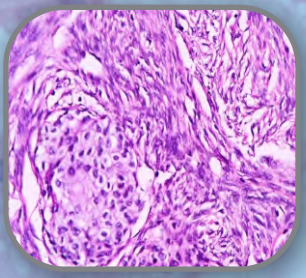
A Simplified Approach in Nutshell











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Dr. Anandraj Vaithy. K
Dr. Rupal Samal

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Handbook of Gynaecpathology – A Simplified Approach in Nutshell

ISBN : 978-93-88022-53-8

Edition : First, 2020

PREAMBLE

Gynaecpathology being a common clinical speciality, it has substantial weightage in exam-oriented sections. The book 'Handbook of Gynaecpathology – A Simplified Approach in Nutshell' aids in catering to the key points in a nutshell to students as well as covering clinico-pathological correlation in a precise and schematic manner.

Dr. Anandraj Vaithy. K
Dr. Rupal Samal

ABOUT THE BOOK

The chapters in this book cover the common lesions encountered in the stream Gynaecpathology with an emphasis on tumours and recent classifications and staging. The book includes tables in coloured background and flowcharts in a simplified approach. Classification and categorization lesions are depicted in a schematic approach aiding the students to review the contents hassle-free. Classical gross and microscopical images from collections with the possible differential diagnosis are also included.

Hope the book caters to the needs of students, residents of Gynaecology and Pathology.

Best Wishes!

ACKNOWLEDGEMENT

Sincere thanks and acknowledgement to all the contributors in preparing this book. We also sincerely thank, **Dr. S. Sowmya**, Head of Department of Pathology, **Dr. Venkat Raghavan ATM**, Assistant Professor, and **Dr. Shanmugasamy. K**, Professor of Pathology, Mahatma Gandhi Medical College and Research Institute, Sri Balaji Vidyapeeth (Deemed to be University), Puducherry for guiding us in preparing the contents. We also sincerely thank **Dr. Mitadru De Sarkar**, Consultant Pathologist SRL Diagnostics, Kolkata for permitting to reproduce few contents in the ovary chapter. We dedicate this book to all the students' fraternity wishing them all the very success in future endeavours. We thank the clerical staff and technocrats of our Pathology Department for their valuable services.

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CHAPTER 1

VULVA

Inflammatory Lesion of Vulva

The initial approach to any inflammatory disorder of the skin or mucosa requires knowledge of the precise anatomic location from which the biopsy was taken, an appreciation of the alterations in the regional mucocutaneous anatomy, effects of occlusion (e.g., clothing, skin folds, etc.) and the dynamic changes effected by chronicity and partial treatment.

The mons pubis/labia majora closely resembles skin from other anatomic regions of the body and is composed of a slightly rugose, keratinizing, stratified epithelium, containing all of the cutaneous adnexal structures and a richly vascular dermis. The labia minora, in contrast, has a stratified, glycogen-rich squamous epithelium. Adnexal structures are absent. The subjacent dermis is highly vascular and contains erectile tissue.

The next step in evaluating an inflammatory process is the identification at low power of the major tissue reaction pattern, followed by the pattern of inflammation. Clinically, *tissue reaction pattern* is a distinctive group of lesions as the clinical signs allows the observer to predict the site of biopsy. The *pattern of inflammation* refers to the distribution of the inflammatory infilrate within the dermis and subcutis.

This approach will be applied to the most common inflammatory disorders of the vulva, and should allow the observer to categorize and generate a rational histopathologic and clinically relevant differential that allows the clinician to develop a meaningful treatment plan.

The following table shows the clinical features and corresponding microscopical features of vulval inflammatory reactions.

Table 1.1: Clinical features with corresponding histopathological pattern of vulval inflammation.

Pattern	Characteristic morphologic feature
Lichenoid	Basal keratinocyte damage
Psoriasiform	Regular epidermal hyperplasia
Spongiotic (eczematous)	Intraepidermal edema
Vesiculobullous	Subepodermal or intraepidermal blister formation
Granulomatous	Granulomatous inflammation
Vasculopathic	Vascular injury

LICHEN SCLEROSUS OF VULVA

Definition

Fibrosing dermatitis with a predilection for the anogenital skin in women.

Incidence

Uncommon.

Morbidity

1. Vanishing of the labia minora and urethral stenosis may occur in long-standing lesions.
2. Secondary epithelial dysplasia and squamous cell carcinoma (4%).
3. More common in fifth decade (perimenopausal).

Clinical Features

"Figure-of-eight" distribution and "porcelain-white" plaques with a wrinkled surface and follicular plugging.

Prognosis and Treatment

1. Chronic waxing and waning clinical course.
2. Topical steroids and calcineurin inhibitors for local control, but uncommon complete resolution.
3. Regular observation of dysplastic areas with conservative treatment (cryotherapy).
4. Surgery for severe introital stenosis or if carcinoma evolves within dysplastic areas.

Lichen Sclerosus – Pathologic Features

Microscopic Findings

Psoriasiform epidermal hyperplasia with band-like lymphohistiocytic infiltrate, papillary dermal fibrosis, and hyperkeratosis in early lesions.

Papillary dermal homogenization, pallor, and vascular drop-out with epidermal atrophy in mature lesions.

Differential Diagnosis

1. Lichen planus.
2. Morphea.
3. Chronic radiation dermatitis.

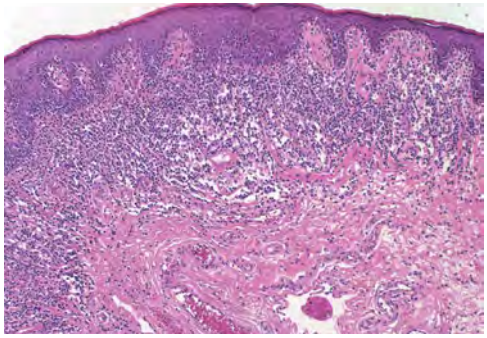


Fig. 1.1: Lichen Sclerosus-Epidermal hyperplasia is accompanied by a dense band-like lymphocytic infiltrate, papillary dermal fibrosis, and hyperkeratosis H&E, 10X.

Vulval Polyp

Mesenchymal lesions that occur in the vulva can be separated into two general categories: (1) those that are relatively site-specific, i.e., they may occasionally occur at extragenital sites; and (2) those that occur more commonly at other sites but which may also involve this region. The former group includes deep "aggressive" angiomyxoma, angiomyofibroblastoma, cellular angiofibroma, and fibroepithelial stromal polyp.

FIBROEPITHELIAL STROMAL POLYP – OF VULVA

Definition

Benign polypoid growth that arises from the distinctive subepithelial stroma of the distal female genital tract.

Incidence and Location

1. Most common during pregnancy.
2. May occur in the vulva, vagina, and, rarely, cervix.
3. Morbidity and mortality.
4. If large, may be disfiguring and cause pain and bleeding.

Gender, Race, and Age Distribution

1. Typically in reproductive-aged women.
2. May occur in postmenopausal women on hormone replacement therapy.
3. There is an association with pregnancy.

Clinical Features

1. Typically polypoid or pedunculated.
2. Usually < 5 cm.
3. May have thin connecting stalk.
4. Multiple polyps may occur during pregnancy.

Prognosis and Treatment

1. Benign lesion.
2. May regress following pregnancy.
3. Complete local excision treatment of choice.
4. Potential for local recurrence if incompletely excised or if continued hormonal stimulation.

Gross Findings

1. Usually < 5 cm.
2. Polypoid or pedunculated with thin connecting stalk.

Microscopic Findings

1. Polypoid with variably cellular stroma, central fibrovascular core, and overlying squamous epithelium.
2. Stellate and multinucleate stromal cells are characteristic.
3. Typically located at the epithelial–stromal interface and around blood vessels.

4. Some polyps may exhibit stromal hypercellularity, stromal cell nuclear pleomorphism, and increased mitotic activity (so-called pseudosarcoma botryoides).

Immunohistochemical Findings

1. Desmin, vimentin, ER and PR typically positive.
2. Actin less frequently positive.

Differential Diagnosis

1. Sarcoma, not otherwise specified.
2. Embryonal rhabdomyosarcoma.
3. Aggressive angiomyxoma.

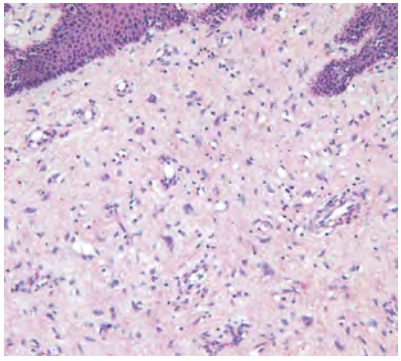


Fig. 1.2: Fibroepithelial stromal polyp. Characteristic stellate and multinucleated stromal cells are prominent near the stromal–epithelial interface.

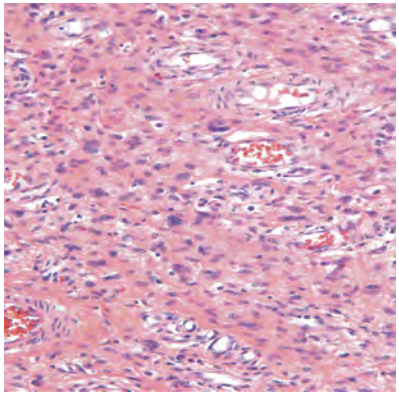


Fig. 1.3: Fibroepithelial stromal polyp. Increased stromal cellularity and atypia are present. Note the presence of the characteristic multinucleated cells.

ANGIOMYXOMA – VULVA

Aggressive Angiomyxoma

Definition

Slow growing polypoid mass or swelling in bartholin gland area.

Infiltrative, nonmetastasizing, hypocellular myxoid tumour of the pelvic–perineal region with potential for local, sometimes destructive, recurrence.

Epidemiology

Common in women in their third or fourth decades of life.

Clinical Features

Mass in vulva.

Gross

Rubbery and white or soft and gelatinous.

Microscopy

1. Stellate and spindle shaped mesenchymal cells embedded in a loose myxoid stroma with a few collagen fibers.
2. Cells are small and bland and lack nuclear atypia.
3. Small or medium sized vessels are grouped together within the tumour and may show medial hypertrophy.
4. Blood vessels are dilated and extravasation of rbcs are usual.
5. It is characteristically hypocellular and lacks necrosis and mitotic figures. Invasion of skeletal muscle and fat is usual.

Differential Diagnosis

1. Neurofibroma.
2. Intramuscular myxoma.
3. Angiomyofibroblastoma.
4. Myxoid smooth muscle tumours.
5. Spindle cell lipoma.
6. Myxoid malignant fibrous histiocytoma.
7. Myxoid liposarcoma.
8. Embryonal rhabdomyosarcoma.

Leiomyoma

Vulvar leiomyomas occur over a wide age range but are most common in the fourth and fifth decades. They usually present as a painless, subcutaneous mass and at the time of surgical excision appear well demarcated from the surrounding soft tissues. Similar to the other entities described herein, they are often thought to represent a vulvar cyst.

Definition

Benign smooth-muscle tumour.

Incidence and Location

1. Infrequent.
2. Vulvovaginal region.

Gender and Age Distribution

Wide age range but most common in fourth and fifth decades.

Clinical Features

1. Typically painless mass.
2. Often thought to represent a cyst.

Prognosis and Treatment

1. Excellent prognosis.
2. Local excision with clear margins.

Gross Findings

1. Well circumscribed.
2. White/tan whorled appearance.
3. Firm, rubbery consistency.
4. Bulging cut section.

Microscopic Findings

1. Intersecting fascicles of spindle-shaped cells with moderate amount of eosinophilic cytoplasm and blunt-ended nuclei.
2. Variable amounts of myxohyaline matrix imparting a “lacy” growth pattern.
3. Epithelioid morphology may be prominent.

4. No cytologic atypia and minimal to absent mitotic activity.
5. No tumour cell necrosis.

Immunohistochemical Features

Desmin, smooth-muscle actin, h-caldesmon typically positive.

Differential Diagnosis

Leiomyosarcoma; in order to classify a smooth-muscle tumour as malignant it should have three of the five following criteria:

1. > 5 cm.
2. Infiltrative margin.
3. Moderate to severe cytologic atypia.
4. > 5 mitoses/10 HPFs.
5. Tumour cell necrosis.

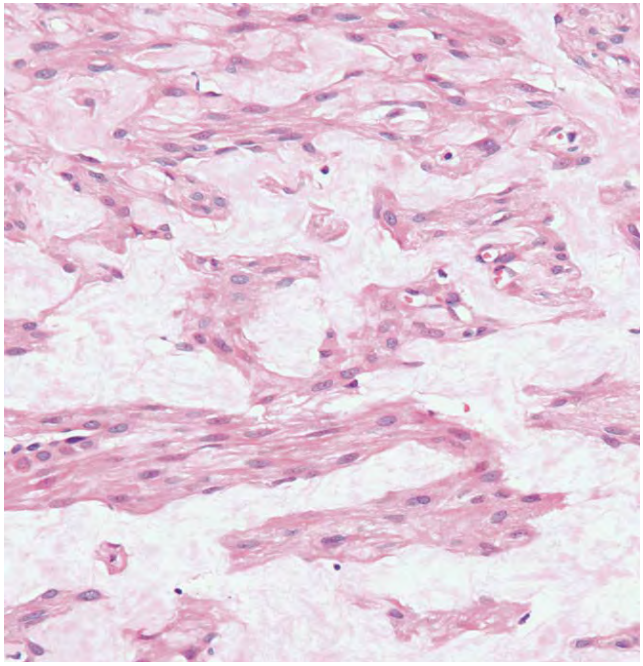


Fig. 1.4: Leiomyoma. Benign-appearing smooth cells show a lacy growth pattern secondary to the abundant myxohyaline matrix associated with the tumour. H&E, 40X.

PREMALIGNANT LESIONS OF VULVA

Condyloma Acuminatum

Clinical Features

Patients are typically asymptomatic but may have pruritus, irritation, or bleeding. Lesions have a predilection for moist surfaces, including introitus, perineal and perianal skin, and, less commonly, vagina and cervix.

They have a very distinct clinical appearance, showing multiple papillary projections and a granular surface.

An association with cervical HPV infection is noted in 30–50% of the patients. Risk factors are similar to those for cervical HPV infection (e.g., sexual activity with multiple partners).

It is Sexually transmitted benign proliferative lesion of squamous epithelium of genital area caused by human papillomavirus (HPV) infection, most often HPV types 6 and 11.

Incidence and Location

Present in approximately 1% of sexually active adults; Most common in vulva, vagina, cervix, anal canal, and perianal skin.

Morbidity and Mortality

1. Benign disease with potential for recurrence.
2. Rarely progression to vulvar intraepithelial neoplasia and invasive squamous cell carcinoma.

Race and Age Distribution

1. No racial predilection.
2. Most common in patients of child-bearing age.

Prognosis and Treatment

1. Benign lesion with protracted course.
2. Small lesions treated with podophyllin therapy.
3. Large lesions treated with surgical removal, laser, or cryotherapy.
4. May recur after excision.

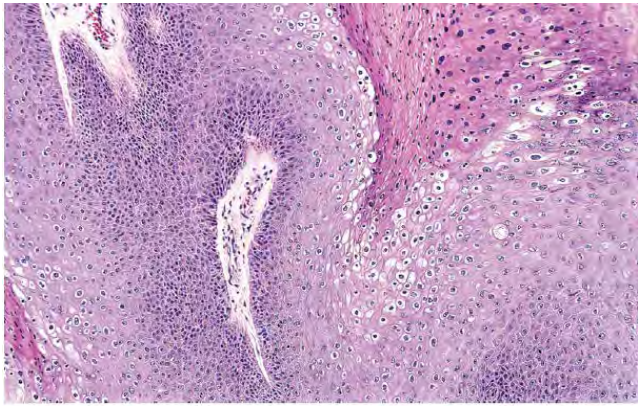


Fig. 1.5: Condyloma acuminatum. prominent papillary architecture is seen. The papillae are lined by hyperplastic squamous epithelium showing hyper and parakeratosis Notice prominent koilocytotic atypia with perinuclear halos and binucleated cells, H&E, 40X.

Vulvar Intraepithelial Neoplasia

The term "vulvar intraepithelial neoplasia" or VIN was endorsed by the International Society for the Study of Vulvar Disease (ISSVD) in 1986 to describeintraepithelial neoplastic proliferations of the vulvar epithelium with the goal of replacing the atypia– carcinoma in situ terminology. Previously, some other terms in the literature that had been used to describe these lesions included Bowen's disease, erythroplasia of Queyrat, bowenoid papulosis, and bowenoid dysplasia.

Similar to their counterpart in the cervix, most of the vulvar lesions are etiologically related to HPV infection (more commonly HPV 16), except the simplex or differentiated type of VIN. This permits the classification of VIN into classic types (with further grading into VIN1, VIN2, and VIN3) and the simplex type which is considered a high-grade lesion (VIN3).

VIN

Intraepithelial neoplastic proliferation of the vulvar epithelium with disordered maturation and nuclear abnormalities

Incidence and Location

1. 2.1 per 100,000 women/year.
2. Increased incidence (× 3) in last two decades in white women < 35 years.
3. Vulvar, perineal, and perianal skin and mucosa.

Morbidity and Mortality

1. Recurrences common.
2. May be difficult to control in immunocompromised patients.

Age Distribution

1. Classic VIN: reproductive age women.
2. Differentiated (simplex) VIN: postmenopausal women.

Clinical Features

1. More commonly pruritus.
2. Risk factors: smoking, immunosuppression.

Prognosis and Treatment

1. Low-grade lesions have minimal or no potential to progress to high-grade VIN.
2. Surgical excision with clear margins for high-grade VIN.
3. Cautery, laser, or cryotherapy, especially if there is multifocal disease.
4. High-recurrence rate after surgical treatment, especially in smokers and immunocompromised patients.
5. Multiple recurrences may progress to invasive carcinoma (interval for progression approximately 4 years; higher frequency for differentiated VIN).

Gross Findings

1. Low-grade classic VIN: single or multiple pale areas.
2. High-grade classic VIN: coalescent white or erythematous papules or verrucous growth with hyperpigmentation in 10–15%.
3. Well-differentiated/simplex VIN: focal discolouration, ill-defined white plaque(s) or discrete elevated nodules.

Microscopic Findings

1. Classical (bowenoid) VIN

1. Epithelial thickening with hyperkeratosis and parakeratosis.
2. Loss of cell maturation, cellular crowding, and dyskeratosis.
3. Nuclear pleomorphism, hyperchromatism, and increased mitoses, including abnormal forms.

4. Involvement of pilosebaceous units, follicles, and Bartholin's glands.
    i. Warty ("condylomatous").
        a. Papillary or "spiky" appearance and prominent koilocytic changes.
    ii. Basaloid.
        a. Flat surface and homogeneous growth of "parabasal" cells with uncommon koilocytosis.

2. Differentiated (simplex) VIN

1. Epidermal hyperplasia with frequent elongation of rete ridges and parakeratosis.
2. Abnormal keratinocytes in all layers; no koilocytosis.
3. Cells with abundant bright eosinophilic cytoplasm and prominent intercellular bridges.
4. Enlarged nuclei with vesicular chromatin and very prominent nucleoli.
5. Whorls including keratin pearls in deeper layers of the epithelium and rete ridges.
6. Smaller cells with high nuclear/cytoplasmic ratio and cytologic atypia in basal layer.

Immunohistochemical Features

1. Increased MIB-1 staining.
2. p16 extensively positive in classic VIN.
3. p53 overexpression in differentiated/simplex VIN.

Differential Diagnosis

1. Classic VIN
    i. Yeast infections.
    ii. Chronic dermatoses.
    iii. Multinucleated atypia of the vulva.
    iv. Bowenoid papulosis (now included as classic VIN).
    v. Paget disease.
2. Differentiated VIN
    i. Squamous hyperplasia.
    ii. Lichen sclerosus.

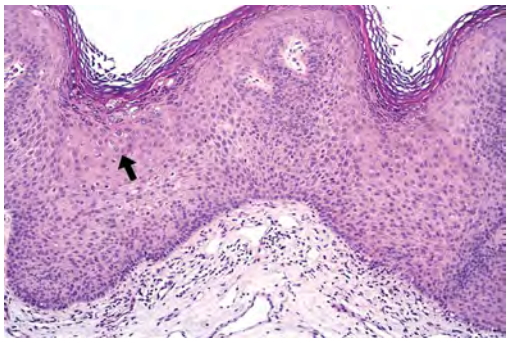


Fig. 1.6: Classic-type high-grade vulvar intraepithelial neoplasia (VIN3). Note full-thickness involvement by highly atypical cells with brisk mitotic activity, including an abnormal mitotic.

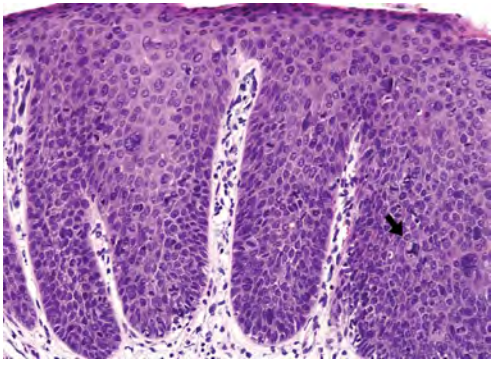


Fig. 1.7: Low-grade vulvar intraepithelial neoplasia (VIN1). Only subtle nuclear changes with focal slight disorganization and koilocytosis (arrow) are seen.

INVASIVE SQUAMOUS CELL CARCINOMA

The majority of vulvar cancers are squamous in origin and they represent 5–8% of all gynaecologic cancers. The current understanding of the clinicopathologic features of two distinct types of high-grade VIN as precursor lesions has contributed to our understanding of the clinical features, pathogenesis, and epidemiology of their invasive counterparts.

Invasive carcinoma of the vulva with squamous differentiation and dimensions greater than superficially invasive tumours.

Incidence and Location

1. Approximately 5–8% of all gynaecologic cancers.
2. Labia minora or majora more commonly involved.

Morbidity and Mortality

1. Local recurrence.
2. Metastasis to inguinal lymph nodes; rarely distant metastasis.

Race and Age Distribution

1. No racial predilection.
2. Higher incidence in patients of low socioeconomic status.
3. Bimodal age distribution.
4. Fifth decade for tumours associated with classic VIN.
5. Sixth to seventh decades for tumours associated with differentiated VIN.

Clinical Features

1. Pruritus or mass in approximately 50% of cases.
2. Bleeding, dyspareunia, dysuria, and unpleasant odour.

Prognosis and Treatment

1. Prognosis stage dependent.
2. Overall 5-year survival > 95% for stage I tumours and 29% for stage IV tumours.
3. Stage, tumour size, depth of invasion, lymphovascular invasion, and lymph node involvement important prognostic factors.
4. Wide local excision with 1 cm gross margin with inguinal lymph node dissection mainstay of treatment.
5. Increased risk of recurrence if positive margins (< 8 mm), lymphovascular invasion, size > 5 cm and depth of invasion.
6. ≥ 11 mm and high-grade VIN at margin.

Gross Findings

1. Typically solitary (multifocal in < 10%).
2. Exophytic cauliflower-like growth or endophytic ulcerated lesion.

Microscopic Findings

Subtypes

1. Keratinizing squamous cell carcinoma, not otherwise specified.
    i. Conspicuous evidence of keratinization with pearl formation.

ii. Neoplastic cells with abundant eosinophilic cytoplasm.

iii. Considerable nuclear atypia and mitotic activity, including abnormal forms.

iv. Invasion as irregular nests and single cells in a desmoplastic stroma.

v. Adjacent lichen sclerosus or differentiated high-grade VIN.

2. Nonkeratinizing squamous cell carcinoma.
   i. Minimal evidence of keratinization with no pearl formation.
3. Basaloid carcinoma.
   i. Broad bands, large or small irregular nests and cords.
   ii. Immature uniform basaloid cells with scant cytoplasm.
   iii. Evenly distributed granular chromatin with no evident nucleoli.
   iv. Occasional focal abrupt keratinization within the tumour nests.
4. Warty (condylomatous) carcinoma.
   i. Multiple papillary projections with fibrovascular cores.
   ii. Papillae lined by keratinized squamous epithelium with koilocytic changes.
   iii. Considerable cytologic atypia including brisk mitotic activity.
   iv. Irregular jagged nests of keratinized squamous cells infiltrating stroma.
   v. Keratin pearl formation in invasive nests helpful clue in excluding pseudoinvasion.
5. Verrucous carcinoma.
   i. Deceptive pushing broad pattern of invasion.
   ii. Bulbous nests of neoplastic cells pushing into underlying stroma.
   iii. Hyperplastic squamous proliferation with prominent hyper and parakeratosis.
   iv. Cells with abundant eosinophilic cytoplasm, but typically lacking nuclear atypia and koilocytosis.

Immunohistochemical Features

1. p16 strongly positive in basaloid and warty squamous cell carcinomas.
2. p53 typically positive in keratinizing squamous cell carcinomas.
3. Cytokeratin, S-100, and HMB-45 and neuroendocrine markers useful in differential diagnosis.

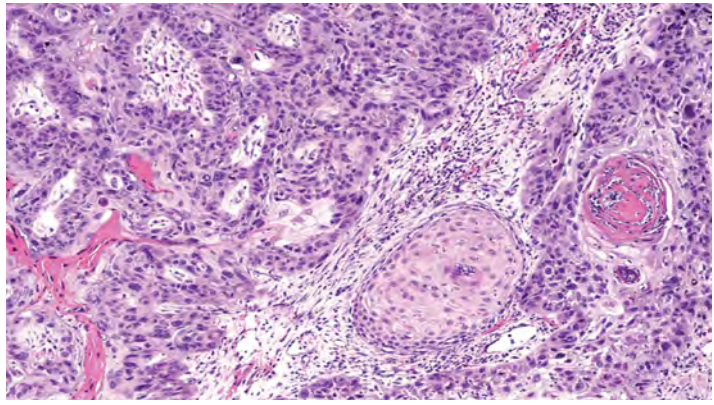


Fig. 1.8: Invasive keratinizing squamous cell carcinoma. Irregular tongues of well to moderately differentiated and keratinizing neoplastic squamous cells infiltrate the stroma in a haphazard pattern, H&E, 40X.

Table 1.2: FIGO staging of carcinoma vulva

TNM	FIGO	
Tis	0	Carcinoma in situ (preinvasive carcinoma).
T1	I	Tumour confined to vulva or vulva and perineum, ≤ 2 cm in greatest dimension.
T1a	IA	Tumour confined to vulva or vulva and perineum, ≤ 2 cm in greatest dimension, with stromal invasion < 1 mm.
T1b	IB	Tumour confined to vulva or vulva and perineum, ≤ 2 cm in greatest dimension, with stromal invasion ≥ 1 mm.
T2	II	Tumour confined to vulva or vulva and perineum, > 2 cm in greatest dimension.
T3	III	Tumour invades any of the following: lower urethera, vagina, or anus.
T4	IVA	Tumour invades any of the following: bladder mucosa, rectal mucosa, upper urethera; or is fixed to public bone.

❑

CHAPTER 2

VAGINA

Benign Lesions of Vagina

Vaginal Cysts

The prevalence of vaginal cysts is estimated to be 1 in 200 women; however, this number is probably inaccurate, since most cysts are not reported. They are more common in women in their third and fourth decades and are usually detected incidentally. When symptomatic, patients may present with mild vaginal discomfort, vaginal pressure or fullness, vaginal mass or swelling, dyspareunia, vaginal bleeding, or urinary symptoms.

Ultrasound, voiding cystourethrogram, CT-scan, and especially MRI are useful to characterize these lesions.

Vaginal cysts are treated with excision. The most common types of vaginal cysts discussed herein include: (1) Müllerian cyst; (2) epidermal inclusion cyst; and (3) Gartner's cyst.

Cysts of Vagina

Cysts lined by different epithelial types occurring in the vagina.

Incidence and Location

1. 1 in 200 women.
2. Müllerian cyst most common; mainly located in anterolateral wall.
3. Epidermal inclusion cyst related to previous surgical procedure.
4. Gartner's cyst typically located in anterolateral wall.

Age Distribution

Most common in the third and fourth decades.

Clinical Features

1. Usually asymptomatic.
2. Mild vaginal discomfort, vaginal pressure or fullness, vaginal swelling or mass, dyspareunia, and urinary symptoms may occur.

Prognosis and Treatment

1. Benign.
2. Possible association of Gartner's cysts with urinary system abnormalities.
3. Excision.

Müllerian Cyst

Gross Findings

1. Müllerian cysts range in size up to 7 cm
2. Epidermal inclusion cysts range in size up to 4 cm, and may contain "cheese-like" material
3. Gartner's cysts typically range in size from 0.1–4 cm

Microscopic Findings

1. Müllerian cyst: Endocervical columnar epithelium, less commonly cuboidal mucinous, endometrioid, or tubal epithelium.
2. Epidermal inclusion cyst: Squamous epithelium associated with keratin debris.
3. Gartner's cyst: Cuboidal or low-columnar nonmucinous epithelium.

Differential Diagnosis

1. Cystocele (vs Gartner's cyst).
2. Urethral diverticulum (vs Gartner's cyst).

Gartner's Cyst

These cysts arise from the remnants of the mesonephric (wolffian) ducts. They are typically located in the anterolateral wall and are small (ranging in size from 0.1 to 4 cm), but rarely may be > 10 cm and be mistaken for a cystocele or an urethral diverticulum. The cysts are lined by cuboidal or low columnar nonmucinous epithelium). In contrast to the epithelium seen in müllerian cysts, the epithelium of Gartner's cysts is devoid of cytoplasmic mucicarmine or PAS-positive material. Gartner's cysts can be associated with urinary system abnormalities such as ectopic ureter, unilateral renal agenesis, and renal hypoplasia.

Bartholin Cyst

Definition/General

1. Due to blockage of duct exiting Bartholin gland, causing accumulation of gland fluid; if infected, may form an abscess.

2. Common infectious agents include sexually transmitted chlamydia and gonorrhoea; *E. coli* and other normal flora.
3. Cyst may occur secondary to gonorrhea or other acute inflammation, which causes abscess, then obstruction of duct.
4. Painful; may be huge; seen in all ages but often women age above 40 years.
5. May be associated with accessory breast tissue.
6. May have mucocele-like changes.

Treatment

Excise in older women because of risk of adenoid cystic carcinoma; otherwise marsupialize.

Microscopic (Histologic) Description

1. Squamous and urothelial epithelium common but may be destroyed by inflammatory infiltrate.
2. Still see residual mucinous glands with non-sulfated sialomucin.
3. May have calcifications resembling malakoplakia.

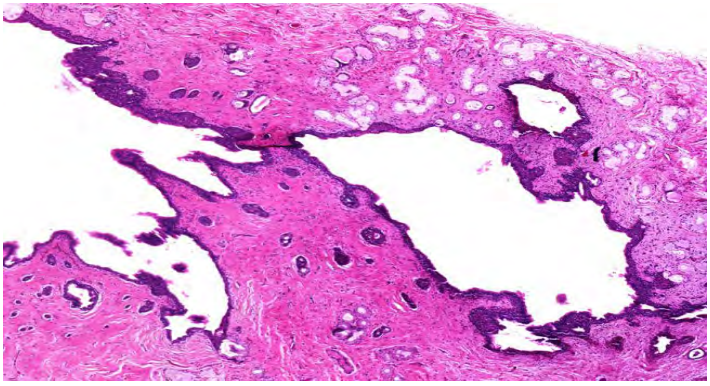


Fig. 2.1: Bartholin cyst lined by transitional type with dilated glands, H&E, 10X.

VAGINAL NEOPLASMS

Pre-malignant Lesions of Vagina

Primary neoplasms of the vagina, whether benign or malignant, are rare. Primary carcinomas are the most common malignant tumours and account for approximately 2% of all gynaecological malignancies. Among vaginal carcinomas, in situ and

invasive squamous carcinomas are the most frequent. As a general rule, when evaluating a primary malignant tumour in the vagina, it is essential to exclude the possibility of a metastasis,especially if it is an epithelial neoplasm.

The vagina is the least common site in the lower genital tract to develop squamous intraepithelial neoplasia.

Risk factors associated with VAIN include concurrent or prior cervical intraepithelial neoplasia or vulvar intraepithelial neoplasia (both present in more than three-quarters of patients), history of HPV infection or sexually transmitted diseases, smoking, immunosuppression, history of radiation therapy or DES exposure. The more common HPVs encountered in VAIN are types 15 and 16.

Vaginal Intraepithelial Neoplasia (VAIN)

Definition

Lesion characterized by variable degrees of atypia and maturation of the keratinocytes which is confined to the epithelium.

Location

Upper third of the vagina most common location.

Morbidity and Mortality

1. 10–42% overall recurrence rate.
2. 2–12% rate of development of invasive squamous carcinoma.

Age Distribution

16–84 (mean 35–55) years.

Clinical Features

1. Commonly asymptomatic.
2. Detection typically following Pap smear.
3. Rarely, vaginal bleeding or discharge.

Prognosis and Treatment

1. If untreated, ≤ 9% of patients followed ≥ 3 years develop invasive squamous carcinoma.
2. Low risk of progression in VAIN I; close observation suffices.
3. Treatment with either carbon dioxide laser or topical 5-fluorouracil if persistent VAIN I.

4. Surgical excision if VAIN II or III.
5. Treatment with carbon dioxide laser or topical 5-fluorouracil if invasion can be excluded in high-grade VAIN.

Gross Findings

1. Often multifocal.
2. Commonly no gross lesion.
3. Less frequently, mucosal irregularities or colour changes.
4. Acetowhite epithelium, punctation, and mosaicism by colposcopy.

Microscopic Findings

1. Exophytic or flat.
2. VAIN I: susperficial koilocytosis and mild squamous atypia confined to the lower third of the epithelium.
3. VAIN II: moderate squamous atypia confined to the lower two thirds of the epithelium or marked atypia confined to the lower third of the epithelium. Koilocytes may be seen.
4. VAIN III: moderate to marked squamous atypia involving the full thickness of the epithelium. Koilocytes may be seen.

Immunohistochemical Features

1. VAIN I: Ki-67 positivity in the superficial two-thirds of the epithelium.
2. VAIN II and III: Ki-67 positivity throughout the entire epithelial thickness.

Differential Diagnosis

1. Nonspecific squamous hyperplasia.
2. Immature squamous metaplasia.
3. Reactive inflammatory atypia.
4. Atrophy.
5. Transitional cell metaplasia.
6. Pseudokoilocytosis.
7. Micropapillomatosis.
8. Radiation atypia.

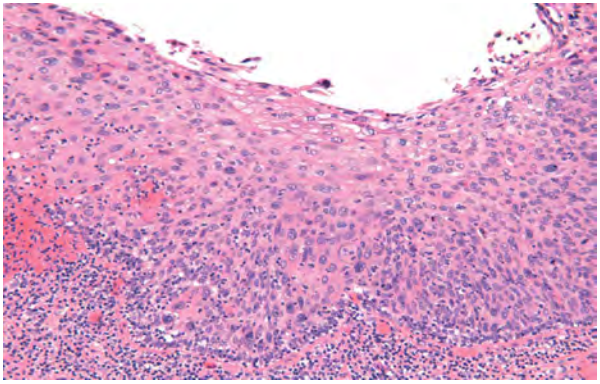


Fig. 2.2: Vaginal intraepithelial neoplasia II. Cellular crowding, nuclear enlargement and hyperchromasia of the lower two thirds of the epithelium are associated with superficial maturation.

Hidradenoma

1. Also called papillary hidradenoma.
2. Most common neoplasm of anogenital mammary-like glands.
3. Exclusively in women.
4. Perianal or vulvar (similar frequency in labia majora and labia minora).
5. Rare ectopic cases from eyelid, nasal area, breast.

Microscopy: Papillary fronds, ducts lined by apocrine type cells that show decapitation secretion and fibrous stroma.

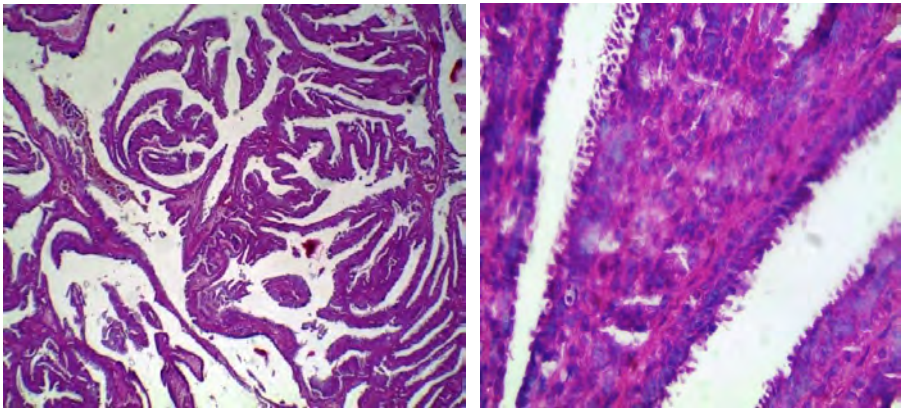


Fig. 2.3: Hidradenoma vagina: Papillary fronds, ducts lined by apocrine type cells that show decapitation secretion and fibrous stroma, H&E.

SQUAMOUS CELL CARCINOMA - VAGINA

Carcinoma demonstrating squamous differentiation (i.e.,keratin formation and/or intercellular bridges).

Diagnosis after exclusion of cervical, vulvar, and urethral origin.

This tumour represents only 1% of all malignant tumours of the female genital tract, but accounts for 80% of those arising in the vagina. According to the International Federation of Gynecologists and Obstetrics (FIGO), a tumour should be classified as a vaginal primary if this organ is the primary site of growth. Thus, a tumour that involves the vagina and cervix should be considered as a cervical primary; a tumour that involves the vagina and the vulva should be considered primary in the vulva, and a tumour that affects the vagina and the urethra should be considered a primary urethral carcinoma.

Furthermore, a squamous cell carcinoma occurring in the vagina within 5 years of treatment for cervical/vulvar cancer is considered to be a recurrence of the cervical/vulvar tumour rather than a new primary.

Morbidity and Mortality

1. Tumour behaviour depends on stage.
2. 73% relative 5-year survival rate for stage I disease.
3. 58% relative 5-year survival rate for stage II disease, and 36% for stages III–IV.
4. Risk factors: trauma, HPV, low social economical status, smoking, pelvic radiation, previous hysterectomy, history of cervical neoplasia or VAIN, and immunosuppression.

Clinical Features

1. Vaginal bleeding, discharge, dyspareunia, or pain.
2. Urinary symptoms.
3. Rarely asymptomatic; may be detected by routine Pap smear or physical examination.

Radiologic Features

1. T1 or T2-predominant images of medium or high signal intensity on MRI.
2. Higher detection of vaginal tumour and abnormal lymph nodes by fluorodeoxyglucose positron emission tomography than CT-scan.

Prognosis and Treatment

1. Radiotherapy, including brachytherapy and external-beam radiation treatment of choice.
2. Surgery in selected cases.

Gross Findings

1. Exophytic, ulcerating, or infiltrative.
2. Variable size (millimeters to > 10 cm).

Microscopic Findings

1. Well, moderately, or poorly differentiated.
2. Keratinizing or nonkeratinizing.
3. Spindle, verrucous, and warty subtypes.

Differential Diagnosis

1. Tangentially sectioned squamous cell carcinoma in situ.
2. Radiation-induced atypia.
3. Epithelioid trophoblastic tumour and placental site trophoblastic tumour.
4. Melanoma.
5. Sarcomas composed of epithelioid cells.

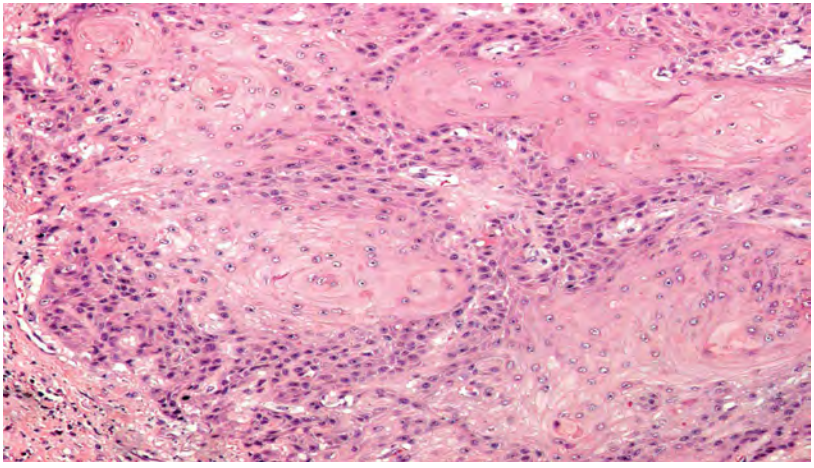


Fig. 2.4: Invasive well-differentiated squamous cell carcinoma. Nests of tumour cells with abundant eosinophilic cytoplasm show central keratinization. H&E, 40X.

Table 2.1: Carcinoma of the vagina: International Federation of Gynecologists and Obstetrics staging nomenclature.

Stage	Description
0	Carcinoma in situ.
I	Carcinoma is limited to the vaginal wall.
II	Carcinoma has involved the subvaginal tissue but has not extended to the pelvic wall.
III	Carcinoma has extended to the pelvic wall.
IV	Carcinoma has extended beyond the true pelvis or has involved the mucosa of the bladder or rectum; bullous edema as such does not permit a case to be allotted to stage IV.
IVa	Tumour invades bladder and/or rectal mucosa and/or direct extension beyond the true pelvis.
IVb	Spread to distant organs.

❑

CHAPTER 3

CERVIX

Cervix is located in the lower end of the uterus and is composed of the ectocervix(outer portion) and endocervix (inner portion). The ectocervix is composed of wet stratified squamous epithelium, which means there are many layers of thin flat cells that make up the lining. It includes:

1. Basal layer.
2. Parabasal layer.
3. Intermediate cell layer.
4. Superficial layers.

The endocervix is comprised of simple columnar epithelial cells that are mucus secreting. In between these portions of cervix is called as the 'transformation zone' also known as the 'Squamocolumnar Junction'.

Squamous cell carcinoma of cervix is one a common malignant neoplasm of cervix originating in or near the cervical transformation zone showing squamous differentiation. Squamous cell carcinoma comprises of 80% of histological subtype of cervical cancer and highly associated with Human Papillomavirus(HPV), most common subtype being 16 and 18, HPV had oncoprotein that leads to unchecked cell growth and genetic instability which can lead to cancer.

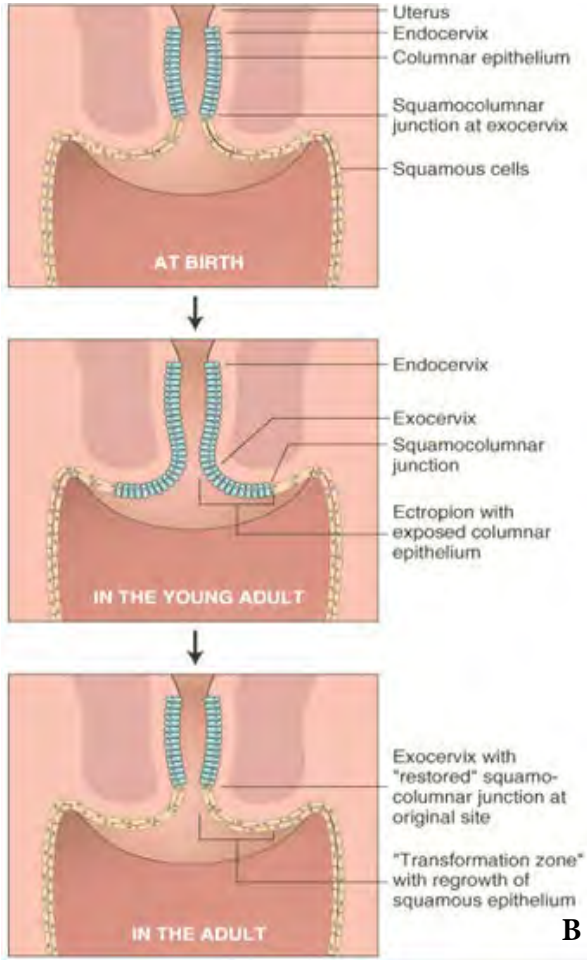


Fig 3.1 : (A) Histological section showing transformation zone; Schematic representation of transformation zone (B) .

BENIGN LESIONS OF CERVIX

The SCJ is constantly subjected to hormonal influences, and as a consequence, its anatomic location varies with age. At birth, most female neonates have endocervical epithelium present in the portion because of intrauterine exposure to maternal hormones but it rapidly moves back into the endocervical canal until menarche. During puberty, pregnancy, or progesterone therapy, the presence of endocervical glandular epithelium in the ectocervix results in what is clinically know as physiologic cervical *eversion* or *ectropion.*

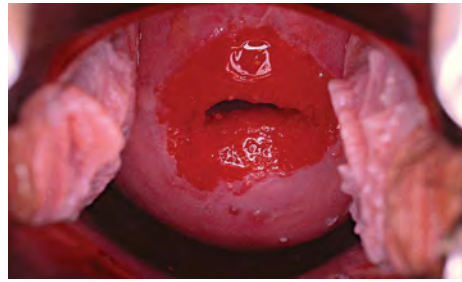


Fig. 3.2: Cervical erosiosn/Ectropion. By colposcopy, the endocervical mucosa has a rough, red appearance, in sharp contrast to the smooth pink surface of the native squamous epithelium.

Throughout the reproductive years, the endocervical epithelium is continuously replaced by metaplastic squamous epithelium due to exposure of the ectropion to the acidity of the vagina and other environmental factors. The degree of ectropion decreases with increasing age and time from onset of sexual activity. During menopause, the transformation zone recedes into the endocervical canal, and in postmenopausal women may be located completely within the endocervical canal. Hence, the transformation zone is the remodelled area of ectropion which undergoes active squamous metaplasia and represents the region between the original and the functional SCJ. It is important to note that the transformation zone is a very dynamic area, which is changing under hormonal and environmental influences. Remodelling of the ectropion does not occur in a uniform fashion, and, in fact, squamous metaplasia can, and often does, occur anywhere within the exposed endocervical columnar epithelium in a patchy fashion. This area is the one most susceptible to HPV infection for several reasons, including higher susceptibility of the advancing edge of the immature squamous epithelium to infection.

CERVICAL POLYP

Definition/General

Benign exophytic proliferation composed of variable admixture of endocervical glandular and metaplastic squamous epithelium with a fibrovascular core.

Essential Features

1. Endocervical polyps are common benign proliferations composed of a fibrovascular core and endocervical glandular or metaplastic squamous epithelium.
2. Chronic inflammation, surface erosion and reactive epithelial changes are common.

3. Rare cases may harbor in situ or invasive squamous or glandular lesions.
4. Lack of leaf-like architecture and periglandular stromal condensation, which are key features of Müllerian adenosarcoma.

Clinical Features

1. Most are found incidentally during a routine gynaecological exam.
2. May also present with abnormal vaginal spotting or bleeding (postcoital or contact) or abnormal vaginal discharge.

Diagnosis

1. Endocervical polyps often protrude through the cervical os and can be detected during routine gynaecologic examination or colposcopy.

Microscopic (Histologic) Description

1. Fibrovascular core with variably sized vasculature (often including thick walled arteries).
2. Variable stromal cellularity often with mixed chronic inflammation.
3. Surface epithelium is endocervical glandular type and may show squamous metaplasia, erosion and reactive/reparative changes.
4. Proliferation of endocervical glands, which may be cystic or may show benign microglandular hyperplasia.
5. Mitotic activity may be noticeable, especially in cases with marked inflammation or florid microglandular hyperplasia.
6. "Epidermal" metaplasia may be seen with skin appendage structures.
7. Stromal cells may be multinucleated, may show decidual change or may contain heterologous elements (fat, cartilage, bone, glial tissue), which could represent retained fetal tissues from a previous gestation.
8. Endocervical polyps may rarely harbor in situ or invasive squamous and glandular lesions, i.e. high grade squamous intraepithelial lesion, adenocarcinoma in situ, squamous carcinoma and adenocarcinoma.

Differential Diagnosis

1. Adenosarcoma:
    i. Leaf-like glandular architecture, resembling phyllodes tumour of the breast, with intraglandular papillary projections and prominent periglandular stromal condensation.
    ii. Stromal cell atypia and stromal mitotic figures are also present.

2. Endometrial polyp:
    i. Proliferation of benign endometrial stromal and glandular elements, protruding into the endometrial cavity.
    ii. Occasionally a larger polyp arising in the lower uterine segment may protrude into the endocervical canal or may be visible through the cervical os, mimicking an endocervical polyp.
3. Polypoid adenomyoma:
    i. Polypoid mass composed of smooth muscle and irregular benign endocervical type glands, often showing a lobular architecture.
4. Condyloma:
    i. Exophytic, warty lesion of the ectocervix with squamous epithelium showing papillomatosis and koilocytosis, commonly associated with low risk human papillomavirus infection.

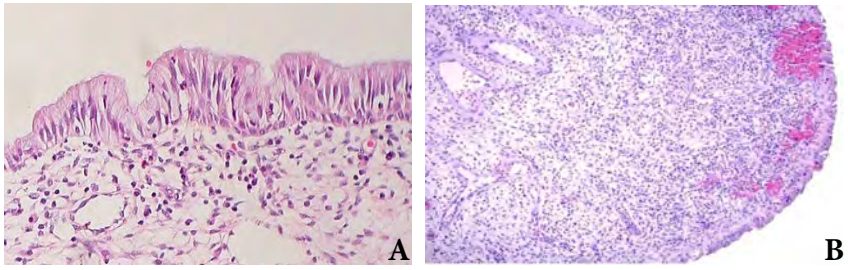


Fig. 3.3: (A) Endocervical polyp, H&E 10X; (B) Benign endocervical polyp with inflammation with ulceration of lining epithelium.

CERVICAL FIBROID POLYP

1. Rare and frequently underdiagnosed biphasic tumour composed of benign endocervical glands and smooth muscle typically located in the endocervix.
2. Usually an incidental finding in women of reproductive or postmenopausal age (mean age 40 years).
3. Presents as a polyp or mass protruding through the external cervical os, resulting in abnormal bleeding or vaginal discharge, causing concern for malignancy.
4. Well circumscribed neoplasm composed of irregularly shaped, benign endocervical-type glands, often in a lobular arrangement, admixed with myomatous smooth muscle.
5. Benign with an excellent prognosis if completely removed.

Epidemiology

Women of reproductive or post-menopausal age (mean age 40 years).

Sites

1. Arises from endocervix.
2. Endometrioid type adenomyomas usually originate from the endometrium, but could also arise from the endocervix.

Clinical Features

1. Usually an incidental finding.
2. May be asymptomatic; usually discovered incidentally during regular gynaecologic examination.
3. May present as a polyp or 'fibroid' protruding through the external cervical os, or may result in abnormal bleeding or vaginal discharge, causing concern for malignancy.
4. Less commonly, there is cervical enlargement by a mural mass without mucosal involvement.

Microscopic (Histologic) Description

1. Well circumscribed, unencapsulated neoplasm composed of irregularly shaped benign endocervical type glands, often in a lobular arrangement, admixed with myomatous smooth muscle.
2. Endocervical cells have basal nucleus with abundant pale cytoplasm and may show tubal or tuboendometrioid metaplasia.
3. The smooth muscle component forms variably sized and shaped fascicles embedded in a collagenous background; cells have bland cytologic features with eosinophilic cytoplasm and spindled cigar shaped nuclei.
4. Mitotic activity is absent in both epithelial and smooth muscle components.
5. No desmoplastic response is evident.

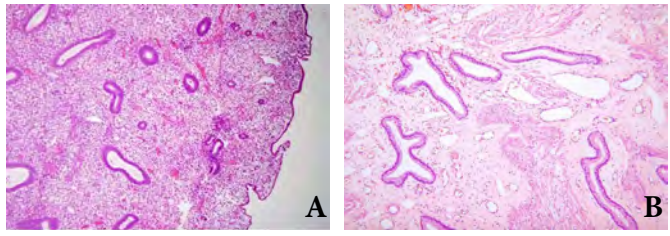


Fig. 3.4: (A) Endocervical fibroid with glands and smooth muscles, (B) Cervical fibroid with inflammation and myxoid change H &E, 10X.

PREMALIGNANT LESIONS OF CERVIX

Human Papillomavirus and the Pathogenesis of Precursor Lesions and Cervical Carcinoma

It is now well established that HPV infection plays an essential role in the development of precancers and cancers of the cervix, as > 99% of all cervical cancers are HPV-related which is independent of racial origin. HPV, a double-stranded DNA virus and a member of the Papovaviridae family, is sexually transmitted disease that predominantly infects squamous epithelia of skin and mucosae. Risk factors associated with HPV infection include early age at first intercourse, early age at first pregnancy, number of sexual partners, cigarette smoking, oral contraceptive use, low socioeconomic class, interval since previous Pap test, increasing parity, nutritional status, immunosuppression (particularly HIV infection), and other sexually transmitted infections.

Use of barrier methods of contraception, including condoms and diaphragms, is associated with a decreased risk of HPV infection. The different subtypes of HPV are divided into “low-risk” and “high-risk” depending on the associated risk of carcinoma. Low-risk subtypes include 6, 11, 42, 43, 44, and 53, whereas high risk subtypes are 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68.

The human papilloma virus enters the basal cells or immature squamous metaplastic cells through defects in the mucosa at the transformation zone. It usually infects the squamous epithelium; however, the virus can also infect subcolumnar reserve cells. The virus can cause either a nonproductive (latent) or a productive infection. In the latter, large amounts of free DNA virus (episomal) are produced in the intermediate and superficial cell layers, which are nonproliferating terminally differentiated squamous cells. As the virally infected cells mature and migrate towards the surface, the characteristic cytopathic effect – the so-called koilocytic atypia – becomes apparent.

Integration of HPV DNA into the host cell genome, with covalent binding of viral genome into host DNA, is thought to be a critical event in the progression tohigh-grade squamous intraepithelial lesions (HSIL). High-risk HPVs produce E6 and E7, two proteins with growth-stimulating and transforming properties. Viral integration into host cell genome results in disruption of the viral DNA with overexpression of E6/E7 genes. Excessive levels of E6/E7 viral oncoproteins result in abrogation of p53/Rb tumour suppressor proteins, with resultant uncontrolled cell cycling and proliferative activity of the squamous epithelium.

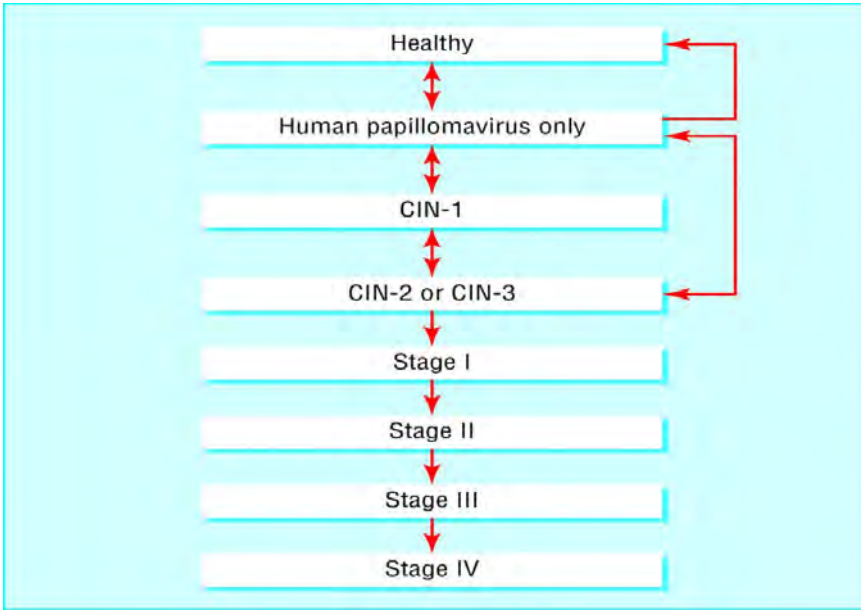


Fig. 3.5: Sequelae of HPV induced cervical lesions in flowchart.

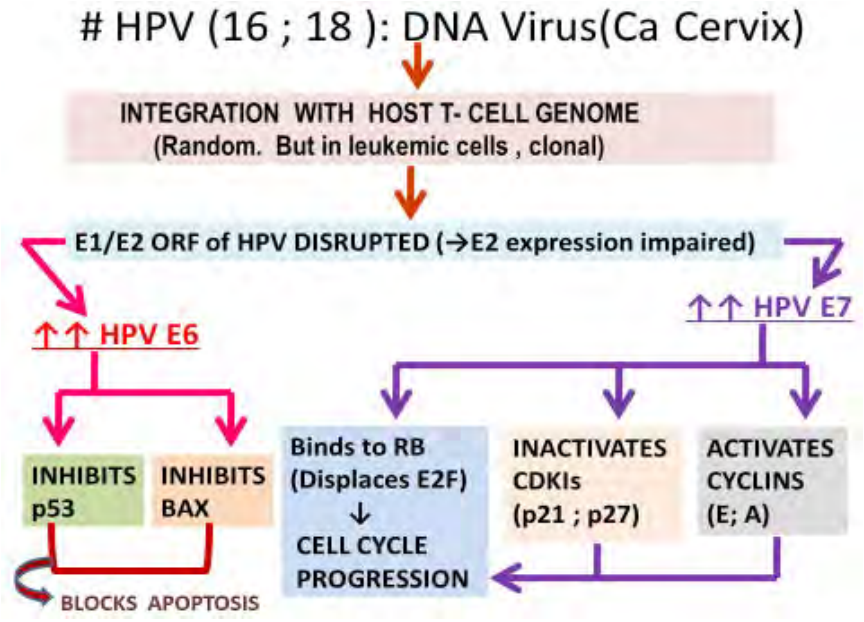


Fig. 3.6: The schematic diagram of pathogenesis of HPV induced carcinoma cervix is depicted below.

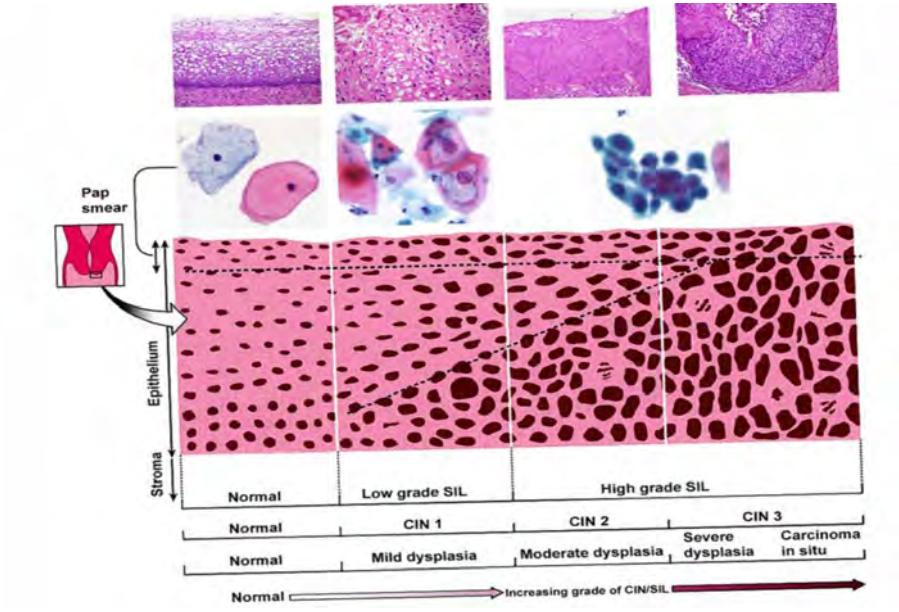


Fig. 3.7: Histological sequence of cervical epithelium transforming to CIN to Ca. (Pc: J Obsterics and Gyneco, 2016)

LOW-GRADE SQUAMOUS INTRAEPITHELIAL LESION

This category includes flat condyloma, condyloma acuminatum (also known as exophytic condyloma), and CIN I. All of these low-grade lesions are the result of productive viral infections in which large numbers of viral particles are generated. They are usually self-limited and all display koilocytic atypia. Among them, condyloma acuminatum is strongly associated with low risk HPV subtypes 6 and 11.

Cervical cancer precursor lesion associated with both low and high-risk HPV subtypes - The category of LSIL includes flat and exophytic condyloma and CIN I.

Prevalence and Location

1. Reproductive age women.
2. Unknown true prevalence; however, up to 3.0% of Pap smear reported as SIL.
3. Mostly at the transformation zone.
4. Ectocervix can also be involved if condyloma acuminatum.

Age Distribution

Peak incidence in mid-20s, decreasing thereafter (5% of women < 30 have LSIL on Pap smear, versus < 0.1% of women ≥ 65 years).

Clinical Features

1. Asymptomatic.

Colposcopic Features

1. Leukoplakia or acetowhite epithelium.
2. Cerebriform or papillary raised lesion with prominent vasculature (condyloma acuminatum).

Prognosis and Treatment

1. Only 15% of LSIL progress to HSIL.
2. Following a diagnosis of LSIL on pap smear, colposcopic exam is performed with biopsy of any lesion to confirm the diagnosis.
3. If confirmatory biopsy, follow-up with Pap smears every 4–6 months.
4. If discordant biopsy, additional sampling may be necessary.

Gross Findings

1. May be uncommonly seen as white irregular plaques (leukoplakia).
2. Tan-white raised papillary or cerebriform lesion (condyloma acuminatum).

Microscopic Findings

1. Koilocytic atypia (nuclear enlargement, nuclear membrane irregularities, coarse chromatin, hyperchromasia, multinucleation, and peripheral cytoplasm condensation) in superficial layers.
2. Epithelial hyperplasia may be present.

Categories of LSIL

In condyloma acuminatum:

1. Epithelial hyperplasia with acanthosis and papillomatosis.
2. Parakeratosis and hyperkeratosis.
3. Koilocytic atypia.

In papillary immature metaplasia:

1. Epidermal hyperplasia with slender filiform papillae.
2. Immature metaplastic squamous cells with regular nuclear spacing +/− nucleoli.
3. Minimal to absent koilocytic atypia.

Cytology Correlation

1. Nuclear but not cytoplasmic changes in mature superficial squamous cells required for diagnosis of LSIL.
2. Nuclear enlargement > three times that of a normal intermediate sized squamous cell, with nuclear hyperchromasia, coarse or smudgy chromatin, frequent binucleation and multinucleation, and inconspicuous nucleoli.

Differential Diagnosis

1. Mature glycogenated squamous epithelium.
2. Postmenopausal squamous atypia.
3. Metaplastic squamous epithelium with reactive changes.
4. High-grade squamous intraepithelial lesion.

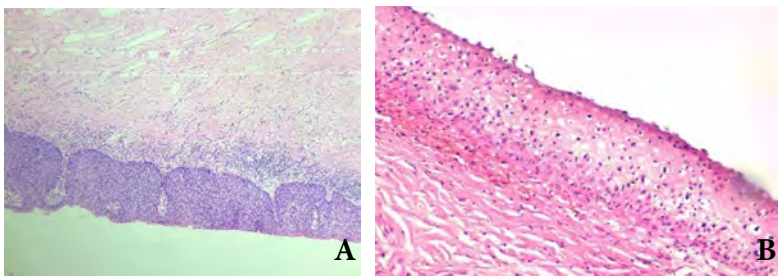


Fig. 3.8: (A) LSIL The lining squamous epithelium shows koilocytic atypia (B).The squamous epithelium shows cellular disorganization with 2/3 of lining thickness, H&E 4X; (B) The lining squamous epithelium shows koilocytic atypia, H& E 10X.

HIGH GRADE SQUAMOUS INTRA EPITHELIAL LESION (HSIL)/CIN III/SEVERE DYSPLASIA OF CERVIX

HSIL – 1–7% are associated with early invasive disease; 10–20% are estimated to progress to carcinoma if untreated.

Poor prognostic factors include extensive involvement of surface epithelium and deep endocervical clefts, luminal necrosis, intraepithelial squamous maturation.

Micro: Epithelium is totally replaced by atypical cells in at least part of the lesion with loss of maturation; koilocytes often have smaller and more concentric halos and denser hyperchromasia; may have less pleomorphism than low grade lesions, although nuclei are uniformly enlarged, crowded or irregularly spaced; hyperchromatic or binucleated; increased mitotic activity is present; may have surface parakeratotic cells with abnormal nuclei; nuclear abnormalities are often more prominent in basal/parabasal cells.

Note: LSIL and HSIL often co-exist.

Positive stains: MIB-1.

EM: Loss of intercellular cohesion due to marked reduction in desmosomes, presence of extremely complex cell surface, loss of surface pseudopodia.

DD of HSIL:

Reactive/reparative changes: Intercellular edema (spongiosis), evenly spaced nuclei, minimal variation in nuclear size, prominent nucleoli, neutrophils, superficial maturation of epithelium, no hyperchromasia; binucleation may be present.

Immature squamous metaplasia: Mucin droplets, neutrophilic infiltration, often overlying mucinous epithelium, minimal variation in nuclear size, no hyperchromasia.

Atrophy: Hyperchromatic but uniform nuclei, elongated and grooved nuclei, minimal atypia in superficial epithelium, no mitotic activity, even spacing of nuclei, conspicuous intracellular bridges, MIB-1 negative; Ki-67/MIB1 and p16 negative are helpful in diagnosis in postmenopausal women in older women, can apply estrogen to induce maturation and rebiopsy.

Adenoid cystic carcinoma.

Radiation changes: Abundant cytoplasm with vacuoles, nuclear enlargement and hyperchromasia with smudged chromatin, prominent nucleoli, uniform nuclear spacing, normal N/C ratio, minimal mitotic activity.

Placental site nodule: (Strongly keratin and PLAP positive).

Sheets of macrophages.

Urothelial hyperplasia.

Iodine effect: Can induce shrinkage, cytoplasmic eosinophilia, vacuolization and epithelial pyknosis.

DD (clinical): Hyperkeratosis and metaplastic squamous epithelium.

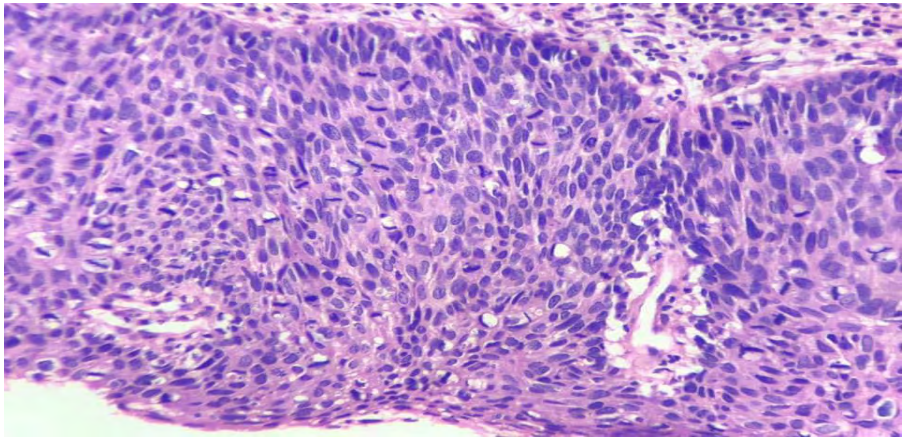


Fig. 3.9: HSIL - The squamous epithelium shows cellular disorganization involving full thickness with loss of polarity and pleomorphism, 40X.

ADENOSQUAMOUS CARCINOMA

Usually arise from subcolumnar reserve cells in basal layer of endocervix. More common during pregnancy. Same prognosis as other cervical carcinomas when stratified by grade and stage, but most cases are high grade. Most undifferentiated cervical carcinomas have ultrastructural features of squamous or glandular differentiation.

Micro: Usually defined as biphasic pattern of well defined malignant glandular and squamous components clearly identifiable without special stains; glandular component usually endocervical and poorly differentiated with cytoplasmic vacuoles or luminal mucin; squamous component also is poorly differentiated; if endometrioid call endometrioid carcinoma with squamous differentiation.

Positive stains: p63 (squamous component), CK7.

EM: Glandular features include mucous secretory vacuoles, true lumen formation and scattered glycogen; also tonofilaments and secretory products.

DD: Squamous cell carcinoma with focal mucin droplets, adenoid basal carcinoma, extension of endometrial adenocarcinoma (bulk of tumour is in endometrium), adenocarcinoma with coexisting SIL (usually no mixing of tumour elements).

HSIL/CIN II/Moderate Dysplasia of Cervix

Micro: Persistent abnormal differentiation towards prickle and keratinizing layers with at least focal maturation; atypical basal cells involve between 1/3 and 2/3 of epithelial thickness or less with disproportionate atypia; increased N/C ratio, pleomorphic nuclei with hyperchromasia, loss of polarity, increased mitotic activity.

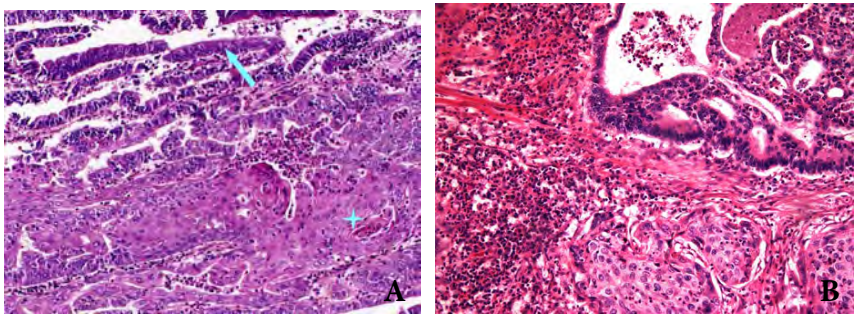


Fig. 3.10: Adenosquamous carcinoma showing squamous and glandular component (A) Squamous morules; (B) Glandular component.

Table 3.1: Dysplasia criteria.

Low-grade dysplasia (previously mild dysplasia)	Architecture	Overall satisfaction is preserved, whereas basal-parabasal layer is abnormal. Basal-parabasal layer is increased, upto lower half of the epithelium. Spinous layer may be increased, with prickle cells usually seen only in upper half of the epithelium.
	Cytology	Limited pleomorphism. Enlarged nuclei with increased nuclear-to-cytoplasmic ratio, but evenly distributed chromatin; vague cytoplasmic pinking with limited intercellular spinous processes. Isolated dyskeratosis cells. Mitoses (typical forms) limited to lower third of epithelium.
High-grade dysplasia (previously moderate and severe dysplasia, and carcinoma in situ)	Architecture	Keratinizing or nonkeratinizing (basal cell) types. Loss of maturation, with disordered stratification and loss of polarity up to full thickness, frequently severe. Basement membrane remains intact (no stromal changes) around irregular-shaped rete (bulbous, downwardly extending).
	Cytology	Often conspicuous pleomorphism with marked variation in cell and nuclear size and shape, marked variation in staining intensity (often hyperchromatic), and increased size and number of nucleoli. High nuclear-to-cytoplasmic ratio. Dyskeratotic cells increased throughout the epithelium. Increased mitoses anywhere in the epithelial, to include atypical forms (the latter qualifies as high-grade by itself).

SQUAMOUS CELL CARCINOMA OF CERVIX

Common cancer of cervix and occurs in mean age 51 years, uncommon before age 30 years but most are ages between 45–55 years.

Risk factors: Early age at first intercourse, multiple sexual partners, male partner with multiple prior sexual partners, history of HSIL; HLA associations in Mexican women.

Also oral contraceptives (some studies), parity, family history, associated genital infections, no circumcision in male partner.

Human papillomavirus (HPV): Causes vulvar condylomaacuminatum (sexually transmitted), found in DNA of 95% of cervical cancers, 90% of condylomas and premalignant lesions.

High risk HPV types for cervical carcinoma: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68 and others.

Low risk HPV types for cervical carcinoma: 6, 11, 42, 44 (associated with condyloma).

HPV acts via E6 and E7 genes, which differ in high vs. low risk HPV types; HPV is integrated in premalignant lesions with tumour DNA vs. present in episomes (not integrated) in condylomas; in HPV 16 and 18, E6 binds to p53, causing its proteolytic degradation; E7 binds to retinoblastoma gene (Rb) and displaces transcription factors normally bound by Rb.

Other co-factors are important, because (a) most with HPV don't get cervical cancer, (b) 10–15% of cervical cancer is not associated with HPV.

HIV or HTLV-1 infection adversely affect the prognosis, may be associated with rapidly progressive course.

Detect clinically via white patches after application of acetic acid to cervix; cervix also has mosaic vascular patterns at colposcopy.

Prognostic factors: Clinical stage, nodal status, size of largest node and number of involved nodes, tumour size, depth of invasion, endometrial extension, parametrial involvement, angiolymphatic invasion; HPV negative patients do poorer; possibly S phase fraction; possibly tissue associated eosinophilia (poorer survival in one study; also squamous cell carcinoma antigen serum level in patients with advanced disease.

Not relevant: Microscopic tumour grade, tumour type, angiogenesis.

Spreads usually through cervical lymphatics in sequential manner; via direct extension to vagina, uterus, parametrium, lower urinary tract, uterosacral

ligaments; distant metastases to aortic and mediastinal lymph nodes, lung, bones, ovary (1%) 2/3 are stage I or II when diagnosed.

Treatment: Surgery (cervicectomy), radiation therapy, radioactive implants (for early lesions), pelvic extenteration (for post-radiation therapy relapse; 5 year survival is 23%; frozen section may be necessary to rule out extra-pelvic spread) 5 year survival by stage: Ia1-Ib1: > 95%, Ib2-IIb: 80–90%, III: 50%, IV: 25–35%.

Micro: See subtypes below; invasion characterized by desmoplastic stroma, focal conspicuous maturation of tumour cells with prominent nucleoli, blurred or scalloped epithelial-stromal interface, loss of nuclear polarity; may have pseudoglandular pattern due to acantholysis and central necrosis; rare findings are amyloid, signet-ring cells, melanin granules Grading does not correlate with prognosis and is optional.

Well differentiated: Predominantly mature squamous cells with abundant keratin pearls, occasional well-developed intercellular bridges, minimal pleomorphism, minimal mitotic activity.

Moderately differentiated: Less distinct cell borders and less cytoplasm than well differentiated tumours; also more nuclear pleomorphism and more mitotic activity.

Poorly differentiated: Small primitive appearing cells with scant cytoplasm, hyperchromatic nuclei and marked mitotic activity; no/rare keratinization; resembles HSIL.

Positive stains: Keratin (almost 100%), CEA (90%).

Negative stains: p53 (usually), MDM2 gene, EBV.

EM: Well developed intracytoplasmic tonofilaments, desmoplastic-tonofilament complexes and intercellular microvilli in well differentiated tumours, lost with decreasing differentiation.

Molecular: Aneuploid, but tumour may exhibit heterogeneity; HPV16 is associated with 3q amplification.

DD:

1. Immature squamous metaplasia (uniform cell size and shape, no significant nuclear atypia);
2. Squamous metaplasia with extensive glandular involvement or marked decidual reaction (no atypia, no/rare mitotic figures);
3. Placental site nodule (well circumscribed nodules of intermediate trophoblast cells, no/rare mitotic activity, HPL+);
4. Clear cell carcinoma (papillary and tubulocystic areas, hobnail cells, no squamous differentiation, may be associated with DES exposure);

5. Small cell neuroendocrine carcinoma (diffuse infiltration of small cells with scant cytoplasm and hyperchromatic nuclei; often rosettes, trabeculae or ribbons;
6. Often crush artifact immunoreactive for neuroendocrine markers).

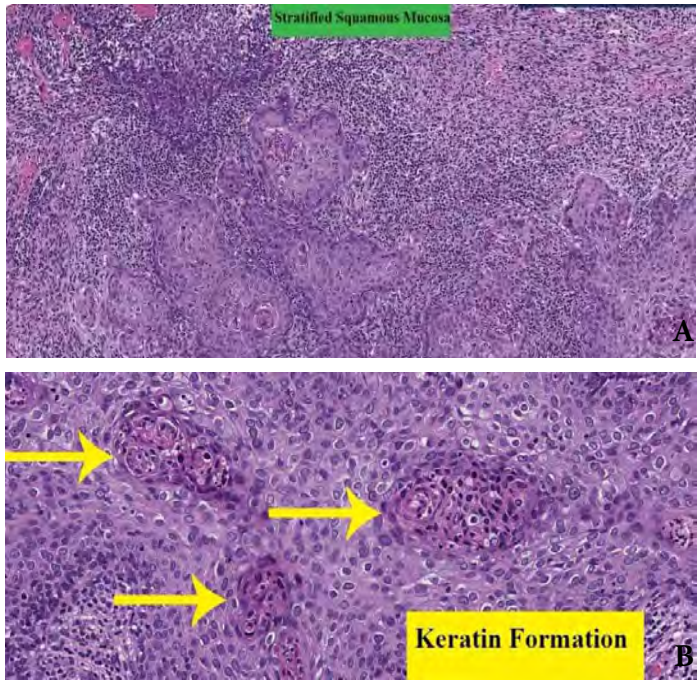


Fig. 3.11: Squamous cell carcinoma showing keratin formation (A) Scanner -4X; (B) 40X.

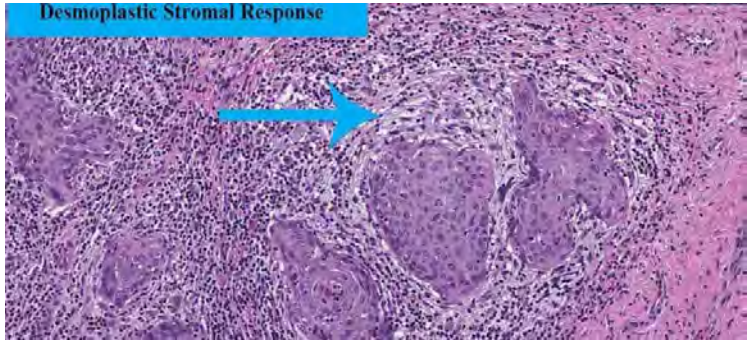


Fig. 3.12: Desmoplastic stromal response(Arrow) in Squamous cell carcinoma, H & E 40X.

LARGE CELL KERATINIZING SQUAMOUS CELL CARCINOMA OF CERVIX

1. Rare, locally aggressive; spreads by direct extension.
2. More radioresistant than nonkeratinizing carcinomas (5 year survival for stage I is 54%).
3. Not associated with HPV or SIL; not associated with sexual risk factors.
4. Often normal Pap smear, but may be large and high stage at diagnosis.
5. Histologically similar to HPV negative vulvar and penile cancers.

Gross: Usually large.

Micro: Must have keratin pearls and intercellular bridges to be keratinizing; keratin pearl is rounded nest of squamous epithelium with circles of squamous cells surrounding a central focus of acellular keratin; cells are large with abundant eosinophilic cytoplasm; nuclei may be enlarged or pyknotic; extensive parakeratosis and hyperkeratosis without atypia in non-malignant portion of cervix, marked hyperkeratosis in invasive area with keratin pearls, intercellular bridges, >25 cells per nest, extensive infiltration of adjacent tissues, relatively low mitotic activity, no vascular invasion.

Large cell nonkeratinizing squamous cell carcinoma of cervix

More radiosensitive than large cell keratinizing (5 year survival for stage I is 84%).

Micro: Rounded nests of neoplastic squamous cells with no keratin pearls, but may have individual cell keratinization or clear cells; relatively uniform cells with indistinct cell borders and numerous mitotic figures.

SMALL CELL SQUAMOUS CELL CARCINOMA OF CERVIX

1. Mean age 50 years.
2. Lower rate of nodal metastases and recurrence than small cell neuroendocrine carcinoma.
3. 5 year survival for stage I is 42%.

Micro: Well-defined nests of basaloid-type cells resembling small cell neuroendocrine carcinoma, but with more cytoplasm, coarser chromatin and prominent nucleoli; 60% also have SIL.

Positive stains: Keratin.

Negative stains: Neuroendocrine markers.

DD: Small cell neuroendocrine (undifferentiated) carcinoma.

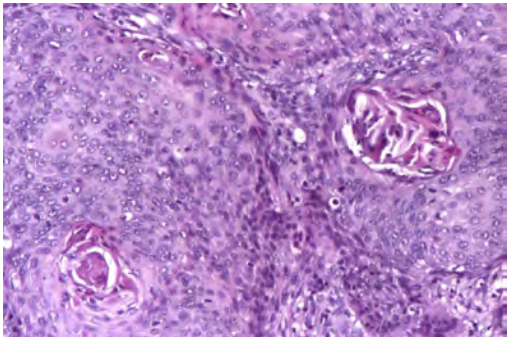


Fig 3.13: Small cell carcinoma of Cervix, H & E, 40X.

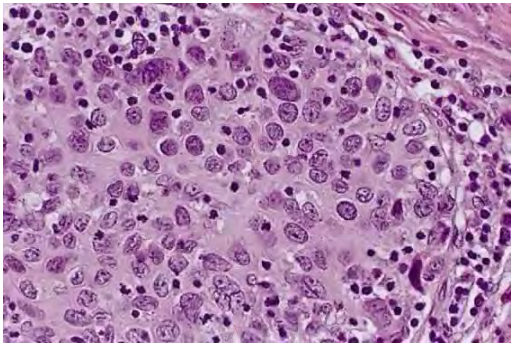


Fig 3.14: Higher power view of Large cell, H & E, 40X.

MICROINVASIVE SQUAMOUS CELL CARCINOMA OF CERVIX

Invasion upto 3 mm or 5 mm (varies by author) or less of stromal invasion.

Also known as "early invasive carcinoma" (WHO), "early stromal invasion" or "superficially invasive".

Approximately 20% of invasive carcinoma cases in US (higher figure than in the past; lower rate where patients typically present with advanced disease, Note: FIGO stage Ia is lesion with maximum depth of invasion of 5 mm and maximum horizontal spread of 7 mm; is subdivided into Ia1 (invasive depth of 3 mm or less; no wider than 7 mm) and Ia2 (invasive depth of more than 3 mm but not more than 5 mm; no wider than 7 mm 1% with 3 mm of invasive disease have nodal metastases (more if angiolymphatic invasion) vs. 13% with 3–5 mm of invasive disease.

In recent study, recurrence in 6% with up to 3 mm vs. 13% with up to 5 mm of invasive disease.

Almost always arises from SIL, usually in anterior lip of cervix; associated with delayed screening.

Prognostic factors: Lymph node metastases; recurrence associated with angiolymphatic invasion, depth of invasion and distance between tumour margin and apex of cone; also positive margins.

Report depth of invasion (measure from most superficial epithelial-stromal interface of adjacent intraepithelial process), length of entire lesion, whether length is composed of one or multiple lesions, presence of vascular invasion (DD: retraction artifact, displacement of tumour into vascular spaces during biopsy or anesthetic injection), margins, presence of SIL, presence of glandular differentiation (i.e. adenocarcinoma).

Treatment: Clinical course resembles HSIL, so treat with cone biopsy or simple hysterectomy (versus radical hysterectomy with pelvic lymph node dissection for more invasive disease).

Gross: Resembles HSIL; often abnormal vessels at colposcopy.

Micro: Irregularly shaped tongues of epithelium projecting into stroma; invasive cells exhibit individual cell keratinization, loss of polarity, pleomorphism, cellular differentiation, prominent nucleoli, desmoplastic stroma rich in acid mucosubstances with metachromatic staining properties, breach of basement membrane by reticulin stains (also type IV collagen or laminin); may also see scalloped margins at epithelial-stromal interface, duplication of neoplastic epithelium or pseudoglands.

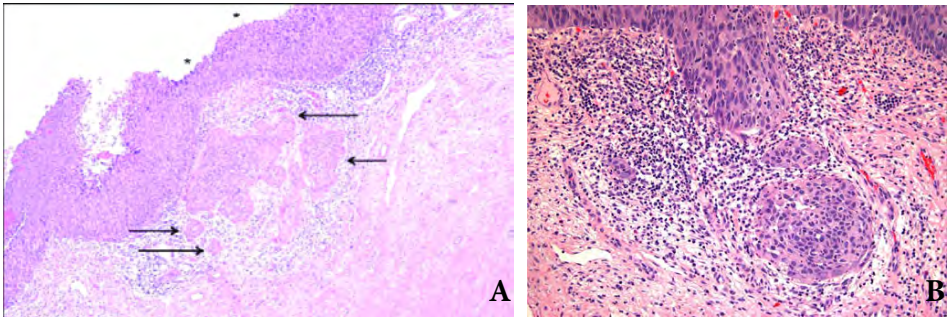


Fig 3.15: Microinvasive carcinoma cervix with stromal invasion by tumour nests (Arrow). (A) 10X; (B) 40X.

DD: Crypt involvement of SIL with tangential sectioning (each nest is discrete and separate from its neighbours), cautery/crush artifact due to prior biopsy, pseudoepitheliomatous hyperplasia or other reactive changes, blurring of epithelial-stromal border by inflammation, placental implantation site.

Table 3.2: Showing criteria for microinvasive carcinoma in various organs.

Criteria for "micro-entites" in various organs	
Diagnosis	**Size criteria**
Breast metastases to lymph nodes	Isolated tumour cells: < 0.2 mm (or < 200 cells)
Lung, atypical adenomalus hyperplasia (AAH)	≤ 0.5 cm (+low-grade cytology, though not all experts agree on an arbitrary size cutoof between AAH and BAC)
Lung, carcinoid tumourlet	≤ 0.5 cm
Gastric microcarcinoid (ECL cell)	≤ 0.5 cm
Pamcrecatic neuroendocrine microadenoma (formely islet cell microadenoma)	≤ 0.5 cm
Pituitary microadenoma versus macroadenoma	≤ cm versus > cm (this is generally a clinical distinction)
Renal cell papillary adenome	≤ 0.5 cm
Thyroid papillary microcarcisoma	≤ 1 cm
Thyroid micromedullary carcinoma	≤ 1 cm
Criteria for micro-invasion in various organs	
Site	**Size criteria for micro-invasion**
Breast	< 1 mm (some experts use 2 mm)
Cervix, squamous cell carcinoma (stage IAI)	≤ 3 mm deep and ≤ 7 mm horizontal extent (controversial) diagnosed by microscopy only, i.e. no grossly visible lesion in a specimen with negative margins
Ovary, serous borderline tumour	< 3–5 mm or < 10 mm^2
Ovary, mucinous borderline tumour	< 3–5 mm or < 10 mm^2 (WHO)
Salivary gland, carcionma ex-mixed tumour	≤ 1.5 mm beyond the tumour capsule (minimally invasive)
Upper aerodigestive tract	1–2 mm below the basement membrance
Lung (minimally invasive adenocarcinoma arising in BAC)	≤ 5 mm focus of invasion in a lepidic tumour (BAC) That is ≤ 3 cm in overall size (new proposal)

Table 3.3: Pitfalls in diagnosis of squamous cell carcinoma cervix.

Pitfalls	
Tumour type	**Pitfall**
Dysplasia	Pseudoepitheliomatous hyperplasia has bulbous rete, but etiologic agent frequently present. Tangential sections must be carefully reviewed. Gland-duct extension is not invasion. Parakeratosis and keratosis in the larynx are abnormal.
SCC	Basement membrane must be breached. Invasive tumour may develop without surface dysplasia. Poorly differentiated tumours must be evaluated for neuroendocrine carcinoma and mucosa melanoma.
Verrucous carcinoma	Inadequate biopsy precludes definitive diagnosis. Tangential sectioning may overestimate thickness. Do not diagnose verrucous hyperplasia on a biopsy because more extensive sampling may reveal carcinoma.
Papillary/exophytic SCC	Orientation is critical. Must make sure you have an adequate specimen (i.e., stalk or base of lesion).
Spindle cell SCC	Surface epithelium generally absent. 30% lack epithelial immuno markers. Hypocellular tumours still show atypia.
Basaloid SCC	Must find squamous differentiation. Mucohyaline material mimics adenoid cystic carcinoima. Superficial biopsy fails to show true tumour appearance.
Adenosquamous carcinoma	High-grade mucoepidermoid carcinoma still shows mucocytes. Two distinct populations are seen.

Table 3.4: Variants on SCC in nutshell.

Pathologic key features of SCC variants					
	Variant				
Feature	Verrucous	Papillary/Exophytic	Spindle Cell (Sarcomatoid)	Basaloid	Adenosquamous
Macroscopic	Broad-based, warty and fungating mass	Polypoid, exophytic, bulky, papillary, fungiform	Polypoid mass	Firm to hard with central necrosis	Indurated submucosal mass
Microscopic	Pushing border of infiltration; abrupt transition with normal; large, blunt club-shaped rete; no pleomorphism; nearly absent mitoses; abundant keratin, including parakeratin crypting and "church-spire" keratosis	>70% exophytic or papillary architecture; unequivocal cytomorphologic malignancy; surface keratinization; invasive by definition; koilocytic atypia	Biphasic; SCC present, but ulcerated; transition of epithelial to atypical spindled cells; hypercellular; variable patterns of spindle-cell growth; pleomorphism; opacified cytoplasm; increased mitoses	Deeply invasive; lobular; basaloid component most prominent; peripheral nuclear palisading; high N:C ratio; abrupt squamous differentiation (metaplasia, dysplasia, CIS or invasive); increased mitoses; central comedonecrosis; hyaline stroma material	Biphasic; SCC and adenocarcinoma; undifferentiated clear-cell component; separate or intermixed with areas of transition; infiltrative
Special studies	No transcriptionally active HPV identified	None	30% negative with epithelial immunohistochemistry markers	Keratin, EMA, CK7, and 34ßE12; negative neuroendocrine markers	Mucin-positive glandular/goblet cells
Differential diagnosis	Hyperplasia; squamous papilloma; conventional SCC; hybrid carcinoma	In situ SCC; squamous papilloma; reactive hyperplasia	Inflammatory myofibroblastic tumor; mucosal melanoma; synovial sarcoma; other malignant mesenchymal tumors	Adenoid cystic carcinoma; neuroendocrine carcinoma (small cell carcinoma); adenosquamous carcinoma; mucoepidermoid carcinoma	Basaloid SCC; mucoepidermoid carcinoma; adenocarcinoma with squamous metaplasia; adenoid SCC

Table 3.5: Morphologic classification of SCC.

Low grade dysplasia	
Architectural	Minimal to slightly elongated/downward extension of rete ridges. Nuclear stratification (polarity is preserved): Transition of basal cells or augmented basal/parabasal cell layer with perpendicular orientation to the basement membrane to prickle cells horizontally oriented in the upper part. Spinous layer: Spectrum of changes ranging from increased spinous layer in the whole thickness up to changes in which prickle cells are seen only in the upper epithelial half. Basal/parabasal layer: Spectrum of changes, from 2–3 unchanged layers to augmentation of basal and parabasal cells in the lower half of the epithelium.
Cytomorphologic	At most minimal cellular atypia. Parabasal cells: Slightly increased cytoplasm compared to basal cells, enlarged nuclei, uniformly distributed chromatin, no intercellular bridges. Rare regular mitoses in or near basal layer. Few dyskeratotic cells present.
High grade dysplasia (encompasses moderate and severe)	
Architectural	Often associated with elongation of rete ridges with bulbous/downward extension. Abnormal maturation. Variable degree of disordered stratification and polarity; such changes vary from case to case including limited to basal zone epithelium to involvement in as much as the whole epithelium. Altered epithelial cells usually occupying from half to the entire epithelial thickness.
Cytomorphologic	Conspicuous cellular and nuclear atypia, including marked variation in size and shape, irregular nuclear contours, and marked variation in staining intensity with hyperchromasia. Increased nuclear-to-cytoplasmic ratio. Increased mitoses at or above the superbasal level, with or without atypical forms. Dyskeratotic and apoptotic cells are frequent throughout the entire epithelium.

❑

CHAPTER 4

ENDOMETRIUM

Techniques of Endometrial Sampling

1. **Abrasive cytology**
   i. Washing/lavage techniques.
   ii. Endometrial brushing procedures (Tao brus).
   iii. Hysterectomy.
2. **Direct endometrial sampling- Dilation and Curretage**
   i. Intra operative cytology- frozen section.
   ii. Hysteroscopic guided endometrial biopsy- infertility.

Table 4.1: Diagnostic approach to abnormal uterine bleeding.

Peri-pubertal and adolescence	Reproductive years	Perimenopausal	Post-menopausal
Dysfunctional uterine bleeding, especially anovulatory cycles	Dysfunctional uterine bleeding: Anovulatory cycles, irregular shedding, luteal phase defects	Dysfunctional uterine bleeding, especially anovulatory cycles	Atrophy
Pregnancy complications	Pregnancy complications	Intrinsic (organic) lesions: neoplasia, hyperplasia, polyps, endometritis	Intrinsic (organic) lesions: neoplasia, hyperplasia, polyps, endometritis
Intrinsic (organic) lesions: especially endometritis	Intrinsic (organic) lesions: neoplasia, hyperplasia, polyps, endometritis	Hormones: Hormone replacement therapy, contraceptives, treatments for hyperplasia, breast cancer, endometriosis, infertility etc	Clotting abnormalities
Clotting abnormalities	Hormones: contraceptives, treatments for hyperplasia, breast cancer, endometriosis, infertility etc	Clotting abnormalities	

Cycling Endometrium

The key clinical issues that are being addressed when a pathologist is asked to evaluate an endometrial biopsy in a reproductive age woman are whether the

patient has ovulated and if so, whether the luteal phase is progressing normally. The pathologist should approach the task of dating endometrial biopsies with the above questions in mind and attempt to assign a date as precisely as possible. To create a reproducible conceptual framework, cycling endometrium may be divided into six categories, based on morphologic features: (1) early proliferative endometrium with residual stromal breakdown (from the previous menstrual cycle); (2) 16-day endometrium; (3) early (vacuolar) secretory endometrium; (4) mid (exhausted) secretory endometrium; (5) late (predecidual) secretory endometrium; and (6) menstrual endometrium.

A prototypical setting of a 28-day cycle is assumed, with day 1 representing the first day of menses. In reality, many women have cycles that differ from the standard 28-day cycle. These differences are most often accounted for within the preovulatory interval of the cycle (proliferative phase), while the postovulatory period (secretory phase to menses) remains remarkably constant at 14 days. When selecting fragments within an endometrial biopsy to use for assigning a date, basalis and lower uterine segment endometrium must be excluded, as these portions of the endometrium do not respond to hormonal stimuli with the same morphologic reproducibility as does the functionalis, which corresponds to the upper portions of the endometrium containing surface epithelium and subjacent glands and stroma.

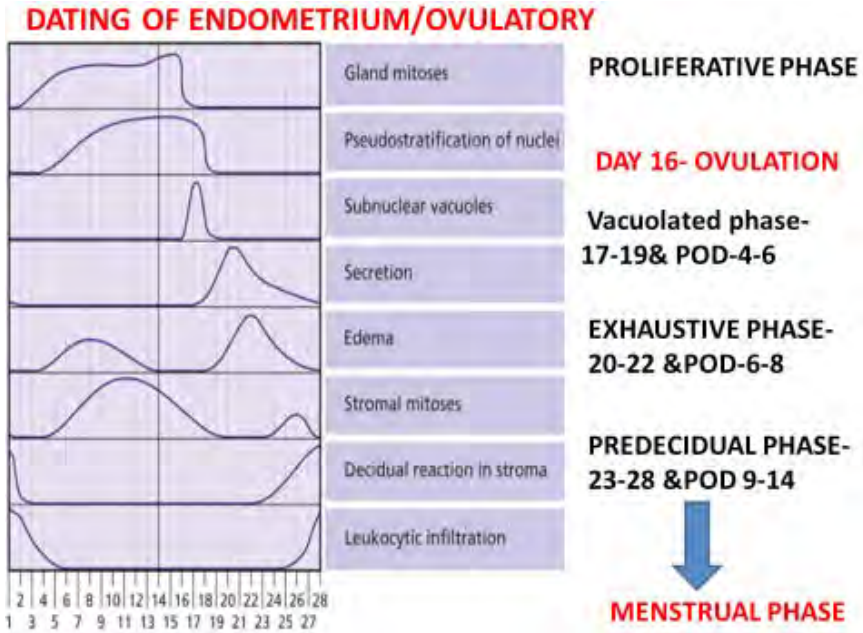


Fig. 4.1: Schematic representation of dating of endometrium.

Proliferative Endometrium

1. Round or tubular glands with pseudostratified nuclei.
2. Abundant mitoses in glands and stroma.

Day-16 Endometrium

1. Tubular glands with pseudostratified nuclei.
2. Frequent mitoses in glands and stroma.
3. Scattered basal cytoplasmic vacuoles.
4. Changes can be caused by estrogen alone and are *not* diagnostic of ovulation.

Early Secretory Endometrium

1. Day-17: Rows of subnuclear vacuoles (piano key) and scattered mitoses.
2. Day-18: Sub- and supranuclear vacuoles and apical discharge.
3. Day-19: Basal nuclei, scattered subnuclear vacuoles, and increased intraluminal secretions. *No* mitotic activity.

Mid Secretory Endometrium

1. Day-20: Rare subnuclear vacuoles and increased gland complexity; intraluminal secretions peak.
2. Day 21: Beginning of stromal edema.
3. Day 22: Maximal stromal edema with "naked" nuclei.

Late Secretory Endometrium

1. Day-23: Predecidual change limited to "cuffing" around spiral arterioles.
2. Day-24: Predecidual change extending from gland to gland, but *not* going to surface.
3. Day-25: *Thin* layer or patch of predecidual change just beneath the surface
4. Day-26: *Thick* layer of predecidual change forming a band beneath the surface.
5. Day-27: Predecidual change extending deep into functionalis.

Menstrual Endometrium

1. Collapsing haemorrhagic stroma with aggregates of necrotic predecidua.
2. Exhausted secretory glands.

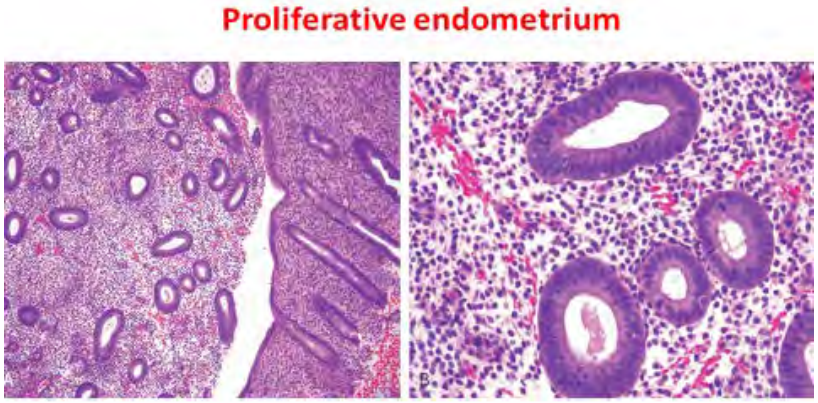


Fig. 4.2: Proliferative endometrium illustrating abundant tubular glands in a dense stroma. B, at higher power, the pseudostratified epithelium contains prominent nuclei with mitoses and stromal cells have oval nuclei and indistinct cytoplasm.

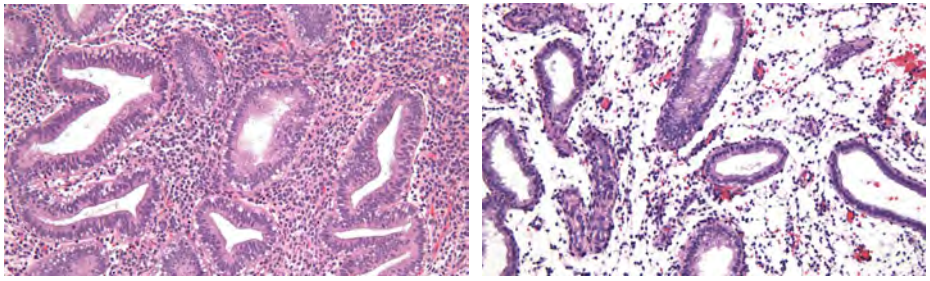


Fig. 4.3: Secretory endometrium showing stromal edema, H & E, 40X.

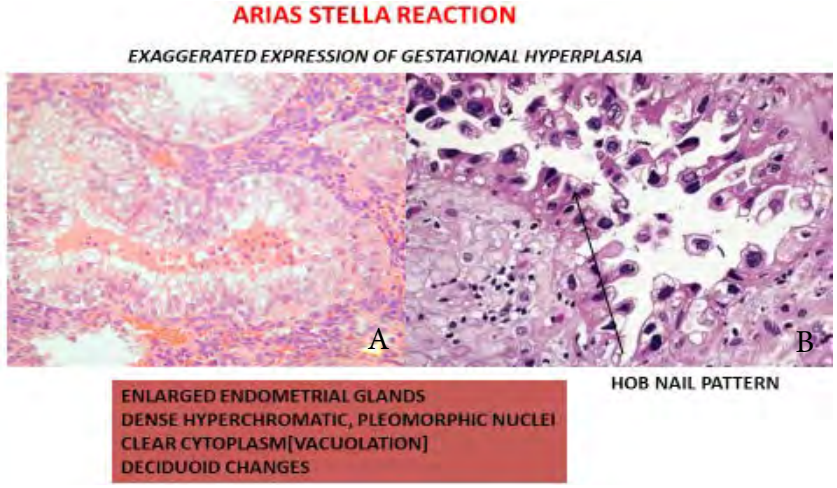


Fig. 4.4: Arias stella reaction, H & E, 40X.

ENDOMETRIAL POLYP

Polypoid proliferation of endometrial stroma and glands with irregular architecture frequently associated with thick-walled blood vessels.

Clinical Features

Endometrial polyps are relatively common, being present in up to 25% of women; however, not all polyps are symptomatic.

They more commonly occur in women ≥ 40 years of age. Less than 5% are associated with neoplasia and almost invariably occur in postmenopausal women. Of those that are symptomatic, the most common manifestation is abnormal bleeding (particularly postmenopausal or intermenstrual).

Gross Findings

1. Pedunculated, polypoid, or sessile.
2. Firm or fleshy.
3. Solid and/or cystic cut surface.

Microscopic Findings

1. Altered gland architecture with cysts and irregular gland outlines.
2. Altered stroma (often with increased fibrosis and collagen deposition).
3. Thick-walled vessels.

Differential Diagnosis

1. Low-grade müllerian adenosarcoma.
2. Atypical polypoid adenomyoma.
3. Lower uterine segment/basalis.

Adenomyomatous Polyp

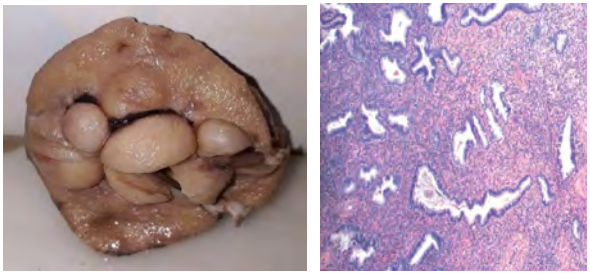


Fig. 4.5: Gross- Endometrial polyp; Scanner view of endometrial polyp with fibrocollagenous stroma.

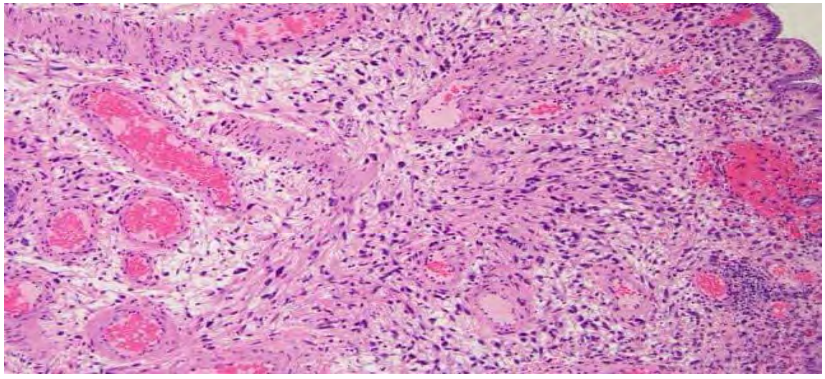


Fig. 4.6: Polyp with thick walled blood vessel, H & E, 40X.

METAPLASIA

Due to chronic and persistent irritation of endometrial mucosa. It includes:

1. Squamous;
2. Eosinophilic;
3. Clear;
4. Hobnail.

Causes includes: degenerative, malignancy etc. with each condition having distinct of metaplasia as shown in Fig. 4.7.

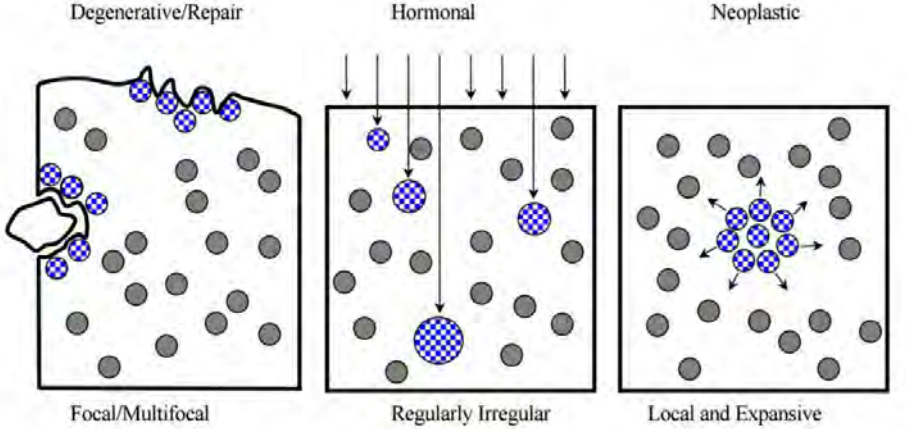


Fig. 4.7: Pattern of metaplasia in underlying etiology.

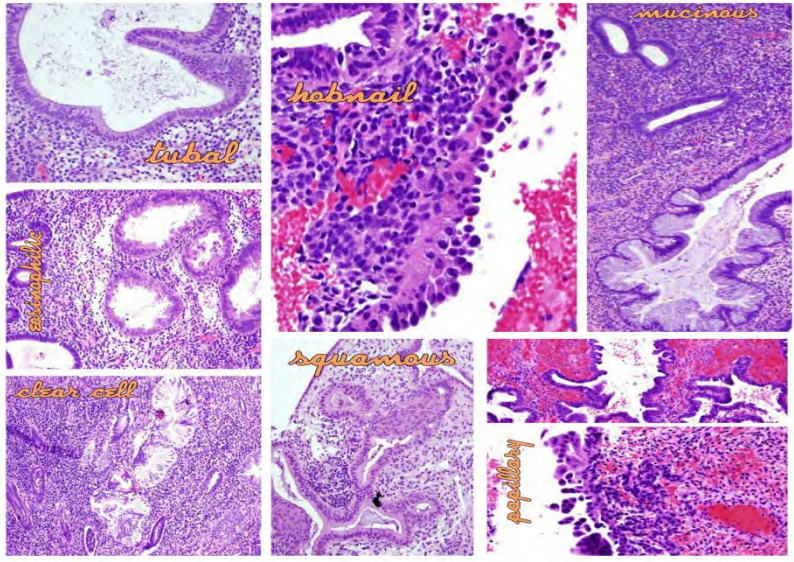


Fig. 4.8: Pattern of metaplasia in endometrium.

ENDOMETRIUM IN INFERTILITY - APPROACH

- **ANOVULATION** – DUB in perimenopausal age

CAUSES: Thyroid disorders. PCOD, granulosa cell theca tumor & metabolic disturbances

PERSISTENT FOLLICLE

↓

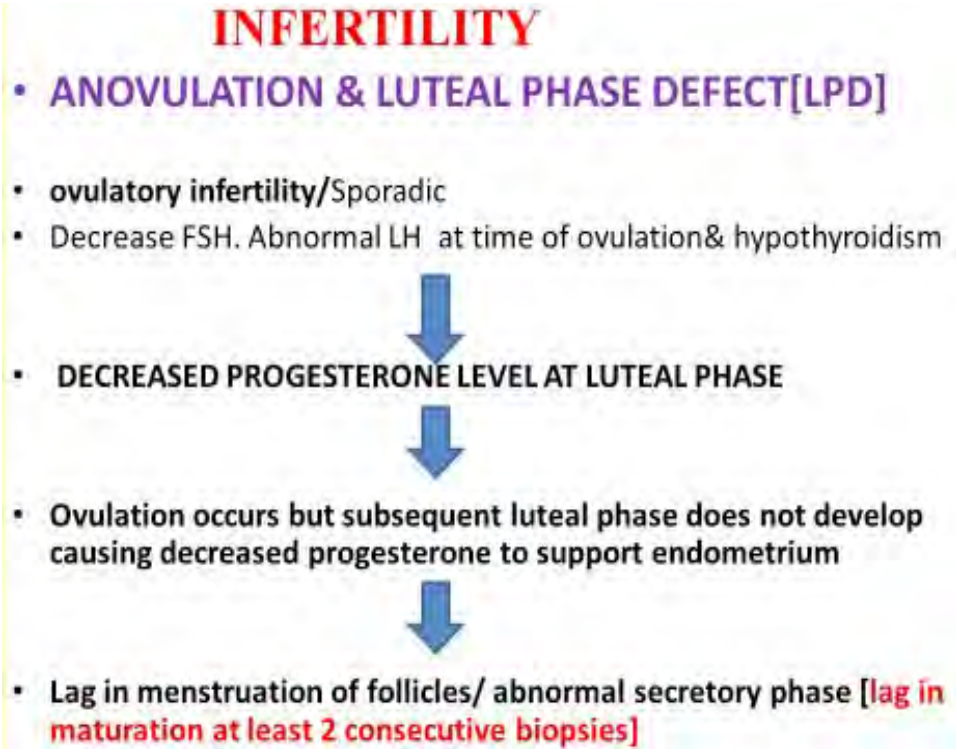
FAILURE OF OVULATION

↓

Prolonged excessive estrogen stimulation without contradictive effect of progestrone

↓

Conformational changes of endo, glands - cystic irregular dilation and stromal breakdown & fibrin thrombi



Endometrial Hyperplasia

Gross Findings

1. Irregular thickening of the endometrium.

Microscopic Findings

World Health Organization Classification

1. *Simple hyperplasia without atypia*: Increased endometrial volume with balanced proliferation of both glands and stroma with absence of cytologic atypia.
2. *Complex hyperplasia without atypia*: Increased volume of glands compared to stroma; glandular crowding with outpouching, papillary infoldings, and back-to-back arrangement.
3. *Simple and complex hyperplasia with atypia*: Architectural features of simple and complex hyperplasia associated with nuclear atypia (loss of axial polarity, large, round nuclei with nucleoli and vesicular chromatin).

Endometrial Intraepithelial Neoplasia (EIN) System.

1. *EIN*: size > 1 mm; volume percentage stroma >55%, cytologic features different from background glands.
2. *Benign hyperplasia sequence*: Generalized, non uniform proliferation of architecturally variably shaped glands +/− cysts, tubal metaplasia, and fibrin thrombi.

Differential Diagnosis

1. Variations/artifact of normal cycling endometrium.
2. Anovulatory cycles/disordered proliferative endometrium.
3. Postmenopausal cystic atrophy.
4. Endometrial polyps.
5. Metaplasias.
6. Chronic endometritis.
7. Well-differentiated endometrioid adenocarcinoma.

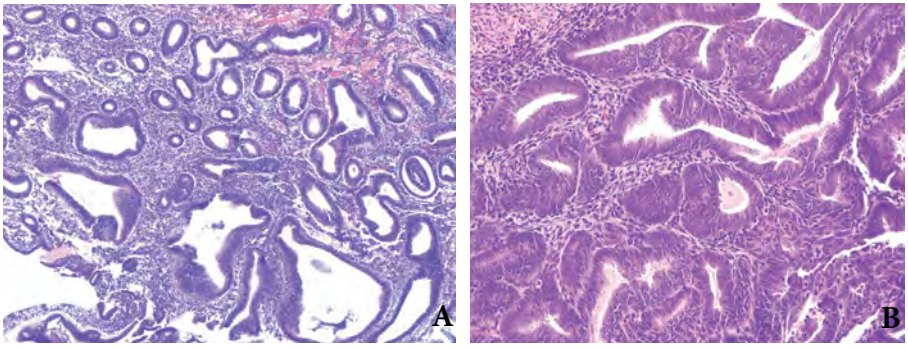


Fig. 4.9: (A) Simple hyperplasia of endometrium, H & E 10X; (B) Complex Hyperplasia, H & E 40.

Endometrial Intra-epithelial Carcinoma

Definition

1. EIC is characterized by markedly atypical nuclei lining the surfaces and glands of the endometrium.
2. The term EIC is preferred than CIS (carcinoma in situ) because EIC can be associated with metastatic potential whereas CIS implies a lesion that does not have malignant potential.

Clinical Features

1. Rare finding without invasive carcinoma; may be associated with extrauterine disease.
2. Usually cured by hysterectomy if no extrauterine involvement by careful staging.
3. May be precursor of invasive serous carcinoma.
4. Must also exclude progesterone related effects (wait 2–4 weeks after cessation of hormones), benign mimics (disordered proliferative endometrium or atrophy) and carcinoma.
5. Prediction of progression versus WHO system varies by study from more accurate to similar.
6. May better classify patients into high and low risk subgroups.
7. Serous endometrial intraepithelial carcinoma arising in adenomyosis is rare; serous EIC may be preceded by p53 signature.

Criteria for EIN Includes

1. A larger glandular area than stromal area (volume percent stroma < 55%).
2. Cytology differs between the crowded glandular focus and the background glands.
3. The premalignant area is at least 1 mm.

Microscopy

1. The surface often demonstrates a slightly papillary contour and some cells display hobnail morphology and smudged hyperchromatic nuclei.
2. The nuclei are enlarged with granular or vesicular chromatin and frequently display prominent eosinophilic nucleoli. Numerous mitotic figures including atypical ones are present.
3. On occasion, the abnormal proliferation can be seen involving only a portion of the endometrial gland.

Positive Stains

1. p53, Ki-67.

Molecular Studies

1. Molecular studies supports the concept that EIC is a precursor lesion of serous carcinoma.

2. Recent studies have demonstrated the over-expression of p53 protein, loss of heterozygosity of chromosome 17p and corresponding p53 gene mutation in EIC and serous carcinomas.
3. The finding of EIC unassociated with invasive carcinoma and presence of identical p53 mutations in both hte lesions support the view that EIC is the precursor lesion of serous carcinoma.

Differential Diagnosis

The distinction of EIC from early serous carcinoma has not been well defined. Crowded glands involved by EIC within a polyp or within the endometrium shoulld be classified as extensive EIC, when the proliferation lacks a confluent glandular pattern and demonstrates no evidence of stromal desmoplasia and is less than 1 cm in greatest dimension. When either glandular confluence or stromal invasion is present and the proliferation exceeds 1 cm in greatest dimension, the lesion qualifies as serous carcinoma. Lesions with glandular confluence and stromal invasion but measuring less than 1 cm in greatest dimension can be sub-classified as minimal uterine serous carcinoma.

EIC must be distinguished from benign metaplastic endometrial lesions that can mimic EIC which includes eosinophilic cell change, hobnail change and tubal metaplasia. All these lesions lack the prominent nucleoli as seen in EIC. Immunohistochemistry for KI-67, is very useful in distinguishing these lesions from EIC. EIC typically displays a high proliferation index.

Treatment and Behaviour

1. There are limited data on the behaviour of pure EIC.
2. A recent study found that patients with pure EIC and those with minimal serous carcinoma lacking myometrial or vascular invasion and no evidence of extra uterine disease, had an overall survival rate of 100%.
3. The majority of these patients received no treatment after hysterectomy.
4. In addition the few patients with involement of the endocervical glands by EIC were also alive without evidence of disease. In contrast, patients with minimal serous carcinoma or evidence of extra uterine disease all died of disease despite intensive chemotherapy.
5. Accordingly, patients with a diagnosis of EIC in an endometrial biopsy or curettings should undergo careful surgical staging at the time of hysterectomy.

Endometrial Cancers

The upper two-thirds of the uterus located above the internal orifice of the uterus is termed the corpus. The fallopian tubes enter at the upper lateral corners of an inverse pear-shaped body. The portion of the muscular organ that is above a line joining the tubouterine orifices is referred to as the fundus. Cancer of the corpus uteri is usually referred to as endometrial cancer, which arises from the epithelial lining of the uterine cavity. Its first local extension concerns the myometrium. Cancers arising in the stromal and muscle tissues of the myometrium are called uterine sarcomas.

Definition: Malignant epithelial tumour of the endometrium.

Incidence

1. Most common malignant tumour of the female genital tract (10–20 per 100,000 women per year in western countries).

Morbidity and Mortality

1. Endometrioid carcinoma and its variants (type I): 5-year survival rate 85–90%.
2. Nonendometrioid carcinomas (type II): 5-year survival rate between 30–70%.

Race and Age Distribution

1. Typically in perimenopausal women (type I), but it may also occur in postmenopausal patients (type II).

Clinical Features

1. Abnormal vaginal bleeding.

Prognosis and Treatment

1. Poor prognostic indicators:
    i. Histologic type (serous and clear cell carcinoma).
    ii. Histological grade.
    iii. Stage.
    iv. Depth of myometrial invasion.
    v. Lymphovascular invasion.
    vi. Serosal and adnexal involvement.
    vii. Lymph node metastases.

2. Hysterectomy with bilateral salpingo-oophorectomy treatment of choice.
3. Pelvic and para-aortic lymphadenectomy in patients with poor prognostic indicators.
4. Omentectomy in serous carcinoma.
5. Radiation therapy added according to extent of disease at surgery.
6. Progestins and/or chemotherapy may be added in advanced.

Histopathologic types (According to WHO/International Society of Gynaecological Pathology Classification)

All tumours are to be microscopically verified.

The histopathologic types of endometrial carcinomas are:

1. Endometrioid carcinoma: adenocarcinoma; adenocarcinoma-variants (with squamous differentiation; secretory variant; villoglandular variant; and ciliated cell variant).
2. Mucinous adenocarcinoma.
3. Serous adenocarcinoma.
4. Clear cell adenocarcinoma.
5. Undifferentiated carcinoma.
6. Neuroendocrine tumours.
7. Mixed carcinoma (carcinoma composed of more than one type, with at least 10% of each component).

Apart from the classification of endometrial carcinoma, carcinoma of the endometrium comprises mixed epithelial and mesenchymal tumours including:

1. Adenomyoma.
2. Atypical polypoid adenomyoma.
3. Adenofibroma.
4. Adenosarcoma.
5. Carcinosarcoma: currently carcinosarcomas, in which both epithelial and mesenchymal components are malignant and aggressive tumours, are considered metaplastic carcinomas, and are treated as aggressive carcinomas.

Endometrial cancers have traditionally been classified in one of the following two categories:

1. Types 1 (grade 1 and 2 endometrioid carcinoma) are the most common endometrial cancers. They may arise from complex atypical hyperplasia and are linked to excess of estrogen stimulation.

   As they are usually diagnosed at early stages, they present a relatively good prognosis.

2. Types 2 are the least common endometrial tumours. They include grade 3 endometrioid tumours as well as tumours of nonendometrioid histology, and develop from atrophic endometrium. Type 2 tumours are less hormone sensitive. Since they are diagnosed in later stages, they are generally more aggressive and have a poorer prognosis than Type 1 endometrial cancer.

Gross Findings

1. Friable mass or irregular thickening involving the endometrium with or without invasion of the uterine wall.

Microscopic Findings

1. Endometrioid adenocarcinoma: variable resemblance to normal endometrial glands depending on degree of differentiation.
2. Grade I: ≤ 5% solid growth.
3. Grade II: 5–50% solid growth.
4. Grade III: 50% solid growth.
5. Assessment based on solid glandular but not squamous component.
6. Endometrioid adenocarcinoma variants.
7. With squamous differentiation.
8. Villoglandular.
9. Secretory.
10. Ciliated.
11. Others.
12. Mucinous adenocarcinoma: 50% of cells with intracytoplasmic mucin.
13. Serous carcinoma: irregular, branching papillae with budding and prominent stratification of pleomorphic cells.
14. Clear cell carcinoma: cells arranged in tubulocystic, papillary, and solid patterns, frequently with clear and hobnail cells.
15. Mixed adenocarcinoma: composed of different types of carcinoma representing 10% each.

16. Squamous cell carcinoma: exclusively composed of squamous cells.
17. Transitional cell carcinoma: similar morphology to tumours of the urinary tract.
18. Small cell carcinoma: similar to small cell carcinoma of the lung.
19. Undifferentiated carcinoma: lacks any recognizable type of cell differentiation.

Differential Diagnosis

1. Atypical polypoid adenomyoma (vs endometrioid carcinoma).
2. Endocervical carcinoma (vs endometrioid carcinoma).
3. Endometrial mucinous epithelial proliferations (vs endometrioid and mucinous carcinoma).
4. Endometrioid carcinoma (vs serous carcinoma).
5. Radiation changes (vs serous carcinoma).
6. Secretory endometrioid carcinoma (vs clear cell carcinoma).
7. Arias Stella effect (vs clear cell carcinoma).
8. Malignant mixed müllerian tumour (vs poorly differentiated endometrioid EC).
9. Metastatic tumours.
10. Trophoblastic lesions (vs poorly differentiated endometrioid EC and squamous cell carcinoma).

Table 4.2: Clinico Pathological features of Type1 and 2 Endometrial ca.

	Type I	**Type II**
Age	Pre and perimenopausal	Postmenopausal
Unopposed estrogen	Present	Absent
Hyperplasia precursor	Present	Absent
Grade	Low	High
Myometri invasion	Minimal	Deep
Histologic types	Endometrioid carcinoma and variants, mucinous carcinoma.	Serous, clear cell, squamous cell, and undifferentiated carcinoma.
Behaviour	Stable	Progressive
Molecular abnormalities	Microsatellite instability, PTEN and k-RAS mutations and beta-catenin nuclear accumulation.	p53 alterations, and loss of heterozygosity (LOH) at different loci.

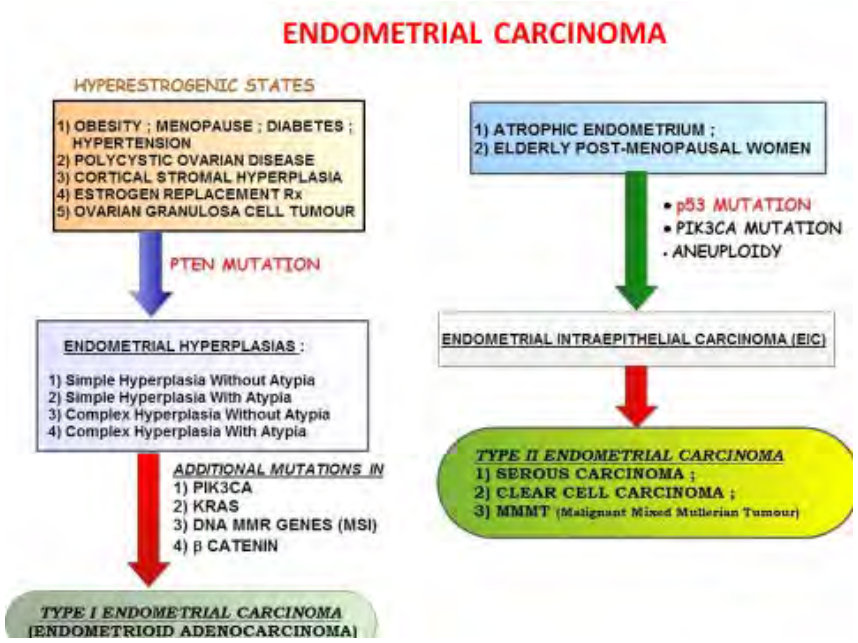


Fig. 4.10: Schematic approach to sequence etiopathogenesis of Endometrial carcinoma.

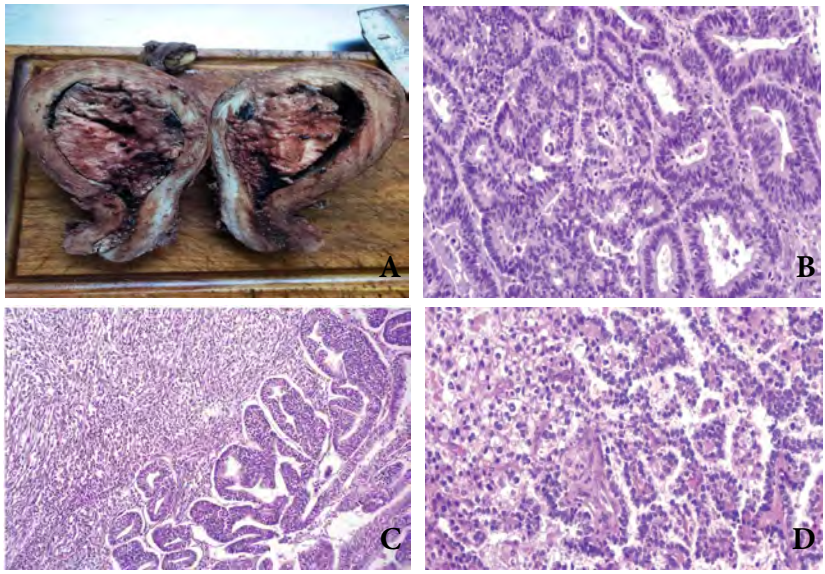


Fig. 4.11: (A) Gross image of endometrial carcinoma showing fleshy friable growth; (B) Endometrial adenocarcinoma, H & E-40X; (C) Carcinosarcoma endometrium –H & E,10X, (D) Clearcell carcinoma endometrium- H & E 10X.

ENDOMETRIAL CARCINOMA IN NUTSHELL

Endometrioid Carcinoma

Introduction

1. Endometrioid carcinoma is the most common form of endometrial carcinoma.
2. These tumours are referred to as endometrioid because they resemble prolifertion phase endometrium and to maintain the consistency to describe with the same histologic appearance in the cervix, ovary or tubes.

Epidemiology

1. Associated with estrogen replacement therapy (usually well differentiated and endometrioid with good prognosis).
2. Rare if ovarian dysgenesis or castration.
3. Rates much higher in white vs black women.

Etiology

1. Both carcinoma and hyperplasia are linked to prolonged estrogenic stimulation without progestational agents; both are also associated with estrogen secreting tumours.

Clinical Features

1. Patients with endometrioid carcinoma range in age from 2nd to 8th decade, with a mean age of 59 yrs.
2. Most women are post-menopausal as the disease is relatively uncommon in young women.
3. The initial manifestation of endometrial carcinoma usually is abnormal vaginal bleeding.

Gross

1. The endometrial surface is shaggy, glistening and tan and may be focally haemorrhagic.
2. It is almost uniformly exophytic even when deeply invasive. The neoplasm maybe focal or diffuse.
3. Sometimes, it can present as polypoidal masses.
4. Necrosis usually is not evident in well differentiated carcinomas but it is usually seen in poorly differentiated carcinomas.

5. Myometrial invasion by carcinoma results in enlargement of uterus.
6. Myometrial invasions appears as well demarcated, firm, grey white tissue with linear extensions beneath an exophytic mass or as multiple white nodules with yellow areas of necrosis.
7. Extension into the endocervical glands are common but involvement of cervix occurs only in 20% of cases.

Microscopy

1. The microscopic appearances of endometrioid carcinoma is determined by the grade of the tumour.

   Grade 1 - No more than 5% of the tumour is composed of solid masses.

   Grade 2 - 6–50% of the tumour is composed of solid masses.

   Grade 3 - More than 50% of the tumour is composed of solid masses.

Staging

Differential Diagnosis

1. Atypical hyperplasias: The stroma interacts in invasive carcinomas and the morphologic changes it undergoes can serve as a means of identifying carcinomas. There are three useful criterion which identifies stromal invasion- (i) irregular filtration of glands associated with altered fibriblastic stroma (desmoplastic reaction), (ii) confluent glandular pattern in which individual glands merges at times creating a crifriform pattern,(iii) extensive complex papillary patterns.
2. Atypical polypoid adenomyoma: Compared to APA, carcinomas show more cytologic atypias,glandular crowding and architectural complexity.
3. Aria-stellar reaction.
4. Menstruating endometrium.
5. Another problem is the distinction of endometrial and endicervical primary. The presence of associated endometrial hyperplasias favours endometrial primary and the presence of adenocarcinoma in situ in the endocervix favours the diagnosis of endocervical primary. Endometrioid carcinomas usually express oestrogen and progesterone receptors whereas endocervical adenocarcinomas are usually negative for hormone receptors by immunohistochemistry.

Prognostic Factors

Intra-uterine factors:

1. Histologic type.
2. Grade.
3. Depth of myometrial invasion.
4. Cervical involvement.
5. Vascular invasion.
6. Presence of atypical endometrial hyperplasia.
7. Hormone receptor status.
8. DNA ploidy and S phase fraction.

Extra-uterine factors:

1. Adnexal involvement.
2. Intraperitoneal metastases.
3. Positive peritoneal cytology.
4. Pelvic and para-aortic lymp node metastases.

Behaviour and Treatment

1. The standard treatment for endometrial cancer is hysterectomy with bilateral salphingo-oopherectomy.
2. The current approach is to treat all patients when feasible by hysterectomy supplemented by surgical staging and to adminster post operative radiation to patients with poor prognostic factors.
3. Post operative oestrogen therapy has been advocated to patients with early stage disease and no significant poor prognostic factors.

Uterine Papillary Serous Carcinoma

Introduction

1. Papillary serous carcinomas displays complex papillary architecture similar to ovarian serous carcinomas.
2. Type 2 (non-endometrioid) carcinoma, often arises in black, multiparous and nonobese women.
3. Associated with endometrioid adenocarcinoma, clear cell carcinoma and ovarian serous carcinoma.
4. They are highly aggressive type of the endometrial carcinomas.

Epidemiology

1. Compared to endometrioid carcinoma, UPSC is less common (10%), older age, and more common in black vs white women.
2. Associated with p53 mutations (considered an early event), usually clinically understaged.

Etiology

1. Not associated with estrogen secretion as endometrioid tumours are; may follow radiation therapy for cervical carcinoma.
2. Associated with atrophic endometria.

Clinical Features

1. More common in post-menopausal women.
2. It is less likely to occur in women who have received oestrogen replacement therapy and more likely to occur in women with abnormal cervical cytology.

Gross

1. The tumours are small and atropic.
2. They present as exophytic masses with papillary structures.

Microscopy

1. The exophytic component part of the serous carcinoma has a complex papillary architecture resembling serous carcinoma of the ovary.
2. The papillary fronds maybe short and densely fibrotic or thin and delicate.
3. The cells covering the papillae and lining the glands form small papillary tufts, many of which are detached and floats freely in spaces between the papillae and gland lumens.
4. The cells are cuboidal or hobnail shaped and contains eosinophilic cytoplasm or clear cytoplasm and they tend to be loosely cohesive.The cells show cytologic atypia with high mitosis(including atypical forms).
5. Multi-nucleated cells,giant cells, bizzare cells and psommama bodies are also seen.
6. Nests of cells in vascular spaces are commonly found.
7. The adjacent endometrium is atrophic in most of the cases.

Differential Diagnosis

1. Villoglandular carcinoma: In VGC, the papillary fronds are thin and delicate and they do not display papillary tufting.
2. Endometrioid carcinomas: Serous carcinomas demonstrates a lack of expression of oestrogen and progesterone receptors and shows a high proliferation index for KI-67 whereas endometrioid carcinomas expresses hormonal receptors and shows low proliferation index.
3. Papillary syncytial eosinophilic change: The papillary processes in eosinophilic change lacks the fibrovascular support and the cells that form these processes are small and lacks cytologic atypia or mitotic activity.

Cytology Description

1. 2/3 have malignant pap smears since buds and tufts break off.
2. Features of high-grade malignancy with readily identified malignant features, but site of origin may be unknown.
3. Positive peritoneal cytology upgrades the stage.

Positive Stains

1. p53 (useful for differentiating from endometrioid carcinoma), CK7, CA125; also p16, Ki67 (high index) and vimentin.

Negative Stains

1. ER (may be low level), PR, CEA, CK20.

Molecular Description

1. Most cases are aneuploid.
2. Mutations of TP53 represent the most well characterized alteration in > 90% of cases, but 50% have loss of p53 (TP53) function.
3. Also HER2/neu overexpression (18–61%), EGFR overexpression, PIK3CA mutations.
4. Claudin-3 and claudin-4 are highly expressed; PTEN mutations are rare.
5. 63% of cases showed loss of heterozygosity of chromosome 1p.

Behaviour and Treatment

1. Serous carcinomas has a propensity for myometrial and lymphatic invasion.

2. The hysterectomy specimens often discloses tumour in lympahatics extensively within myometrium, cervix, broad ligament, fallopian tubes and ovaries.
3. In addition, intra-epithelial carcinomas similarly involving the endometrium has been reported on the surfaces of the ovaries, peritoneum, tubes and endocervix in the absence of gross diseases in these sites.
4. The current approach is hysterectomy along with bilateral salphingo-oopherectomy and careful surgical staging including peritoneal cytology and pelvic and para-aortic nodes sampling.
5. In view of the highly aggressive behaviour of the tumour, adjuvant chemotherapy should be considered for all tumours.

Carcinosarcoma

Introduction

1. Carcinosarcoma or MMMT (Malignant Mixed Mesodermal Tumours) represent less than 1% of the endometrial neoplasms.
2. By definition, they are composed of malignant epithelial and mesenchymal components as recognised by light microscopy.

Epidemiology

1. Rare, almost always in postmenopausal women (median age 65 years), small number of women < age 40 years.
2. Constitutes half of all uterine sarcomas.

Etiology

1. Associated with chronic estrogen stimulation.
2. 30% with heterologous MMMT and 13% with homologous MMMT have history of radiation therapy (median 16 years previous, often pelvic).
3. Other predisposing factors include nulliparity, diabetes, obesity.
4. Cases of tamoxifen associated uterine MMMTs have been reported.

Clinical Features

1. Occurs mostly in post-menopausal women and the most common symptom is post-menopausal bleeding.
2. An enlarged uterus with the tumour protruding through the cervical os is commonly encountered.

3. Some tumours are associated with the history of irradiation.
4. Women with post-irradiation MMMTs are younger and tend to present with advanced stage disease.

Gross

1. MMMTs are frequently polypoidal and usually fills the entire endometrial cavity.
2. Many invades the myometrium and some are confined to polyps.
3. The protruding tip of the tumour is necrotic.
4. The tumours are soft to firm with necrosis and haemorrhage.

Microscopy

1. MMMTs are composed of intimate admixtures of histologically malignant and mesenchymal components.
2. The most common type of epithelial component is endometrioid carcinomas which is often accomponied by squamous differentiation.
3. Half the cases demonstrates the homologous type of stromal component, which is high grade endometrial stromal sarcoma or fibrosarcoma in most and occasionally leiomyosarcoma.
4. When heterologous elements present, rhabdomyosarcoma and chondrosarcoma are the most common types encountered.

Immunohistochemistry

1. MMMTs are always diffusely and strongly positive for cytokeratin and epithelial membrane antigen.

EM Description

1. Hybrid epithelial/stromal cells.

Molecular Description

1. p53 alteration occurs early before clonal expansion.
2. Loss of heterozygosity involving 17p, 17q, 11q, 15q and 21q.
3. Overexpression of c-myc.
4. Altered methylation of H19 gene.
5. Stromal and glandular cells may have same cell of origin; identical alleles are lost in epithelial and mesenchymal cells.

6. Mutations (loss of immunostaining): PTEN (39%), MLH1 (33%), MSH2 (22%), MSH6 (21%); p53 overexpression.

Differential Diagnosis

1. Teratoma: younger age, components include skin appendages, glia, thyroid; MMMT only rarely contains neuroectodermal elements.
2. Botryoid rhabdomyosarcoma: children/teens, cervical or vaginal primaries, no carcinomatous component.
3. Metastatic ovarian serous cystadenocarcinoma: papillae and psammoma bodies present; also anaplastic carcinoma; keratin may not be helpful.

Treatment

1. TAHBSO with pelvic lymphadenectomy.
2. Radiotherapy and chemotherapy (initially chemosensitive, but relapse quickly).
3. Recurs in lung and abdomen.

Prognostic factors:

Highly aggressive:

1. 5 year disease-free survival by stage is poor (stage I, 56%; stage II, 31%; stage III, 13%; stage IV, 0%) with most patients developing extrapelvic disease.
2. Cure possible only if tumour is restricted to inner half of myometrium.
3. Heterologous differentiation has no prognostic importance.

❑

CHAPTER 5

MYOMETRIUM

Pure mesenchymal tumours of the uterus consist mainly of smooth muscle and endometrial stromal tumours, leiomyomas being by far the most common. As benign smooth muscle tumours have a wide spectrum of microscopic appearances as well as unusual growth patterns, distinction from their malignant counterparts as well as from endometrial stromal tumours may become challenging in routine practice. Mixed müllerian tumours of the uterus represent the other main category of tumours with an important mesenchymal component. It encompasses a wide spectrum of tumours, with low-grade müllerianadenosarcoma, malignant mixed müllerian tumour, and adenomyoma being the best known. Malignant mixed müllerian tumours are the most common in this category, at the same time being associated with a worse prognosis.

Accurate classification of the different categories of tumours is crucial for both prognostic and therapeutic purposes and morphology remains the cornerstone in the classification of all these tumours.

LEIOMYOMA

Leiomyoma is the most common solid tumour in women and the most frequent among smooth muscle tumours, with an estimated incidence of 70% in hysterectomy specimens for noncancer related conditions. Fibroids are also a common reason for hysterectomy.

Definition

1. Benign smooth muscle tumours of the uterus with variable gross and microscopic appearances.

Incidence

1. Most common uterine neoplasm.
2. Present in 70% of hysterectomy specimens removed for noncancer related conditions.

Age Distribution

1. Present in 20–30% of women over 30 years of age and > 40% in women > 40 years of age.

Clinical Features

1. Asymptomatic in 40–60% of cases.
2. Abnormal uterine bleeding (menorrhagia or hypermenorrhoea).
3. Abdominal pain due to acute haemorrhage (apoplectic leiomyoma).
4. Infertility, frequent spontaneous abortions, and pregnancy-related.
5. Problems - Pelvic mass, rupture into peritoneal cavity, or rapid enlargement (risk of misinterpretation as leiomyosarcoma).
6. Cardiac manifestations in intravenous leiomyomatosis.
7. Rarely erythrocytosis, infection, or ascites (pseudo-Meigs' syndrome).

Radiologic Features

1. Hypoechoic or heterogeneous mass (transvaginal ultrasonography).
2. Low signal intensity on T2 and thin hyperintense rim due to compression of adjacent muscle (MRI).
3. High signal intensity on T1 in acute infarction.

Prognosis and Treatment

1. Excellent outcome for typical leiomyoma, leiomyoma variants, and most of the unusual growth patterns.
2. Pelvic or cardiac recurrences up to 15 years later in intravenous leiomyomatosis.
3. Association with benign smooth muscle nodules in lungs (benign metastasizing leiomyoma) in typical leiomyoma, leiomyoma with vascular invasion, and intravenous leiomyomatosis.
4. Myomectomy, hysterectomy, hormone therapy (gonadotropin releasing hormone agonists: GnRHa), or uterine artery embolization based on symptoms and risk factors.
5. Hysterectomy, excision of extrauterine tumour, bilateral adnexectomy, and GnRHa in intravenous leiomyomatosis.
6. 5-year recurrence rate as high as 60%.

Gross Findings

1. Intramural, submucosal, or subserosal in order of frequency.
2. Fundus most common location.
3. Often multiple; wide range of sizes.
4. Pedunculated if subserosal; torsion with secondary necrosis of its pedicle with loss of connection to the uterus (parasitic leiomyoma).
5. Sharply circumscribed and easily shells out.
6. Bulging white to slightly pink, firm and whorled cut surface.
7. Degenerative changes include ulceration, edema, cystic change, calcification, or ossification.
8. Red degeneration characteristic of pregnancy, postpartum, and oral contraceptives.

Leiomyoma Variants

1. Highly cellular leiomyoma: often tan to yellow soft cut surface.
2. Mitotically active leiomyoma: frequently soft and fleshy; may have cystic areas and visible haemorrhage.
3. Apoplectic or haemorrhagic leiomyoma: prominent stellate haemorrhage and cystic change.
4. Leiomyoma with hydropic change including diffuse perinodular: multinodular growth present within the main mass with edematous tissue separating nodules; watery fluid on sectioning.
5. Epithelioid leiomyoma: frequently soft and tan to pink cut surface; if ≤ 1 cm: "plexiform tumourlet".
6. Myxoid leiomyoma: soft, gray, jelly-like cut surface.
7. Lipoleiomyoma: soft yellow areas admixed with firm white areas.

Unusual Growth Patterns

1. Dissecting leiomyoma including cotyledonoid leiomyoma ("Sternberg tumour"): irregular indistinct margins dissecting the myometrium with associated extrauterine exophytic extension as multiple bulbous red nodules attached to each other by thin adhesions resembling placental tissue.
2. Diffuse leiomyomatosis: diffuse and symmetrical thickening of the myometrium due to innumerable poorly circumscribed nodules typically < 1 cm.

3. Diffuse leiomyomatosis peritonealis: multiple small (typically <2 cm) nodules with a white firm cut surface present in pelvic peritoneum and omentum.
4. Intravenous leiomyomatosis: multiple well-demarcated masses and sometimes visible coiled worm-like plugs of white tissue filling and distending myometrial and/or parametrial vessels outside the confines of or in the absence of a leiomyoma.
5. Benign metastasizing leiomyoma: small white and firm nodule(s) in lungs (more frequent), retroperitoneal and mediastinal lymph nodes, soft tissues, and bone (less frequent).

Microscopic Findings

1. Well circumscribed.
2. Intersecting fascicles of spindled cells intermixed with variable amounts of collagen.
3. Abundant large blood vessels (when very numerous, vascular leiomyoma or angiomyoma).
4. Abundant eosinophilic cytoplasm (when transversely cut, paranuclear vacuole) and elongated "cigar"-shaped nuclei.
5. Nuclear palisading may be seen.
6. Mild to absent cytologic atypia and mitoses.
7. Infarct-type necrosis: "mummified" and homogeneous appearance, area of transition between necrotic and viable tumour composed of granulation tissue or fibrous or hyalinized tissue.
8. Other findings: skeletal-like or rhabdoid cells, extramedullary hematopoiesis, collections of lymphocytes, mast cells, eosinophils, numerous histiocytes, acute infl ammatory cells (pyomyoma).

Leiomyoma Variants

Cellular Leiomyoma

1. Significantly more cellular than normal myometrium.

Highly Cellular Leiomyoma

1. Fascicles and sheets of cells with cellularity similar to that seen in endometrial stromal tumours.
2. Small cells with oval to spindle nuclei and scant cytoplasm.

3. Large and thick blood vessels as well as cleft-like spaces.
4. Imperceptibly merges with surrounding myometrium Leiomyoma with Bizarre Nuclei ("Symplastic," "Atypical," or "Bizarre").
5. Multinucleated or mononucleated cells.
6. "Spotty" distribution of cells with bizarre nuclei, although on occasion uniformly throughout the tumour.
7. Atypical nuclei and abundant eosinophilic cytoplasm.
8. Prominent nucleoli, coarse chromatin, and average mitotic count of 1–2/10 HPFs; but may reach 7/10 HPFs by highest count.
9. Other nuclear features: pseudoinclusions, pyknotic nuclei with dense smudged chromatin (may simulate abnormal mitoses).
10. Uniform and bland cytologic features of spindled cells in areas uninvolved by bizarre cells.

Mitotically Active Leiomyoma

1. Spindled cells with bland nuclear features.
2. Increased mitotic activity (5–15/HPFs).
3. No tumour cell necrosis.
4. Frequent haemorrhage or degenerative changes.

Leiomyoma with Hormone-Related Changes
("Apoplectic Leiomyoma" or "Hemorrhagic Cellular Leiomyoma")

1. Stellate hemorrhagic areas.
2. Edema and/or myxoid change around haemorrhage.
3. Hypercellularity surrounding hemorrhagic areas.
4. Mild to moderate nuclear atypia and up to 9 mitoses/10 HPFs.
5. Decreased cellularity and mitoses away from haemorrhage (zonation phenomenon) and no nuclear atypia.
6. Abnormal arteries with intimal thickening, fibrosis, and myxoid degeneration.

Treated Leiomyomas with

1. Gonadotropin-releasing hormone agonists.
2. Reduced tumour size.
3. Increased hyalinization.

4. Smaller cell size, nuclear crowding, and increased apoptosis.
5. Infarct-type necrosis and lymphocytic infiltrate.
6. Vascular changes with fewer vessels, decreased vessel diameter, thickening and fibrosis, myxoid and fibrinoid changes, luminal narrowing, and thrombosis.
7. Uterine artery embolization.
8. Infarct-type necrosis.
9. Aggregates of embolized material in necrotic leiomyomas and myometrium.
10. Foreign body-type giant cells and macrophages.

Leiomyoma with Diffuse Perinodular Hydropic Change

1. Poorly defined areas of edematous connective tissue alternating with conventional areas of smooth muscle neoplasia.
2. Perinodular appearance or extensive effacement of architecture if prominent.
3. Occasional fibroblasts, sparse collagen fibers and vessels.

Epithelioid Leiomyoma

1. At least 50% of the tumour cells are epithelioid.
2. Sheets, nests, cords, and trabeculae.
3. Polygonal or round cells.
4. Eosinophilic, granular, or clear cytoplasm.
5. Mild cytologic atypia, < 3 mitoses/10 HPFs.
6. No tumour cell necrosis.

Myxoid Leiomyoma

1. Hypocellular with abundant acellular myxoid matrix (positive for alcian blue or colloidal iron).
2. May coexist with areas of conventional leiomyoma.
3. Oval to elongated or stellate cells.
4. Bland cytology with < 2 mitoses/10 HPFs.
5. No tumour cell necrosis.

Leiomyoma with Heterologous Elements

1. Adipose tissue: "lipoleiomyoma".
2. Skeletal muscle.
3. Osseous or cartilaginous differentiation.

Leiomyomas with Unusual Growth Patterns

1. Dissecting Leiomyoma Including Cotyledonoid Leiomyoma ("Sternberg Tumour").
2. Fascicles of disorganized smooth muscle with a swirled growth.
3. Marked vascularity and extensive hydropic degeneration.
4. Large number of large muscular vessels in delicate fibrous matrix separating smooth muscle nodules.

Diffuse Leiomyomatosis

1. Multiple closely packed small nodules that tend to merge imperceptibly with each other.
2. Variable cellularity, but frequently cellular.
3. Perivascular arrangement of spindled cells.
4. Mature, mitotically inactive smooth-muscle cells.
5. Diffuse Leiomyomatosis Peritonealis.
6. Multiple small to 10 cm (majority < 2 cm) nodules.
7. Spindled cells with minimal cytologic atypia and mitoses.
8. Decidual cells frequently admixed with smooth muscle cells.
9. Rarely, malignant transformation.
10. Leiomyoma with vascular invasion.
11. Microscopic intravascular growth of benign-appearing smooth muscle cells within the tumour.

Intravenous Leiomyomatosis

1. Endothelium covered protrusions of smooth muscle.
2. Intersecting fascicles or appearance of a leiomyoma variant.
3. Clefted or lobulated contour, extensive hyalinization or hydropic change, and numerous thick-walled vessels.

4. Benign cytologic features and rare mitoses, except in cellular intravenous leiomyomatosis (up to 4/10 HPFs).
5. Occasionally subendothelial proliferation of benign smooth muscle.

Benign Metastasizing Leiomyoma

1. Fascicles of smooth muscle cells.
2. Cells with no cytologic atypia or mitotic activity.
3. In the lung, alveolar spaces may be entrapped at the periphery.

Immunohistochemical Features

1. Actin, desmin, smooth-muscle myosin, HDCA8, h-caldesmon and oxytocin positive.
2. ER and PR positive.
3. Keratin and EMA frequently positive.
4. Variable CD10 expression (more commonly in highly cellular leiomyoma).
5. Androgen receptor positive in 30% of cases.
6. Low MIB-1 expression, except in mitotically active leiomyoma.
7. Minimal p53 expression.

Cytogenetic Features

1. Simple karyotypic abnormalities in 40% of typical leiomyomas.
2. t(12;14)(q15;q24).

Differential Diagnosis

1. Endometrial stromal tumour (vs highly cellular leiomyoma and intravenous leiomyomatosis).
2. Spinded leiomyosarcoma (vs mitotically active leiomyoma and leiomyoma with bizarre nuclei).
3. Myxoid leiomyosarcoma (vs hydropic leiomyoma and myxoid leiomyoma).
4. Epithelioid leiomyosarcoma (vs epithelioid leiomyoma).
5. Perivascular epithelioid cell tumour (vs epithelioid leiomyoma).
6. Lymphangiomyomatosis (vs diffuse leiomyomatosis).
7. Metastatic leiomyosarcoma (vs benign metastasizing leiomyoma).

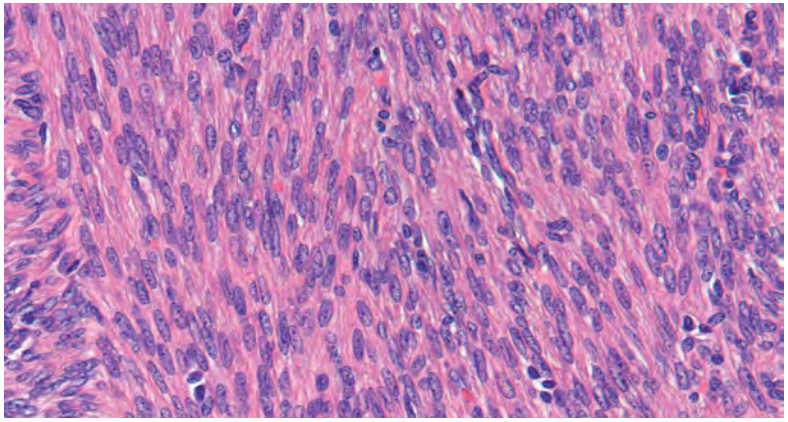


Fig. 5.1: Typical leiomyoma. Long fascicles of spindle-shaped cells with elongated "cigar-shaped" nuclei, eosinophilic cytoplasm, and no cytologic atypia, H & E 40X.

LEIOMYOSARCOMA

1. It is a malignant neoplasm of smooth muscle.
2. Age - It usually occurs in the elderly-median age 54 yrs.
3. Site - uterus,soft tissues.
4. Gross - large, wellcircumscribed, soft or fleshy with areas of haemorrhage and necrosis.
5. Microscopy - hypercellular with nuclear atypia and pleomorphism,with areas of necrosis.
6. IHC - positive for vimentin, SMA, desmin, calponin, h-caldesmon, low molecular weight keratin and EMA.
7. Cyto genetics - break point clusters in 1q32 and 10q22.
8. D.D - leiomyoma.

Variants

1. Epithelioid (clear cell) leiomyosarcoma.
2. Myxoid leiomyosarcoma.
    i. Leiomyosarcoma with osteoclast like giant cells.
    ii. Intravenous leiomyosarcomatosis.
    iii. Leiomyosarcoma with skeletal muscle differentiation.

Treatment

Total abdominal hysterectomy with bilateral salpingo-opherectomy.

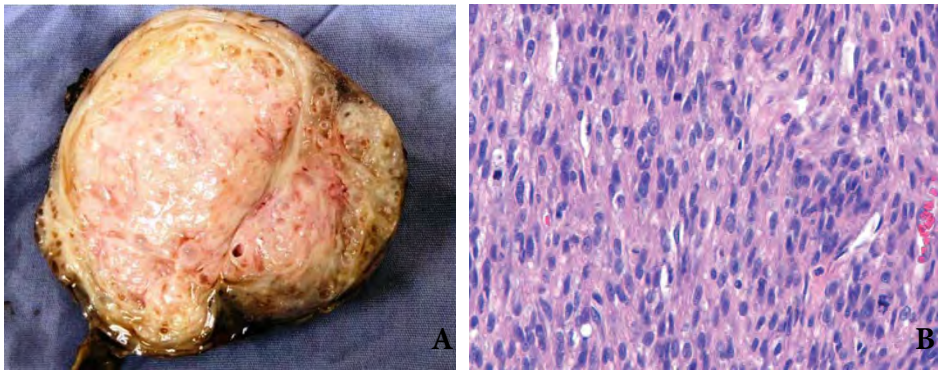
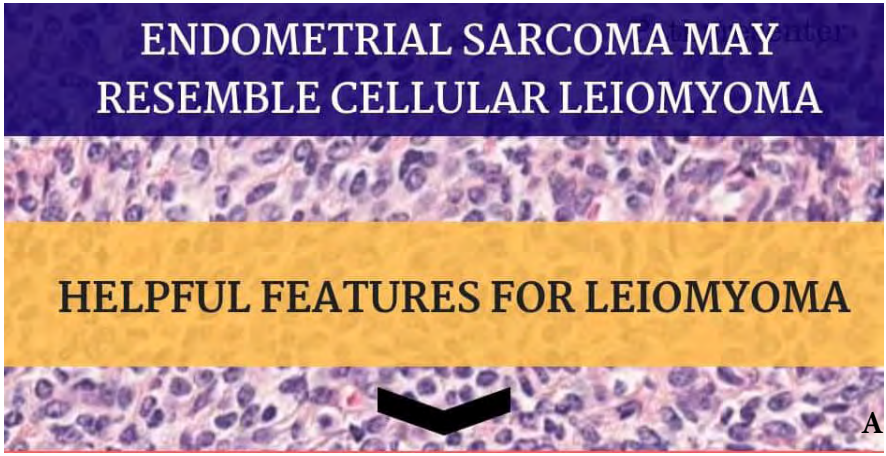


Fig. 5.2: (A) Gross image of leiomyosarcoma showing fleshy mass with necrosis and haemorrhage; (B) Histology of leiomyosarcoma, H & E, 40X.

Points to Ponder in Stromal Tumours



1. Coexistence of hypercellular area with typical fascicular area of smooth muscle tumours.
2. Reticulin fibers that tend to parallel the fascicles of cells (not individual cell as in ES).
3. Lager calibre blood vessels with thick muscle walls.
4. Strong and multifocal or diffuse positivity for SM market (desm, h-caldesmon).

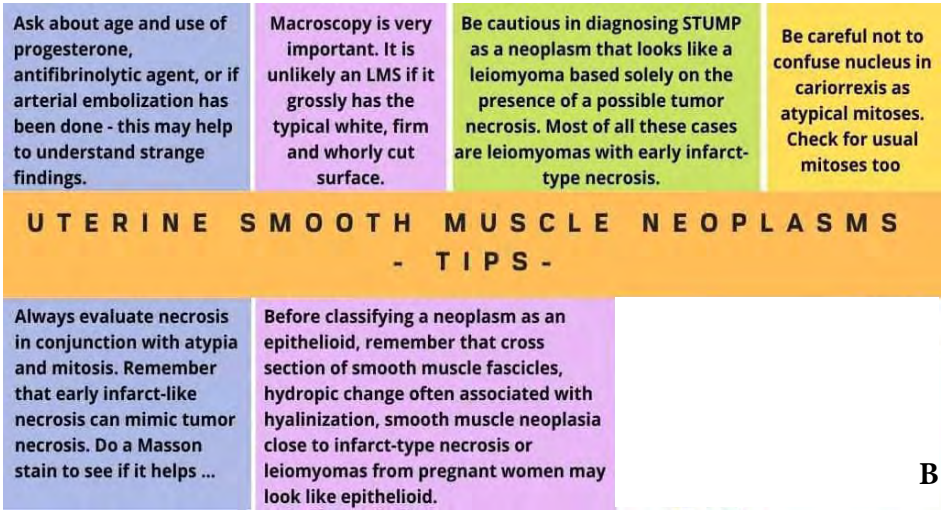


Fig. 5.3: (A) Histological points to be noted in reporting leiomyoma; (B) Schematic depiction in pointsb to be noted while reporting myometrial sarcomas.

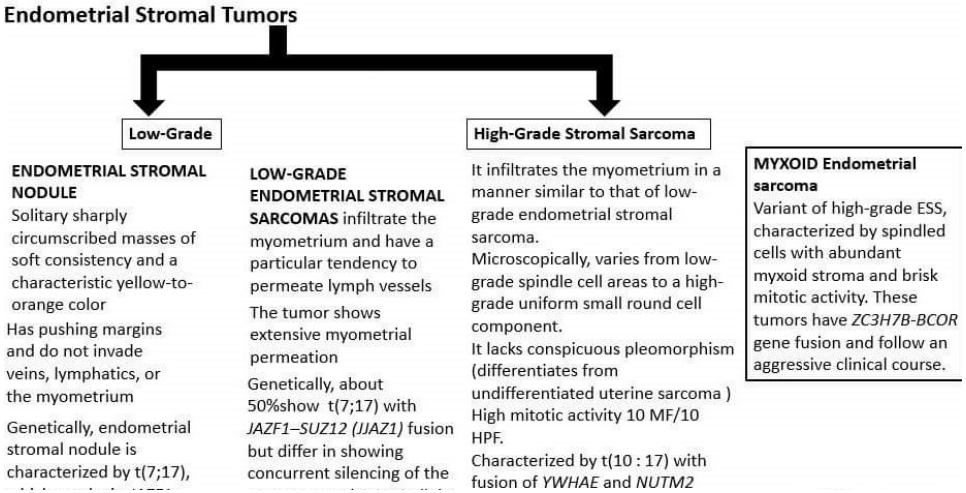


Fig. 5.4: Histological classification of endometrial stromal.

❑

CHAPTER 6

OVARY

Nonneoplastic lesions of the ovary may be entirely asymptomatic incidental findings identified on gross or microscopic examination of the ovary, or they may be associated with a pelvic mass, pain, or manifestations of abnormal hormonal regulation. Many occur during the reproductive years and may be associated with infertility.

Cysts of Follicular Origin

Definition

1. Physiologic (functional) follicle cyst or corpus luteum cyst measuring > 3 cm in diameter.

Incidence and Location

1. Common, especially during prepubertal and reproductive years.

Morbidity and Mortality

1. Often self-limited condition, but may cause acute abdominal pain secondary to rupture and hemoperitoneum, or torsion.
2. Persistence requires intervention in order to exclude a borderline or malignant surface epithelial tumour.

Age Distribution

1. Prepubertal and reproductive-age women.

Clinical Features

1. Menstrual irregularities, occasionally amenorrhoea.
2. Precocious pseudopuberty in prepubertal patients.
3. Sudden onset of abdominal pain if cyst ruptures with consequent hemoperitoneum.

Radiologic Features

1. Unilocular cyst > 3 cm.

Prognosis and Treatment

1. Benign.
2. Most solitary cysts resolve spontaneously.
3. Cystectomy if persistence or rupture.

Polycystic Ovarian Disease

Definition

1. Clinicopathologic syndrome characterized by anovulation, menstrual dysfunction, hyperandrogenism, and enlarged polycystic ovaries (Stein–Leventhal syndrome). Heterogeneous etiology, more commonly insulin resistance of peripheral tissue and/or an abnormality of the hypothalamic–pituitary–ovarian axis.

Incidence and Location

1. Very common, affecting up to 10% of reproductive-age women.
2. Increased incidence among first-degree relatives suggesting autosomal-dominant mode of inheritance in some cases.

Morbidity and Mortality

1. Infertility, insulin resistance (when present), and sequelae of increased peripheral conversion of androgenic to estrogenic compounds (e.g., endometrial hyperplasia, well-differentiated endometrial adenocarcinoma).

Age Distribution

1. Age of onset typically perimenarchal.

Clinical Features

1. Anovulation, infertility, menstrual disturbances.
2. Obesity.
3. Hirsutism, acne, male-pattern baldness (some patients).

Radiologic Features

1. Enlarged, multicystic ovaries with cystic follicles lining up at the periphery of the ovaries on ultrasound.

Prognosis and Treatment

1. Ovulation induction, weight loss, hormonal therapy (oral contraceptives or progestins), treatment of underlying insulin resistance, medical treatment for hirsutism.

The following figure shows Ovarian tumours in nutshell.

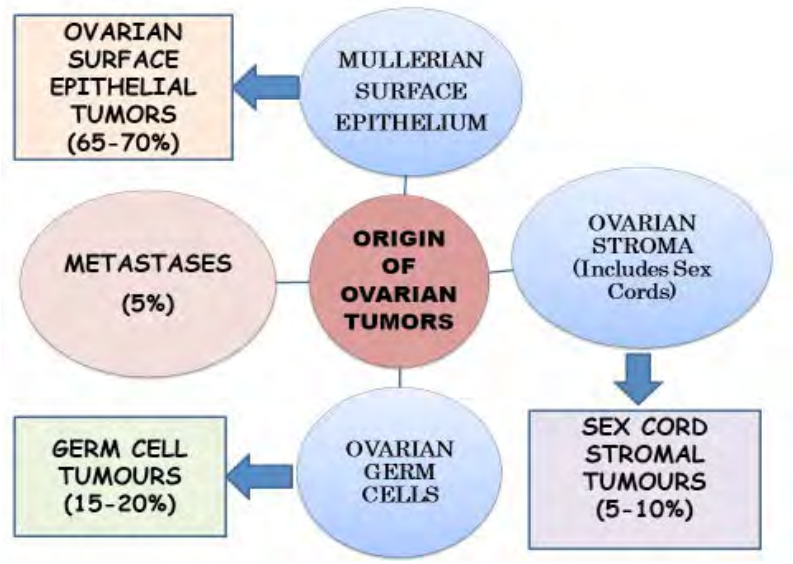
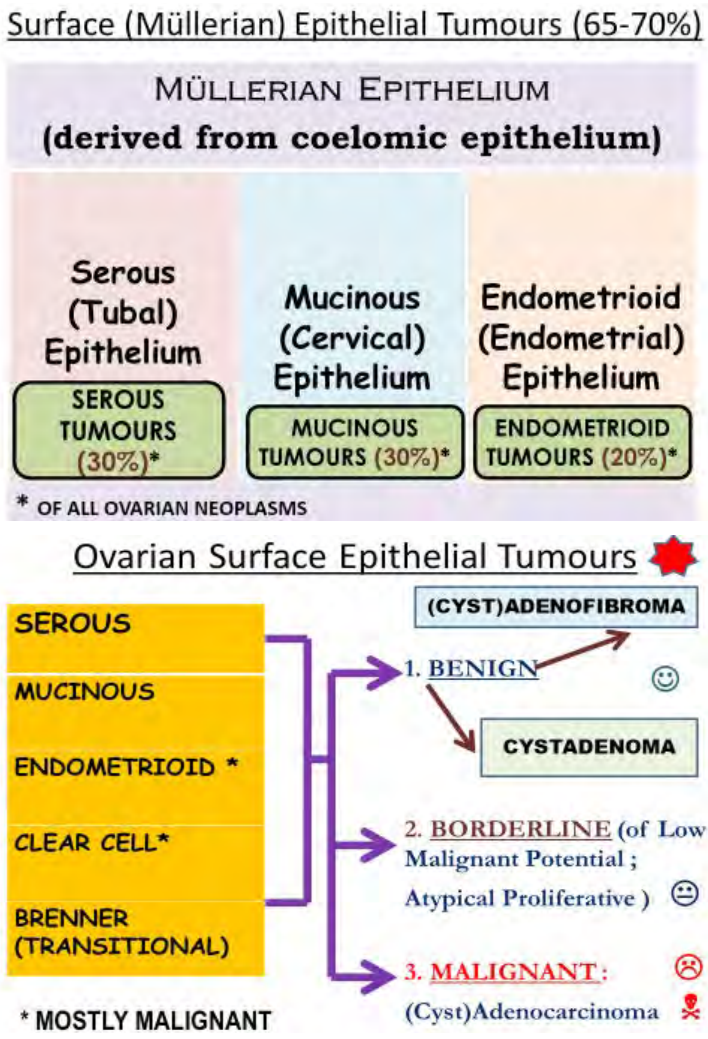


Fig. 6.1: Approach to ovarian tumours.

Table 6.1: WHO classification of ovarian tumours (simplified).

Surface epithelial tumours	Germ gell tumours	Sex cord stromal tumours
Serous	Teratomas (mature; immature; monodermal)	Granulosa cell tumour
Mucinous	Dysgerminoma	Thecoma
Endometrioid	Embyronal carcinoma	Fibrothecoma
Clear cell	Endodermal sinus tumour	Fibroma
Brenner	Primary choriocarcinoma	Sertoli-leydig cell tumour
Undifferentiated	Polyembryoma	Leydig cell tumour (hilar; nonhilar)
	Gonadoblastoma	



Ovarian Serous Tumours: Overview

1. 30% of all ovarian tumours.
2. 50% of surface epithelial tumours.
3. Benign + borderline cases approx. 70%.
4. 30% malignant (Accounts for 40% of all cases of Ca ovary).
5. 20–45 years age (serous ca inelderly age groups).
6. Risk factors: Nulliparity (OCP; tubectomy protective, pprotective)
7. Familial cases (BRCA1; BRCA2 mutations) → High Grade Ca (de novo).

8. KRAS; BRAF mutations → Low grade Ca (often with an assoc. borderline serous component).

Table 6.2: Gross features of serous ovarian tumours.

Benign serous tumours	Borderline serous	Malignant: serous ca
58% of cases (commonest serous tumour) 20% cases bilateral Smooth walled cyst; serous clear fluid (cystadenoma) Cystadenoma + solid fibrous areas (cystadenofibroma) Hard white, solid fibrous + spongy, fluid filled cut surface (adenofibroma)	10% of ovarian serous neoplasms 30% cases B/L Exuberant. Friable, papillary projections from cyst wall Endophytic > exophytic papillae: exophytic surface papillae in 70% Solid tumour component not well appreciable	30% of ovarian serous neoplasms (2nd commonest serous tumour) 66% cases B/L Solid + papillary tumour mass in cyst wall Irregularity within tumour mass; variegation(haemorrhage; necrosis etc) Ovarian capsular fixation; nodularity: capsular invasion

Table 6.3: Histopathological features of serous tumours.

Benign vs Borderline vs Malignant Serous Tumour: Microscopy		
Benign serous tumours	**Borderline serous**	**Malignant: serous Ca**
Cysts lined by single layer of bland cuboidal- flattened cell (± Cilla) Uniform basal nuclei; true stratification rare Fibrous stromal proliferation ± (as in adenofibroma; cystadenofiboma	Extensive epithelial stratification → architecturally complex papillae (with tufting; budding) Mild nuclear atypia Stromal micronivasion (ie.≤ 3 mm/ < 10 mm^2 max. focus of invasion) may occur However, destructive stromal invasion (and stromal desmoplasia) not seen	Complex papillae; confluent gland and solid (non glandular) architecture Micropapillary pattern ± Variable nuclear atypia (+++ in high grade) Destructive stromal invasion; stromal desmoplasia +ve Capsular invasion

Table 6.4: Clinical behaviour of serous tumours.

Benign vs Borderline vs Malignant Serous Tumour: Clinical Behaviour			
Benign serous tumours		**Borderline serous**	**Malignant: Serous Ca**
Associated peritoneal Lesions	None	May exhibit: Endosalpingiosis (benign glandular inclusions). Peritoneal implants (usually noninvasive peritoneal implants: 31% cases).	Invasive peritoneal implants (esp. in high grade serous Ca)
5-Yr survival rates	-	If confined to ovary : 100% With peritoneal involvement: 40%	If confined to ovary: 100% With peritoneal involvement: 90%

Mucinous Ovarian Tumours: Overview

1. 30% of all ovarian neoplasms; mid adult life; assoc. with H/O smoking; KRAS mutation ±.
2. Mostly U/L (≈ 5% of mucinous ca B/L).
3. Usually stage I at Dx (peritoneal involvement uncommon).
4. Surface involvement rare.
5. May be hormonally active (stromal luterinization in pregnancy → virilization; carcinoid syndrome).
6. May be assoc. with coexistent dermoid cyst; pseudomyxoma peritone II.
7. Mostly benign (75%) or borderline (20%); 5% malignant.

Table 6.5: Gross classification of mucinous tumour.

Benign vs Borderline vs Malignant Ovarian Mucinous Tumours		
Benigh mucinous (Cystandenma)	**Borderline mucinous**	**Primary ovarian mucinous carcinoma**
75% cases; 3rd, 5th decade	20% cases; 5th–6th decade	5% cases; 4th–7th decade

Large; Multiloculated cysts (oftern > 10 cm). Smooth external surface; inner cyst wall. Thick; viscid; mucoid secretions. No papillary excrescences/solid areas in cyst wall.	Grossly often identical to mucioun cystademna. Cyst wall thickening; papillary excrescences ±.	In addition, reveals Solid areas in cyst wall (intracystic nodules); papillary excrescences. Haemorrhage; necrosis ±.

Table 6.6: Histological features of mucinous tumours.

Benign mucinous (cystadenoma)	**Borderline mucinous**	**Primary ovarian mucinous carciona**
Single layer of lining tall columnar cells (intestinal type > endocervial type). Complex papillae rare. Assoc, fibroclollagenous stroma in mucinous cystadenofibroma. No e/o destructive stromal invasion or desmoplasia.	Epithelial cell stratification (at least 3 cell layer); complex papillage; back to back glands. Mild to moderate nuclear atypia. Stromal micronivasion ± (no invasive focus ≥ 3 mm in diameter). Destructive stromal invasion; desmoplasia absent (as in benign mucinous).	Confluent back to back crowded glands (cribriform pattern). Marked cytologic atypia; Mt activity ±(esp. in PD forms). Unequivocal stromal invasion (more than 5 mm); desmoplasia.

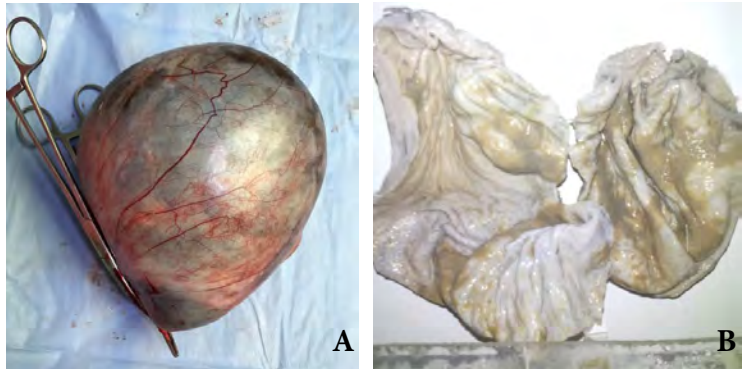


Fig. 6.2: Gross image of serous tumour: (A) External surface smooth and glistening; (B) Cut surface- smooth and grey white.

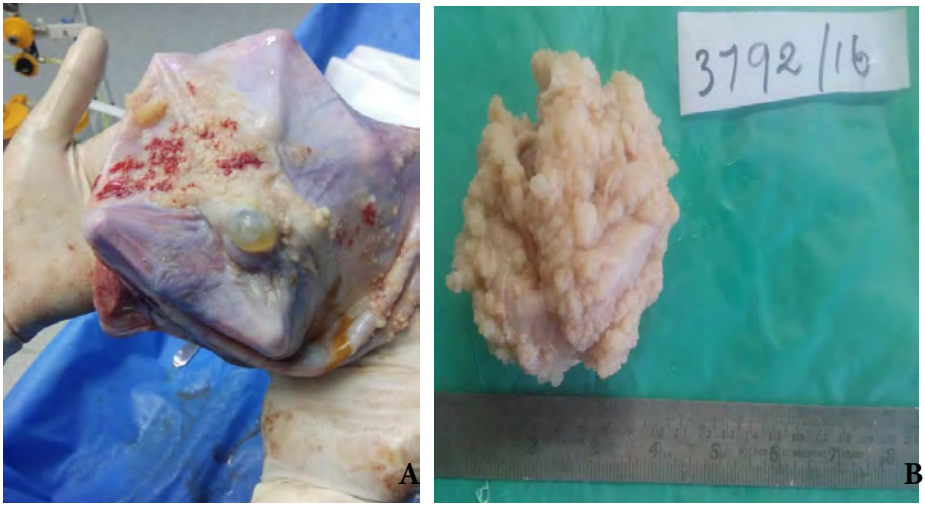


Fig. 6.3: Borderline tumour ovary: (A) Cut section showing solid papillary areas; (B) Papillary excrescences.

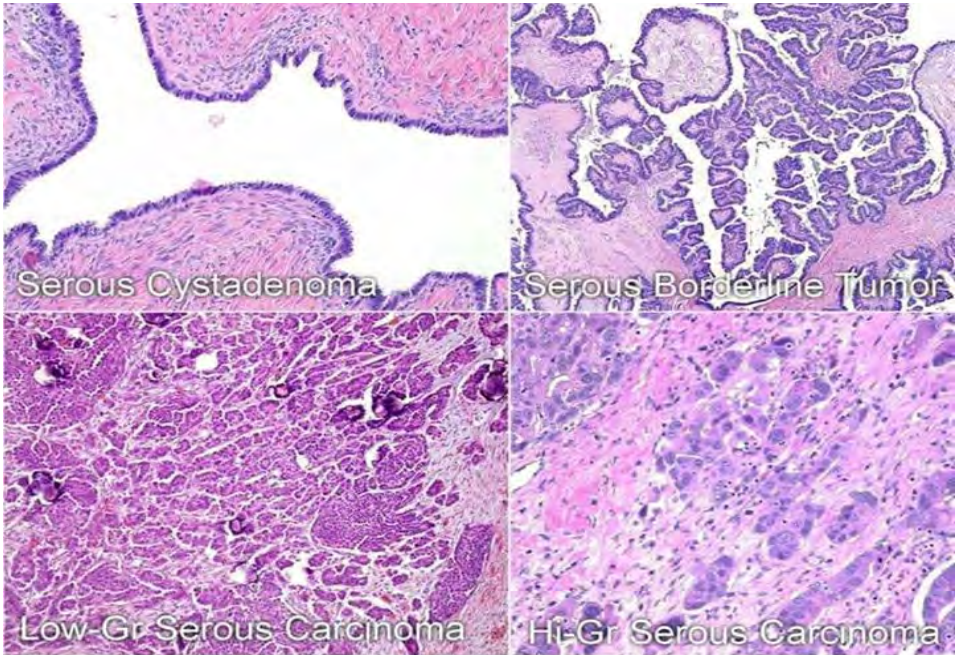


Fig. 6.4: Histological patterns of serous tumours.

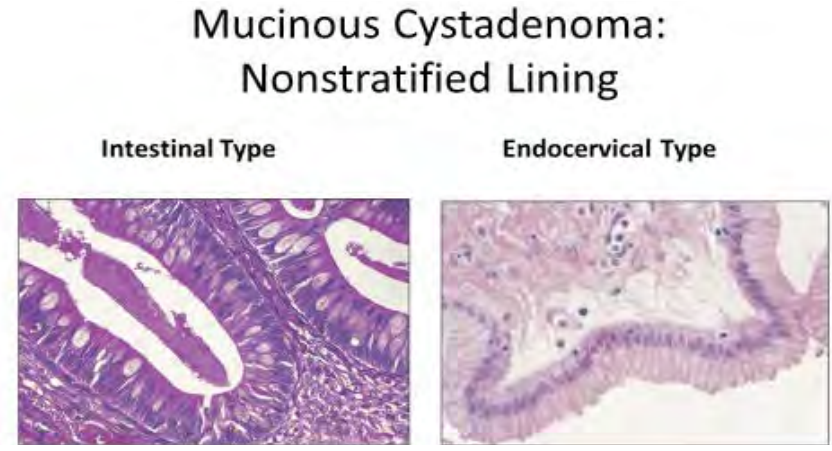


Fig. 6.5: Histological pattern of borderline mucinous tumours, H & E, 40X.

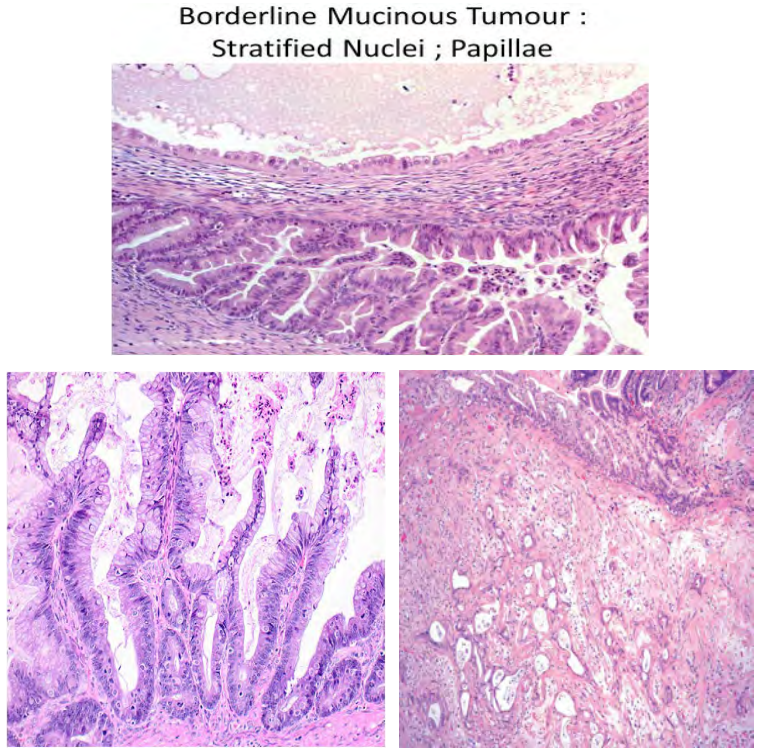


Fig. 6.6: Histological features of borderline mucinous tumour.

Table 6.7: Criteria for differential diagnosis of mucinous tumours.

Histological type	Location of mucin	Growth pattern
Mucinous Carcinoma	Extracellular	Clusters of cells in mucin lakes
Mucinous cystadenocarcinoma	Intra and Extracellular	Large cysts, columnar cells, epithelial stratification,palillae, serous areas
Columnar mucinous carcinoma	Intracellular	Round and convoluted glands lined by columnar cells

Table 6.8: Classification of mucinous tumour based on type of mucin.

Mucinous Carcinoma	Mucinous Cystadenocarcinoma	Signet Ring Cell Carcinoma
Extracellular mucin floating cell groups in pools of mucin low grade nuclei.	Intracellular and extracellular mucin papillary architecture endocervical type epithelium with pseudostratified basally oriented nuclei with little or no atypia.	Intracellular mucin displacing nucleus to periphery of cytoplasm do not form cystic spaces can have abandoned extracellular mucin.

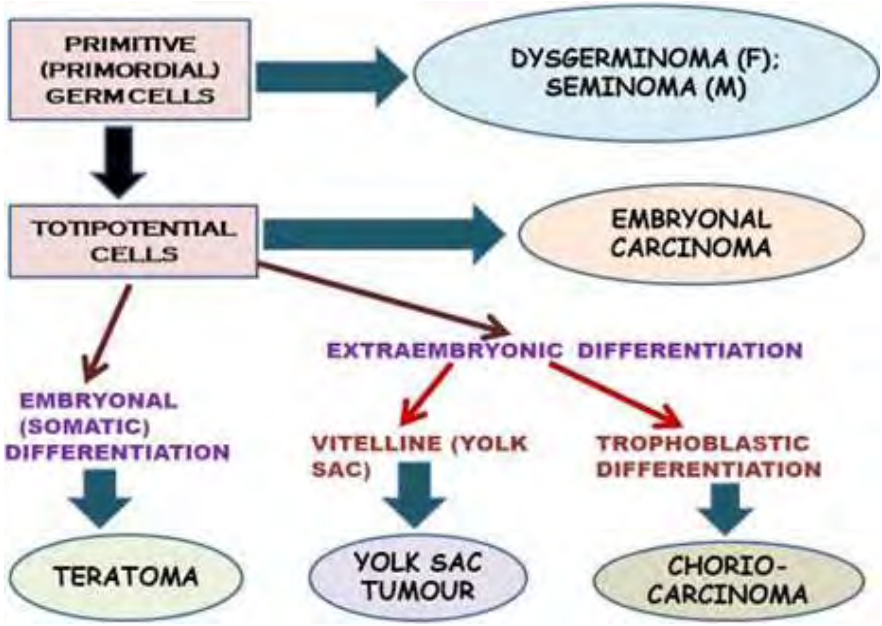


Fig. 6.7: Schematic representation of germ cell tumour of ovary.

Endometrioid Adeno Carcinoma

Gross Findings

1. Smooth outer surface.
2. C/S solid-cystic (with mural solid nodule).
3. Coexistent endometriotic cyst of ovary (chocolate cyst) ±.

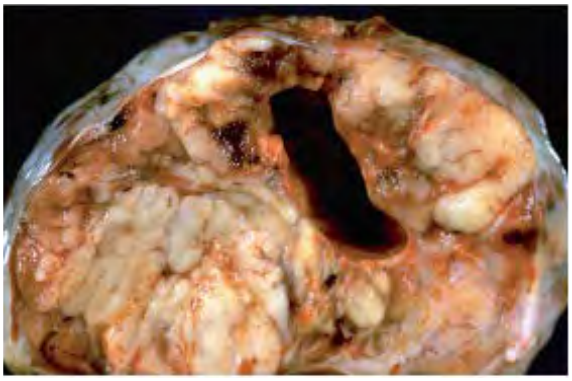


Fig. 6.8

Microscopy

1. Tubules; cribriform/confluent glands; (resembling endometrial glands).
2. Stromal desmoplasia; destructive stromal invasion.
3. Figo grade 1 (WD) to grade 3 (PD) depending upon % of non-glandular; non-squamoid solid component.

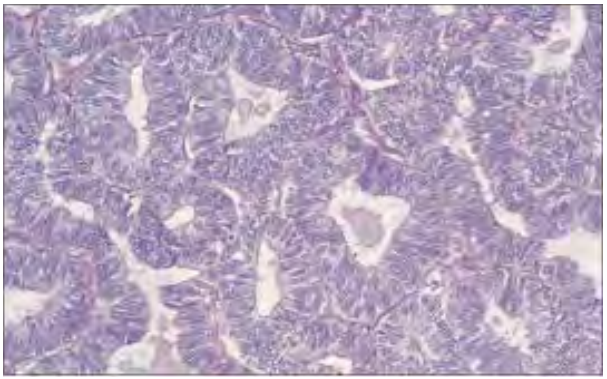


Fig. 6.9

Brenner Tumours of Ovary

1. Ovarian surface epithelial tumours with transitional (urothelial like) lining
2. 3 categories: Benign, borderline (proliferating brenner) and malignant brenner.

Gross

1. Benign brenner: U/L; solid; well circumscribed; small; pale yellow (often present within a serous/mucinous cystadenoma). Cystic change ±.
2. Borderline: Solid-cystic with polypoidal protrusion into cyst cavity (friable papillae).
3. Malignant: Solid-cystic; friable; fleshy; haemorrhagic necrotic.

Microscopic Findings

1. Benign Brenner:
   i. Transitional cell nests in ovarian stroma (solid; solid-cystic); glandular spaces within nests.
   ii. Tumour cells have longitudinal nuclear grooves.
   iii. Stromal fibrosis often marked.
2. Borderline brenner: Features of benign brenner + broad papillae arising from cyst wall (TCC like); no stromal invasion.
3. Malignant brenner: Feature of benign; borderline brenner + solid invasive nests; desmoplasia.

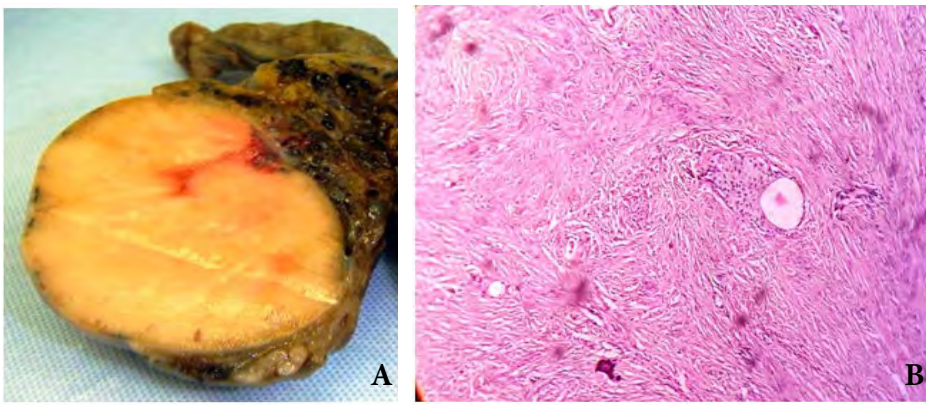


Fig. 6.10: Brenner tumour ovary: (A) Gross; (B) Histology at 10X.

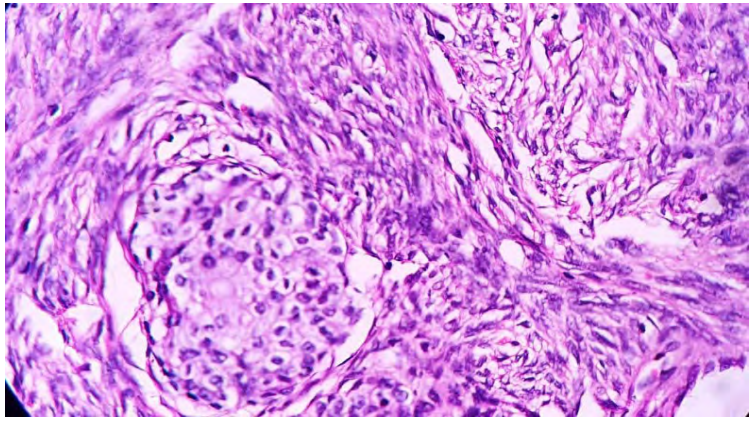


Fig. 6.11: Nests of transitional epithelium in stroma showing grooving.

Table 6.9: Ovarian germ cell tumours simplified classification scheme.

Dysgerminoma (Seminoma equivalent in females)		Mixed germ cell tumours (10% cases)
Yolk sac tumour (Endodermal sinus tumour)		
Embryonal carcinoma		
Choriocarcinoma		
Teratoma	Mature (cystic): Dermoid cyst. Immature (solid): < 1% cases. Monodermal (specialized): Struma ovarii; carcinoid; stromal carcinoid. With malignant transformation.	
Polyembryoma		

Germ Cell Tumour - Overview

1. 15–20% of all ovarian tumours.
2. Majority are unilateral.
3. Predominantly benign: Dermoid cysts (2/3rd in Ist two decades).
4. Malignant GCTs relatively uncommon (3% of Ca ovary): Dysgerminoma commonest pure malignant GCT.
5. Unlike testicular GCT: Ovarian GCTs are predominantly pure (mixed forms rare: 10% cases approx).

6. Uncommon tumour (2% of Ca Ovary): Esp. in 1st two decades (adolescence to early adulthood).
7. Commonest pure malignant germ cell tumour of ovary.
8. Non-specific symptoms (abdominal mass); rapid growth in pregnancy.
9. Trophoblastic elements ± (→ hCG → isosexual precocity; menstrual abnormalities).
10. May be assoc. with gonadal dysgenesis.
11. Dysgerminoma: Clinical behaviour.
12. Rapid growth; but metastatic spread if occurs, is late.
13. Metastatic spread: Lymphatic system (along common iliac a.; Abdominal aorta → SC l. node; mediastinal nodes) → Haematogenous (lung; liver; bone).
14. 75–90% 5 yr survival.
15. Recurrences may occur (mostly within 1–2 years of diagnosis).
16. Highly sensitive to CT/RT: CT Rx of choice (3–4 cycles of BEP).

Dysgerminoma

Gross Findings

1. U/L (80–90%).
2. Pure forms.*
   i. Solid; Well circumscribed.
   ii. Lobulated; soft; fleshy – firm rubbery.
   iii. Homogenous; necrosis/haemorrhage ± (but cystic change rare).
3. Mixed forms: Cystic change; Hge/Necrosis.

*Pure forms of dysgerminoma commoner.

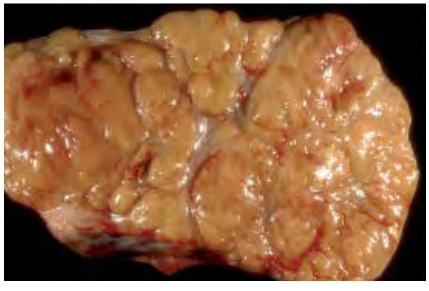


Fig. 6.12

Microscopy

1. Sheets-islands of dysgerminoma cells.
   i. Large; oval-round; well defined cell borders.
   ii. Abundant clear cytoplasm (glycogen- PAS+).
   iii. Prominent eosinophilic nucleolus.
2. Interspersed fibrovascular connective tissue septae - prominent lymphocytic infiltrate; granulomatous reaction.
3. Syncytiotrophoblastic giant cells ± (6–8%).

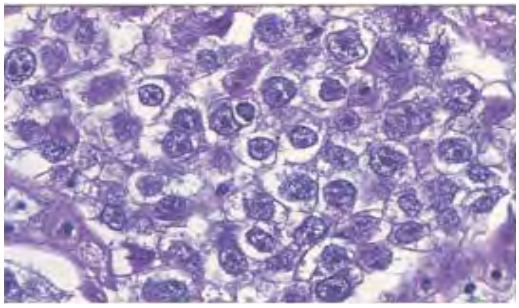


Fig. 6.13

Ovarian Teratoma

Table 6.10: Ovarian germ cell tumour derived from all three germ cell layers (± organoid pattern).

Mature (cystic) teratoma: Dermoid cyst	Extodermal derivatives	Skin: Stratified squamous epithelium; sweat glands; sebaceous glands; hair follicles. Neuroepithelium: Neuroglia; ganglion cells; neuroblasts; n. trunks.
Immature (solid) teratoma	Mesodermal derivatives	Cartilage. Bone; smooth muscle; skeletal muscle; fibroadipose tissue.
	Endodermal derivatives	G.I.T; respiratory tract epithelium. Thyroid; salivary gland tissue

Dermoid Cyst

Microscopy

1. Cyst wall cavity lining: Skin; bronchial or G.I. Epithelium.
2. Rokitansky protuberance: Max. tissue diversity (ectoderm; mesoderm and endoderm).
3. Immature neuroepithelium (primitive neural tubules; rosettes) ±. Assoc. with an immature teratoma (aggressive unlike a mature cystic teratoma).

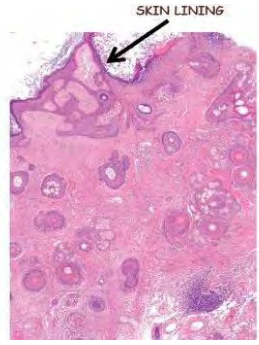


Fig. 6.14

Table 6.11: Misc. ovarian germ cell tumours.

Embroyonal Ca	Yolk sac tumour	Choriocarcinoma
Rare; highly malignant. Least differentiated form of ovarian GCT Painful abd. mass (↑hCG; AFP ±) Often component of a mixed GCT	2nd most common malignant GCT (after dysgerminoma) Approx. 19 yrs (children to adolescents) ↑↑↑AFP (↑hCG±) lymphatic metastases; pelvic recurrences frequent	Gestational choriocarcinoma commoner; pure ovarian chorioca rare (< 1% cases) ↑↑↑↑ hCG (isosexual precocity) Mostly a component of mixed GCT
Often grossly haemorrhagic; necrotic	Almost always U/L Large; encapsulated round-oval; smooth; firm; lobulated Cystic change common Haemorrhage; necrosis±	Often assoc. with marked haemorrhagic necrosis

Table 6.12

Embryonal Ca	Yolk sac tumour	Choriocarcinoma
Solid; syncytial or sheet like aggregates; pseudoglandular spaces. Large anaplastic cells Pale; vacuolated cytoplasm; cellular overlapping Hyperchromatic, markedly atypical nuclei; prominent nucleoli; Mt activity Assoc. tumour giant cells; syncytiotrophoblastic giant cells Haemorrhage; necrosis common	Multiple architerctural patterns: Reticular-microcystic; endodermal sinus pattern (with schiller duvall bodies); solid patterns common Pleomorphic; hyperchromatic cells (cuboidal-low columnar) Hyaline globules characteristic: Intra/ extracellular (+ve for AFP; α1-AT)	Biphasic pattern composed of solid aggregates of cytotrophoblast + syncytiotrophoblast Vascular invasion by neoplastic trophoblastic cells → Haemorrhagic necrosis ++++

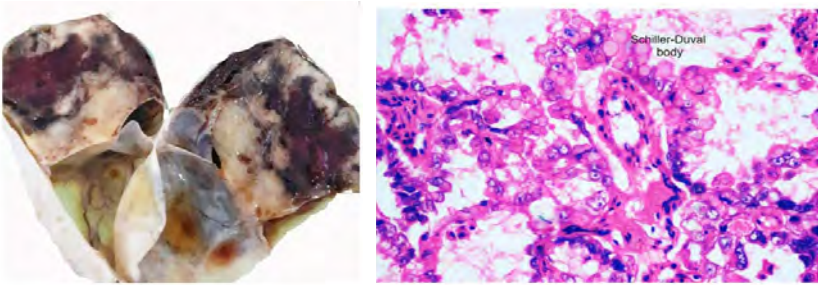


Fig. 6.15: Yolk sac tumour- Gross and histology.

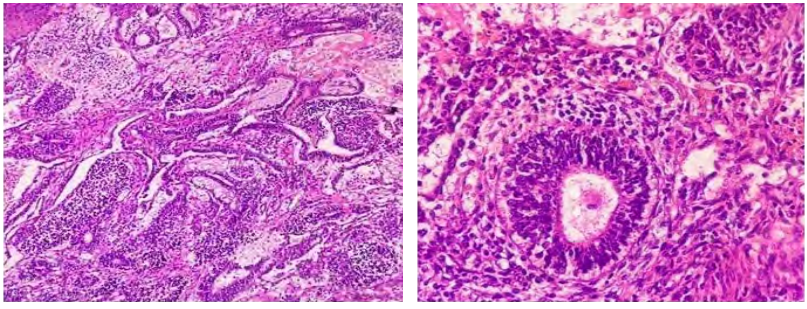


Fig. 6.16: Immature teratoma showing rosette formation.

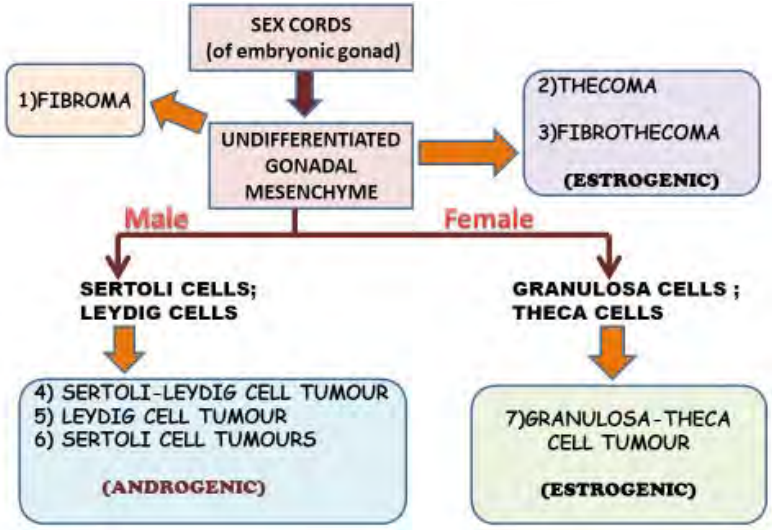


Fig. 6.17: Overian sex cord stromal tumours: Histogenesis.

Table 6.13: Ovarian sex cord stromal tumours: A functional approach.

Androgenic (Hirsutims; virilization)	Sertoli-leydig cell tumour Sertoli cell tumour Leydig cell tumour (Hilar; nonhilar)
Estrogenic (precocious puberty; DUB)	Granulosa-theca cell tumour
	Thecoma
	Fibrothecoma
Nonfunctional (ascites; hydrothorax etc.)	Fibroma (assoc, with MEIG's syndrome)

Sex Cord Stromal Tumours: Overview

1. Mostly in postmenopausal women (Exception: Juvenile granulosa cell tumour; pregnancy luteoma).
2. Usually U/L; encapsulated; firm-solid tumours (Exception: Granulosa cell tumour – solid cystic).

3. Yellow tan to brown (Esp. androgen producing tumours); fibromas gray-white.
4. Often Hormonally functional.
5. Imp: Predominantly estrogenic tumours may sometimes produce androgen (and vice versa).
6. IHC: +ve for inhibin; calretinin.

Table 6.14: Estrogenic sex cord stromal tumours: Microscopy.

Granulosa cell tumour (Adult; Juvenile)	**Fibroma; Thecoma; Fibrothecoma**
Adult Granulosa cell tumour Diffuse sheets; microfollicles(call-exner bodies); macrofollicles Neoplastic mature granulosa cells - small cuboidal cell with high N:C; angulated nuclei (longitudinal nuclear grooves- coffee bean appearance)	**Fibroma** Interlacing fascicles; bundles of well differentiated Fibroblasts Stromal collagen **Thecoma** Sheets of lipid laden theca cells (round-plump spindled stromal cells) → Oil Red O+ve Stromal luteinization ±
Juvenile granulosa cell tumour Solid sheets; immature follicles ± Immature neoplastic granulosa cells- More atypia; Mt activity +++ Stromal luteinization common	**Fibrothecoma**

Ovarian Tumours– Points to Ponder

Parameters which may be included on pathology report of serous borderline tumour

1. Unilateral or bilateral.
2. Integrity of capsule.
3. Intracystic or surface tumour or both.
4. Percentage of neoplasm involved by borderline tumour.

5. Usual type or micropapillary architecture.
6. Microinvasion.
7. Autoimplants.
8. Endosalpingiosis.
9. Implants (presence or absence and type).
10. Nodal involvement.
11. Peritoneal washings.
12. Stage.

Gross Points

Yellow Tumours of Ovary

1. Granulosa tumours of ovary.
2. Thecoma.
3. Steroid cell tumours.
4. Sertoli-leydig cell tumour.
5. Brenner tumour.
6. Carcinoid tumour.
7. Sclerosing stromal cell tumour.

Table 6.15: Ovary- Tumour with dominant solid component.

Friable necrotic tumours	Solid, firm white to tan tumours	Variegated cut surface with haemorrhage and necrosis
Malignant germ cell tumour	Fibroma, thecoma	Embryonal carcinoma
Granulosa cell tumour	Brenner tumour, Leiomyoma	Yolk sac tumour
Sertoli cell leydig tumour	Sclerosing stromal tumour, disseminated peritonneileiomyomatosis	
Metastatic tumours from colon- (with cystic necrosis)		

Table 6.16: Cystic ovarian masses with solid component.

Cyst wall with solid nodule	Cyst with protrusion nodule/papillary excrescence	Cyst with mucin material
Decidualisedendometriotic cyst	Papillary serous cystadenoma	Mucinous cystadenocarcinoma
Mullerianseromucinous tumours with endometriosis	Sero-mucinous endometrioid borderline	Metastatic mucinous carcinoma
	Cystic strumaovarii	

Table 6.17: Cystic ovarian masses.

Single smooth translucent cyst	Smooth walled haemorrhagic cyst	Cyst with mucinous material
Serous cyst	Endometriotic cyst	Mucinous cystadenoma – borderline
Para-ovarian cyst	Degenerated corpus luteum	Endocervical mucinous cystadenoma
Hydrosalpinx		Metastatic mucinous carcinoma
Follicular cyst (>3 cm)		

Solid and Cystic Ovarian Tumours

1. Sertoli-Leydig cell tumour.
2. Mature cystic teratoma.
3. Germ cell tumour.
4. Granulosa cell tumour.
5. Surface epithelial cell tumours.
6. Yolk sac tumours (variegated).

OVARIAN TUMOURS IN NUTSHELL

Luteinized Thecoma

Definition

1. Densely cellular tumour composed predominantly of spindle cells admixed with less prominent small lutein cells (steroid hormone producing cells) typically associated with sclerosing peritonitis.

Incidence and Location

1. Rare.
2. Typically bilateral but can be unilateral.

Morbidity and Mortality

1. Bowel obstruction and enterocutaneous fistulae secondary to sclerosing peritonitis.
2. No recurrence or metastases.
3. Death secondary to surgical complications.

Age Distribution

1. Reproductive age (mean 25 years; frequently < 40 years).

Clinical Features

1. Abdominal pain or swelling.
2. Symptoms secondary to bowel obstruction.

Prognosis and Treatment

1. Prognosis related to intestinal/peritoneal disease.
2. Bilateral oophorectomy and resection of adhesions.
3. Bowel obstruction managed by surgical intervention, conservative measures, or hormonal therapy.
4. Extensive and multiple surgeries if adhesions with increased risk.

Pathologic Features

Gross Findings

1. Typically bilateral.
2. Slightly enlarged to nodular ovaries or large masses (up to 31 cm).
3. Cerebriform surface.
4. Solid and edematous cut surface.

Microscopic Findings

Frequent diffuse ovarian involvement.

1. Densely cellular with diffuse or loose fascicular architecture.
2. Predominant population of spindle cells admixed with small groups of lutein cells.

3. Absent to mild cytologic atypia.
4. Brisk mitotic activity in spindle cells (up to 80/10 HPFs).
5. Not infrequently, edema with microcyst formation.
6. May entrap normal ovarian structures.

Immunohistochemical Features

1. Inhibin, calretinin and CD56 positive in luteinized cells, smooth muscle actin, desmin, calretinin, CD56, and AE1/3 focally positive.
2. Inhibin negative in spindle cells.

Differential Diagnosis

1. Stromal hyperthecosis.
2. Massive edema/fibromatosis.
3. Edematous cellular fibroma.
4. Sclerosing stromal tumour.
5. Fibrosarcoma.

Sclerosing Stromal Tumour

Definition

1. Benign stromal tumour with cellular areas composed of fibroblasts and lutein cells separated by hypocellular edematous or collagenized areas imparting a pseudolobular appearance.

Incidence and Location

1. 2–6% of ovarian stromal tumours.
2. < 1% of all primary ovarian tumours.
3. Unilateral.

Age Distribution

1. 80% of women < 30 years of age.

Clinical Features

1. Pain, pelvic mass.
2. Very rarely, estrogenic or androgenic manifestations.

Radiologic Features

1. Solid mass with a pseudolobular pattern by CT scan and MRI.
2. Medium signal intensity of tumour periphery and high signal in centre by nonenhancing MRI.
3. Initial enhancement of tumour periphery with centripetal progression of contrast by dynamic enhanced MRI.

Prognosis and Treatment

1. Excellent prognosis.
2. Unilateral oophorectomy.

Gross Findings

1. 1.5–20 cm.

Well-defined border with normal ovarian tissue

1. White to yellow and solid, or solid with multiple cystic spaces, occasionally large central cyst.

Microscopic Findings

Pseudolobular architecture

1. Cellular nodules alternating with hypocellular edematous or collagenized areas.
2. Numerous thin-walled vessels, some branched and dilated (hemangiopericytoma-like vascular network).
3. Cellular areas with heterogeneous admixture of spindle and round cells.
4. Round cells with vacuolated to eosinophilic cytoplasm and round nuclei with vesicular chromatin and prominent nucleoli.
5. Minimal cytologic atypia and low mitotic rate.

Immunohistochemical Features

1. Calretinin, ER, PR, vimentin and smooth muscle actin positive.
2. Variable inhibin and desmin expression.
3. Keratin and EMA negative.

Ultrastructural Features

1. Variegated appearance of cells.
2. Abundant membrane-bound lipid granules and rough endoplasmic reticulum.

3. No desmosomes.
4. Basal lamina adjacent to cell membranes.

Differential Diagnosis

1. Fibroma, thecoma, krukenberg tumour, carcinoid tumour.

Sex Cord Tumour with Annular Tubules

Definition

1. Sex cord tumour characterized by simple and complex ring-like tubules.

Incidence and Location

1. In Peutz–Jeghers syndrome (PJS):
   i. Very common.
   ii. Bilateral in two-thirds.
2. Without PJS:
   i. Rare.
   ii. 95% unilateral.

Morbidity and Mortality

1. Complications in patients with PJS secondary to adenoma malignum of cervix (15% of cases) or other tumours.
2. In the absence of PJS, 20% malignant with lymph node metastases.
3. Late recurrences and death from disease.

Age Distribution

1. 4–76 years.
2. If associated PJS, younger age at presentation (average 27 years).
3. If no association with PJS, average age at presentation 34 years.

Clinical Features

1. Association with PJS in one-third of cases.
2. Typically incidental finding in patients with PJS.
3. Palpable mass if no PJS.
4. Estrogenic manifestations in 40%, including isosexual pseudoprecocity.
5. Rarely progesterone production.

Prognosis and Treatment

1. If associated with PJS, conservative management; however,significant risk of adenoma malignum.
2. Unilateral salpingo-oophorectomy with staging, including lymph nodes, for patients without PJS and stage Ia tumours.
3. Tumours with nuclear atypia and increased mitotic activity more likely to behave aggressively.

Gross Findings

In Patients with Peutz–Jeghers Syndrome (PJS):

1. Incidental finding.
2. Multiple and bilateral small ≤ 3 cm yellow nodules.

In Patients without PJS:

1. 0.5–33 cm.
2. Solid yellow cut surface.
3. Cystic change, haemorrhage, or necrosis.

Microscopic Findings

1. Simple tubules or complex patterns with multiple anastomosing tubules.
2. Tubules surround central hyaline material, with nuclei oriented, both peripherally and centrally, leaving an intervening pale anuclear zone.
3. In PJS, multiple tumourlets with scattered simple tubules or clusters of tubules associated with calcifi cations.
4. Nuclear pleomorphism and up to 10 mitoses/10 HPFs in malignant tumours.
5. Foci of typical Sertoli cell tumour or microfollicular granulosa cell tumour in some cases.

Immunohistochemical Features

1. Inhibin and calretinin positive.

Differential Diagnosis

1. Gonadoblastoma.
2. Sertoli cell tumour.
3. Granulosa cell tumour cytoreductive surgery for recurrence.

Sertoli–Leydig Cell Tumour

Definition

1. Tumours composed of Sertoli cells showing varying degrees of differentiation admixed with variable numbers of Leydig cells.

Incidence and Location

1. 1% of ovarian neoplasms.
2. Most common neoplasm in the category of Sertoli stromal cell tumours.
3. Most unilateral.

Morbidity and Mortality

1. Approximately 12% clinically malignant.

Age Distribution

1. Average age 25 years.
2. Well-differentiated, older age at presentation (average 35 years).
3. Retiform variant, younger age at presentation (average 15 years).

Clinical Features

1. Commonlynonspecifi c symptoms, including abdominal swelling and pain.
2. 1/3rd androgenic manifestations (less frequently in retiformSertoli–Leydig cell tumours).
3. Occasionally estrogenic or associated with increased AFP levels.

Prognosis and Treatment

1. 80% of tumours stage Ia.
2. Prognosis related to stage, degree of differentiation of the tumour, and presence of heterologous elements or retiform component.
3. Almost all malignant tumours are poorly differentiated, retiform, or contain heterologous mesenchymal elements.
4. Salpingo-oophorectomy for well-differentiated stage I tumours.
5. Chemotherapy for poorly differentiated tumours, unusual variants and ruptured intermediate differentiated tumours.
6. Early recurrences, more often confined to pelvis and abdomen.

Gross Findings

1. 15 cm average size.
2. Solid, lobulated, yellow cut surface.
3. Retiform variant and those with heterologous elements more commonly soft and "spongy" or cystic with intracystic papillae and polypoid excrescences.

Microscopic Findings

Well Differentiated

1. Lobules separated by fibromatous tissue.
2. Lobules composed of solid or hollow tubules.
3. Tubules may resemble endometrioid-type glands.
4. Sertoli cells with abundant eosinophilic or pale and vacuolated cytoplasm and round nuclei with small nucleoli.
5. Minimal cytologic atypia and absent mitotic activity.
6. Leydig cells in between lobules.

Intermediate Differentiated

1. Cellular "blue" lobules separated by hypocellular edematous stroma.
2. Lobules composed of Sertoli cells with diffuse or tubular (poorly developed), nested or cord-like arrangements.
3. Microcystic pattern reminiscent of thyroid tissue.
4. Immature Sertoli cells with scant cytoplasm and small round to oval nuclei.
5. Leydig cells either admixed with Sertoli cells or more frequently at the periphery of lobules.

Poorly Differentiated

1. Diffuse or sarcomatoid growth of poorly differentiated Sertoli cells.
2. Rarely, small areas of poorly formed tubules.
3. Sparse to absent Leydig cells.

Retiform Variant

1. Frequently associated with moderately to poorly differentiated Sertoli–Leydig cell tumours.
2. Often slit-like tubules and cysts with short and rounded or blunt papillae.
3. Cysts may resemble thyroid tissue due to luminal eosinophilic secretion.

4. Papillary cores often hyalinized.
5. Tubules, papillae, and cysts lined by a single layer of cuboidal cells with round to oval nuclei.
6. Variable mitotic rate.
7. With Heterologous Elements.
8. In ~20% of Sertoli–Leydig cell tumours, typically in intermediate and poorly differentiated tumours.
9. Gastrointestinal-type mucinous epithelium most common.
10. Carcinoid tumour.
11. Immature cartilage or skeletal muscle.
12. Very rarely, hepatoid and neuroblastoma foci.

Immunohistochemical Features

Sertoli Cells

1. Vimentin, cytokeratin, inhibin, calretinin and CD56-positive.
2. CD99, WT-1, CD10, smooth muscle actin variably positive.
3. EMA negative.

Leydig Cells

1. Vimentin, inhibin, and calretinin positive.
2. Melan A, CD10 frequently positive.
3. Keratin and smooth muscle actin rarely positive.

Ultrastructural Features

Sertoli Cells

1. Basal lamina, tight junctions, abundant rough endoplasmic reticulum, lipid and microvilli.
2. Rarely noncrystalline parallel arrays of Charcot–Böttcher microfilaments.

Leydig Cells

1. Oval nuclei with regular contours and large nucleoli.
2. Abundant smooth endoplasmic reticulum, lipid droplets, mitochondria and secondary lysosomes containing lipochrome pigment.
3. Sometimes Reinke crystals and their filamentous precursors.

Differential Diagnosis

1. Endometrioid carcinoma with sex cord-like differentiation.
2. Sertoli cell tumour.
3. Tubular Krukenberg tumour.
4. Serous neoplasia (vs retiform variant).
5. Yolk sac tumour (vs retiform variant).

Immunohistochemistry Profile

Table 6.18: Metastatic ovarian adenocarcinomas.

Tumour	CK7	CK20	CDX-2	PAX-8	Mammaglobin	CA-125	WT-1
Primary Ovarian Carcinoma							
Serous	+	-	-	+	-	+	+
Endometrioid	+	-	-	+	-	+	-
Mucinous	+	+, +/-	+, +/-	-	-	-/+	-
Metastatic Carcinoma							
Colon-rectum	-	+	+	-	-	-	-
Appendix	-/+	+	+	-	-	-	-
Stomach	+	+/-	-/+	-	-	-	-
Breast	+	-	-	-	+	-/+	-

OVARY PATHOLOGY

Features that favour metastasis to the ovary:

1. Billateral ovarian involvement or < 10 cm.
2. Multinodular growth on gross or microscopic examination.
3. Surface involvement frequently associated with a desmoplastic reaction.
4. Hilar vascular invasion as primary ovarian tumours, even when high grad, uncommonly exhibit extensive lymphatic or vascular invasion.
5. Infiltration of preexistent structures as well as single cells.
6. Different histologic patterns of the tumour in different nodules.

Features that favour a primary ovarian tumours:

1. Unilateral or > 10 cm (with exception, mostly bowel and endocervical carcinoma).

2. Expansile pattern of invasion.
3. Complex papillary pattern.
4. Size > 10 cm.
5. Borderline or benign appearing areas at least in most cases.

Tumours of Ovary

Three ovarian cell types

1. Surface epithelium.
2. Germ cell.
3. Sex cord tissues (theca, granulosa cells).

Most common type of ovarian tumour

1. Surface epithelial tumour.

Two most common types of surface epithelial tumours

1. Mucinous (mucous fluid).
2. Serous (watery fluid).

   *Both are cystic.

Classification of mucinous and serous tumours

1. Benign (cystadenoma) – simple, flat lining.
2. Borderline – in between.
3. Maligant (cystadenocarcinoma) – complex, shaggy lining.

Psammoma body tumours

1. PSaMMoma
   i. P = Papillary cancer of the thyroid.
   ii. S = Serous cystadenocarcinoma of the ovary.
   iii. M = Meningioma.
   iv. M = Mesothelioma.

Mutation associated with serous ovarian carcinoma

1. BRCA1.

Associated with intestine-like tissue

1. Mucinous cystademoma.

Tow tumours associated with massive mucous accumulation in peritoneum

1. Mucinous cystadenocarcinom.
2. Appendiceal tumour.

Ovarian tumour associated with bladder-like epithelium

1. Brenner tumour.

Serum marker for ovarian cancer

1. CA-125.

Four germ cell tumours

1. Dysgerminoma.
2. Cystic teratoma.
3. Endodermal sinus tumour (yolk sac).
4. Choriocarcinoma.

Four tissues that female germ cells are capable of producing

1. Fetal tissue.
2. Oocytes.
3. Yolk sac.
4. Placental tissue.

Tumour associated with sheets of uniform cells with clear cytoplasm and central nuclei

- Dysgerminoma.

Associated with elevated LDH

- Dysgerminoma.

Associated with Turner's syndrome

- Dysgerminoma.

Associated with elevated beta-HCG

- Choriocarcinoma.

Associated with the formation of theca-lutein ovarian cysts

- Choriocarcinoma.

What age do germ cell tumours normally occur in women?

- Women of reproductive age.

Associated with elevated AFP

- Endodermal sinus tumour (yolk sac).

Most common ovarian tumour in children

- Endodermal sinus tumour (yolk sac).

Associated with Schiller Duval bodies

- Endodermal sinus tumour (glomerulus like structures).

Described as "yellow friable solid masses"

- Endodermal sinus tumour.

Most common germ cell tumour in females

- Cystic teratoma.

What is a struma ovarii?

- Subtype of ovarian teratoma with thyroid tissue.

Associated with hyperthyroidism

- Teratoma (struma ovarii).

Associated with ascites, hydrothorax and ovarian fibroma

- Meig's syndrome.

Associated with a "pulling sensation in groin"

- Ovarian fibromas.

Associated with estrogen production and signs of estrogen excess

- Granulosa-theca cell tumour.

Call-Exner bodies vs. schiller Duval bodies

1. Schiller-duval bodies= Yolk sac tumours.
2. Call-exner bodies = granulosa-theca cells.

Associated with Reinke crystals

- Sertili-Leydig cell tumours.

Associated with hirsutism and virilisation

- Sertoli-Leydig cell tumour.

Germ Cell Tumours of the Ovary

1. Dysgerminoma.
2. Yolk sac tumour (endodermal sinus tumour).
3. Embryonal Carcinoma.
4. Polyembryoma.
5. Choriocarcinoma.
6. Teratoma:
    i. Mature teratoma:
        a. Solid.
        b. Cystic (benign cystic teratoma; dermoid cyst).
        c. Malignant tumour arising in a mature teratoma.
    ii. Immature teratoma.
    iii. Neuroectodermal tumours.
7. Monodermal teratoma:
    i. Struma ovarii.
    ii. Carcinoid tumour.
8. Mixed germ cell tumour.
9. Gonadoblastoma.
10. Unclassified germ cell tumour.

ADENOMATOID TUMOUR

Definition

1. Benign tumour derived from mesothelial cells.

Incidence and Location

1. Most frequent benign tumour of fallopian tube.
2. Beneath the serosa.

Age Distribution

1. Middle-aged or elderly woman.

Clinical Features

1. Usually an incidental finding.

Prognosis and Treatment

1. Excellent prognosis.
2. It can be treated successfully by surgery alone.

Adenomatoid Tumour – Pathologic Features

Gross Findings

1. Most commonly subserosal.
2. Well circumscribed but unencapsulated.
3. Round or oval, gray to yellow nodule.
4. Typically ≤ 2 cm.

Microscopic Findings

1. Gland-like and slit-like spaces.
2. Single signet ring-like cells and cysts less common.
3. Cuboidal to flat cells with bland cytologic features.
4. Sprinkling of lymphocytes.

Immunohistochemical Features

1. Low-molecular-weight keratin, calretinin and WT1 positive.
2. Negative for CEA, factor VIII, CD15, TAG-72.

Differential Diagnosis

1. Adenocarcinoma (frozen section).
2. Lymphangioma.
3. Leiomyoma.

❑

CHAPTER 7

GESTATIONAL TROPHOBLASTIC DISEASES (GTDs)

Development of Chorionic Villi – A Brief Introduction

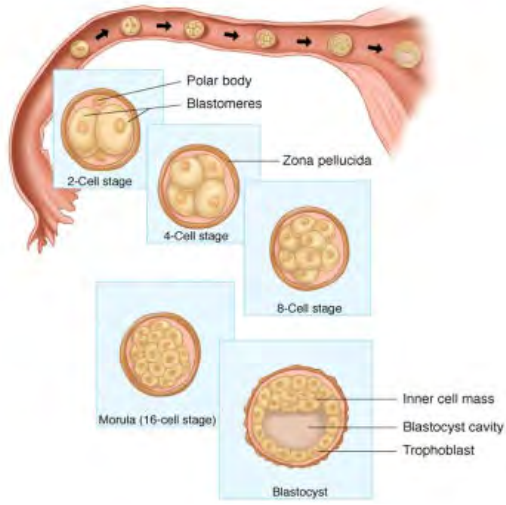


Fig. 7.1

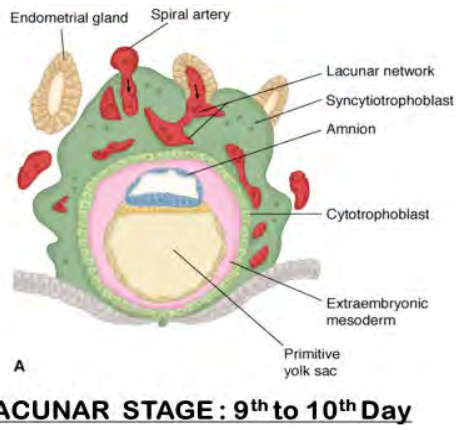


Fig. 7.2: Lacunar stage: 9th–10th day.

Lacunar Stage (9th–10th Day)

1. Cytotrophoblast.
2. Syncytiotrophoblast.
3. Spaces between syncytiotrophoblast (lacunae).
4. Maternal vessel.

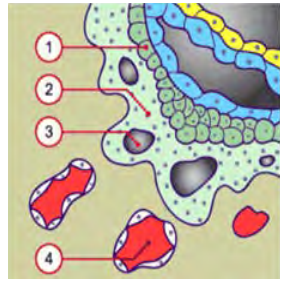


Fig. 7.3: Lacunar stage: 9th–10th day.

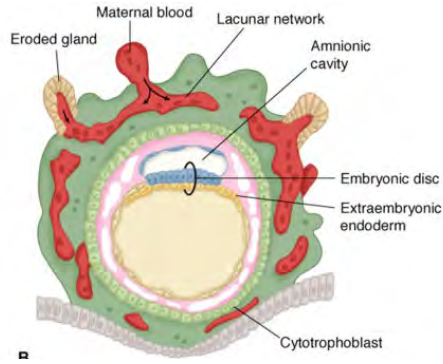


Fig. 7.4: Lacunar stage: 9th–10th day.

Primary Villus (9th–10th Day)

Maternal vessel, eroded by the ST, which form the maternal sinusoids through communication with the lacunae.

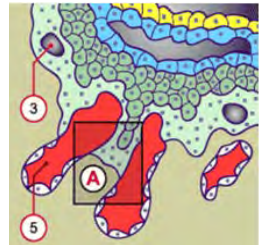


Fig. 7.5: Primary villus (9th–10th Day).

Primary Villus (11th–13th Day)

Cytotrophoblast penetrates into the processes of the syncytio-trophoblast, forming the primary trophoblast villi. (1-CT; 2-ST)

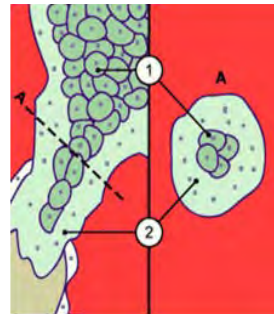


Fig. 7.6: Primary villus (11th–13th Day).

Secondary Villus (13th–16th Day)

1-Extra embryonic mesoblast (→ Connective tissue; BV); 2-CT; 3-ST.

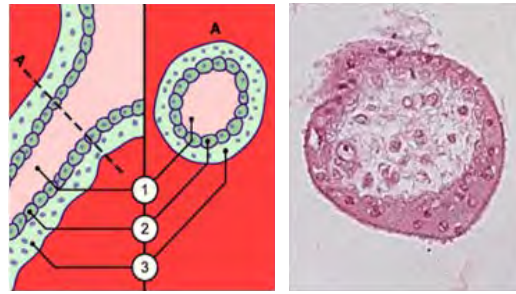


Fig. 7.7: Secondary villus (13th–16th Day).

Tertiary Villus: Placental Barrier (21st Day)

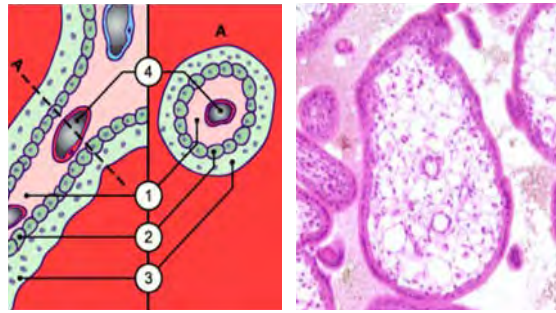


Fig. 7.8: Tertiary villus: Placental barrier (21st Day).

Free Villus (After 4th Month)

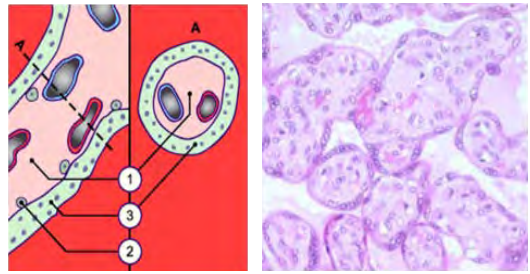


Fig. 7.9: Free villus (After 4th Month).

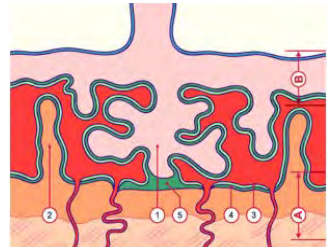


Fig. 7.10

1. Anchoring villus.
2. Septum.
3. Syncytiotrophoblast (ST).
4. Cytotrophoblast (CT).
5. Cytotrophoblast layer.
    i. Basal plate; myometrium.
    ii. Chorionic plate.

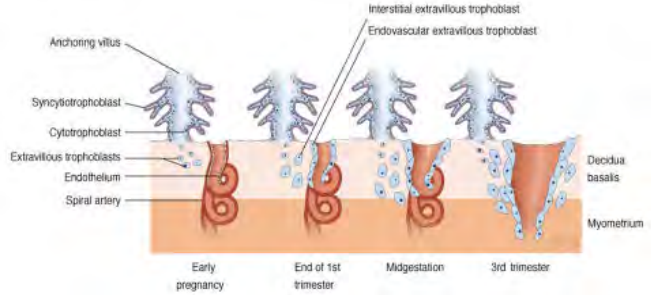


Fig. 7.11

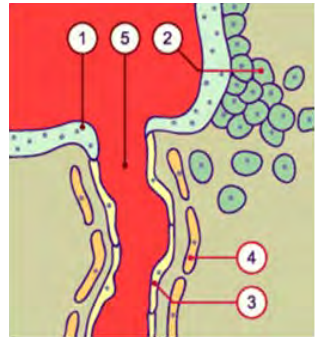


Fig. 7.12A: Growth of CT into the walls of the maternal vessels (spiral arterioles).

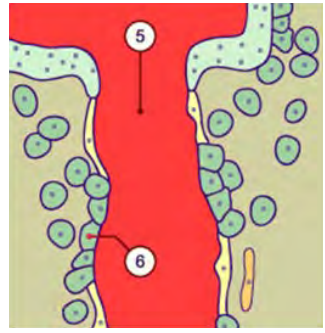


Fig. 7.12B: Growth of CT into the walls of the maternal vessels (spiral arterioles).

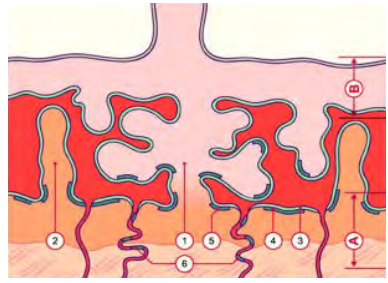


Fig. 7.13

1. Anchoring villus.
2. Septum.
3. Syncytiotrophoblast (ST).
4. Cytotrophoblast (CT).
5. Cytotrophoblast layer.
6. CT in the spiral artery wall.

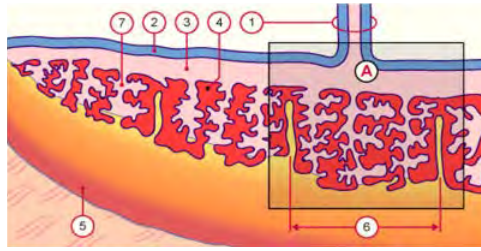


Fig. 7.14

1. Umbilical cord.
2. Amnion.
3. Chorionic plate.
4. Intervillous space (maternal blood).
5. Basal plate.
6. Cotyledon.
7. Villus.

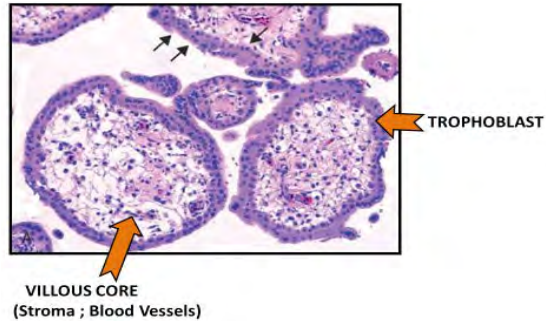


Fig. 7.15: A normal chorionic villus.

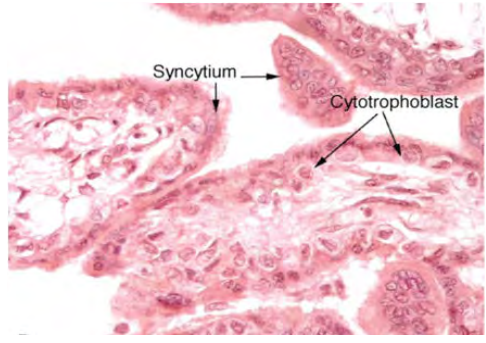


Fig. 7.16

Gestational Trophoblastic Diseases

Hydatidiform mole: Complete; partial; invasive (Gestational) Choriocarcinoma

1. Placental Site Trophoblastic Tumour (PSTT).
2. Epithelioid Trophoblastic Tumour (ETT).
3. Exaggerated Placental Site (EPS) Reaction.
4. Placental Site Nodule (PSN).

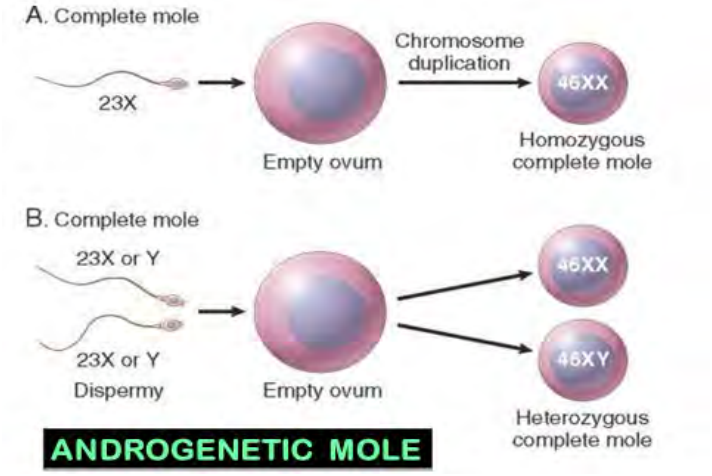


Fig. 7.17: Androgenetic mole.

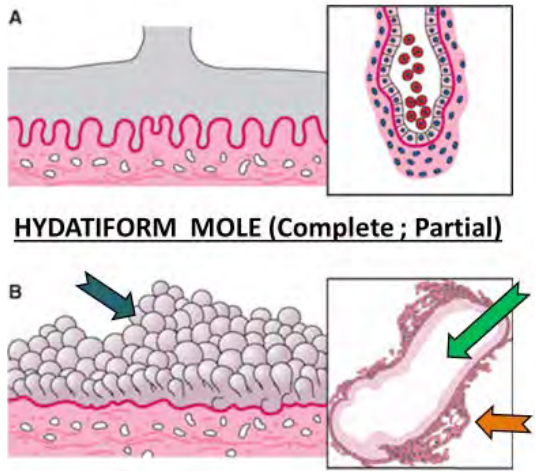


Fig. 7.18

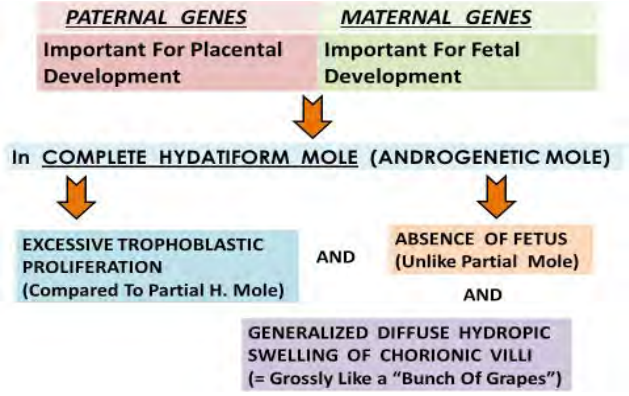


Fig. 7.19

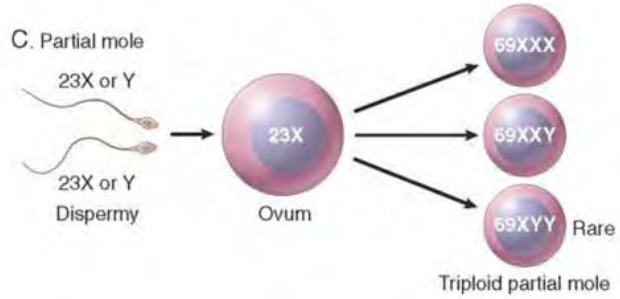


Fig. 7.20: Partial mole.

Partial Mole

Definition

1. Admixture of two populations of villi enlarged and edematous villi normal sized villi that may be fibrotic.
2. Evidence of fetal development is always present.
3. Diandric polyploidy.

Epidemiology

1. Usually present between the 9th and 34th weeks of pregnancy.

Clinical Features

1. Similar in signs and symptoms as complete mole.
2. Vaginal bleeding is the presenting symptom.
3. b-HCG is usually increased but some patients have normal or decreased levels.

Gross

1. Volume of tissue is small.
2. Villi are smaller than complete mole.
3. Fetal parts or fetal membranes may be present.

Microscopy

1. Molar changes are focal.
2. Mixture of edematous and normal shaped villi.
3. Trophoblastic hyperplasia is less marked scalloped pattern of the enlarged villi yielding a pattern of trophoblastic invagination into villous stroma.
4. Presence of fetal structures.

Differential Diagnosis

1. Complete mole.
2. Nonmolar hydropic abortion.
3. Hydropic abortus.
4. Choriocarcinoma.
5. Placental site trophoblastic tumour.

Prognosis: 4% may develop in to invasive mole or metastatic GTD if missed.

Treatment: Evacuation of partial mole and follow up of patients.

Complete Mole

Definition

1. An abnormal placenta characterised by enlarged, edematous and vesicular chorionic villi accompanied by a variable amount of proliferative trophoblast.
2. Characterised by hydropic swelling of the majority of villi and a variable degree of trophoblastic proliferation and atypia.
3. Fetal tissue is usually not present.

Epidemiology

1. Seen in 100 out of 100000 pregnancies.

Clinical Features

1. Diagnosed by USG - appears as “Snow Storm” pattern.

Other features are:

1. Increase in uterine size.
2. Hyperemesis.
3. Preeclampsia.
4. Vaginal bleeding.
5. Elevated b hcg levels (100000 miu/ml).
6. Benign theca lutein cysts.
7. Passage of molar vesicles.

Gross

1. "Grape Like Appearance" of placenta due to massively enlarged and edematous villi.

Microscopy

1. Two key features:
   i. Trophoblastic proliferation.
   ii. Villous edema.
2. Many villi display central cistern formation characterised by a prominent central space that is entirely acellular.
3. Trophoblasts shows cytologic atypia.
4. There is higher level of apoptosis in cytotrophoblast indicating a complex but delicate regulation of the cell population.

Differential Diagnosis

1. Partial mole.
2. Invasive mole.
3. Choriocarcinoma.
4. Placental site trophoblastic tumour.

Prognosis

1. Severe respiratory distress after uterine evacuation.
2. Persistent or metastatic GTD's.
3. Transformation in to choriocarcinoma.

Treatment

1. Evacuation and follow up of the patient monitoring b-HCG levels.

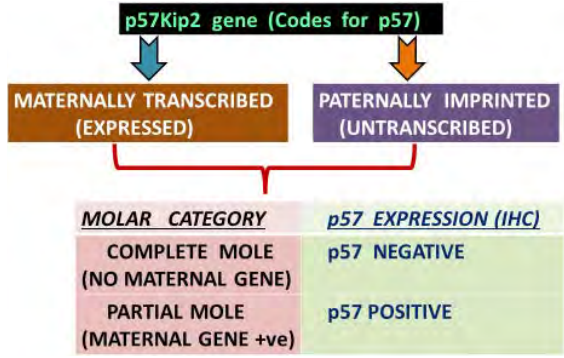


Fig. 7.21

Table 7.1: Complete mole vs Partial mole.

Diagnostic feature	Complete mole	Partial mole
Fetal or embryonic tissue	Absent	Present
Hydatidiform swelling of chorionic villi	Diffuse	Focal
Blood vessels	Absent	Present
Trophoblastic hyperplasia	Diffuse	Focal
Scalloping of chorionic villi	Absent	Present
Trophoblastic stromal inclusions	Absent	Present
Karyotype	46XX; 46XY	69XXY; 69XYY

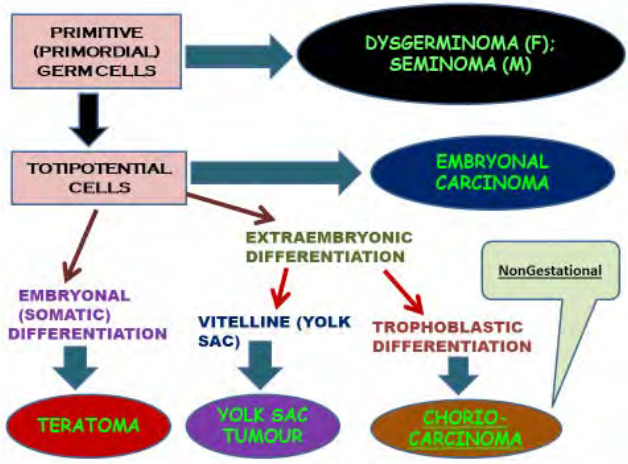


Fig. 7.22

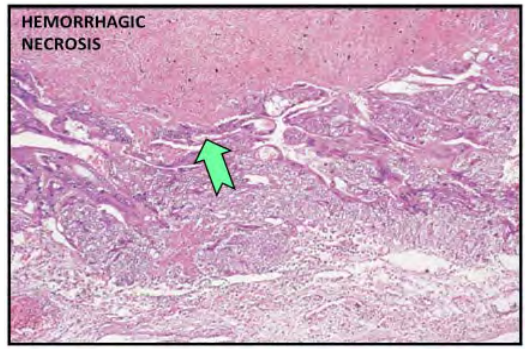


Fig. 7.23: Choriocaricinoma: Extensive necrosis.

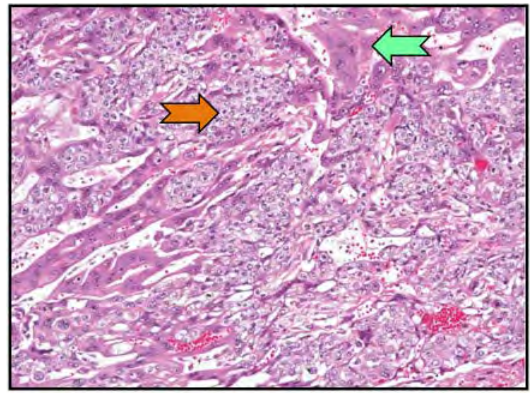


Fig. 7.24: Solid sheets of neoplastic cyto and syncytiotrophoblast.

Table 7.2: Modified WHO prognostic scoring system for GTNs.

Scores	**0**	**1**	**2**	**4**
Age (yr)	< 40	40	-	-
Antecedent pregnancy	Mole	Abortion	Term	-
Interval months from index pregnancy	< 4	4–6	7–12	13
Pretreatment serum hCG (mIU/mL)	$< 10^3$	10^3–< 10^4	10^4–< 10^5	10^5
Largest tumour size (including uterus)	-	3–<5 cm	5 cm	-
Site of metastases	Lung	Spleen kidney	Gastro-intestinal	Liver, brain
Number of metastases	-	1–4	5–8	> 8
Previous failed chemotherapy drugs	-	-	1	2
Low Risk = WHO score 0–6; High Risk = Score ≥ 7				

Table 7.3: FIGO anatomic staging of GTNs.

Stage I	Disease confined to the uterus.
Stage II	GTN extends outside of the uterus but is limited to the genital structures (adnexa, vagina, broad ligament).
Stage III	GTN extends to the lungs, with or without known genital tract involvement.
Stage IV	All other metastatic sites (brain, liver).

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