Molavi Notes

Table of Contents

10
11
20
21
23
27

Chapter 9 – Liver

Normal Histology

- Normal hepatocytes contain
  - Nucleoli
  - Variable nuclear size
  - Uni- or bi-nucleated cells
- The hepatocytes immediately surrounding the portal tracts are called the limiting plate
- Zone 1 = Peri-portal
- Zone 3 = Peri-central

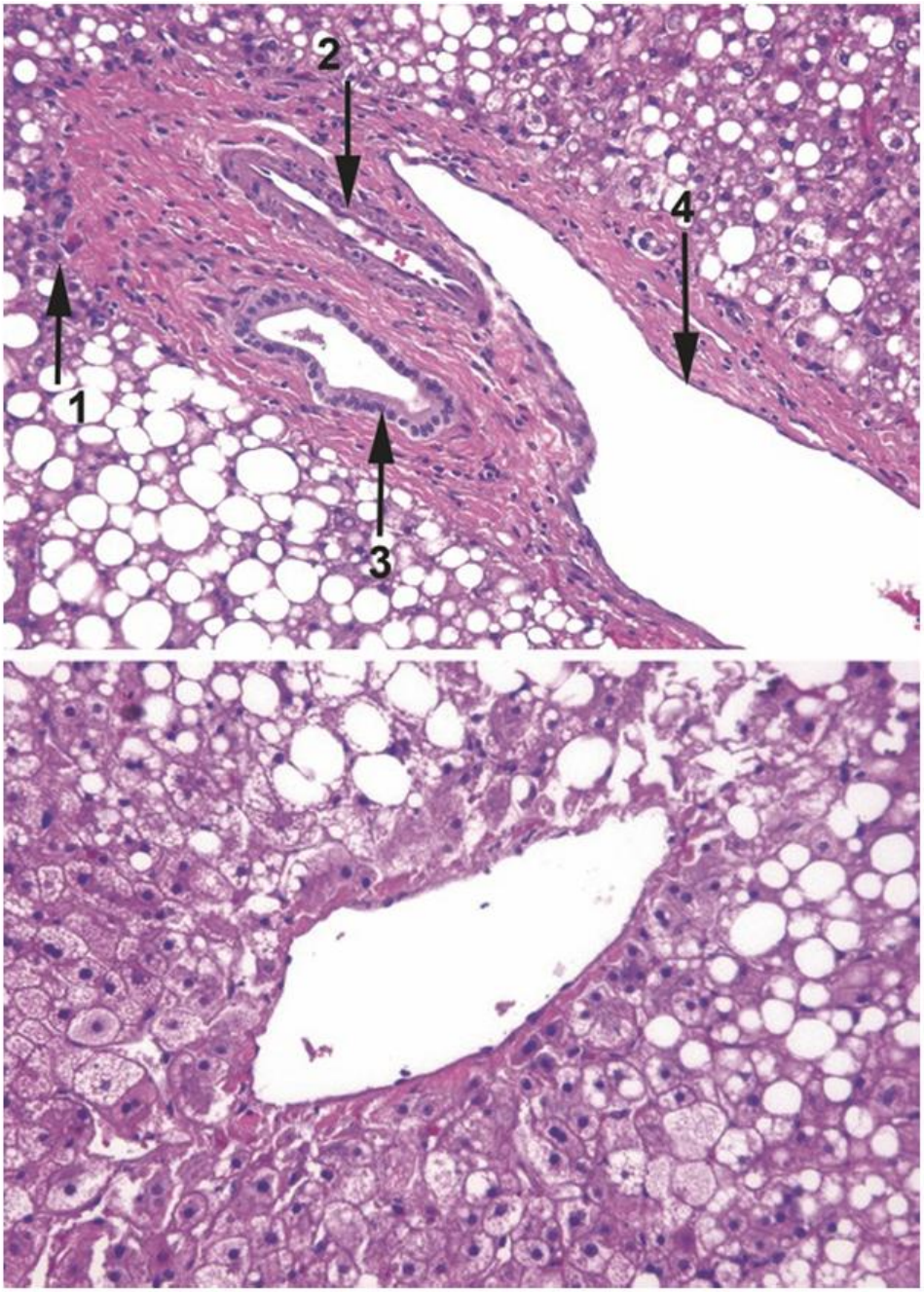


FIGURE 9.1. Portal tract and central vein. The *upper* panel shows a typical portal tract surrounded by the limiting plate of hepatocytes (*1*) and containing a branch of the hepatic artery (*2*), bile ductule (*3*), and portal vein (*4*). The *lower* panel shows a central vein from the same liver. Both panels show extensive macrovesicular steatosis.

- Acute liver injury
  - Similar to any other organ
    - Widespread edema
    - acute and chronic inflammation
    - necrosis
  - Sub-acute or chronic injury
    - mononuclear inflammatory cells
    - individual hepatocyte necrosis
    - final stage is cirrhosis. Cannot tell the etiology of cirrhosis

Hepatocellular Compartment

- Portal information: inflammatory cells within the portal tract
  - viral hepatitis/autoimmune disorders = predominantly mononuclear infiltrate
  - autoimmune hepatitis = plasma cells
  - drugs = eosinophils
- interface activity
  - interface activity is defined as peri-portal hepatitis, usually lymphocytic inflammation that occurs at the limiting plate and damages the paddle sites along that boundary
  - looks like portal information spilling out into a parasites
  - in the liver activity =/= neutrophils

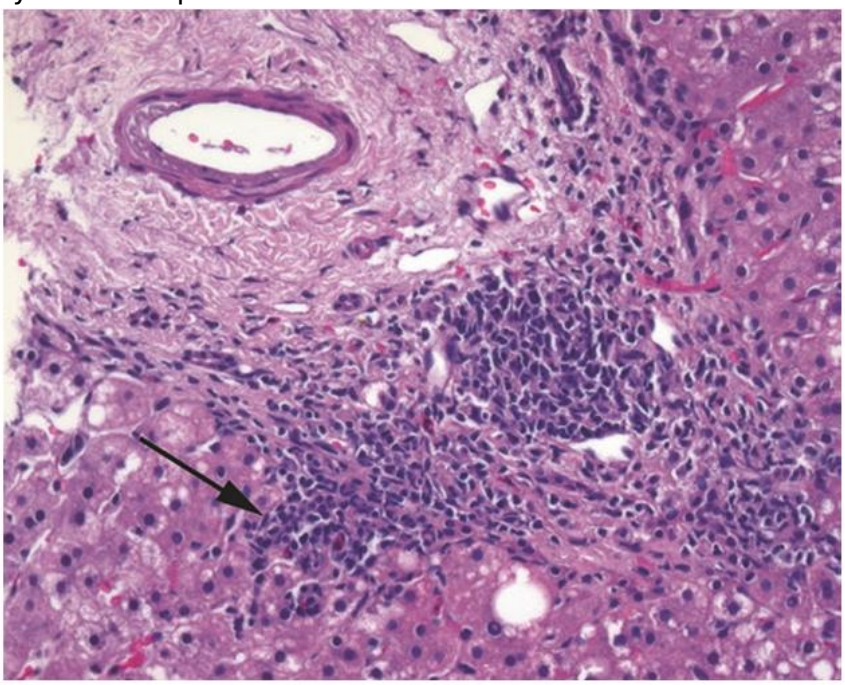


FIGURE 9.3. Portal inflammation. This is an example of chronic viral hepatitis. Lymphocytes in the portal tract spill out into the limiting plate of surrounding hepatocytes (*arrow*).

- Lobular Inflammation
  - *Spotty necrosis* - characterized by little clusters of luma sites and or macrophages destroying individual hepatocytes in the lobules. Do not count lymphocytes in the sinuses, as they are physiologic
- Vacuolar degeneration
  - (balloon cell change, or ballooning degeneration)
  - is one of the ways in which parasites become injured and die
    - the cells swell and the cytoplasm becomes feathery and pale to clear
- Acidophilic bodies
  - another way in which hepatocytes die

- fibrosis
  - starts at portal tracts and spreads to connect adjacent portal tracts or central veins

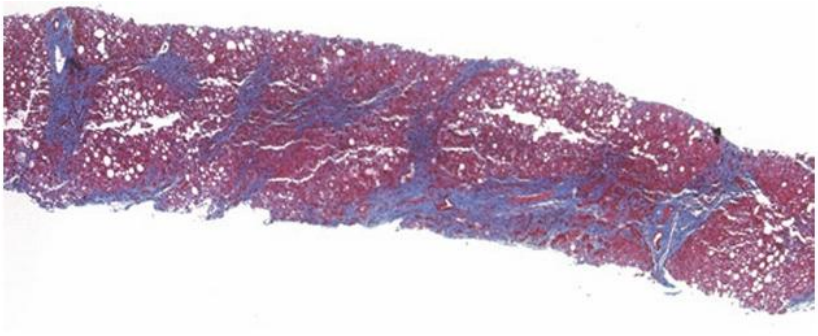


FIGURE 9.4. Cirrhosis in a biopsy specimen. In this trichrome stain, collagen is blue, while hepatic parenchyma is red. Collagen can be seen outlining the lobules of regenerative hepatocytes, bridging the portal tracts and creating a nodular pattern.

- Steatosis
  - Physiologic: <5%
  - Mild: 5-33%
  - Moderate: 33-66%
  - Severe: 66%
  - Macrovesicular steatosis:
    - large lipid vacuoles in each hepatocyte
    - typical of AFLD and NAFLD
  - Microvesicular steatosis:
    - Looks like foamy cytoplasm
- Steatohepatitis
  - Steatohepatitis = steatosis + inflammation *and/or* hepatocyte injury
    - Hepatocyte injury could be necrosis, balloon cells, fibrosis, Mallory's Hyaline, etc.

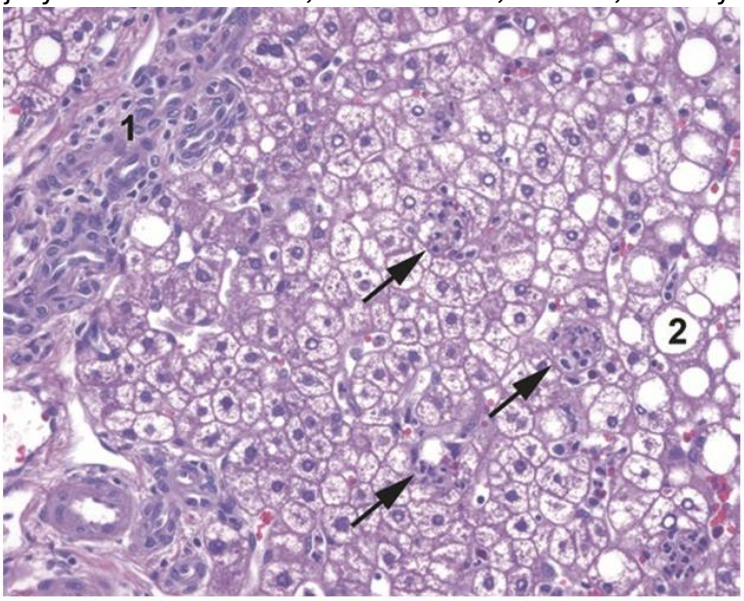


FIGURE 9.5. Steatohepatitis. An adjacent portal tract (*1*) shows minimal mononuclear inflammation. In the lobule, there is macrovesicular steatosis (*2*) and collections of neutrophils attacking individual hepatocytes (*arrows*).

  - Old steatohepatitis
    - Signalled by lipogranulomas
  - Mallory's Hyaline

- Irregular worm-like pink blobs of condensed cytoskeleton in the cytoplasm, especially in balloon cells

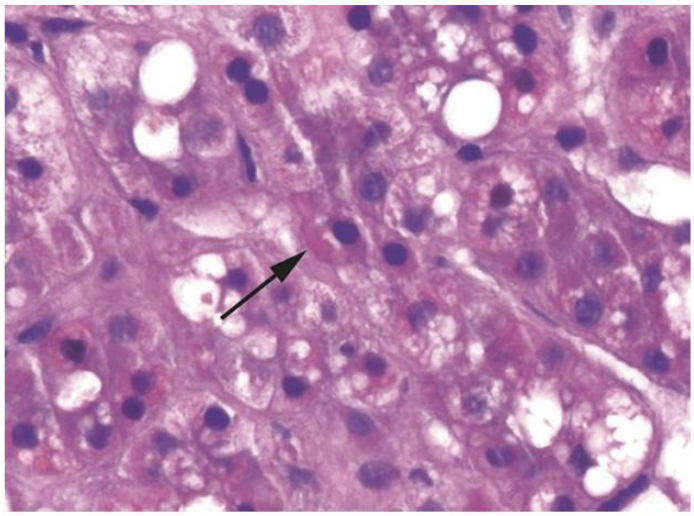


FIGURE 9.6. Mallory's hyaline. In the background of steatosis and inflammation, a pink refractile wormlike structure in the hepatocyte (*arrow*) is evidence of cytoskeletal collapse and condensation.

- Megamitochondria
  - Markedly enlarged mitochondria
  - Looks like rbc trapped in hepatocytes
- Iron accumulation
  - More predominant in Kupffer cells
  - Can be associated with many diseases
- Other storage diseases
  - Alpha-1 antitrypsin, Wilson's, Gaucher, etc need special stains

Biliary Compartment

- Cholestasis
  - Can be a response to blockage,
  - Yellow globs (bile) in hepatocytes

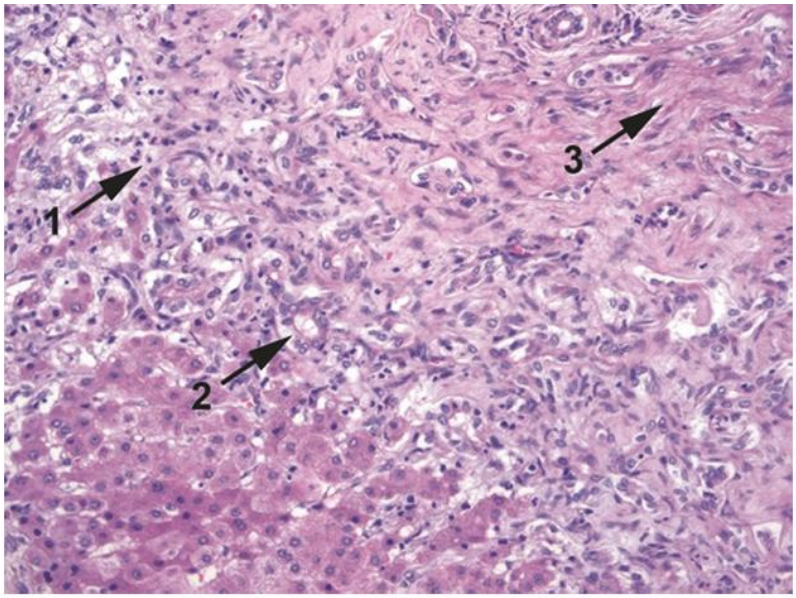


FIGURE 9.7. Bile stasis. In this example of congenital biliary atresia, the downstream obstruction to flow creates the triad of acute inflammation (*1*), a proliferation of poorly formed bile ductules (*2*), and the accumulation of golden globs of bile (not seen here). This will progress to fibrosis (*3*) and eventually loss

- of ductules.

- Bile duct proliferation
  - Ductular reaction
  - Increase more than 2 ductules per portal tract
  - New ductules are small, poorly formed, with compressed or inconspicuous lumina
  - Is a Response to obstruction
- Bile duct injury
  - Identified by
    - Lymphocytes in the bile duct epithelium
    - Vacuolar degeneration
    - Dropout of epithelial cells
  - Usually is patchy
  - End stage is ductopenia
- Ductopenia
  - Loss of ducts in 80% of portal tracts
  - Chronic injury indicator
  - CK7 can help with bile duct identification

Vascular Compartment

Chronic Hepatitis

- Sign-out of a hepatitis biopsy specimen should include 3 key diagnostic and prognostic factors:
  - etiology (if known),
  - grade (degree of inflammation and necrosis),
  - stage (extent of fibrosis)

Inflammation	Fibrosis	Score
None	None	0
Minimal Inflammation	Portal fibrosis	1
Mild Inflammation	Peri-portal fibrosis	2
Moderate Inflammation	Brigding fibrosis	3
Severe Inflammation	Cirrhotic fibrosis	4

Transplant biopsy

- Acute rejection
  - 5 to 30 days after transplant
  - Mixed portal tract inflammation
  - Venulitis
  - Bile duct inflammation and damage

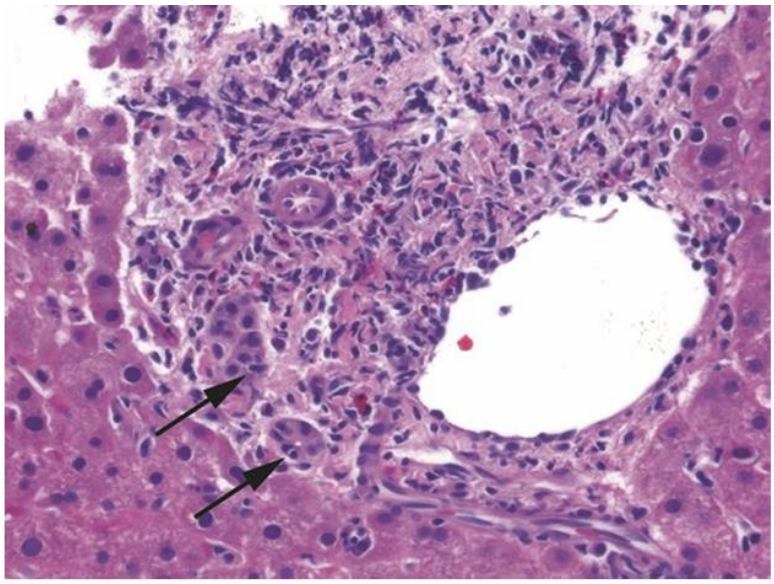


FIGURE 9.8. Acute rejection. Acute rejection refers to the attack on the bile ducts and venules by lymphocytes, which are seen invading the duct epithelium (*arrows*). Note how plump the endothelial cells are as well.

- Chronic rejection
  - More than 1 year later
  - Ductopenia and fibrosis
  - Hep C recurrence (3-9 months) is inevitable and must be differentiated from transplant rejection

PSC and PBC and AIH

- PBC
  - AMA +ve
  - F > M
  - Non-specific findings, portal inflammation, predominantly granulomatous injury to bile ducts → ductular proliferation and cholestasis → ductopenia and cirrhosis

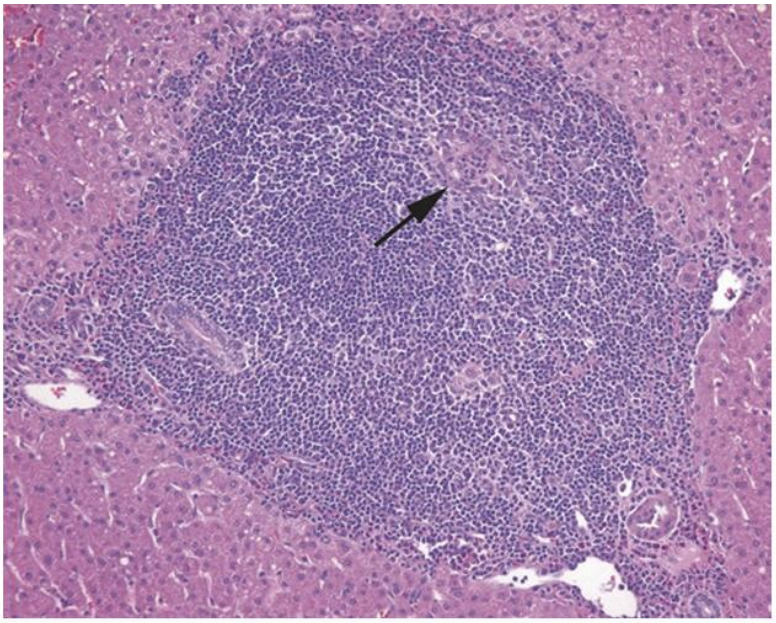


FIGURE 9.9. Primary biliary cirrhosis. There is a mononuclear and granulomatous inflammation of the portal tract, with destruction of a bile ductule (*arrow*).

- PSC

- p-ANCA +ve, Smooth Muscle Actin +ve
- M > F
- Both extrahepatic and large intrahepatic ducts
- IBD association, esp UC
- Not super specific picture histologically
  - Ductular proliferation
  - Cholestasis
  - "Onion skin" concentric periductal fibrosis

❖ Autoimmune Hepatitis (AIH)
- F > M
- Leads to chronic hepatitis with portal inflame, interface activity, and prominent plasma cells
- ANA and SMA +ve

Hepatocellular Neoplasms and Mimickers

❖ FNH
- Island of cirrhosis in background of normal liver
- Multiple cell types present
- Fibrous septae
- Central stellate scar
- Bile ducts and capsule present

❖ Adenoma
- Females on OCP
- Masses are
  - Circumscribed
  - Partially encapsulated
  - Bland looking hepatocytes
    - May be pale due to steatosis or glycogen storage
  - "orphan arteries" or "naked arteries"
    - Prominent arterioles
  - No bile ducts or central veins
  - 1 cell thick plates (every cell touches reticulin)
  - 4 classes molecularly
    - Steatotic adenomas (HNF1α mutated)
    - Inflammatory (telangeiectatic) adenomas
    - β-catenin activated adenomas
    - None of the above

❖ Well differentiated HCC
- Can look like adenoma but occurs in setting of cirrhosis
- No bile ducts of central veins
- Large hyperchromatic nuclei
- Plates are 3 cells thick, unlike in adenoma which are 1 cell thick
- Pseudo-acinar formation may suggest adenocarcinoma
- Aka Hepatoma

- Fibrolamellar HCC
  - A variant in children and young adults
  - Oncocytic cells with prominent nucleoli in fibrotic stroma

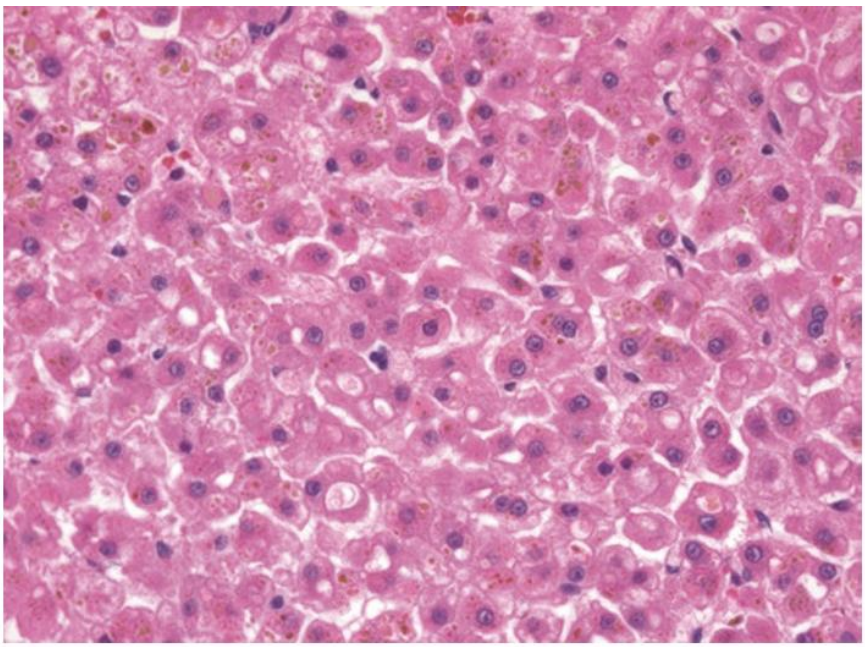


FIGURE 9.10. Well-differentiated hepatocellular carcinoma. Golden bile can be seen in the tumor cells, as well as pseudo-acinar formation. Portal tracts are absent.

- Poorly differentiated HCC
  - Very pleomorphic, can be hard to identify as liver

Biliary Neoplasms and Mimickers

- Bile duct adenoma
  - <1cm in size
  - Subcapsular
  - NO bile production, may have mucin production
  - Bile duct proliferation

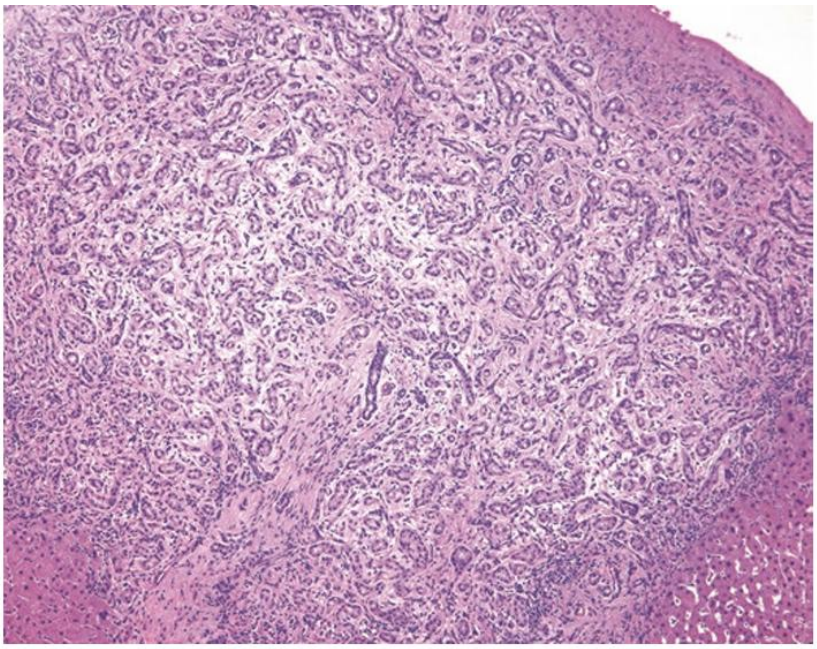


FIGURE 9.11. Bile duct adenoma. This is a benign, well-circumscribed tangle of proliferating bile ducts with associated edema, which may mimic desmoplasia. Bile is absent, and there is no significant cytologic atypia.

- Bile duct hamartoma
  - aka “von Meyenburg complex”
  - <1cm
  - Subcapsular
  - BILE
  - More tortuous bile duct proliferation than bile duct adenoma
- Mucinous cystic neoplasm
  - Females
  - Large cyst lined with bland mucinous epithelium over an ovarian type stroma
- Cholangiocarcinoma
  - History is the best way to distinguish this lesion
  - No bile
  - Mucin is common

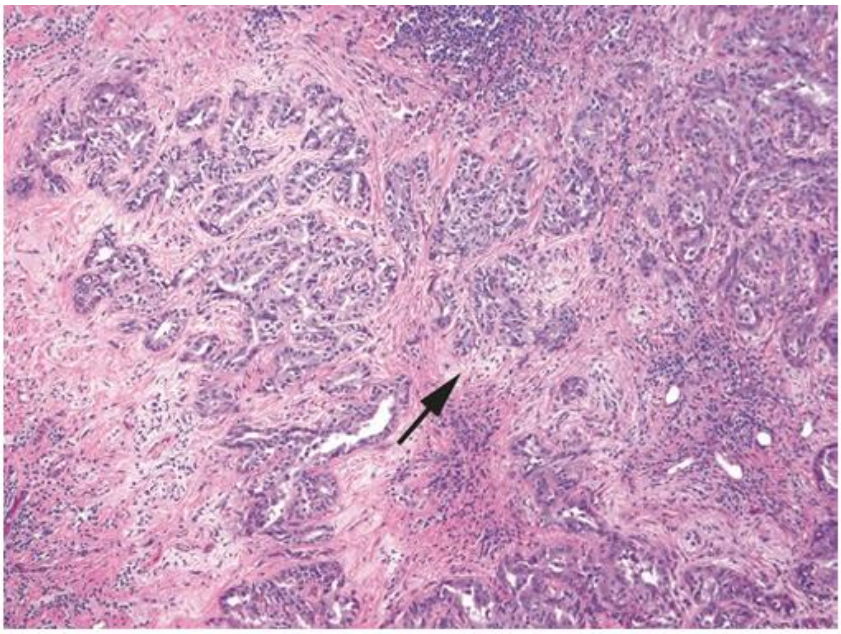


FIGURE 9.12. Cholangiocarcinoma. Although this is a generic adenocarcinoma without unique features, cholangiocarcinoma produces an intense desmoplastic response in the stroma (*arrow*; the pale swirling fibrosis surrounding the malignant glands).

Vascular Neoplasms and Mimickers

- See Text for commentary on cavernous hemangioma, epithelioid hemangioendothelioma, angiomyolipoma, angiosarcoma

***Chapter 10* – Pancreas**

***Chapter 11* – Prostate**

***Chapter 12* – Bladder**

Normal

- TC epithelium
  - 5 to 7 layers thick
  - cells do not significantly mature as they go superficial
  - oblong nuclei, with "polarity"
  - nuclei 2x – 3x The size of lymphocytes
  - mitoses only at the basal layer
  - Umbrella cells have a typical nuclei

von Brunn Nest – invaginated urothelial epithelium

Cystitis cystica – von Brunn Nest with a lumen

Cystitis glandularis – cystitis cystica with goblet cells or metaplasia where cells are columnar

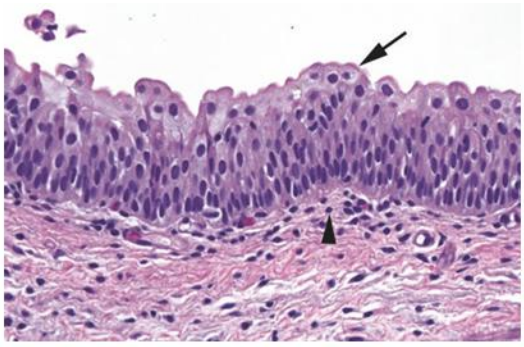


FIGURE 12.1. Normal urothelium. The urothelial cells form a layer five to seven cells thick, with large umbrella cells sitting on top (*arrow*). The urothelial nuclei are generally polarized and oriented perpendicular to the surface, with the exception of the umbrella cells. The nuclei are two to three times the size of a lymphocyte (*arrowhead*).

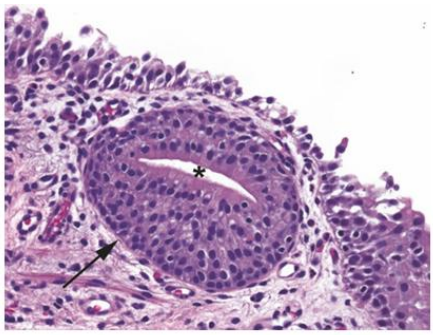


FIGURE 12.2. Von Brunn's nest and cystitis glandularis. The normal urothelium has invaginated down into the lamina propria, forming a rounded von Brunn's nest (*arrow*). The center of the nest has acquired a lumen and columnar cell metaplasia (*asterisk*), which is known as cystitis glandularis.

Cystitis

Granulomatous cystitis - secondary to BCG therapy

Polyploid cystitis

- associated with anything that injures the bladder such as catheters calculi or fistula's
- Akin to inflammatory polyps but in the bladder

Interstitial cystitis - usually diagnosed on cystoscopy. Diagnosis of exclusion on Histology

Schistosoma induced cystitis

- Eggs are extruded into the bladder wall
- Eggs are visible at 4x
- the eggs are dark purple oval bodies with single spines

Malakoplakia

- Rare
- due to a defective inflammatory response
- yellow plaques seen on cystoscopy
  - Yellow plaques are due to sheets of epithelioid histiocytes
  - *Epithelioid histiocytes have inclusions that look like archery targets, "Michaelis-Gutmann bodies"*

Urothelial Neoplasms

Urothelial Carcinoma

- Classified as flat or papillary
- 90% of bladder neoplasms

❖ Carcinoma in situ (= flat CIS)
- ➢ Can go develop directly into Invasive Urothelial Carcinoma
- ➢ Features
  - ▪ Increased nuclei size
    - at worst 4 -5x the size of lymphocytes
  - ▪ hyperchromatic nuclei with irregular "boulder like" outlines
  - ▪ denuded urothelium
  - ▪ partial or full thickness
    - even a few malignant cells are enough to justify the diagnosis

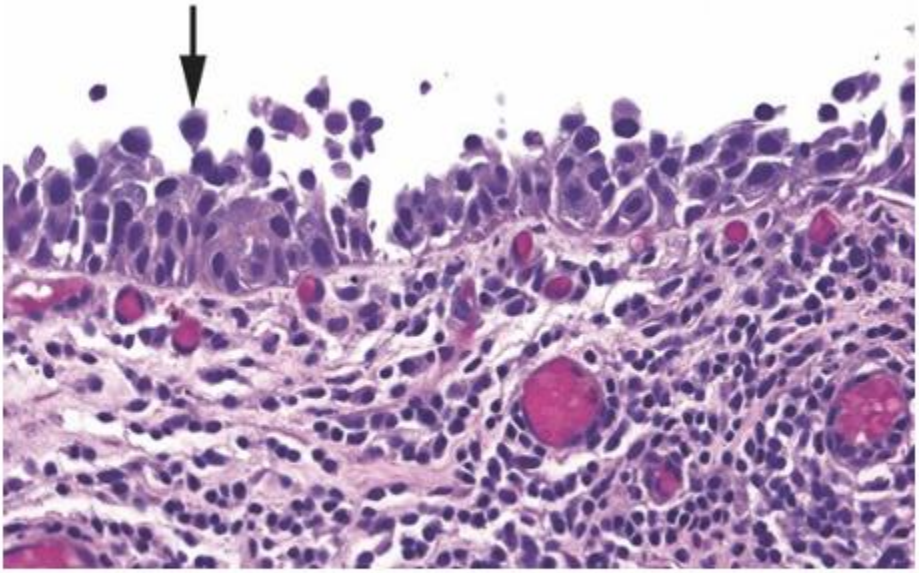


FIGURE 12.3. Flat carcinoma in situ. The urothelium is partially denuded (stripped of cells), but the cells that remain show enlarged, round, hyperchromatic nuclei appearing to pop off the surface (*arrow*).

- ➢ Compare the nuclear size to the underlying lymphocytes.

Papillary lesions

❖ **Papilloma**
- ➢ Nuclei
  - ▪ small
  - ▪ Polarized
  - ▪ often with nuclear grooves
- ➢ No mitoses
- ➢ Epithelium = normal thickness
- ➢ No risk of malignant transformation
- ➢ Papillary hyperplasia is a mimicker: Undulating wave-like urothelium without true fibrovascular cores

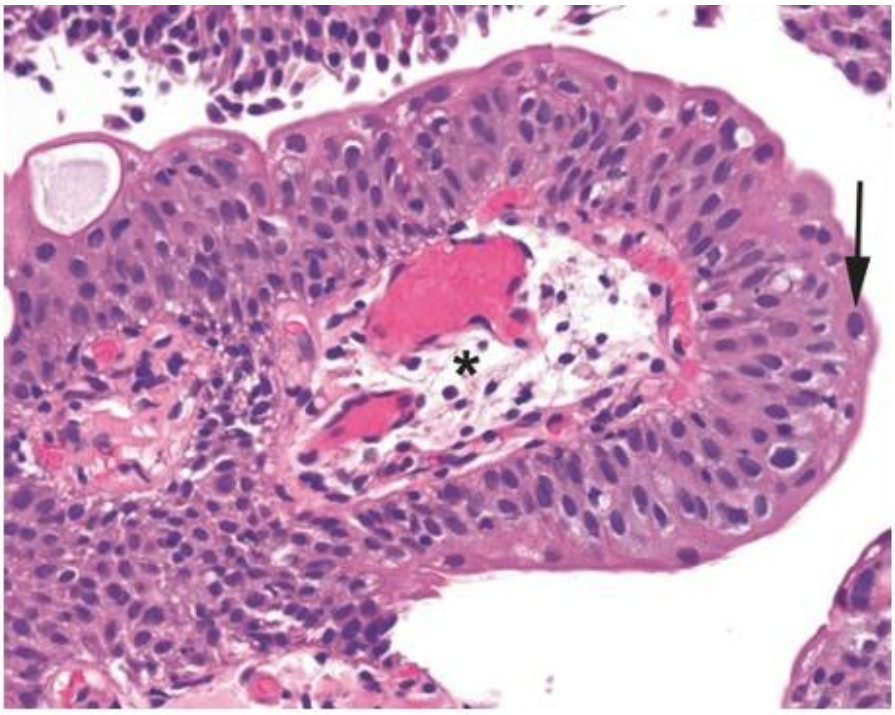


FIGURE 12.4. Papilloma. There is a prominent fibrovascular core (*asterisk*), and the urothelium resembles normal urothelium both in thickness and in bland cytology. Some large umbrella cells are visible (*arrow*).

- **PUNLMP**
  - Nuclei
    - Every nuclei looks the same, unlike low-grade papillary urothelial carcinoma
    - Normal NCR
    - Only rare mitoses
    - Polarized
  - Increase thickness of epithelium, But still appears well organized

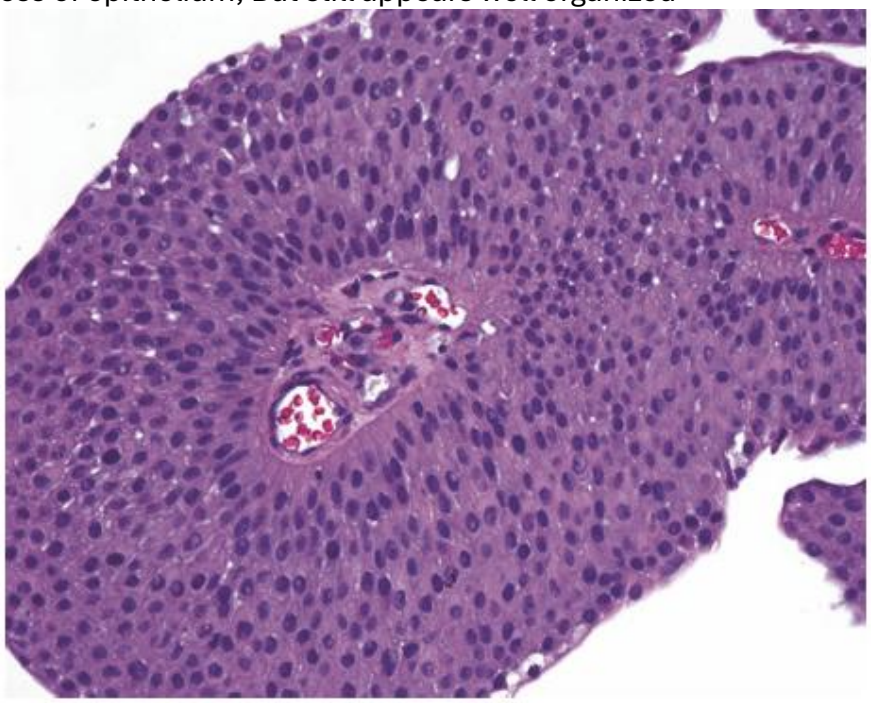


FIGURE 12.5. Papillary urothelial neoplasm of low malignant potential. This papillary lesion shows an increased thickness relative to normal urothelium, but the cells remain uniform and organized.

- **Low Grade Papillary Urothelial Carcinoma**
  - Increased epithelial thickness
  - Nuclei
    - Mostly polarized
    - Atypical
      - random slightly hyperchromatic, slightly enlarged nuclei
      - Unlike PUNLMP where every nuclei looks the same
    - Mitoses uncommon but present

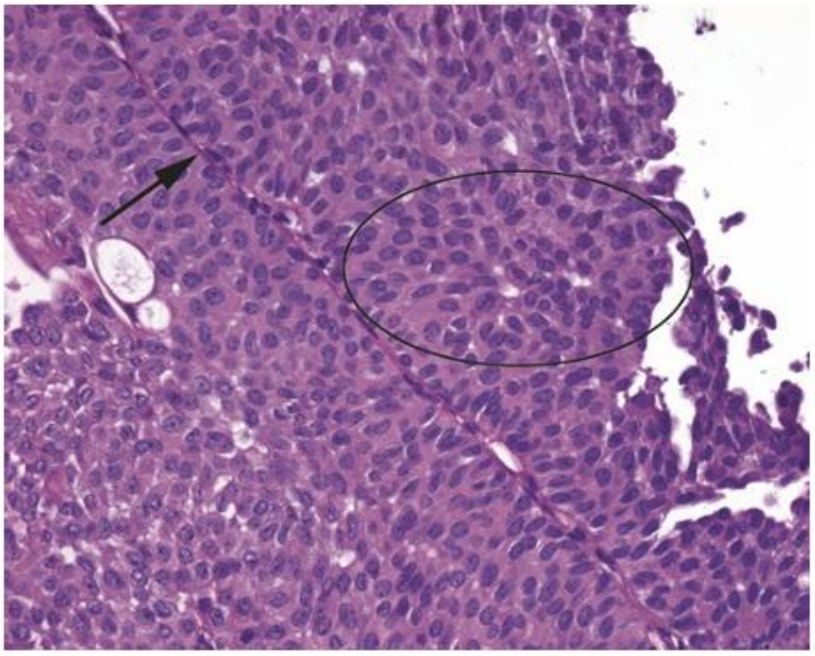


FIGURE 12.6. Low-grade papillary urothelial cancer. The fibrovascular cores (*arrow*) are lined by urothelium that is thicker than normal, increasingly disorganized (*circle*), and with enlarged nuclei.

- **High Grade Papillary Urothelial Carcinoma**
  - Characteristics
    - Disordered epithelium
    - No nuclear polarity
    - ± Nucleoli
    - Hyperchromatic
    - Nuclear pleomorphism
    - Mitosis is present at all levels
    - Non-urothelial differentiation possible (Squamous or glandular)
  - Only 5% needed to define lesion as high grade

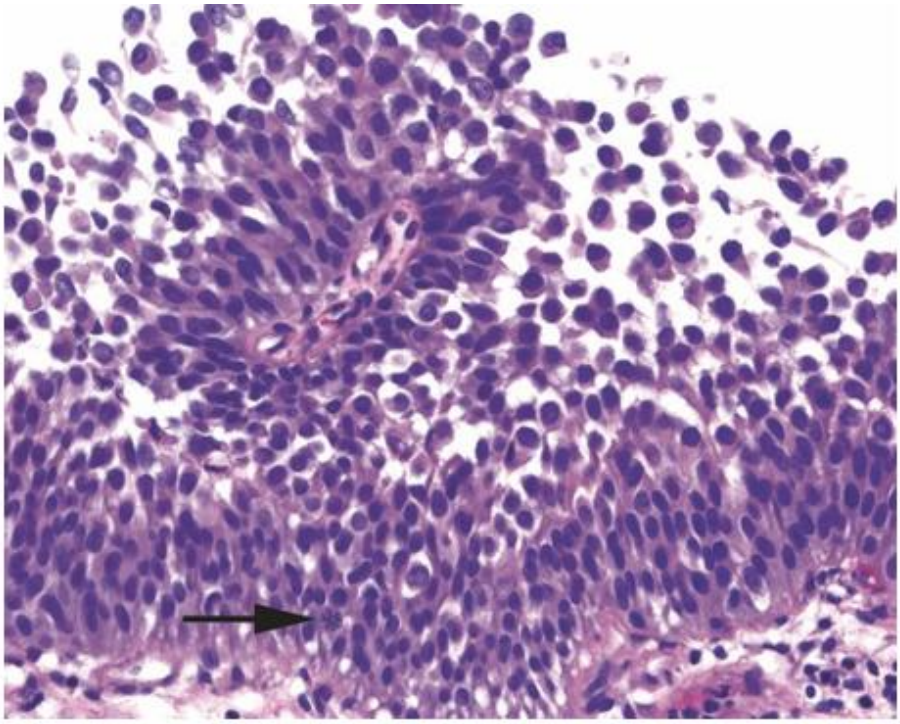


FIGURE 12.7. High-grade papillary urothelial cancer. This papillary lesion shows large, dark, pleomorphic nuclei popping off the surface, similar to carcinoma in situ (see Figure 12.3). A large mitotic figure is visible (*arrow*).

- **Invasive Urothelial Carcinoma, formerly TCC**
  - mostly arises from CIS or HGPUC
  - irregular tongues of cells pushing into lamina propria
  - retraction artifact
  - ± desmoplastic stroma
  - Paradoxical Differentiation: deep invasive cells acquire increasingly eosinophilic cytoplasm, mimicking maturing surface cells

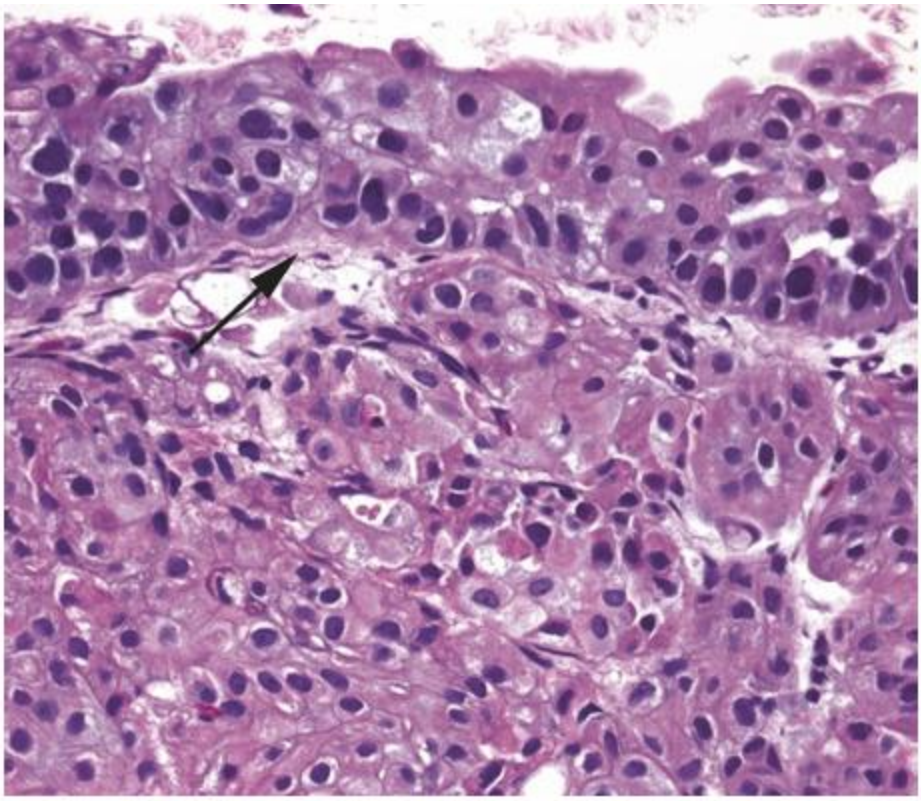


FIGURE 12.8. Invasive urothelial carcinoma. In this case, the carcinoma is arising out of flat carcinoma in situ, seen above the basement membrane (*arrow*). The nests of tumor in the lamina propria appear more pink than the surface carcinoma in situ, corresponding to paradoxical differentiation.

- More pink than the surface carcinoma in situ, corresponding to paradoxical differentiation.

Benign but Mimics Cancer

- **Inverted papilloma**
  - Urothelium looks benign, like in papilloma
- **Nephrogenic adenoma**
  - *A **Single** layer epithelium* that can take many forms:
    - Cuboidal cells lining papillary fronds
    - hobnail cells lining vessel like structures
    - small infiltrative looking tubules, sometimes with thyroid like colloid
    - small tubules mimicking signet ring cell carcinoma
- **Reactive changes**
    - Enlarged, euchromatic nuclei
    - Chromatin evenly blue-grey
    - Nuclear contour smooth and oval
    - Nucleoli may be prominent
  - Should raise your threshold for CIS when inflammation is high
- **Inflammatory pseudotumors - Post-op Spindle Cell Nodule**
  - Arises after a procedure
- **Inflammatory pseudotumors - Inflammatory Myofibroblastic Tumour**
  - true neoplasm
- Both of the 2 above:
    - Myxoid stroma

- tissue culture like pattern,
- inflammatory cells
- frequent mitosis

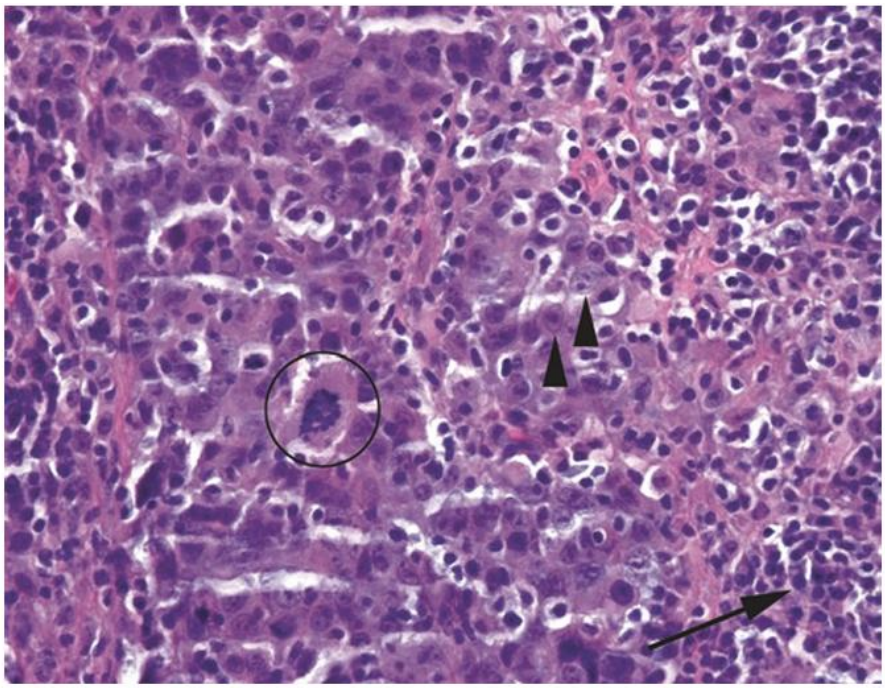
➢ Can be infiltrative

➢ Unlike Sarcoma
- Pale nuclei with smooth round contours
- nucleoli

Cancerous but Mimics Benign

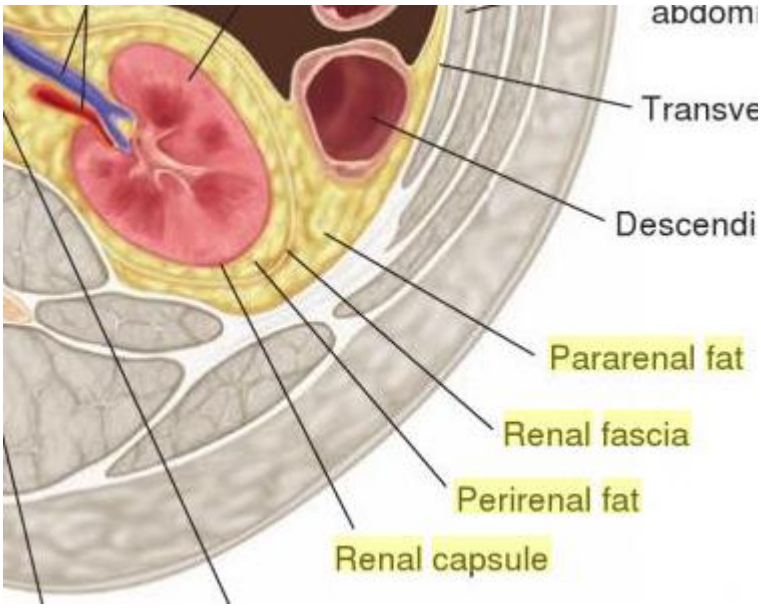
❖ Nested TCC
- ➢ Looks like von Brunn nests but is actually an aggressive carcinoma
- ➢ Look for
  - Infiltrative pattern at the base
  - architecturally complex, closely packed small nests

❖ Lymphoepithelial-like Carcinoma
- ➢ Easy to mistake for raging inflammation with tissue destruction
- ➢ Atypical carcinoma cells seemingly fade into the background
  - The nuclei tend to be large and bubbly
  - The nuclei are not very carcinoma-like



➢ **FIGURE 12.12.** Lymphoepithelial-like carcinoma. The malignant cells (*arrowheads*) are almost obscured by the background of lymphocytes (*arrow*). Atypical mitoses are present (*circle*).

Chapter 13 **– Kidney**



Cystic Lesions

- Simple cysts
  - Very common
  - Essentially a dilated tubule with low cuboidal or flattened epithelium lining
  - No clear cells

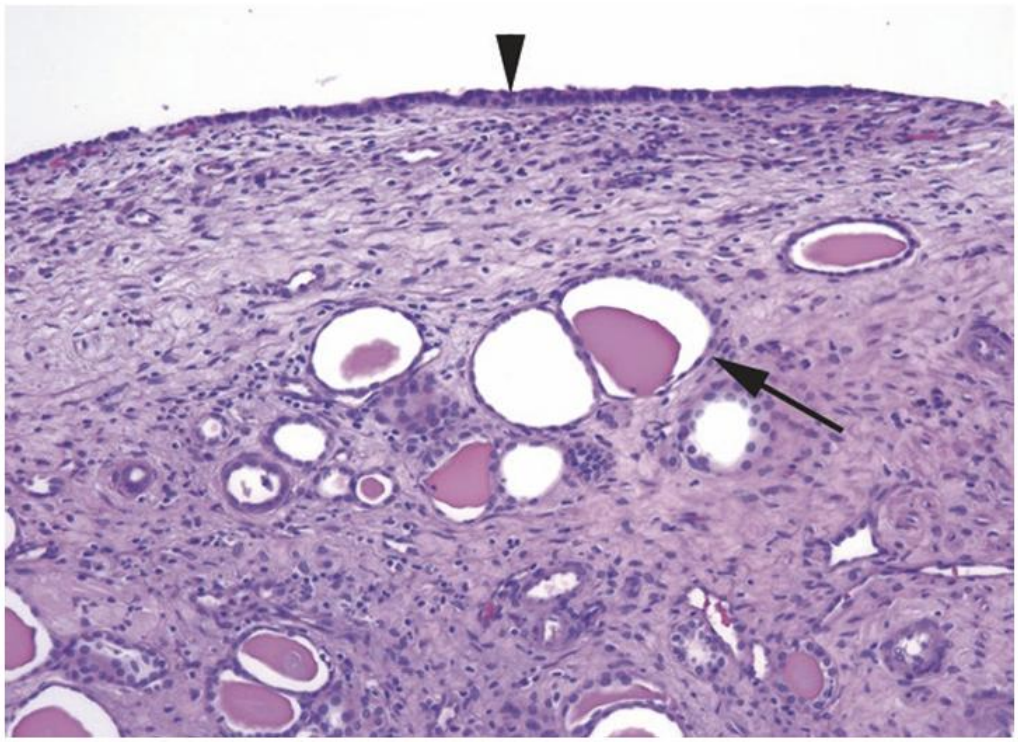


FIGURE 13.1. Simple cyst. The cyst lining (*arrowhead*) consists of a *thin* layer of cuboidal cells. Below the cyst, dilated tubules filled with proteinaceous fluid are visible (*arrow*).

- Cystic Nephroma
  - Found mostly in women (ectopic ovarian stroma lesion)
    - Related to MEST

- Is a multilocular cyst with a background of ovarian type stroma
  - ER and PR positive
  - Lining is cuboidal to hobnail
  - No clear cells

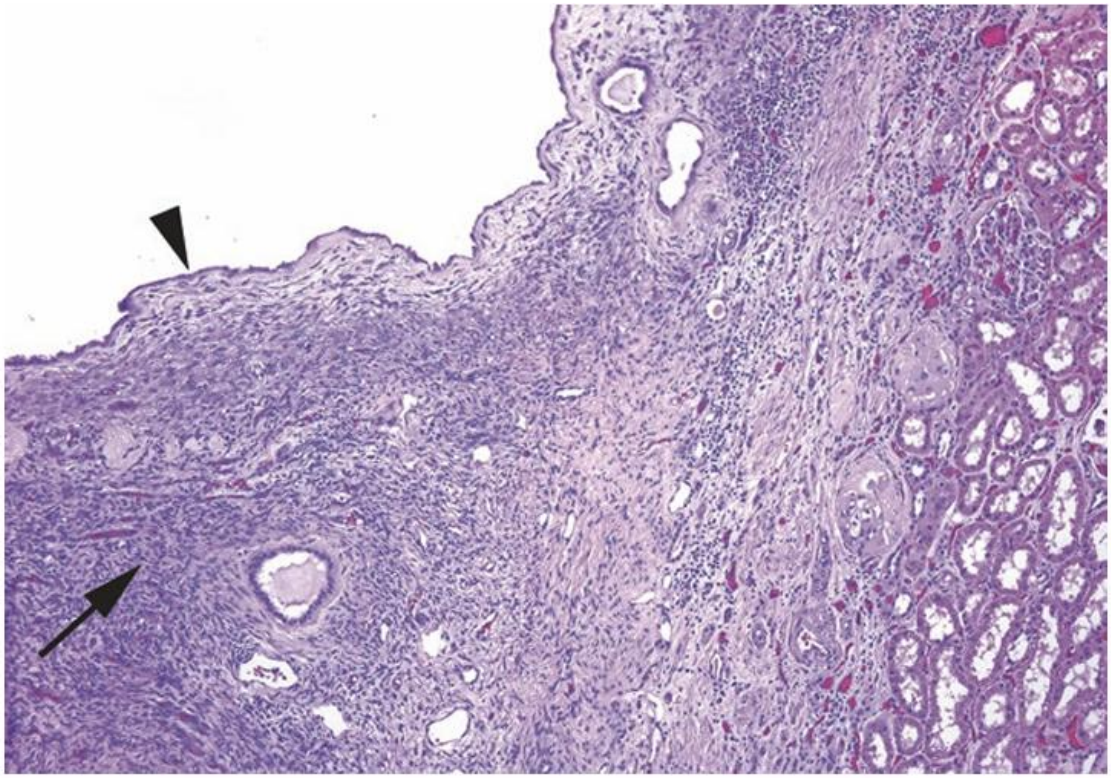


FIGURE 13.2. Cystic nephroma. Like the simple cyst, this cyst is lined with bland epithelial cells (*arrowhead*). However, there is adjacent spindly stroma, similar to ovarian stroma (*arrow*). Kidney parenchyma is seen at the *right*.

❖ Multi-locular cystic neoplasm of low-malignant potential (cc-RCC lining a cyst)
  ➢ cc-RCC can also undergo cystic degeneration

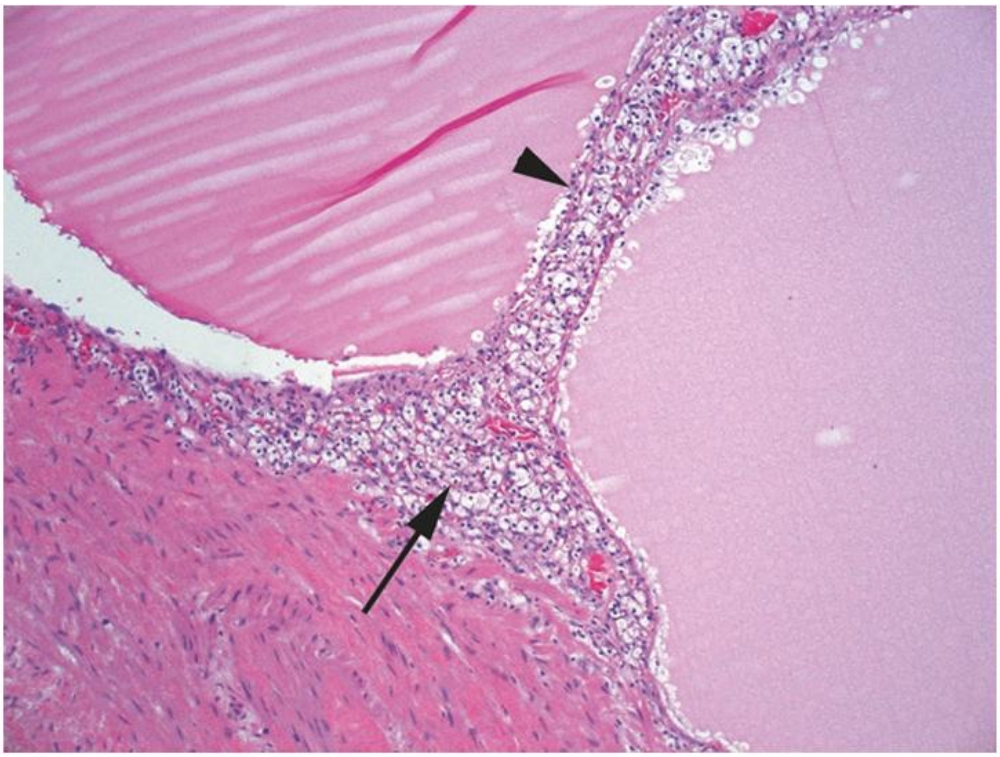


FIGURE 13.3. Multilocular cystic renal neoplasm of low malignant potential. The cyst lining and fibrovascular septa (*arrowhead*) are composed of clear cells with small dark nuclei (*arrow*); compare these cells to conventional renal cell carcinoma (see Figure 13.6).

Lesions with Multiple Cell Populations

- Angiomyolipoma
  - Can be dominated by one or two of the 3 components.
  - KEY: recognize that you have a mass lesion and the unusual vessels that go with
  - Features
    - Large, tangled, tortuous, thick walled, high analysed vessels
    - smooth muscle cells that seem to spin off of the vessel walls
    - pushing borders but not encapsulated
    - HMB-45 and MelanA +ve, S100 -ve
  - Part of PEComa family, all of which are melanoma marker +ve and S100 negative

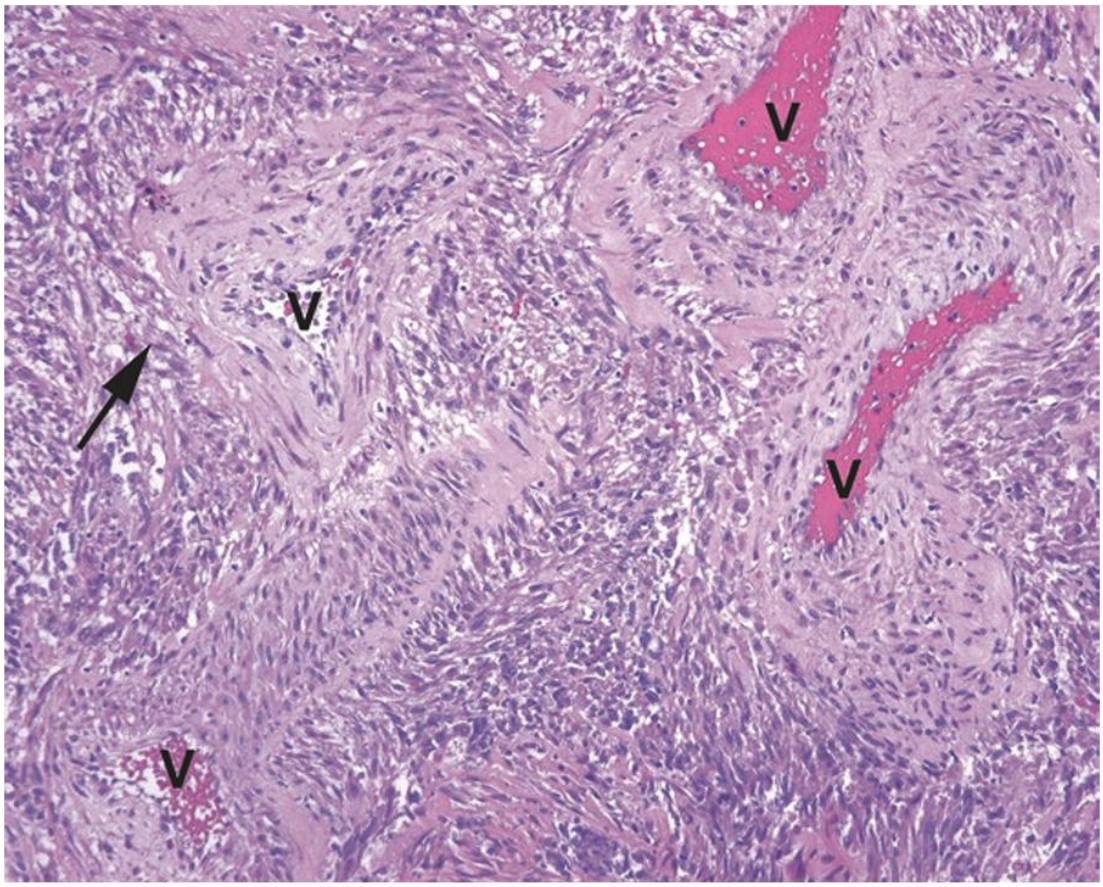


FIGURE 13.4. Angiomyolipoma. This example does not show the fatty component, but the prominent vessels (*V*) and smooth muscle components here are classic. In angiomyolipoma, the spindle cells seem to merge with, or spin off from, the thick-walled vessels (*arrow*).

- Mixed-Epithelial & Stromal Tumour (MEST)
  - Rare
  - Like a fibroadenoma of the kidney
  - Cytologically benign tubules of various size set in a background of bland spindled stroma
    - Stroma may have smooth muscle, fibroblasts or myofibroblasts
  - ER PR positive like the cystic nephroma (may be on a spectrum with cystic nephroma)

Solid Lesions

- There are no clear cell adenomas, even small focus of clear cells is carcinoma
- Scrub mistake 101
  - Mistaking the zona fasciculata of the adrenal for RCC

- RCC = no cytoplasmic vacuoles coming off the nuclei … adrenal DOES!

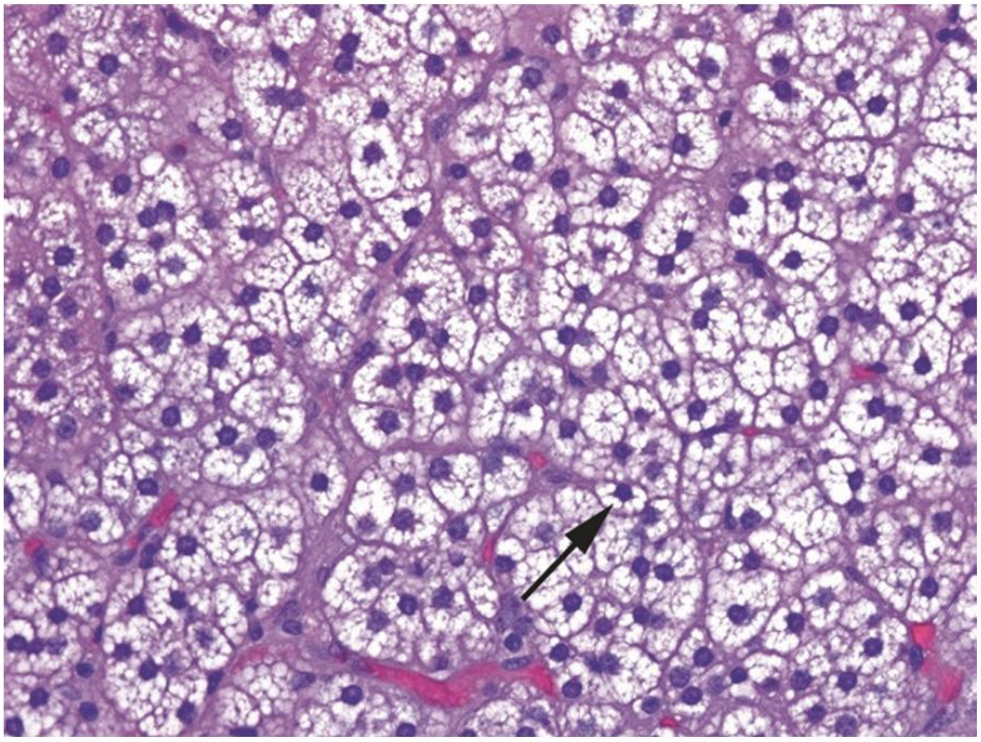


FIGURE 13.5. Normal adrenal cortex. Unlike clear cell carcinoma, the cells of the adrenal cortex have discrete cytoplasmic vacuoles that indent the nuclei, creating a stellate outline around the nucleus (*arrow*).

❖ cc-RCC
- Acini of cells separated by capillaries
- No desmoplasia
- Distinct cell membranes
- Celar cells at least focally
- Grading
  - I: nuclei resemble lymphocytes, no nucleoli
  - II: nuclei still small, +/- tiny nucleoli, but with open chromatin
  - III: nuclei still small, +/- tiny nucleoli, but with open chromatin
  - IV: easily recognizable nucleoli, larger nuclei
  - V: pleomorphic and hyperchromatic nuclei with large nucleoli

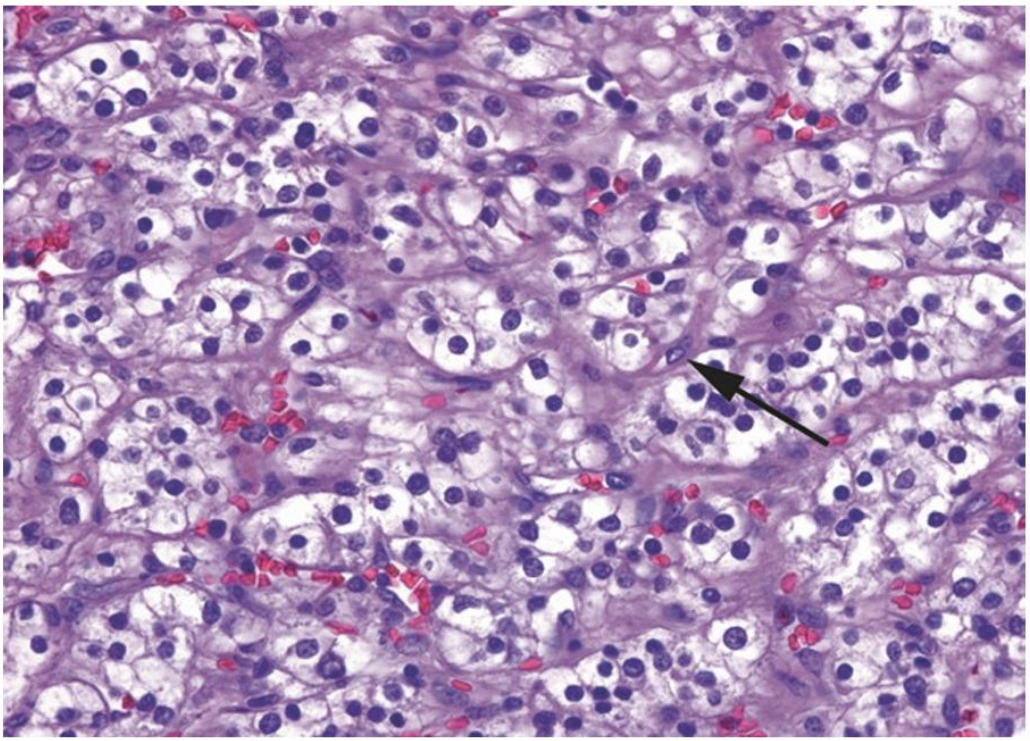


FIGURE 13.6. Clear cell renal cell carcinoma. The tumor is composed of packets of clear cells, divided by delicate fibrovascular septa (*arrow*). These septa are characteristic of renal cell carcinoma and are seen even in high-grade or metastatic tumors. The nuclei in this example are enlarged, but nucleoli are visible only at high power, consistent with ISUP grade II.

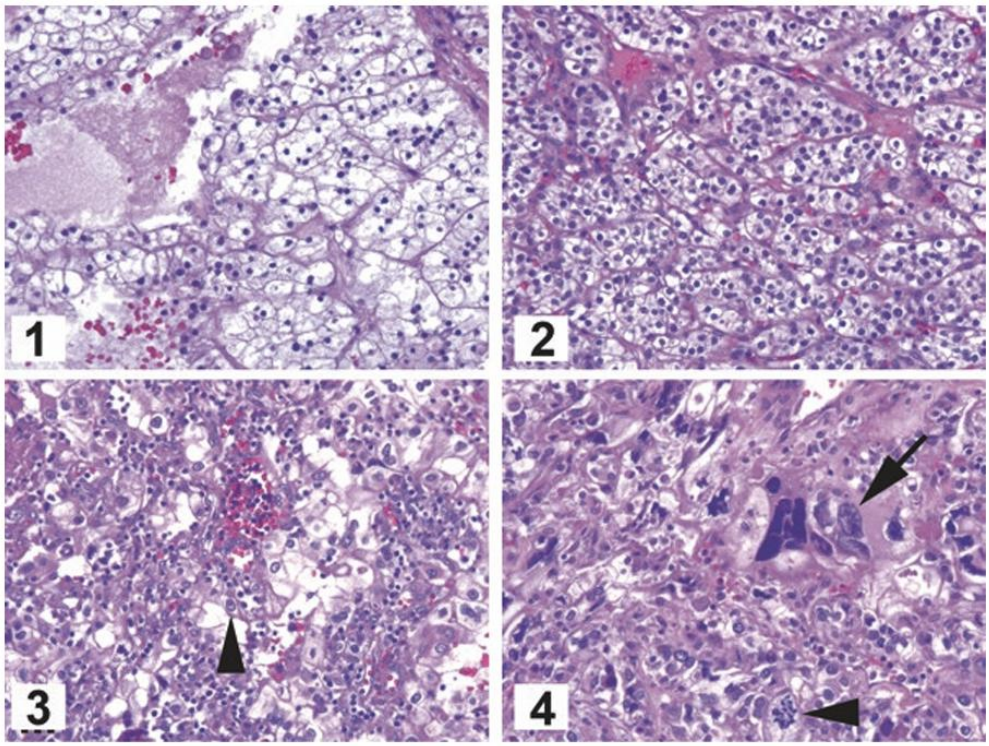


FIGURE 13.7. ISUP grades shown at 10×. *1* Grade I: Nuclei are small and dense, resembling lymphocyte nuclei. *2* Grade II: Nuclei are larger, but no nucleoli are visible at this power. *3* Grade III: Nuclei are even larger, now with some visible nucleoli (*arrowhead*). *4* Grade IV: Nuclei are frankly anaplastic (*arrow*) with large atypical mitoses (*arrowhead*). All images are taken at the same magnification.

❖ chromophobe-RCC
- regular variant is pale pink to clear
- not encapsulated
- eosinophilic variant possible
  - resembles oncocytoma but has perinuclear clearing (unlike oncocytoma)

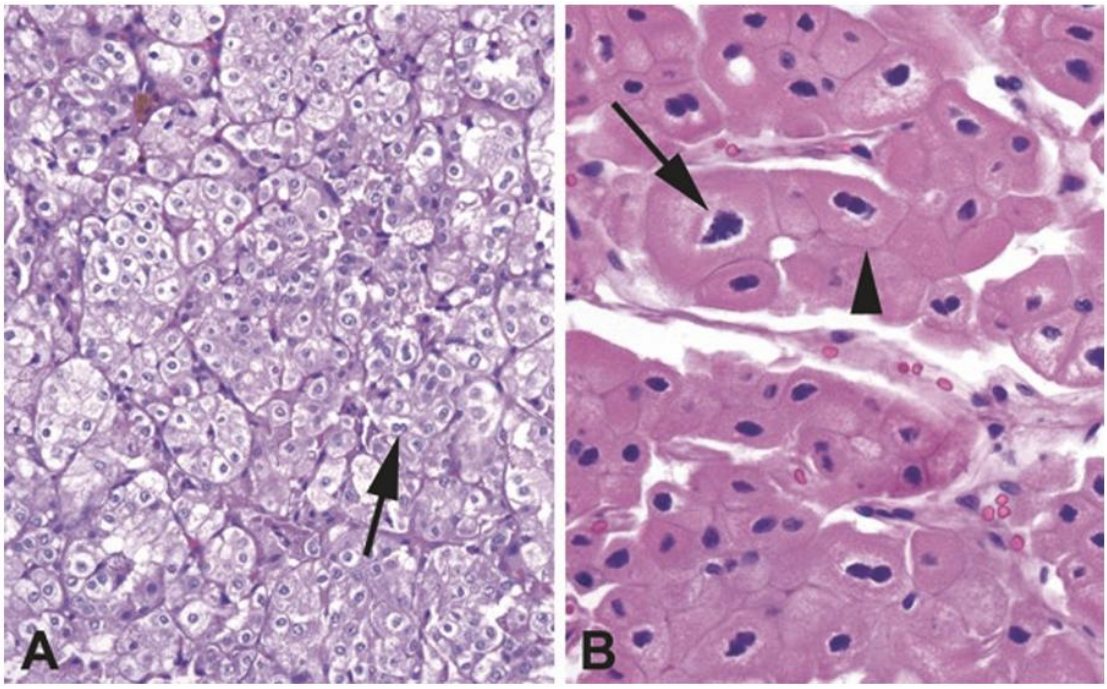


FIGURE 13.8. Chromophobe renal cell carcinoma. (**a**) Low power view of chromophobe, showing packets of cells with clear-to-pink cytoplasm, perinuclear halos, and occasional binucleate cells (*arrow*). The cell membranes are distinct, giving the tumor a cobblestone or alligator skin texture. (**b**) High power view of a chromophobe carcinoma, eosinophilic variant. Although the granular pink cytoplasm resembles an oncocytoma (see Figure 13.12), the nuclei are distinctly koilocytic, with crinkly outlines and perinuclear halos (*arrow*). In addition, the fine cellular membranes are preserved (*arrowhead*).

❖ Clear-Cell-Papillary RCC, aka Tubulopapillary, RCC
- Low grade clear cell neoplasm with papillary or tubular architecture
- Features include:
  - clear cells with small, dense, dark nuclei, often **oriented with the nucleus on the luminal surface, and the cytoplasm towards the base**
  - fibrovascular cores or in small closely packed tubules
  - me show cystic degeneration
  - well circumscribed, often encapsulated

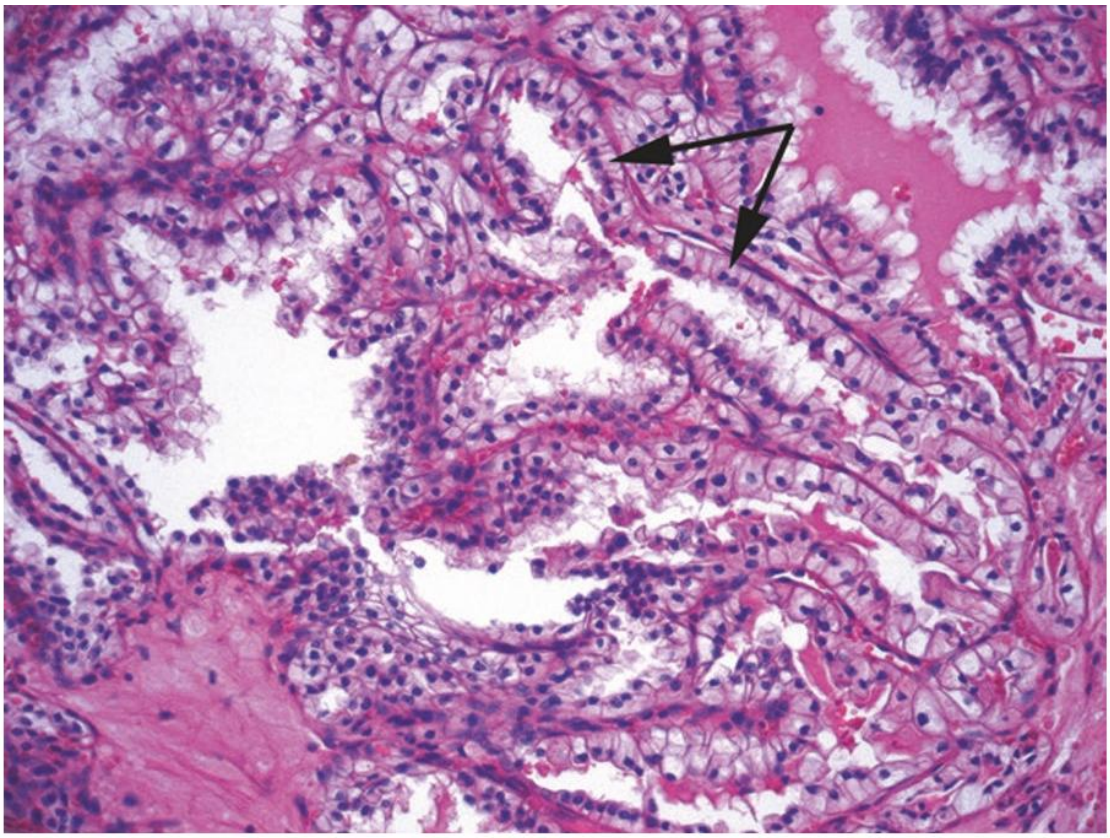


FIGURE 13.9. Clear cell papillary renal cell carcinoma. There are clear cells arranged on fibrovascular cores, creating a papillary pattern. The small dark nuclei are classically lined up at the luminal surface of the clear cells, rather than at the base (*arrows*).

- Mucinous Tubular Spindle Cell Carcinoma
  - Rare
  - Pale & bland overall
  - Mucin may no be prominent (∴ may not recognize it as a mucinous neoplasm)
  - Long array of narrow tubules
  - Indistinct cell borders
  - Nuclei are small round and pale

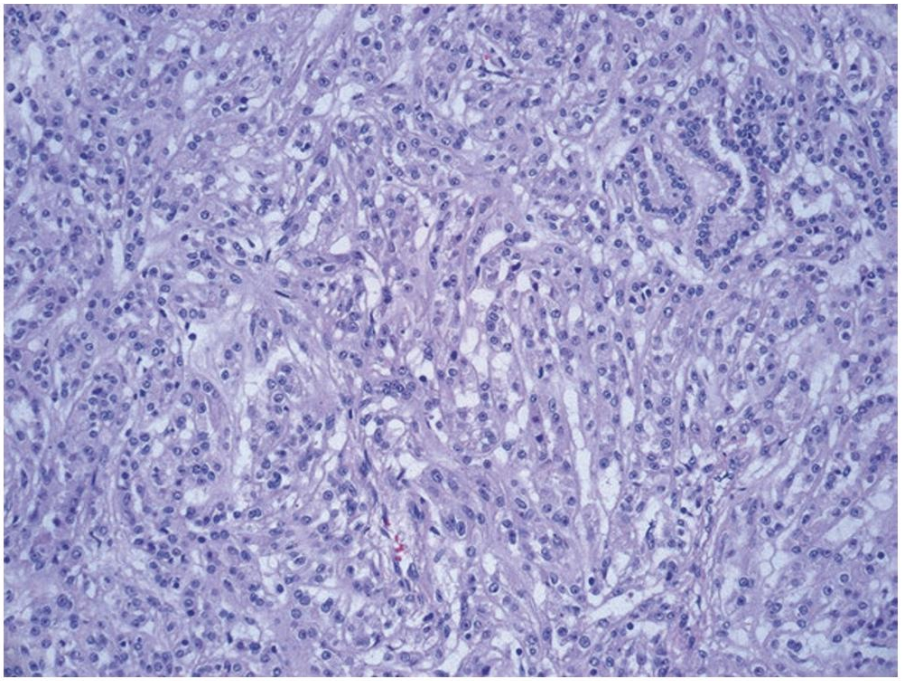


FIGURE 13.10. Mucinous tubular and spindle cell carcinoma. In an overall pale tumor, the nuclei are small and euchromatic and arranged in long tubules and areas of spindling.

- Oncocytoma
  - Gross
    - Mahogany-brown
    - Well circumscribed
    - Not encapsulated
    - ± stellate scar
  - Micro
    - Hypocellular stroma
    - Cells in nests/cords
    - Round cells w Regular round nuclei in dense pink cytoplasm
      - This regularity should strike you at low power, very diffrenent from a chromophobe
    - Features incompatible with the diagnosis
      - Perinuclear clearing†
      - Mitoses
      - PVI
    - Therefore, oncocytoma has
      - **No** perinuclear clearing
      - **No** Mitoses
      - **No** PVI

†Eosinophilic chromophobe has perinuclear clearing

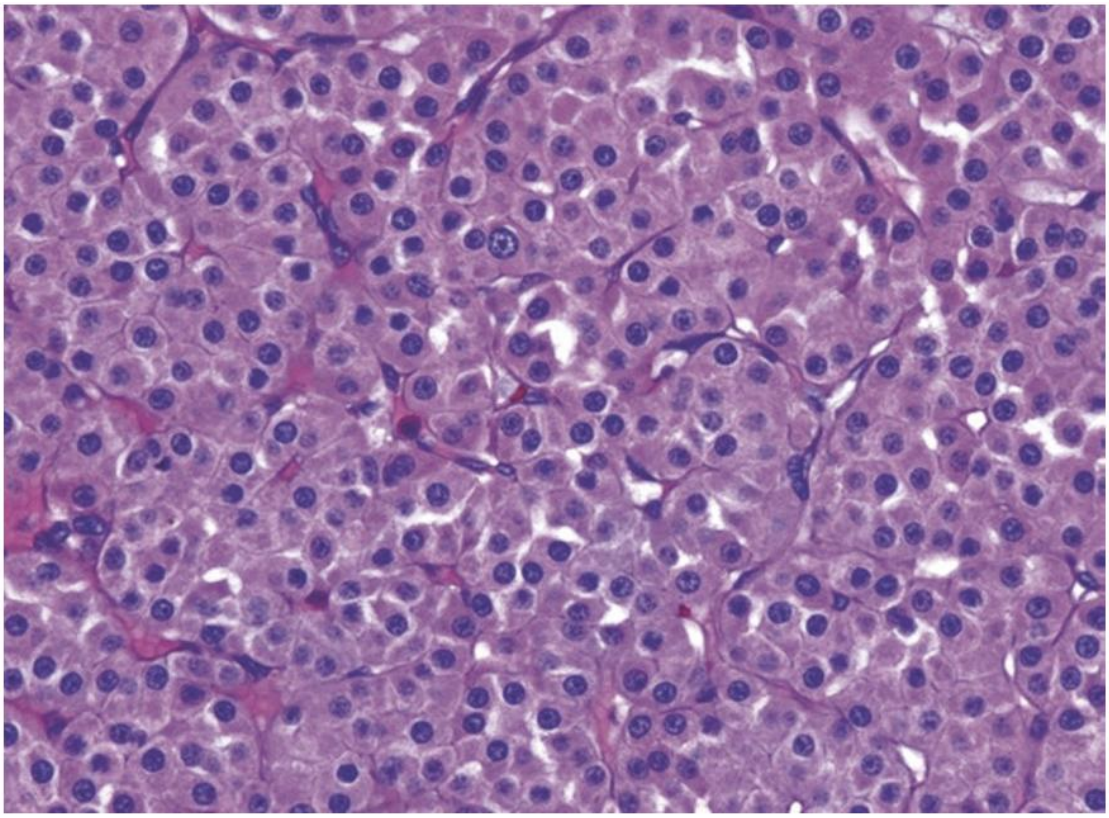


FIGURE 13.12. Oncocytoma. The nuclei are typically very round, uniform in size, and evenly spaced. Nucleoli may be seen, but there are no perinuclear halos. The cytoplasm is pink and granular, similar to oncocytic neoplasms elsewhere in the body.

- Papillary RCC
  - Type 1: blue at low power / low nuclear grade
  - Type 2: pink at low power / high nuclear grade
  - Architecture
    - Papillary
    - Solid
    - Trabecular
  - Classic (pathognomonic) image:
    - Fibrovascular cores packed with foamy macorpahges; lined by cuboidal cells with round nuclei
    - ± psammoma bodies
    - ±hemosidern-laden cells
    - ± focal clear cells

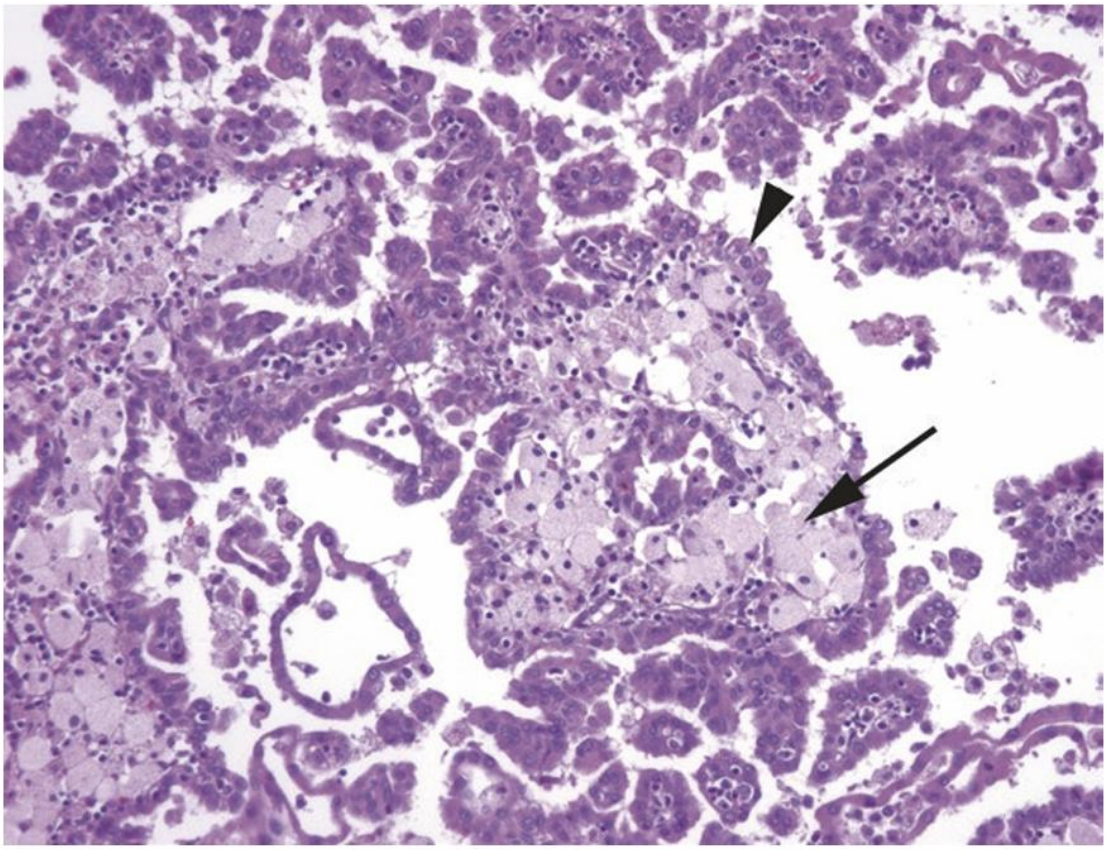


FIGURE 13.13. Papillary renal cell carcinoma, Type 1. The tumor cells are pink, not clear, and range from cuboidal to columnar (*arrowhead*). This tumor may grow as solid sheets and tubules, but finding papillary structures with central cores packed with foamy histiocytes (*arrow*) is diagnostic. Although the tumor in this example is of low nuclear grade, the cells have a relatively high N/C ratio, and therefore this would be somewhat blue on low power.

- Papillary Adenoma
  - A papillary and non-clear cell neoplasm of low grade
  - ≤15mm by definition
- Tubulocystic Carcinoma
  - Rare
  - A spongy collection of dilated tubules lined by fat pink apocrine-looking cells

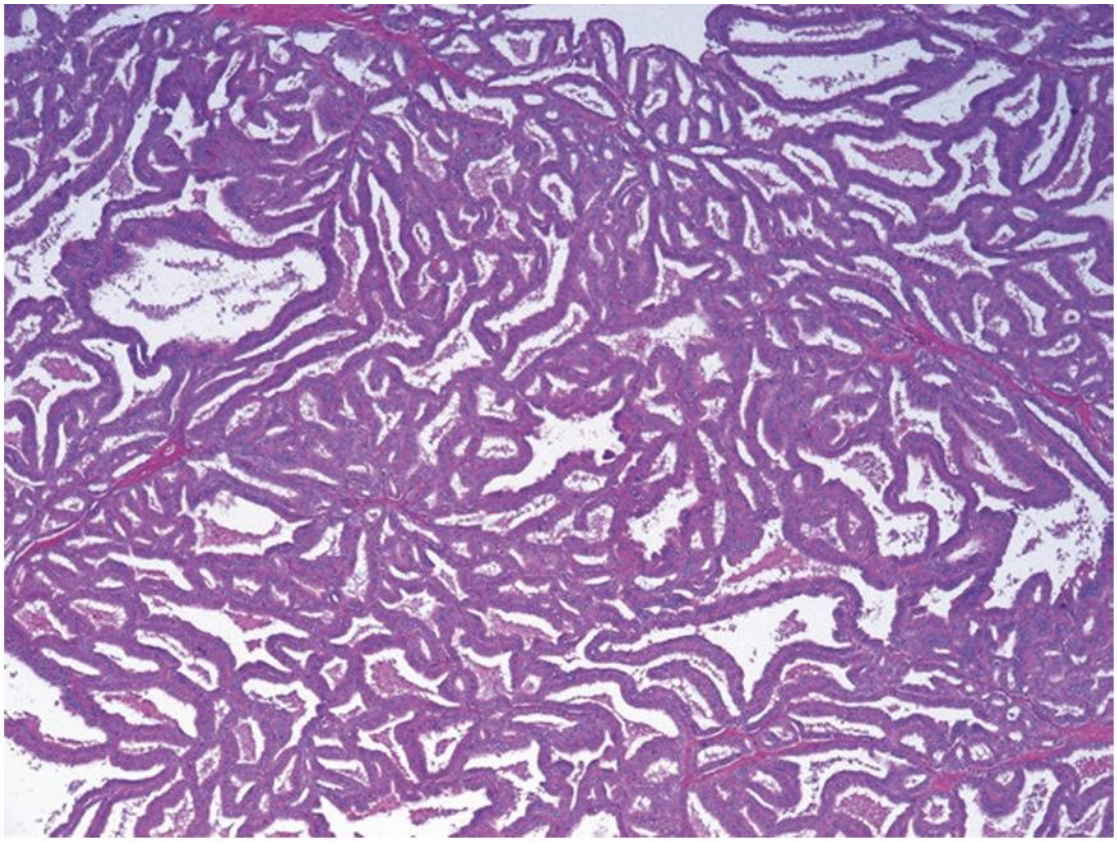


FIGURE 13.14. Tubulocystic carcinoma. This tumor consists of a spongy collection of dilated tubules lined by plump pink apocrine-looking cells with round nuclei.

- Collecting Duct Carcinoma
  - Rare
  - High grade
  - Arises from the medulla
  - Desmoplasia
  - CEA stain +ve
  - May stain for mucin
- Metanephric Adenoma
  - 1x diagnosis (very blue)
  - Looks like a Wilm's Tumour (may be related)
  - Small, round blue cell tumour
  - Not encapsulated but circumscribed
  - Patterns: Tiny tubules to serpiginous gland-like structures

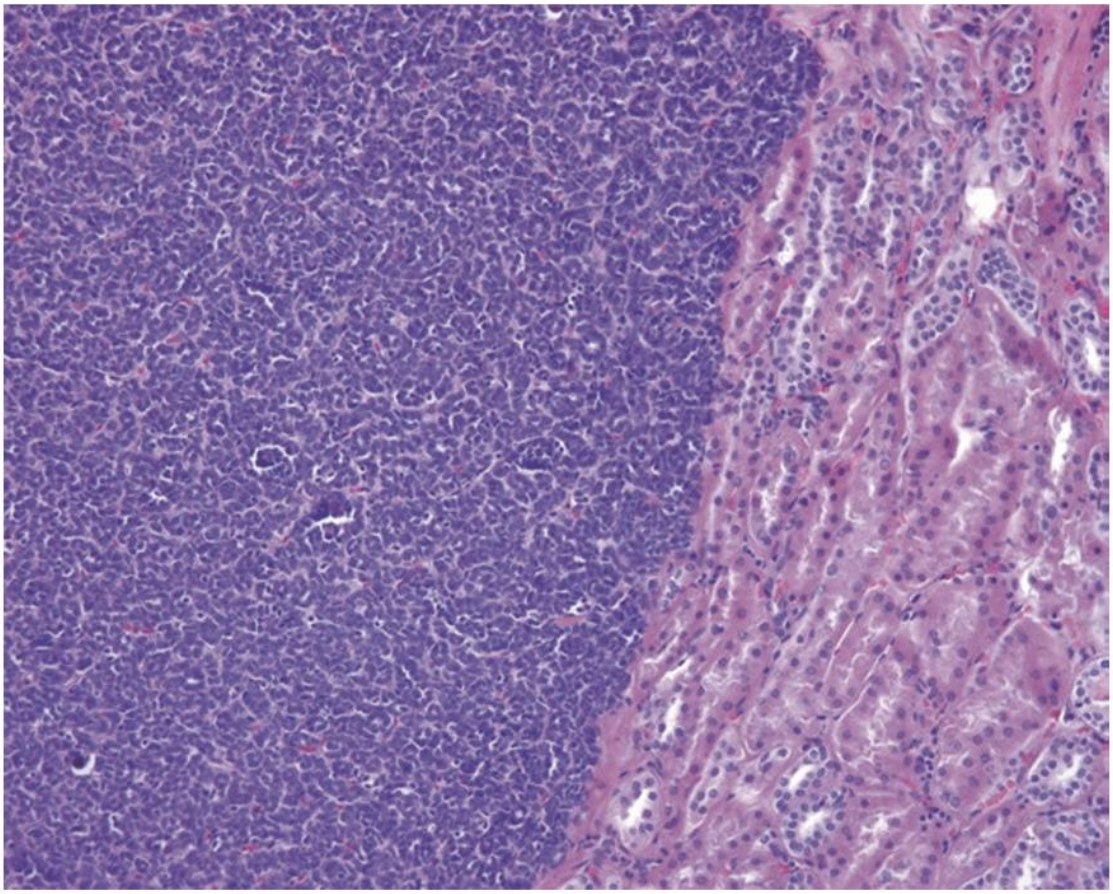


FIGURE 13.15. Metanephric adenoma. This benign tumor is the bluest of them all because of the very high N/C ratio of the cells. Here you can see tiny primitive blue tubules on the *left*, adjacent to the normal kidney on the *right*.

Pediatric Kidney

- Wilms Tumour
  - Key terms
    - Nephrogenic rests: abnormally persistent foci of embryonal cells
    - Blastema:
      - sheets of undifferentiated embryonal cells
      - The prototypical small round blue cells
    - Anaplasia:
      - defined by large hyperchromatic nuclei and abnormal mitotic figures.
      - Histology is defined as favourable or unfavourable based on the presence of anaplasia
  - Micro
    - Triphasic (blastema, stroma, epithelium)
    - One component may predominate
    - Should be encapsulated
      - Infiltration would suggest a hyperplastic nephrogenic rest
    - Post chemotherapy changes
      - *Skeletal muscle maturation*
      - Necrosis, fibrosis, histiocytes

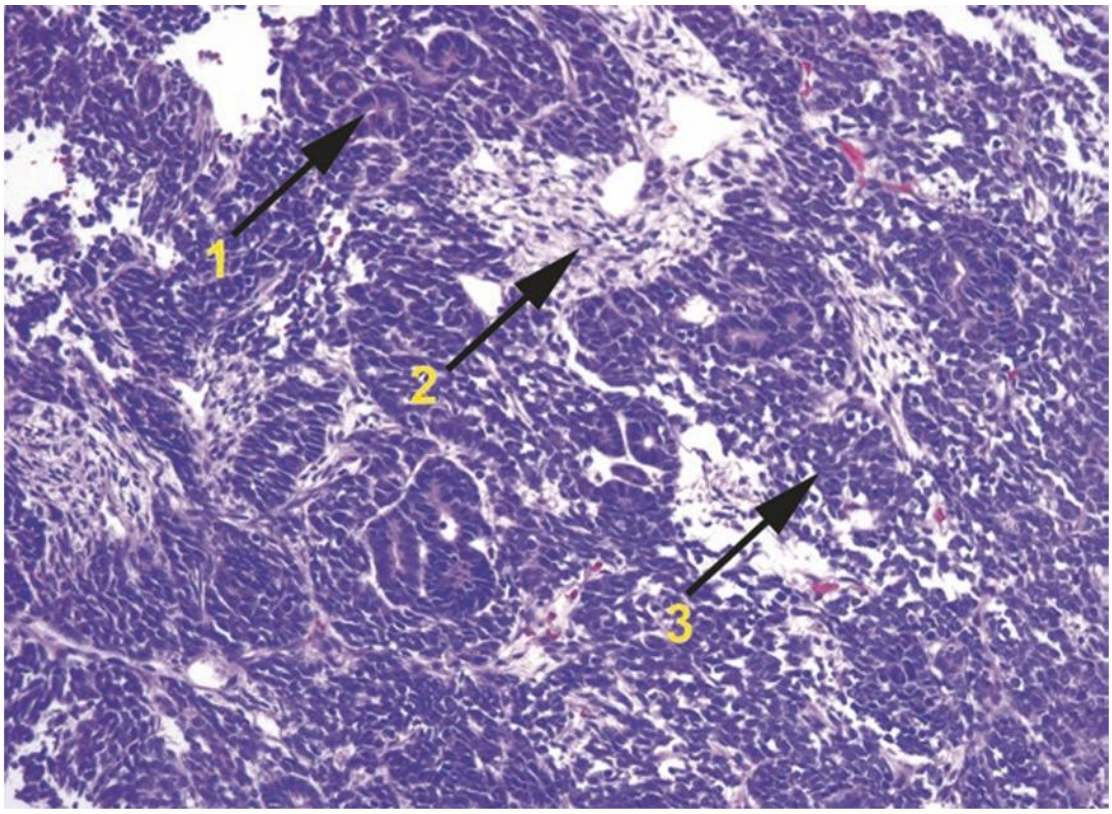


FIGURE 13.16. Wilms tumor. This small round blue cell tumor classically has three components: *1* epithelium, in which the cells form primitive tubules; *2* stroma, the mesenchymal component; and *3* blastema, the most primitive and undifferentiated component. Ratios may vary by tumor.

Medical Kidney

Skipped most of this part. More notes on Google Drive/Notes On Cases/Medical Kidney. ***Grand***.

- The four main compartments of the kidney
  - Glomeruli
    - Assess for percentage involved, focal vs diffuse ; segmental vs global
    - Hypercellularity (mesangial vs endocapillary)
    - Inflammatory cells, hyalinosis, thrombi
    - changes of the basement membrane
  - Tubules
    - Acute and chronic inflammation in epithelium or lumen
    - injury (epithelial vacuolization, necrosis or sloughing)
    - Cellular or hyaline casts
    - drop out (atrophy)
  - Interstitium
    - Inflammation, fibrosis, edema
  - Arteries and arterioles
    - Intimal thickening
    - hyaline deposits
    - emboli

- Thrombotic microangiopathy (Fibrin thrombi, RBC fragments in capillary walls, fibrinoid necrosis)

❖ Diabetes
- Thickened basement membranes
- increased mesangial matrix
- glomerulosclerosis – nodular (Kimmelstiel-Wilson bodies) or global

❖ Hypertension
- intimal fibrosis of the arteries
- hyaline deposits in arterioles

Chapter 14 – Testicle

Normal Histology

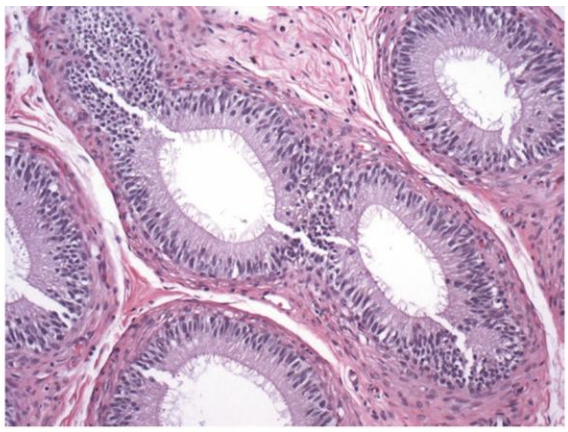


FIGURE 14.3. Normal epididymis. Columnar epithelium with cilia. This epithelium continues into the vas deferens.

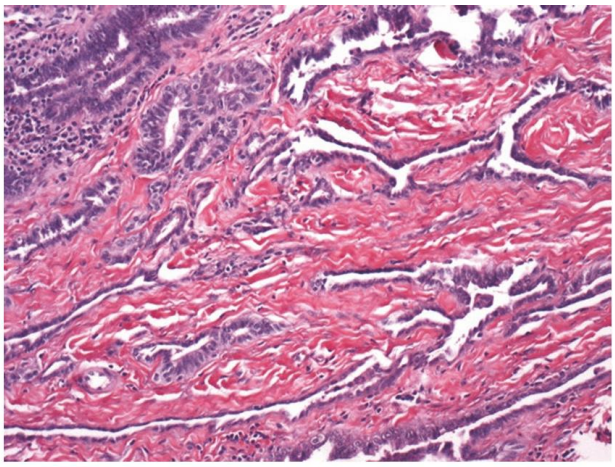


FIGURE 14.2. Normal rete testis. Slit-like spaces with cuboidal epithelium.

Features of GCNIS vs Normal Spermatogenesis	
Normal **Spermatogenesis**	**GCNIS**
Clear cytoplasm	More abundant clear cytoplasm
Fine grained chromatin (spermatogonia) or Visibly condensed chromosomes (spermatocytes)	Coarse chunky chromatin
Smooth nuclear membrane, if any	Irregular nuclear membrane
Tiny nucleolus, if any	Prominent nucleolus
Mature into spermatids	Little to no maturation
PLAP negative	c-kit, OCT3/4, PLAP positive

- Cryptorchid testis†
  - Small atrophic seminiferous tubules, fibrosis, widened interstitial spaces

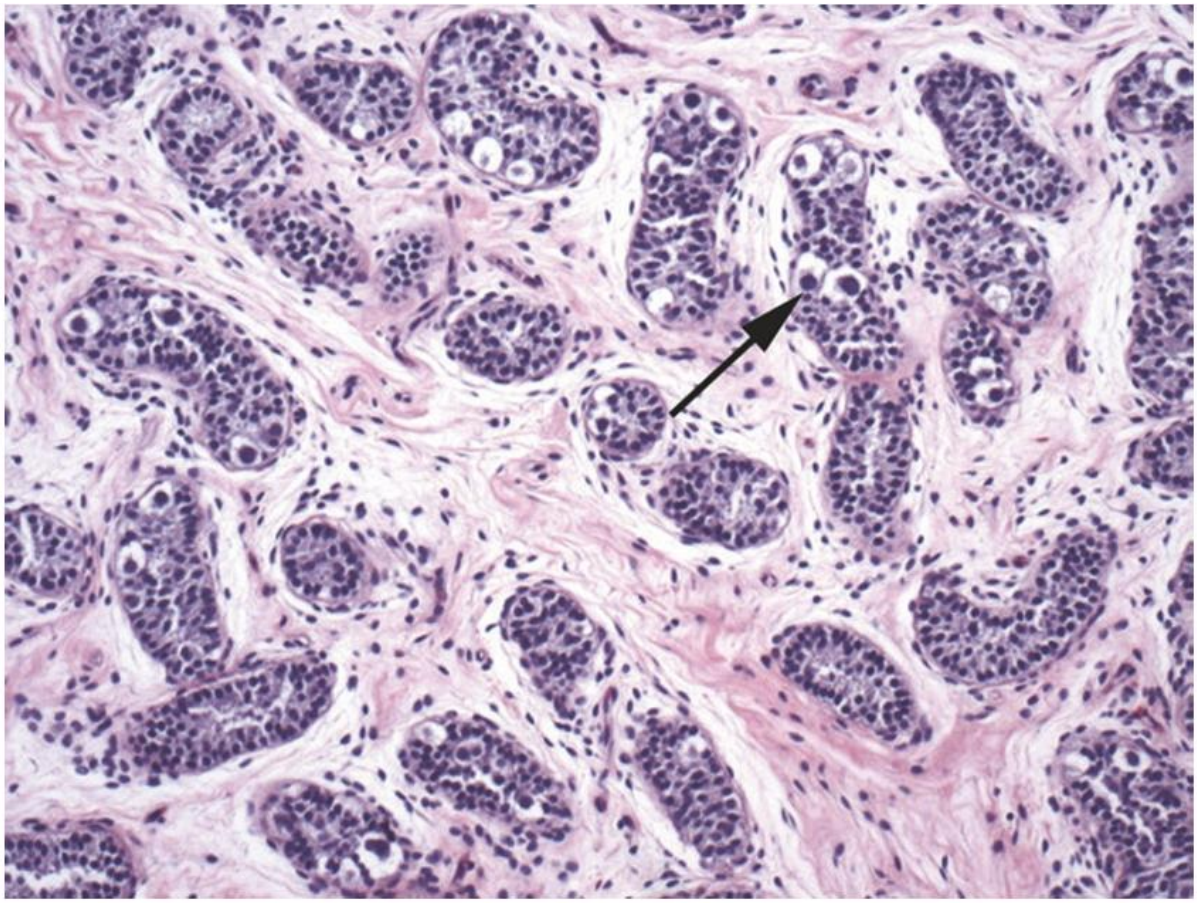


FIGURE 14.4. Cryptorchidism. In the infant testis, large dark spermatogonia are visible (*arrow*).

- Vanishing testis syndrome†
  - Nub of fibrosis and dystrophic calcification after surgical removal of undescended testis

† Generally signed out descriptively

Infertility

Causes include:

- Sertoli-only syndrome (a total lack of germ cells)
- Hypospermatogenesis (decrease per metal genesis in most tubules)
- Maturation arrest (when there is partial maturation but no spermatids produced)
- End-stage testis (global sclerosis and atrophy, no functioning tubules)
- Normal spermatogenesis (implies a distal obstruction)

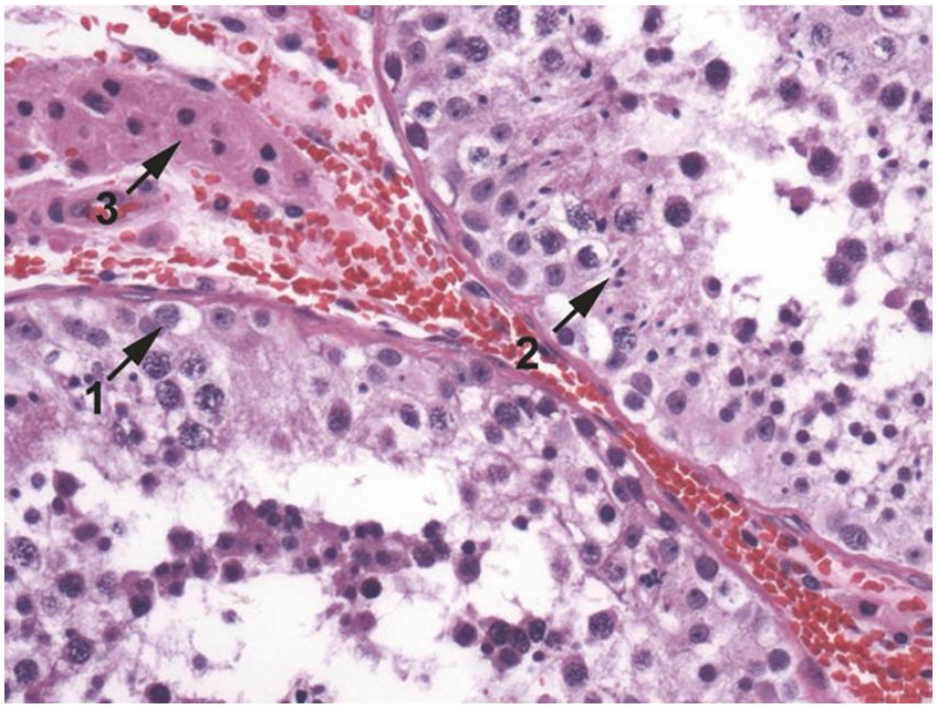


FIGURE 14.1. Normal seminiferous tubules. Large spermatogonia with clear cytoplasm are present at the tubule periphery (*1*). The developing spermatocytes have a wide range of morphologies, ending with the tiny spermatids (*2*), a marker of successful spermatogenesis. Plump pink Leydig cells are seen in the interstitium (*3*).

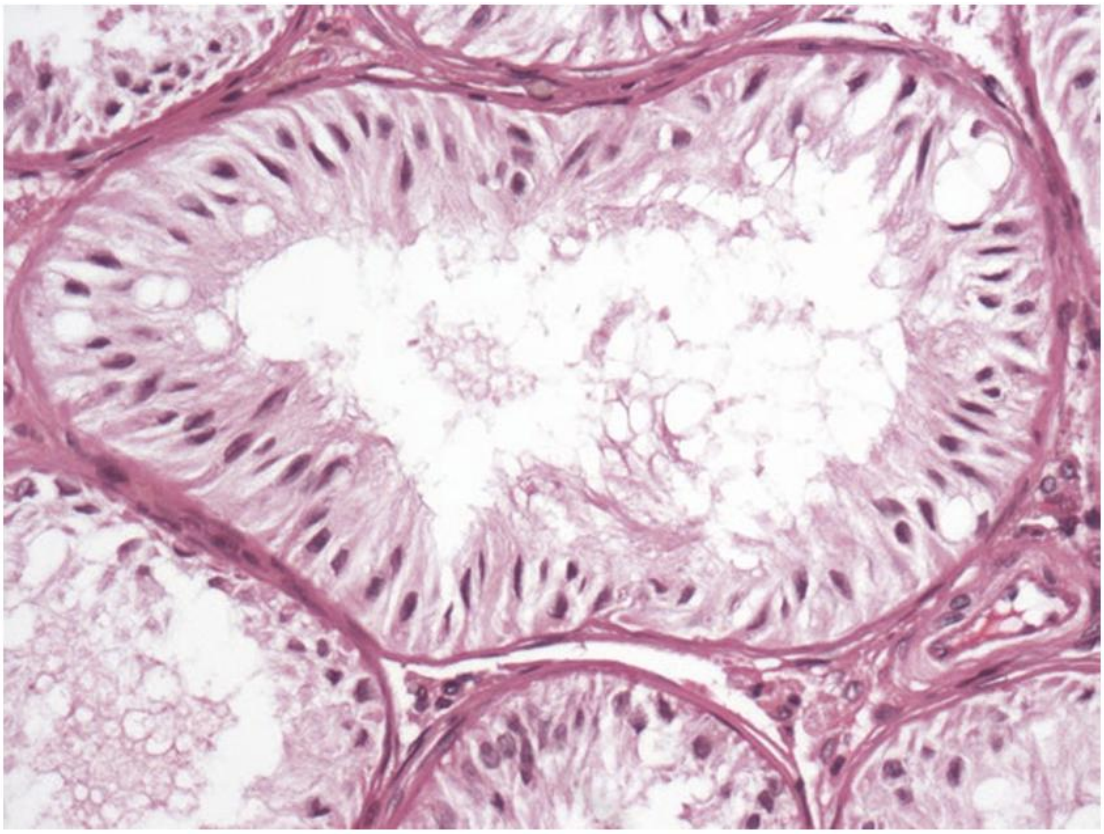


FIGURE 14.5. Sertoli-only syndrome in an adult. The tubules are lined with spindly Sertoli cells, and no germ cells are visible.

Tumours

This chapter only covers germ cell origin tumours. Others include mesothelial, epithelial and connective tissue origin.

- Mixed Germ Cell Tumours
  - The GCTs - seminoma, teratoma, yolk sac tumor, choriocarcinoma, and embryonal carcinoma - can all occur as pure tumors or mixed
- GCNIS
  - Looks like seminoma in the tubules
  - May be subtle with pagetoid spread (single malignant spread)
  - Not seem in prepubertal teratoma, prepubertal YST or spermatocytic seminoma
  - Best way to find it is to scan the tubules at 4x
  - See table above

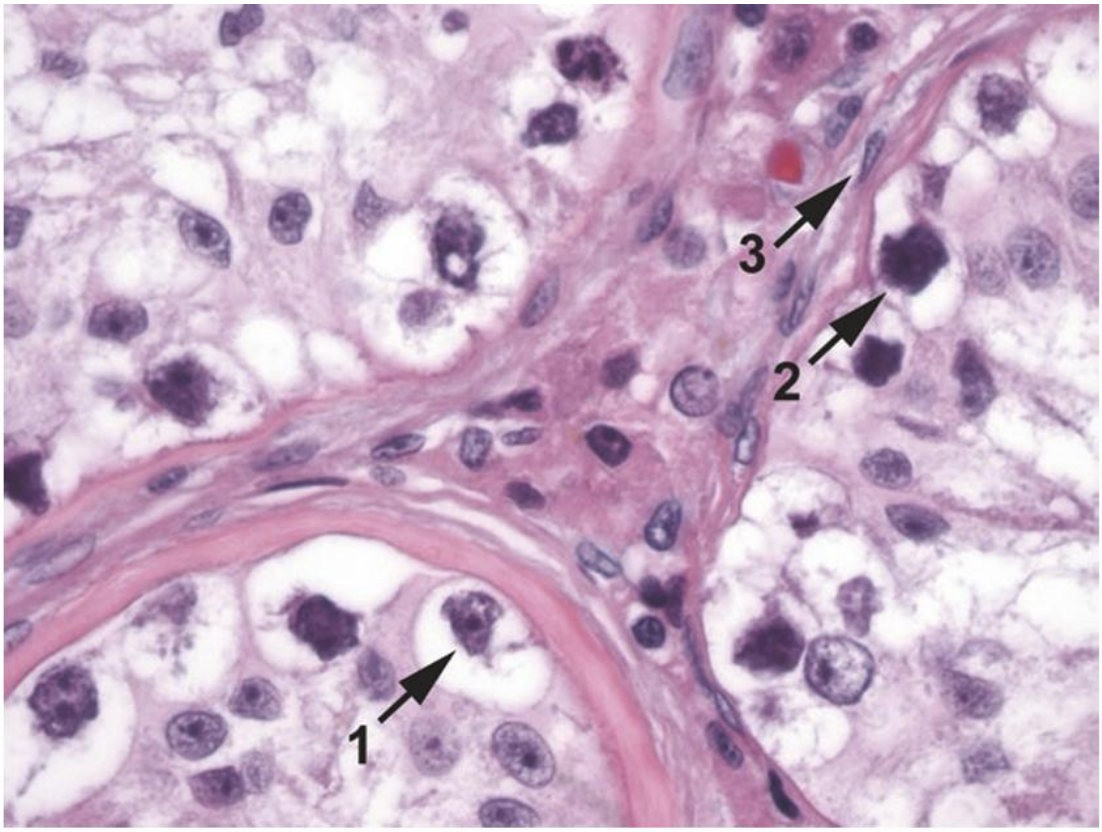


FIGURE 14.7. Germ cell neoplasia in situ. Large cells with clear halos of cytoplasm and prominent nucleoli are seen at the tubule perimeter (*1*). Other malignant nuclei appear hyperchromatic and solid (*2*). Compare the malignant cells to the euchromatin of nearby endothelial cells (*3*).

- Seminoma
  - An array of large, round corase nuclei, non-overlapping and non-molding, suspended ina network of delicate cell membranes
  - 1 or 2 prominent central nucleoli
  - Delicate branching fibrovascular septae
  - Associated inflammation, especially lymphocytes, granulomas and fibrosis
  - Monomorphic cells

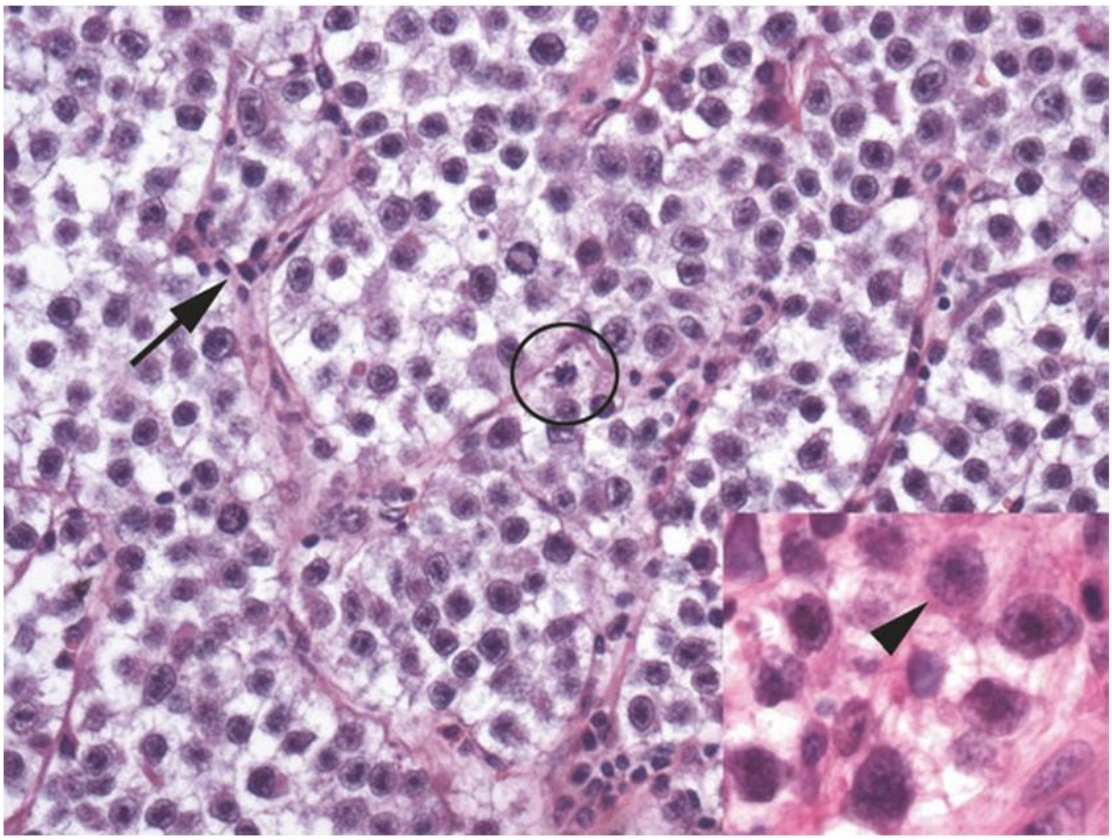


FIGURE 14.6. Seminoma. Delicate fibrovascular septae divide the cells into packets (*arrow*); collections of lymphocytes can be seen along the septae. The nuclei are widely spaced, with clear cytoplasm. Mitoses are common (*circle*). Nuclei have distinct nuclear membranes and prominent nucleoli (*arrowhead*).

- Spermatocytic Seminoma
  - Aka "spermatocytic tumour"
  - Old men
  - Indolent
  - Cytologically looks like seminoma but has 3 cell sizes – (Small, Medium, Large)
  - In comparison to seminoma, has NO lymphocytes & is PLAP -ve
- Embryonal Carcinoma
  - Histologically is the "ugly one"
    - Pleomorphic cells
    - Hyperchromatic
    - Nuclear molding
    - Nucleoli
  - 3 architectures
    - Solid
    - Glandular
    - Papillary
  - Beware as it is keratin +ve, thankfully does stain for germ cell markers

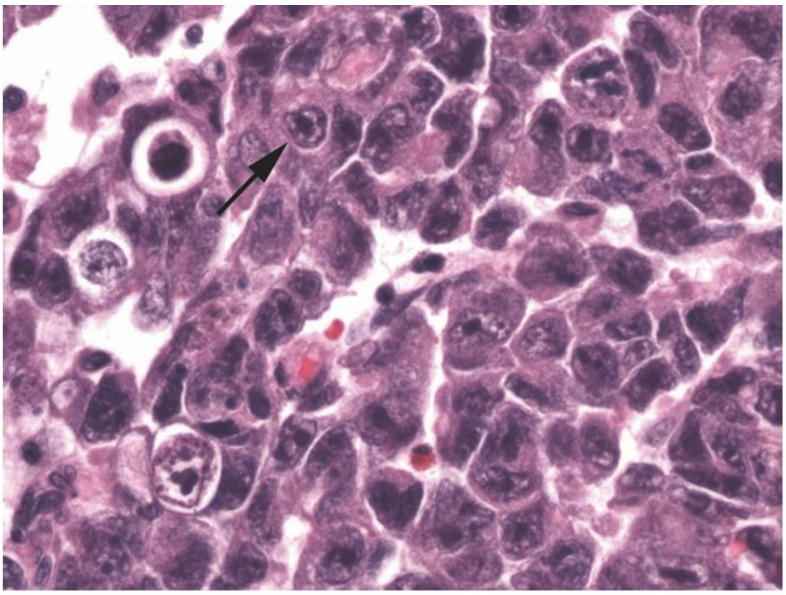
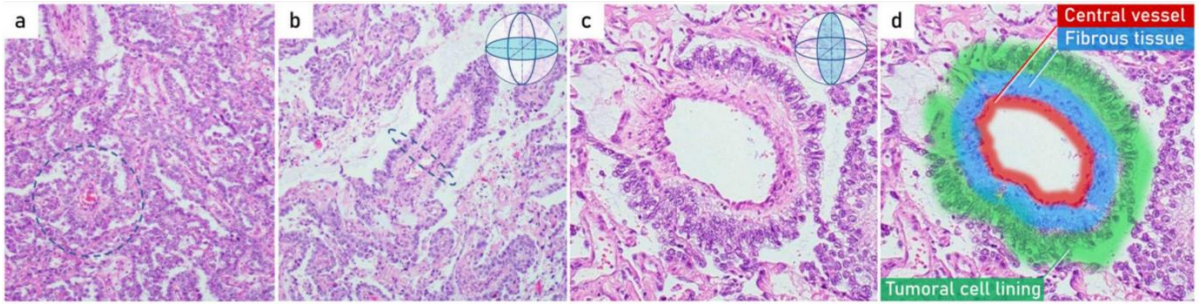


FIGURE 14.8. Embryonal carcinoma. Large epithelioid cells with pleomorphic nuclei grow in sheets. Unlike in seminoma, the cytoplasm is dense, and the nuclei have irregular shapes and sizes, some showing nuclear molding. Many have coarse chromatin with dark nuclear membranes and prominent nucleoli (*arrow*).

- Yolk Sac Tumour
  - Most common pure testicular neoplasm in peds
  - Seen as MGCT in adults
  - Has many forms
    - Microcystic and reticular are the most well known
  - Schiller-Duval Bodies
    - Central vessel *surrounded by* fibrous tissue *surrounded by* layers of tumour cells
    - 

      , usually in cystic space
  - YST nuclei are usually smaller and more regular than in EC but more typical than in seminoma
    - YST look hypocellular & myxoid when adjacent to EC

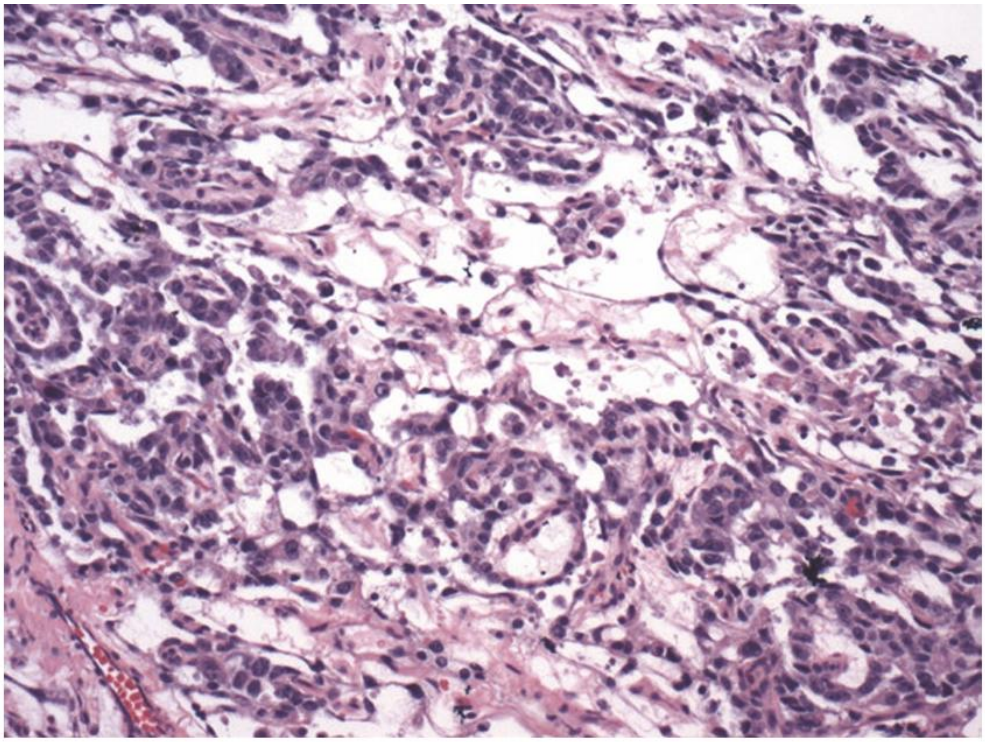


FIGURE 14.9. Yolk sac tumor. The cells of yolk sac tumor often appear more bland than other germ cell tumor types. The cells are cuboidal, with pink cytoplasm, and have a tendency to pull apart into a microcystic pattern (shown here).

- Choriocarcinoma
  - Like placental choriocarcinoma
    - Syncytiotrophoblast and cytotrophoblast layers
      - Syncytiotrophoblasts – multinucleated giant cells and stain for β-hCG
      - Cytotrophoblasts – look like EC cells but paler cytoplasm and less pleomorphic
    - Produces β-hCG
    - Preferentially invades blood vessels
- Teratoma
  - G/L for monster tumour
  - Composed of three primitive germ layers: ectoderm, mesoderm, endoderm
    - not all layers must be present. For example, a teratoma monolayer of ectoderm would be an epidermoid cyst (skin) or dermoid cyst (skin+hair+adnexal glands)
  - Pre-pubertal
    - always benign
  - post-pubertal
    - always malignant
- Sex Cord Stromal Tumours
  - Most SCS tumours are benign in the testis. 10% malignant
  - They resemble their normal counterparts
    - Leydig: looks like oncocytoma
    - Sertoli: tries to recreate seminiferous tubules

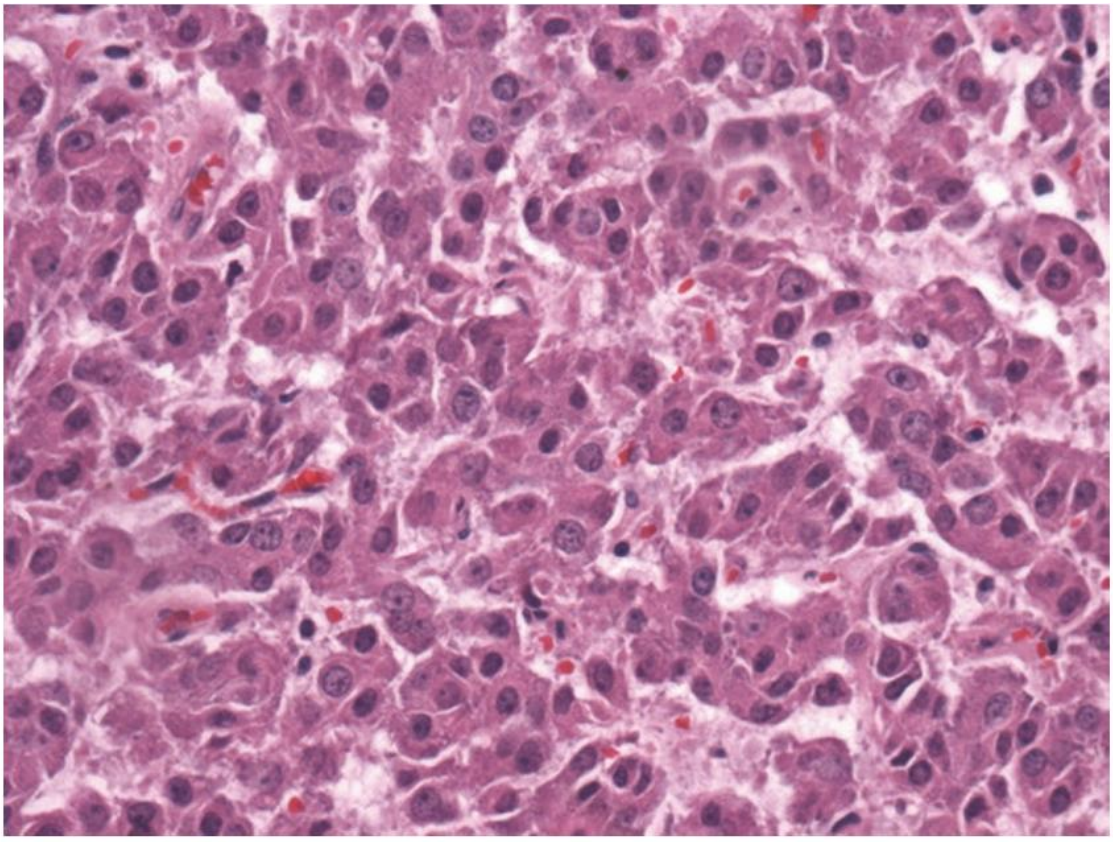


FIGURE 14.10. Leydig cell tumor. These neoplasms are reminiscent of oncocytomas in other sites. Most are benign.

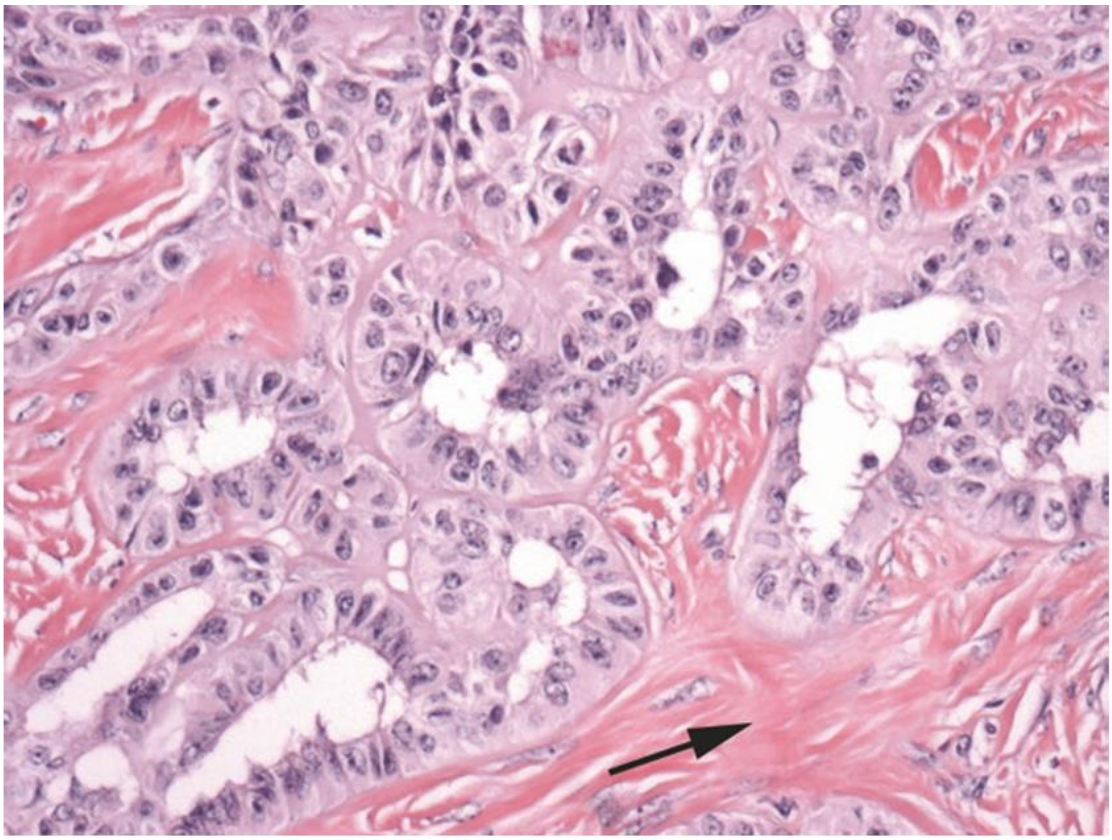


FIGURE 14.11. Sertoli cell tumor. This tumor attempts to recreate the seminiferous tubules. The stroma may become hyalinized (*arrow*).

- Lymphoma
  - Can resemble seminoma but cells not as homogenous
  - Usual lymphoma of the testis is DLBCL
  - No GCNIS

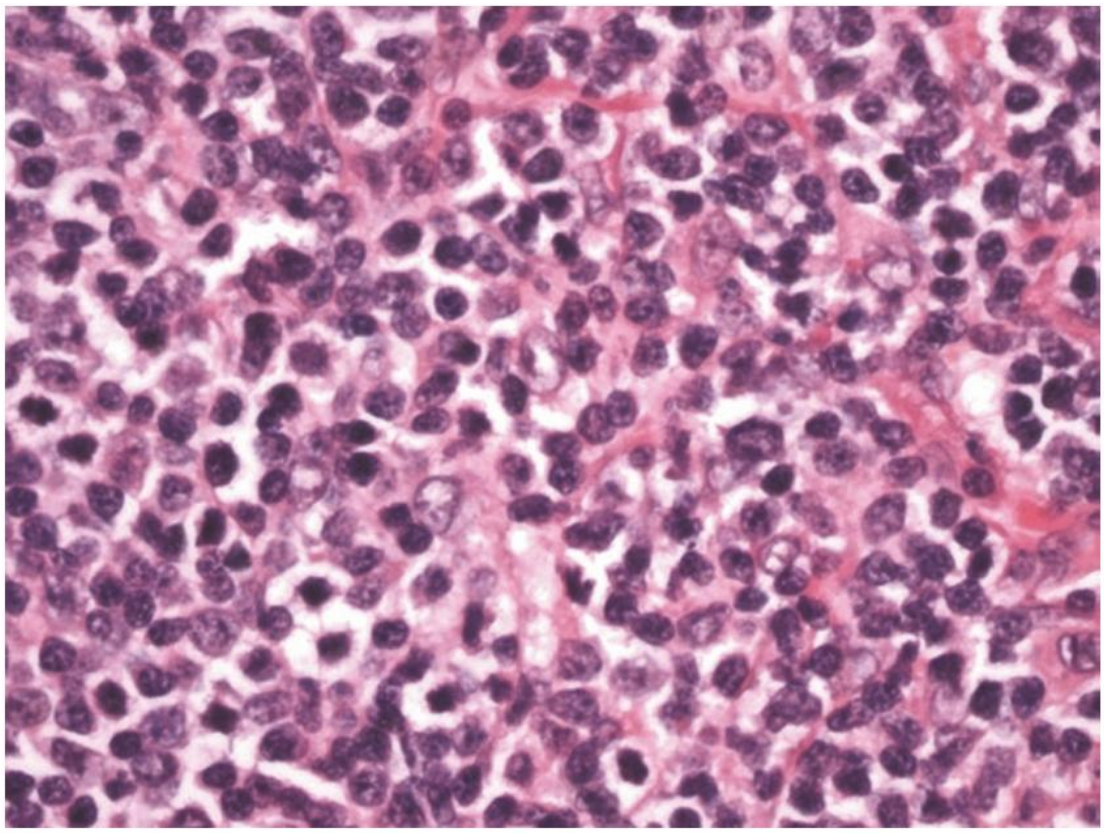


FIGURE 14.12. Diffuse large B cell lymphoma. The main histologic feature is sheets of discohesive tumor cells. Nuclear chromatin is chunky.

***Chapter 15* – Ovary**

Normal histology

- LH – Theca and Leydig
- FSH – Granulosa and Sertoli

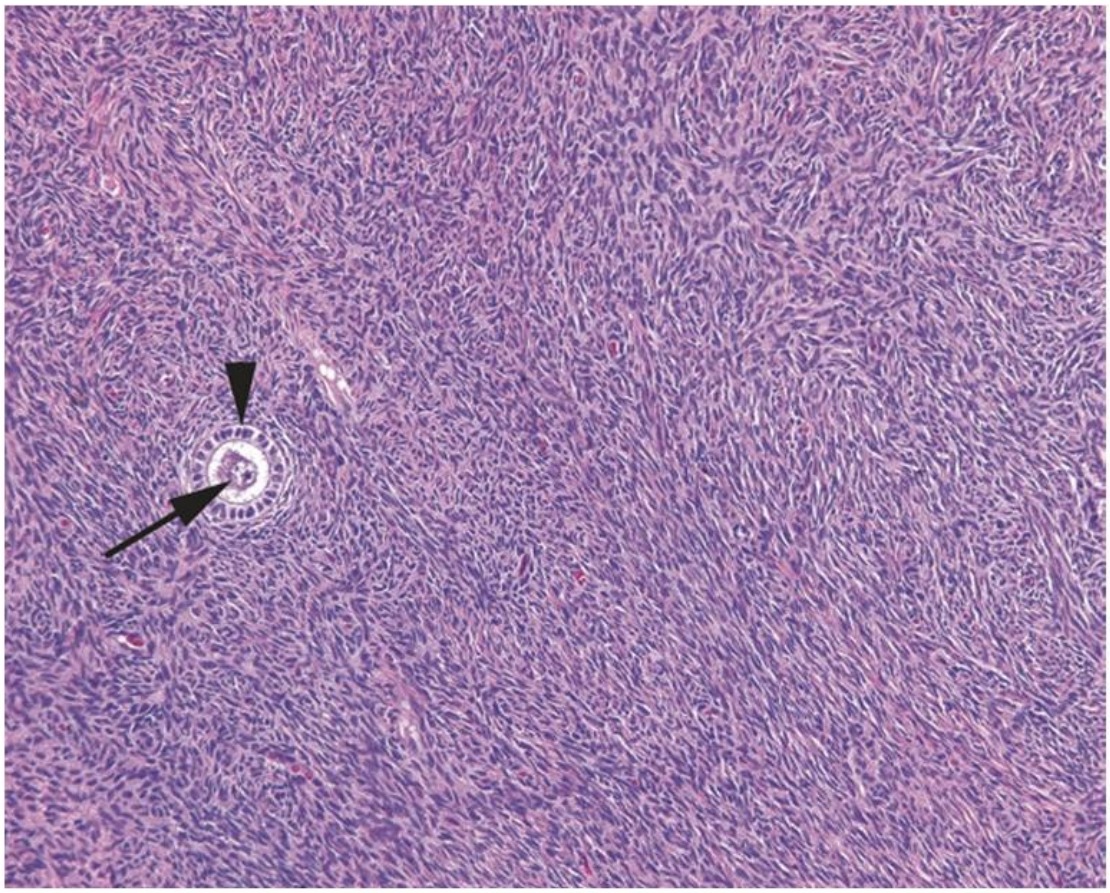


FIGURE 15.1. Ovarian stroma with follicle. Typical ovarian stroma is blue and cellular, with a vaguely fascicular or storiform pattern. A small primary follicle is seen with the central oocyte (*arrow*) and a ring of granulosa cells (*arrowhead*).

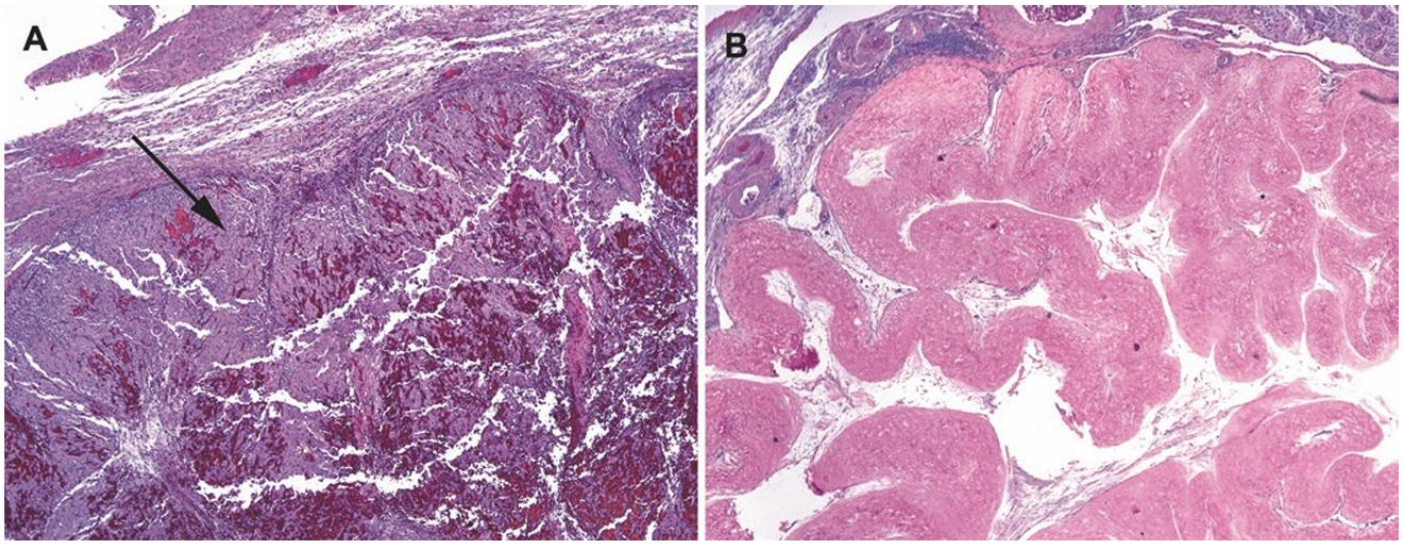


FIGURE 15.2. (**a**) Hemorrhagic corpus luteum, with undulating layers of luteinized granulosa cells (*arrow*) and associated blood. (**b**) A corpus albicans, the remnant of a prior corpus luteum.

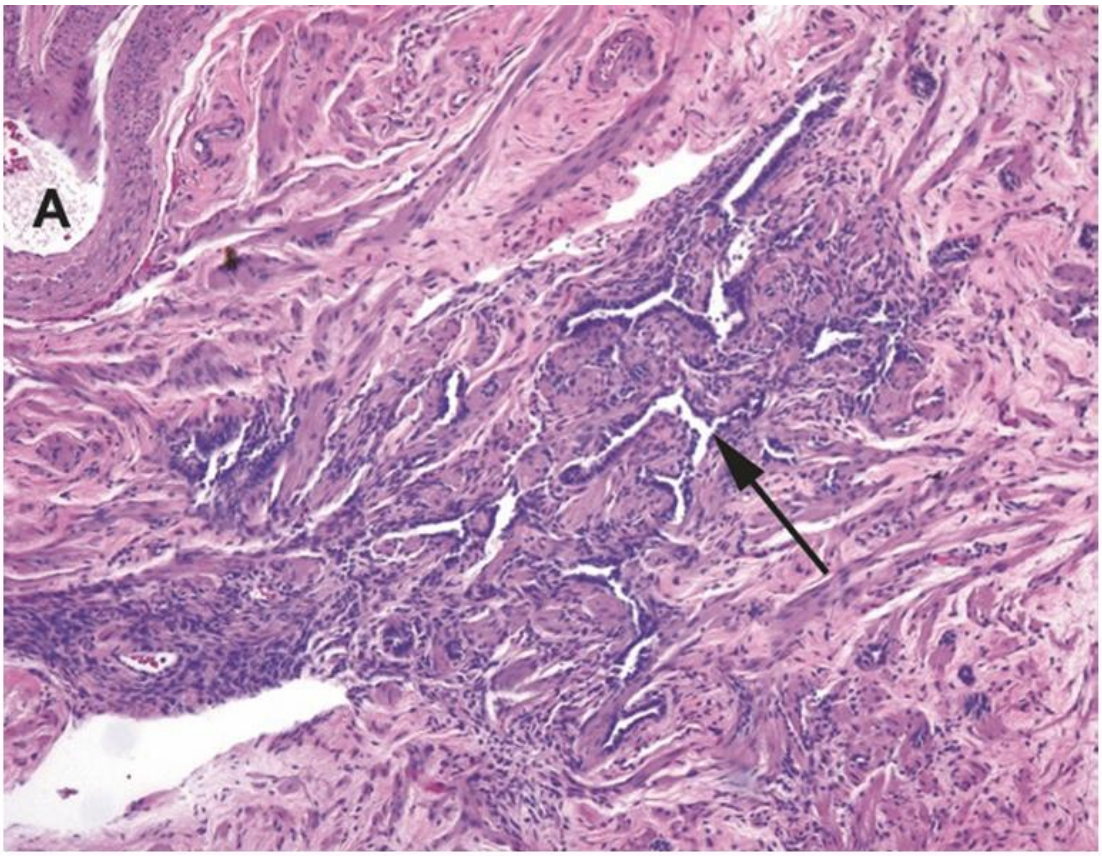


FIGURE 15.3. Rete ovarii. This vestigial structure is found at the hilum of the ovary, adjacent to large arteries (*A*) and veins. The rete consist of slit-like channels with a cuboidal cell lining (*arrow*).

❖

❖

Epithelial Neoplasms

Surface epithelial Tumour	Germ Cell Tumours	Sex cord stromal tumours	Metastases
Serous	Teratoma	Fibroma	GI
Mucinous	*Dysgerminoma	Thecoma	Pancreatic
Endometroid	*Yolk Sac	Granulosa cell tumour	Breast
Clear Cell	*Choriocarcinoma	*Sertoli cell	Others
Brenner	*Embryonal Carcinoma	*Leydig cell tumour	
		*Sertoli-Leydig cell tumour	

* Rare tumors that are not discussed in this chapter. See Chapter 14 for Germ Cell Neoplasms

The approximate frequency of benign, borderline & malignant neoplasms for the 5 types of epithelial neoplasms

	Serous	Mucinous	Endometroid	Clear Cell	Brenner
Benign	60%	80%	Rare	Rare	> 90%
Borderline	15%	15%	Rare	Rare	Rare
Malignant	25%	< 5%	> 95%	> 95%	5%

❖ Micropapillary architecture
  - ➢ Papilla without fibrovascular cores growing off of true papillary structures
  - ➢ Non-specific

❖ **Serous Cystadenoma**
  - ➢ Simple or multilocular cysts linde by a tubal-like epithelium with columnar and/or ciliated cells. They can be large but the lining remains simple

- Serous cystadenofibromas are also common

❖ **Non-invasive LGSC**

- LGSC But confined to the cystic cavity
- stroll invasion if present would bump this up to LGSC
- Psammoma bodies

❖ **Borderline Serous Tumour**

- Papillary frond architecture
- Can have a micro papillary structure
  - > 5mm of micropapillary structure bumps this up to Non-invasive LGSC
- Epithelium should look typical (no atypia)
- Invasion would bump this up to LGSC
- May shed cells into the peritoneum which stick on to other cells and begin to grow. They are "implants". Implants by definition do not invade so if they do invade they are metastases not implants.
- has a T stage despite not qualifying as carcinoma

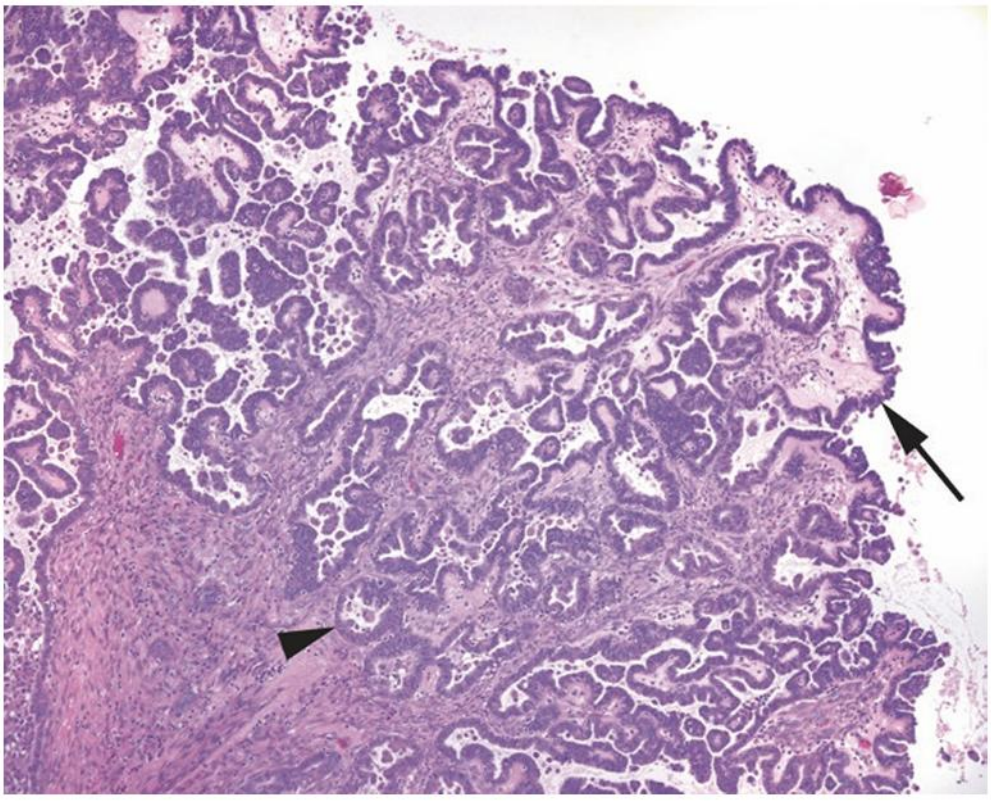


FIGURE 15.5. Borderline serous tumor. The epithelial lining is composed of serous, or nonmucinous, cells (*arrow*). The overall architecture is quite complex, with papillary branching and invaginated folds that should not be mistaken for invasion (*arrowhead*). However, the epithelial component is mostly a monolayer.

❖ **Low-Grade Serous Carcinoma**

- Cystic
- Slowly progressive
- Uniform nuclei unlike HGSC
- BRAF/KRAS +ve

- P53 -ve
- True invasion often shown by micropapillary invasion pattern

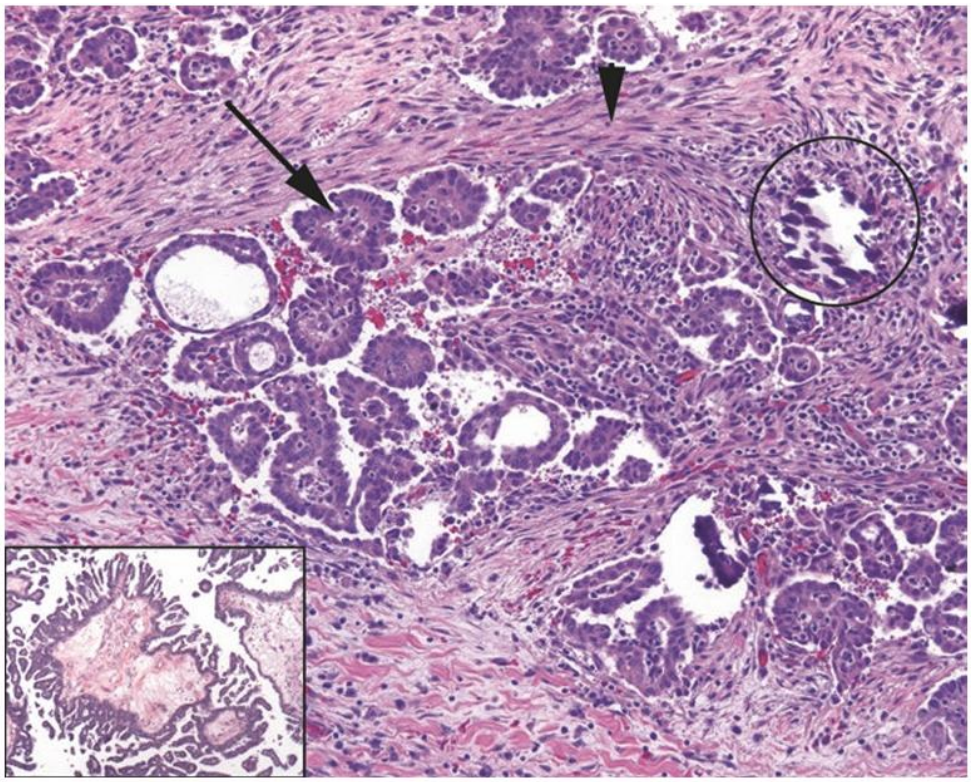


FIGURE 15.6. Micropapillary serous carcinoma. When invasive, micropapillary serous carcinoma looks like tiny florets of cells (*arrow*) in a desmoplastic stroma (*arrowhead*). Psammoma bodies are common (*circle*). *Inset*: the medusa head, or micropapillary, pattern is indicative of micropapillary serous carcinoma.

- Compare the epithelial micropapillae to the simple epithelium of the borderline tumor (see Figure 15.5.).

❖ **High-Grade Serous Carcinoma**

- Genetically distinct from LGSC
- Significant nuclear atypia
- Present at high stage
- p53 +ve
- BRCA association
  - HGSC appears to arise from fallopian tube epithelium
  - They do SEEFIM to exclude tiny foci of serous tubal intraepithelial carcinoma

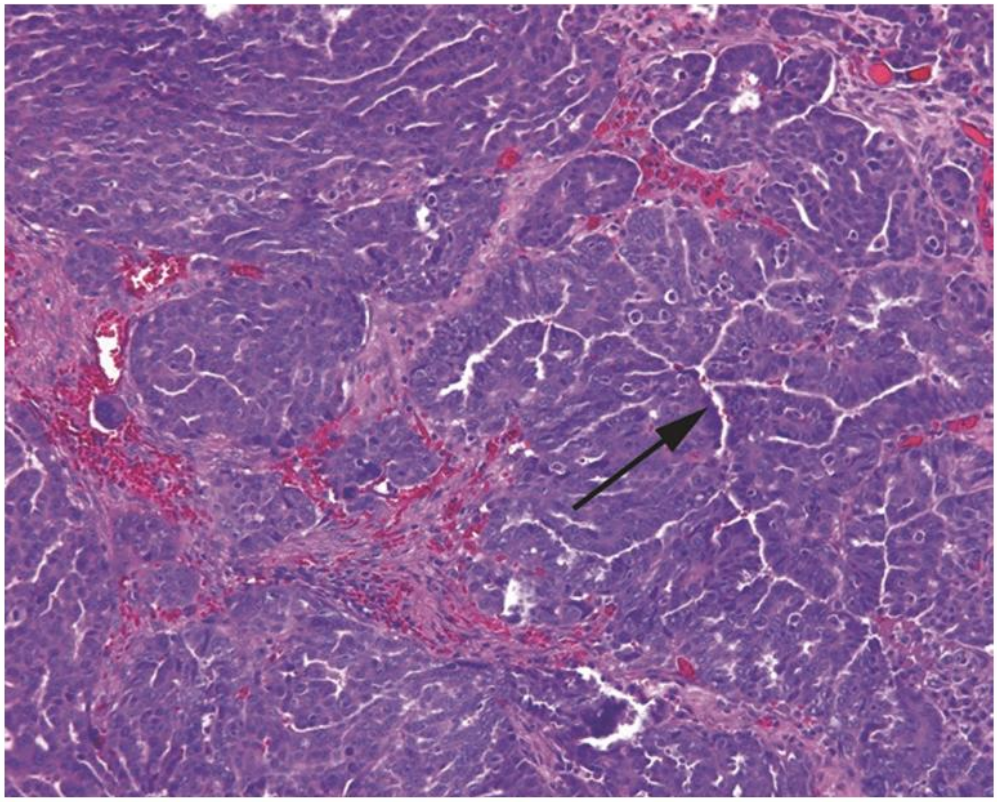


FIGURE 15.7. High-grade serous carcinoma. This tumor is shown invading the stroma. The cells are pleomorphic and dark, with prominent nucleoli, and grow in solid nests with slit-like spaces (*arrow*).

- **Mucinous Cystadenoma**
  - *Note that in the ovary mucinous does not imply nests of epithelial cells floating in extravasated mucin, as it does in other organs. In the ovary, mucinous simply describes the type of cell found in the tumour
  - Lined with fairly flat mucinous epithelium, simple tubules or papillae are acceptable
- **Mucinous Borderline**
  - *Note that in the ovary mucinous does not imply nests of epithelial cells floating in extravasated mucin, as it does in other organs. In the ovary, mucinous simply describes the type of cell found in the tumour
  - Like in serious, mucinous borderline has more complex epithelial lining and than the cystic counterpart.
    - In this case look for pseudo stratified nucleoli and papillary architecture, Or even, gastric foveolar type epithelium, intestinal epithelium, or paneth cells

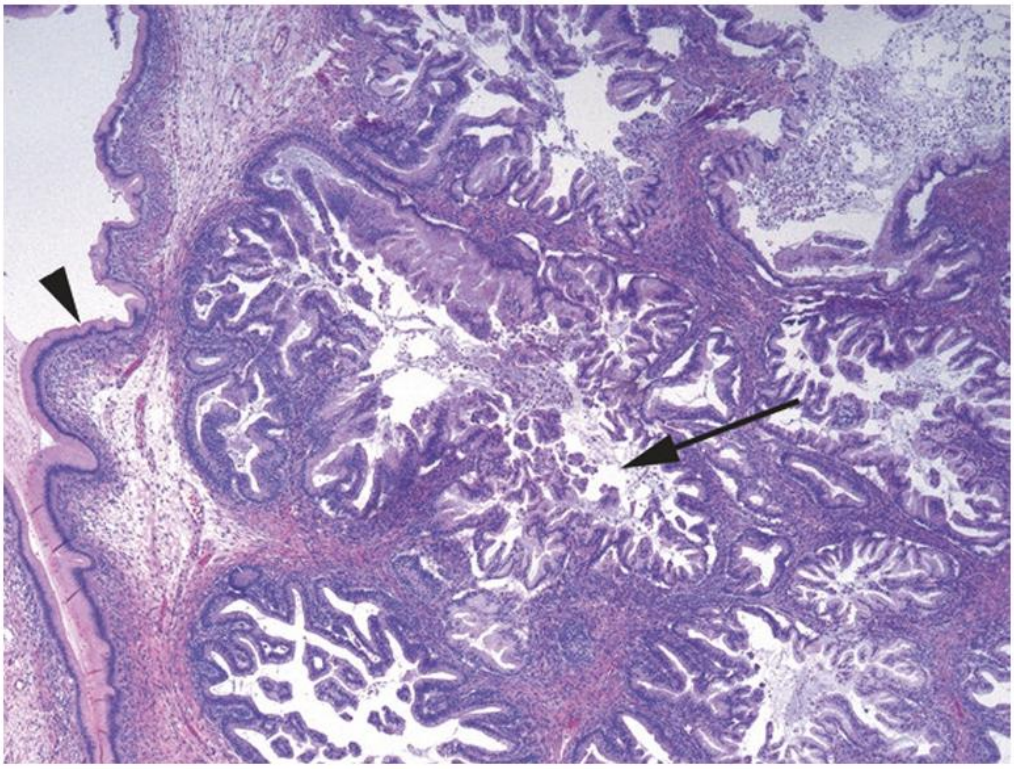


FIGURE 15.8. Borderline mucinous tumor. Although parts of the tumor resemble cystadenoma (*arrowhead*), the adjacent epithelial proliferation shows complexity and epithelial tufting (*arrow*). As with the borderline serous tumor, invaginations into the stroma are not necessarily invasion.

- ❖ **Mucinous Malignant -** rare
- ❖ **Endometroid Carcinoma of the Ovary**
  - ➢ 95% malignant
  - ➢ Resembles endometroid carcinoma of endometrium
    - In fact uses the same FIGO grade system
  - ➢ Tubular or cribriform glands
  - ➢ Nuclei – pleomorphic, vesicular
  - ➢ Can co-occur with or occur within endometriosis

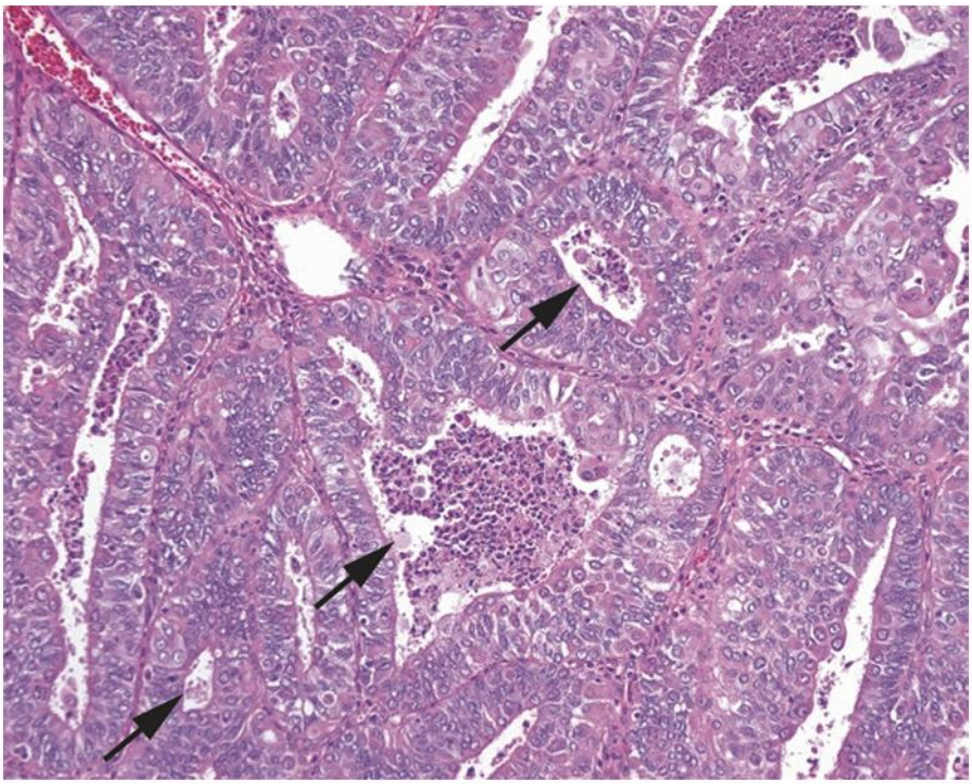


FIGURE 15.9. Endometrioid carcinoma. The nuclei are cleared out and pleomorphic, like endometrioid carcinoma of the endometrium. Distinct glandular spaces are visible (*arrows*), some with central necrosis.

- **Clear Cell Carcinoma**
  - High grade by definition
  - Marked nuclear atypia
  - Monolayer of cells unlike the nuclear stratification other high-grade ovary lesions

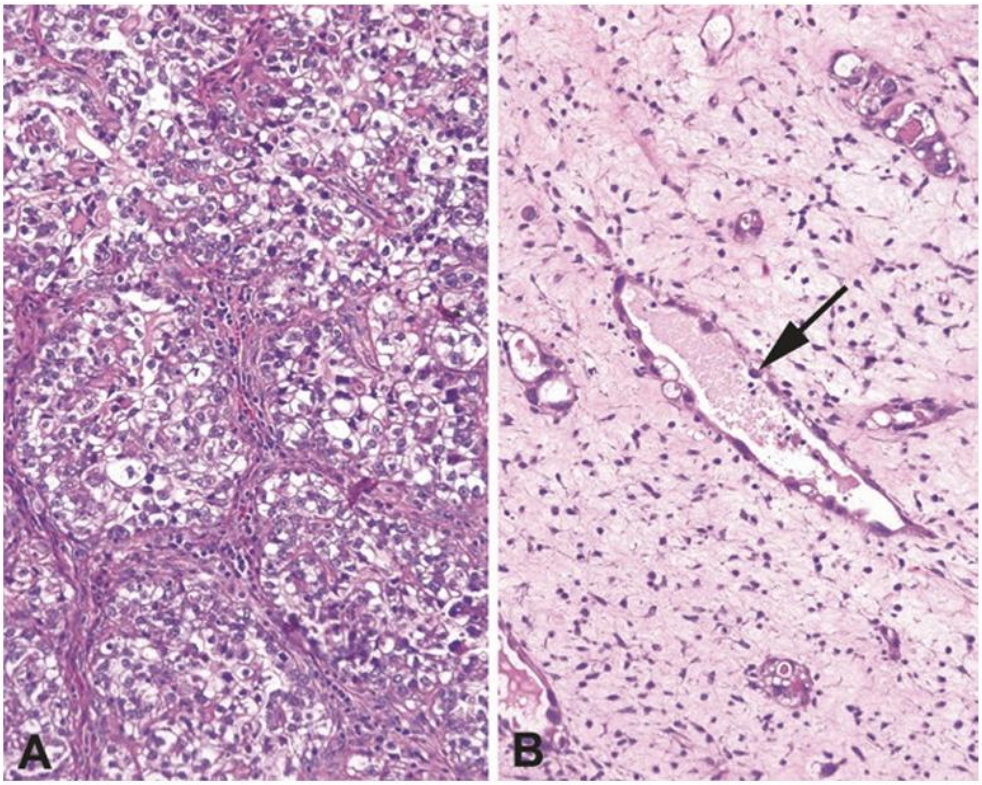


FIGURE 15.10. Clear cell carcinoma. (**a**) In this field, nests of clear cells are seen separated by fibrovascular septa. (**b**) A less cellular area of the same tumor shows vessel-like spaces lined by atypical cells that protrude into the lumen in hobnail fashion (*arrow*).

- ❖ **Brenner Tumours**
  - ➢ 95% benign
  - ➢ A Brenner tumor is an adenoma of urothelial type epithelium, possibly arising from Walthard rests
  - ➢ Walthard rests: benign nests of urothelium in the ovary and fallopian tube

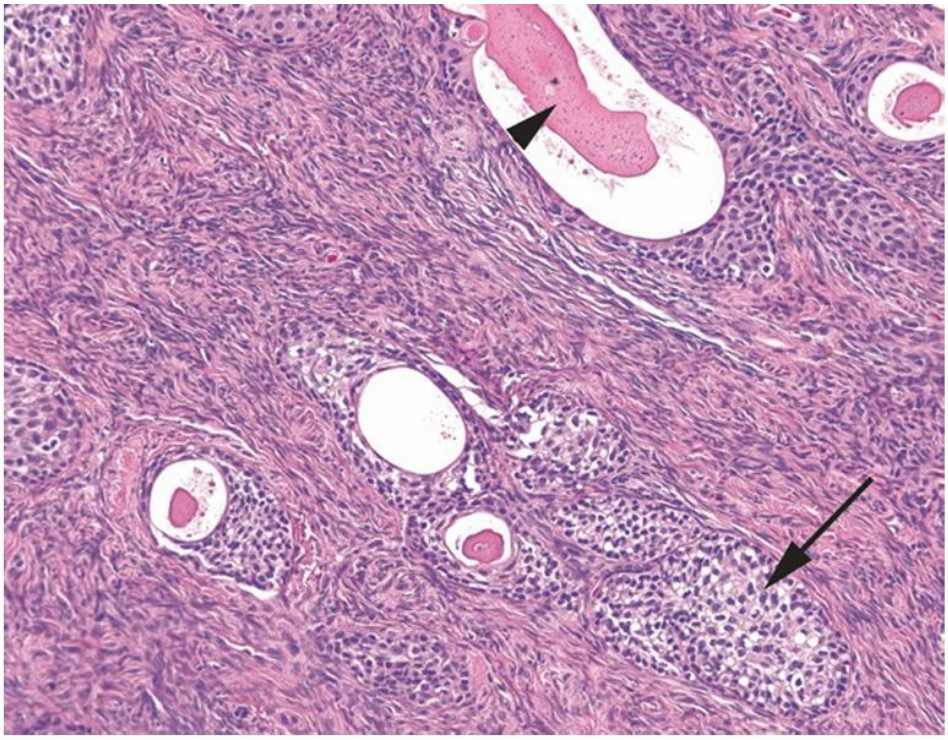


FIGURE 15.11. Brenner tumor. Nests of urothelial-type epithelium (*arrow*) in a fibrotic stroma are typical. Some form gland-like spaces with pink secretions (*arrowhead*).

Table 15.13. The surface epithelial tumours can have overlapping features

If you see…	**Think of…**
Clear cells with very atypical	Clear cell
Clear cells with bland nuclei	Endometrioid or Brenner
Hobnail cells lining glands or papillae	Clear cell
nuclei Intestinal-type cells	Mucinous
Mucinous cells with papillary fronds	Mucinous
Intracytoplasmic mucin	Mucinous or endometrioid
Papillary fronds	Any tumor (see Figure 15.12)
Micropapillary pattern	Serous
Sheets of high-grade nuclei	Serous
Solid growth with slit-like spaces	Serous
Squamous-like nests of cells	Brenner
Squamous metaplasia in glands	Endometrioid
Round gland lumens	Endometrioid
Tall villi	Endometrioid or mucinous

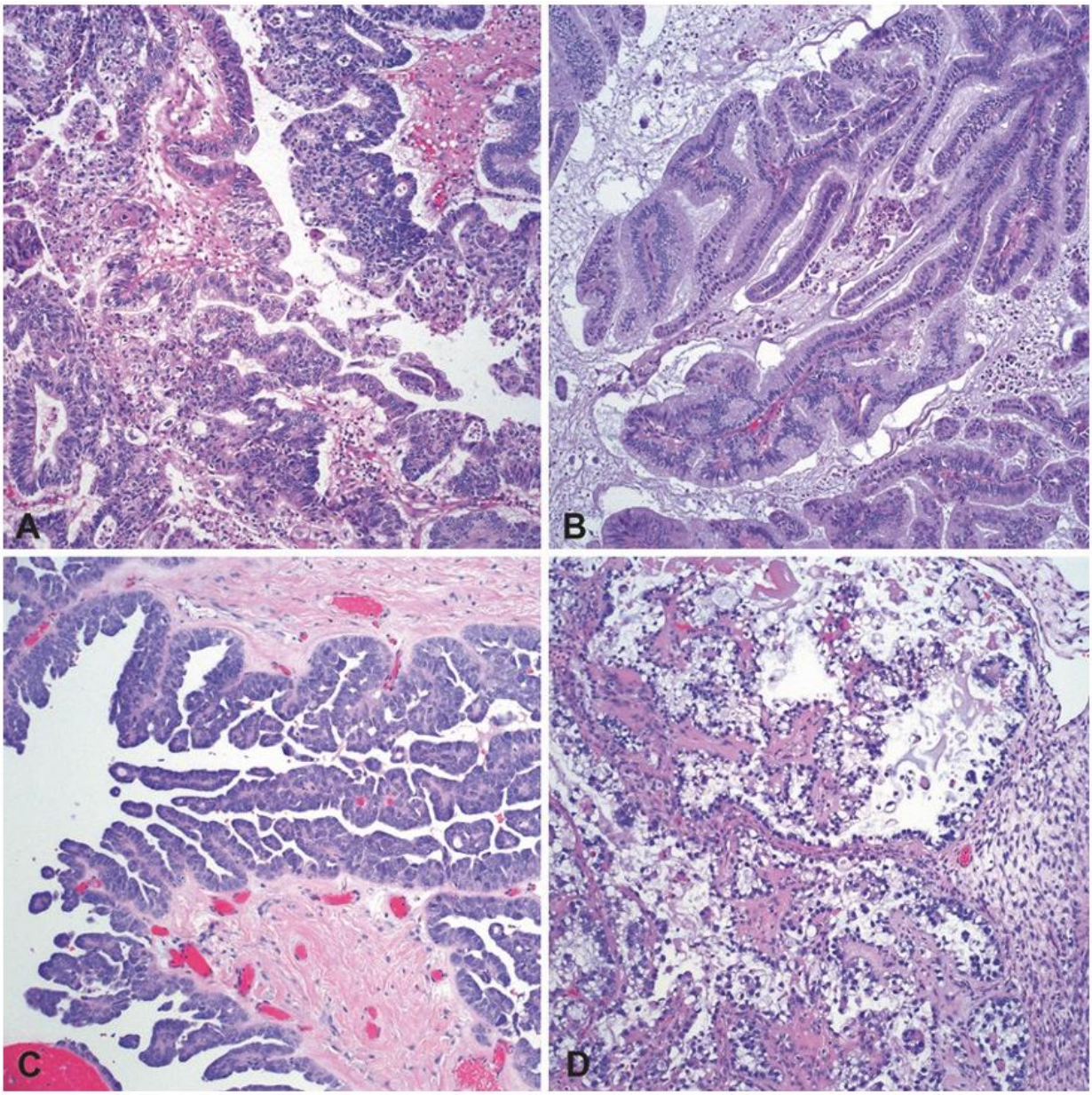


FIGURE 15.12. Papillary architecture is completely nonspecific. Compare the papillae which can be found in (**a**) endometrioid carcinoma, in which fibrovascular cores are lined by columnar endometrial-type cells; (**b**) mucinous carcinoma, in which papillae are lined by tall cells with apical mucin; (**c**) serous carcinoma, in which there are both papillae and micropapillae with jumbled, high N/C ratio nuclei; and (**d**) clear cell carcinoma, in which there is a single layer of cuboidal clear cells with very atypical nuclei. All photos are taken at the same magnification.

Non-Epithelial Neoplasms

- **Teratoma**
  - Composed of 2/3 embryonal derivatives
  - Usually benign but can be malignant
  - Can be malignant if has a
    - Secondary malignancy from a tumour component
    - An association with a malignant germ cell tumour
    - Immature component (usually neuro)

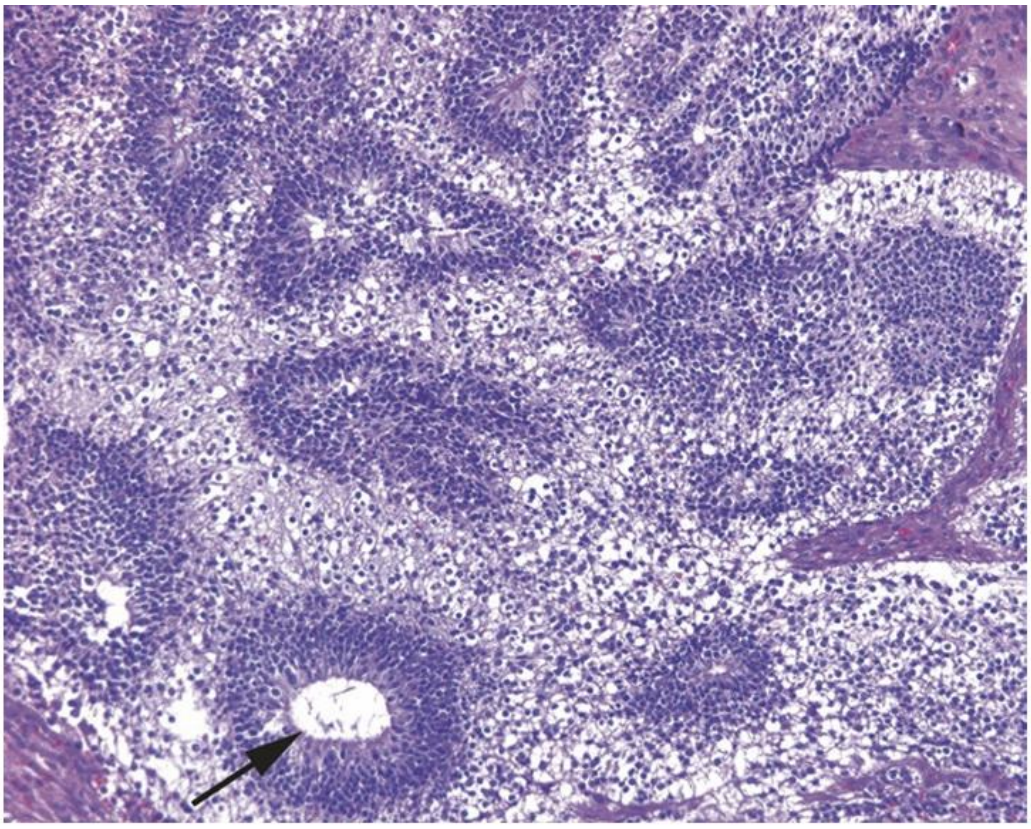


FIGURE 15.13. Immature neural tissue, teratoma. The combination of hypocellular areas and dense small round *blue* cell areas is suggestive of fetal brain. Rosettes (*arrow*) may also be seen. Finding this histology in a teratoma indicates an immature component.

- **Fibrothecoma**
  - Mix of fibroma and thecoma
  - Either part can be a pure tumour
  - Kinda looks like ovarian stroma

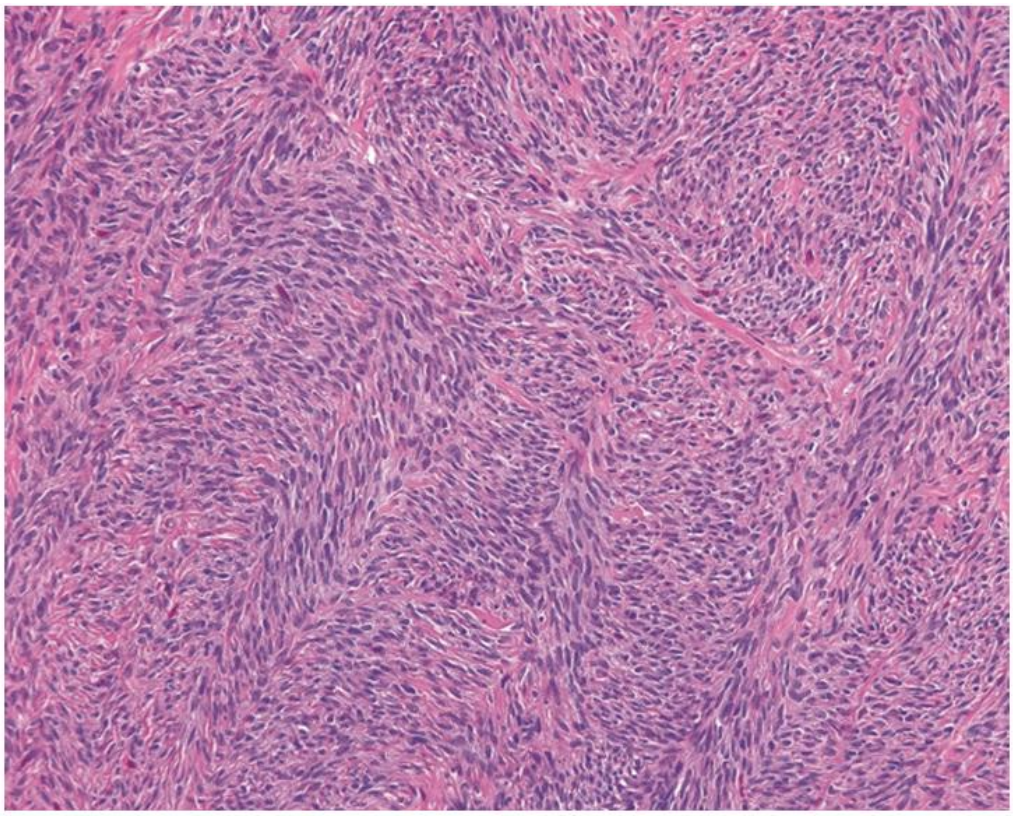


FIGURE 15.14. Fibrothecoma. This specimen shows mainly the fibroma component, with fascicles of bland spindled cells.

- ❖ **Granulosa Cell tumours**
  - ➢ Cytologically look loke normal granulosa cells but with a nuclear groove
  - ➢ Malignant but indolent
  - ➢ Grows in zig-zag pattern, but not a perfect zig-zag
  - ➢ Rarely can see pathognomonic Call-Exner bodies

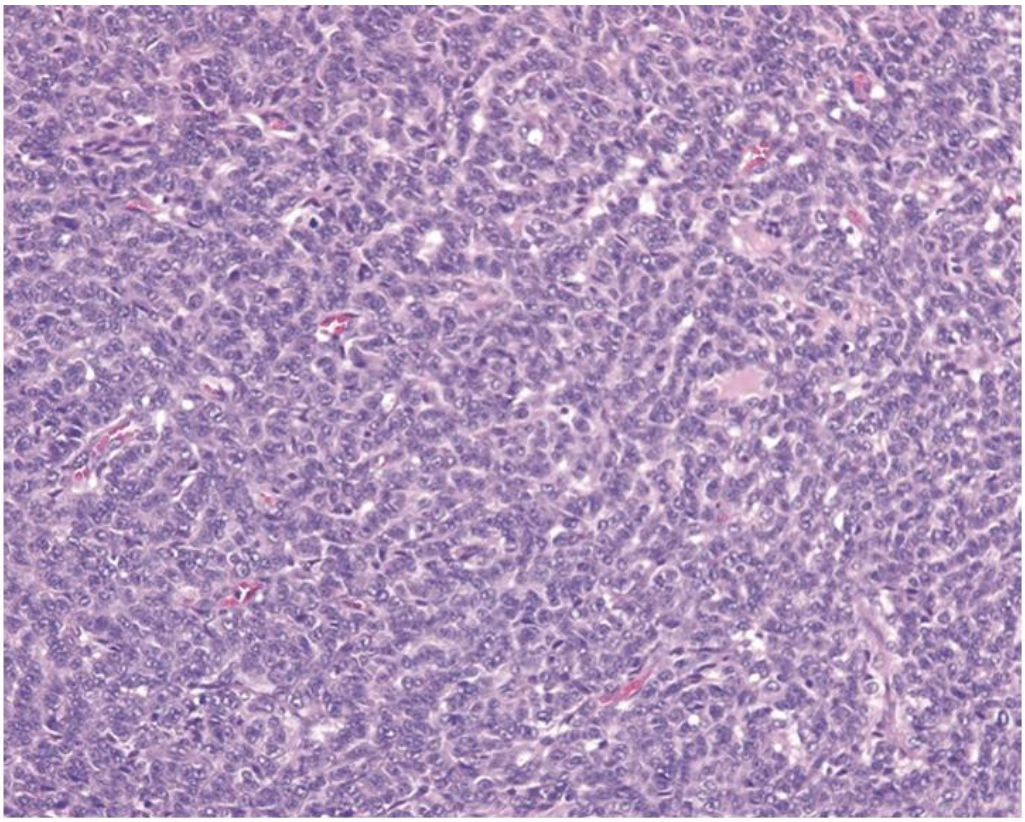


FIGURE 15.15. Granulosa cell tumor, low power. This section shows the characteristic cords and rows of granulosa cells, creating a pattern like watered silk, or (for those not frequenting fabric stores) a topographic map.

Chapter 16 – Cervix & vagina

Squamous Lesions

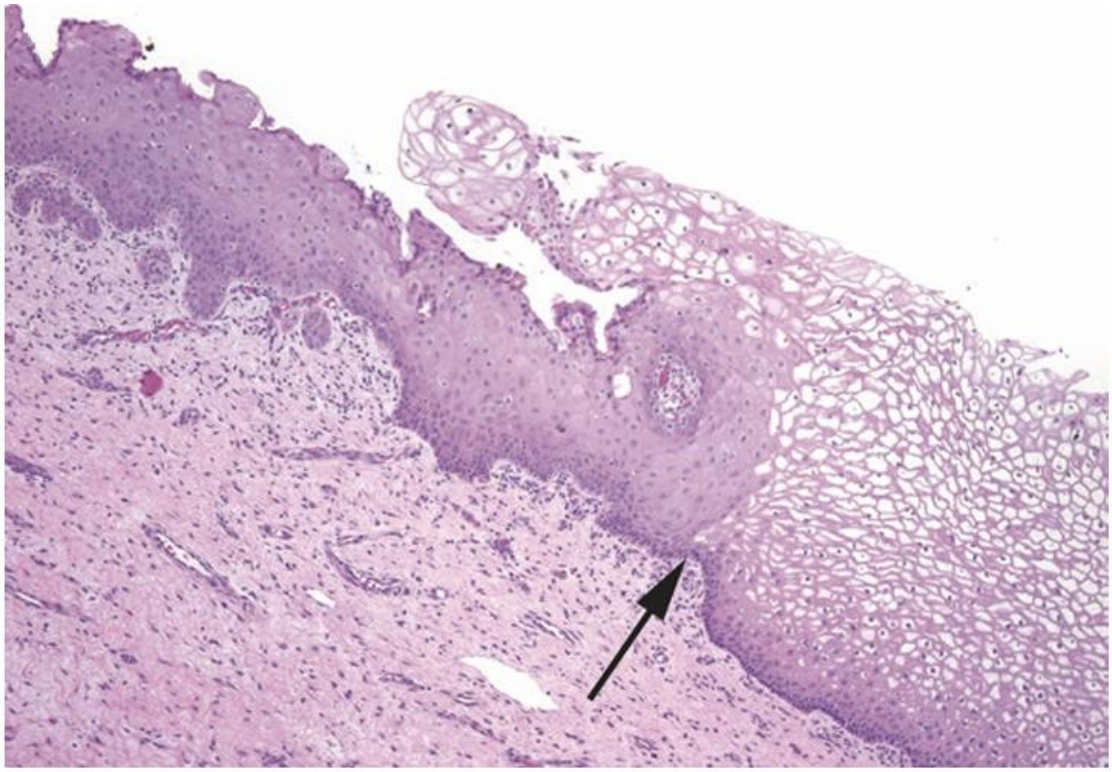


FIGURE 16.1. Squamous metaplasia at the transition zone. Mature squamous epithelium is seen to the *right* of the *arrow*, and squamous metaplasia is seen to the *left*. In squamous metaplasia, the nuclei may be larger and more immature-appearing and the cytoplasm more dense.

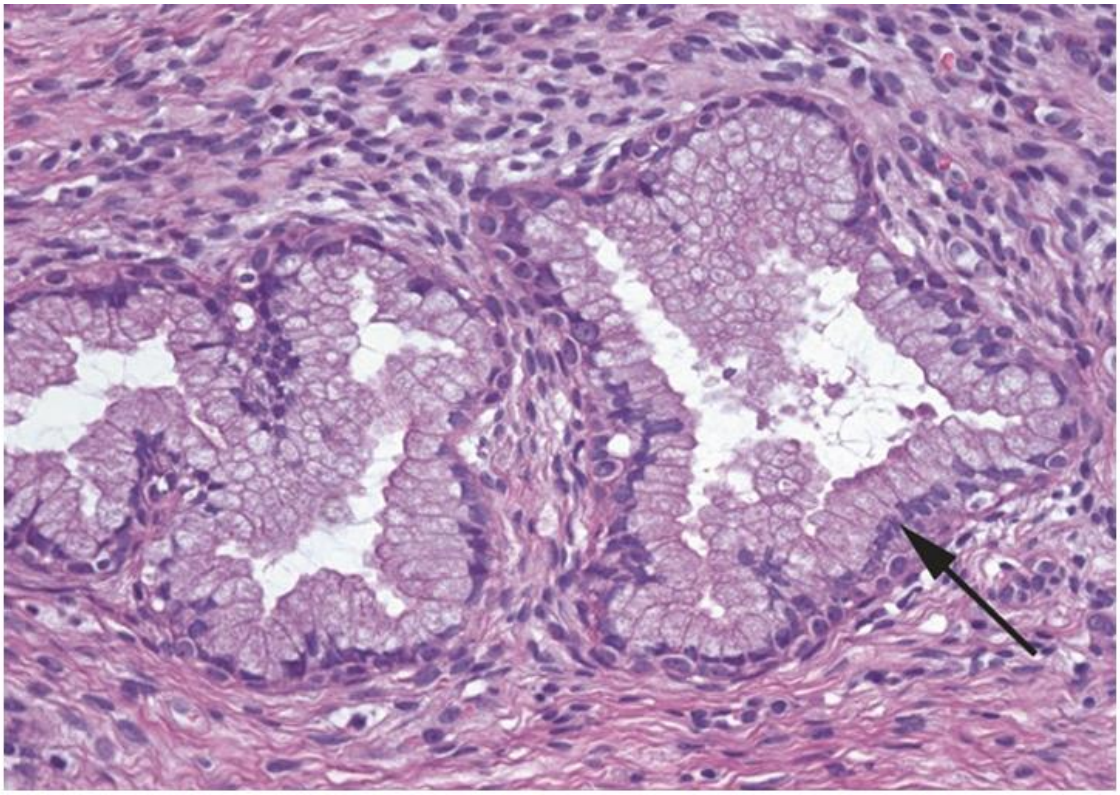


FIGURE 16.2. Endocervical glands. Normal endocervical glands are composed of tall columnar cells with apical mucin and small basal nuclei (*arrow*).

- **<u>LSIL</u>**
  - Immature cells / mitoses in the lower 1/3 of the epithelium only
  - Cells (koilocytes) have pleomorphic, wrinkled (raisonoid nuclei), hyperchromatic nuclei with a perinuclear cleared halo, binucleated nuclei are common
  - NCR remains low, despite marked atypia of the nuclei. Nuclear atypia doesn't upgrade it to HSIL

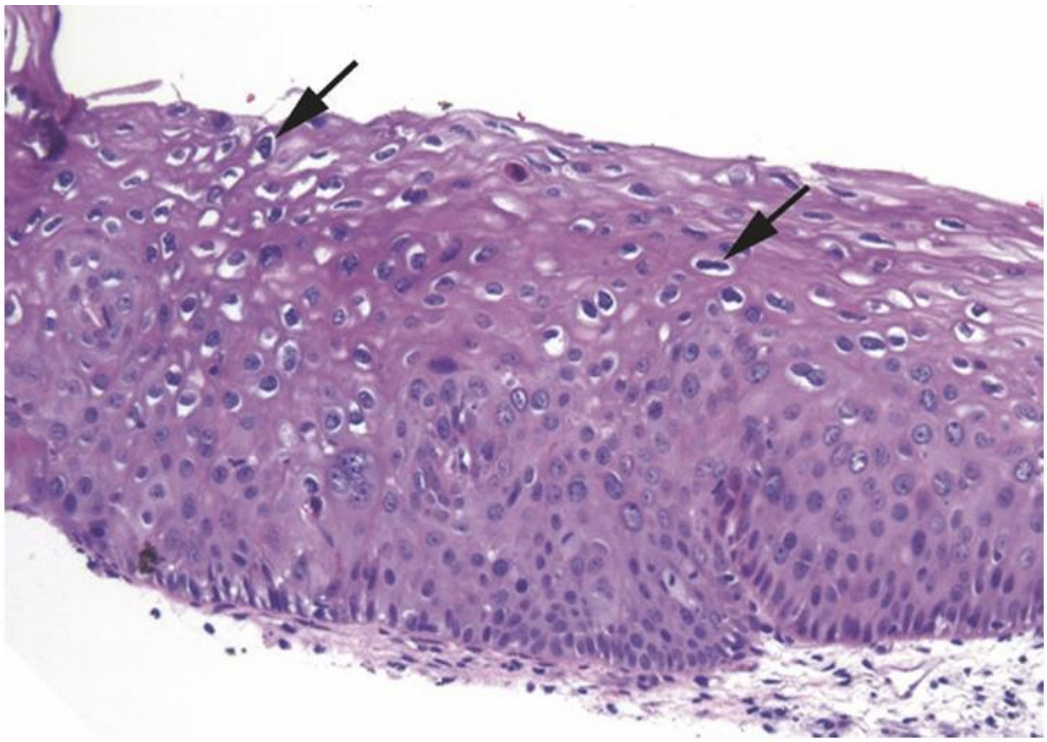


FIGURE 16.3. LSIL. The hallmark of LSIL is the koilocyte, which is a squamous cell with HPV viral cytopathic effect. The nuclei are hyperchromatic (dark) and raisinoid (crinkly; see *arrows*), with a surrounding clear halo in the cytoplasm. Other good features include superficial nuclei that are larger than the nuclei below them, and binucleated cells.

- **HSIL**
  - Immature cells / mitoses above the lower 1/3rd of the epithelium
  - Higher NCR
  - Atypia in all cell layes, although the nuclei may not be as large or as bizarre as LSIL but are uniformly crowded, enlarged, and hyperchromatic with clumped chromatin. Nuclei membranes are "boulder"
  - HSIL can grow into endocervical glands which should be mentioned in the diagnosis
  - Extensive HSIL analogous to CIS
- HSIL vs Immature Squamous Metaplasia
  - Do not confuse them!!
    - Well-defined cell border and low NCR
    - "Boiling mud look"
    - Pinker than HSIL due to having more cytoplasm
    - Bird egg nuclei (smooth, round, with even chromatin)
    - Surface mucin or columnar layer

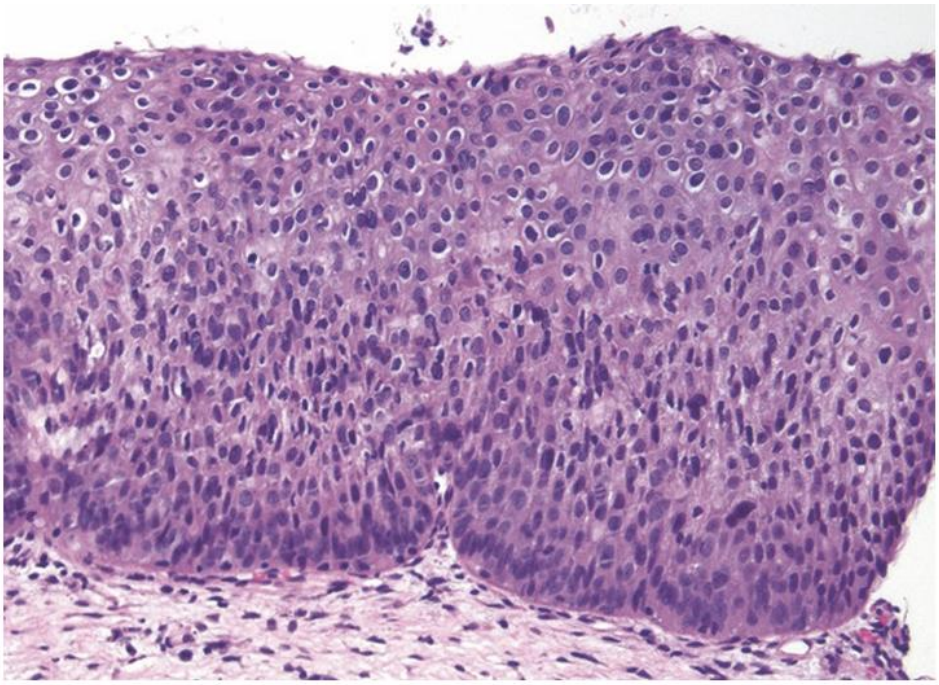


FIGURE 16.4. HSIL. In a high-grade lesion, paradoxically, the nuclei may not look as abnormal as in LSIL. The hallmark of HSIL is a persistence of immature-appearing cells throughout the epithelium. The nuclei are hyperchromatic and may have slightly irregular nuclear outlines, but the most striking feature at low power is the high N/C ratios present from top to bottom.

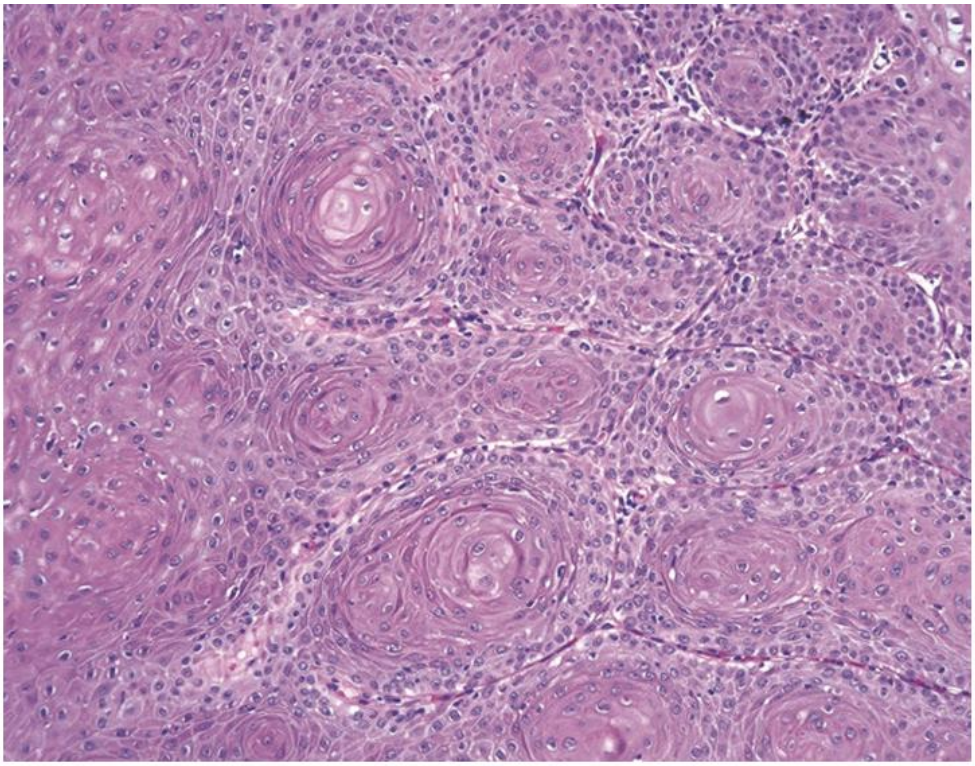


FIGURE 16.5. Immature squamous metaplasia. A tangential cut of squamous metaplasia can look like a lesion. However, this pattern of concentric whorls of cells with central pools of pink cytoplasm (resembling the boiling mud puddles of Yellowstone) is typical of benign squamous metaplasia.

❖ **Dysplasia vs Reactive changes**

Dysplastic	Reactive
Boulder in rockwall appearance	Smooth round nuclei
Clumpy chromatin with nuclei	Fine chromatin
Hyperchromatic nuclei	Pale colour in comparison
nucleoli	nucleoli
	Spongiotic between squamous ccells

- acute information should skew towards reactive

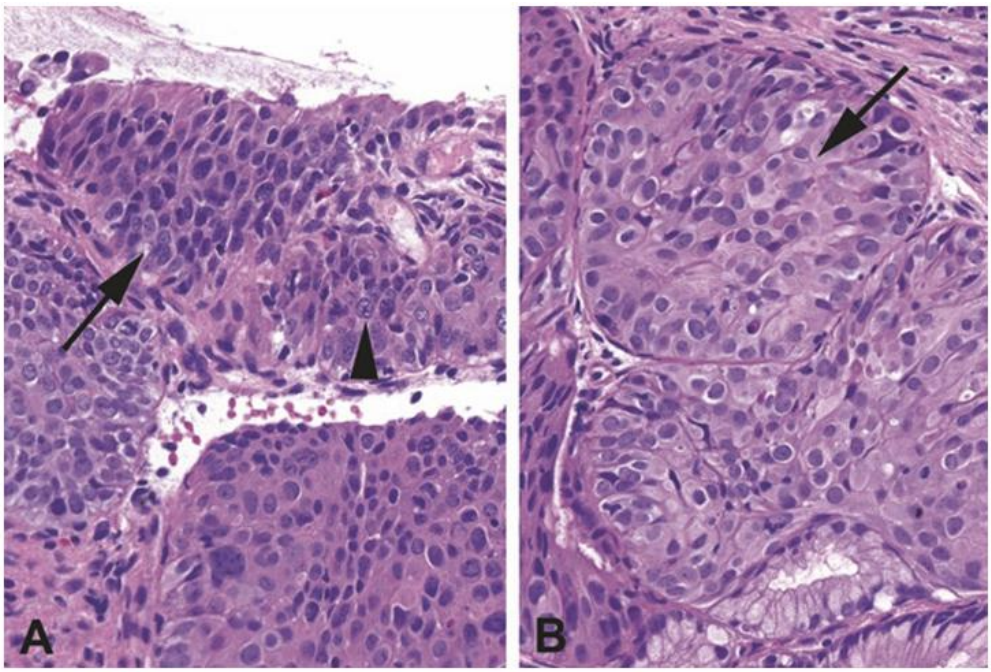


FIGURE 16.6. Dysplasia versus reactive changes. (**a**) In this example of HSIL, the dysplastic nuclei are irregularly shaped and appear to interlock together like stones in a wall (*arrow*). The quality of the chromatin is characteristic as well; it is dark and granular. Occasional nucleoli are visible (*arrowhead*), but they are surrounded by clumpy chromatin within the nucleus. (**b**) In reactive changes, the nuclei may be enlarged, but each nucleus remains smooth and oval in shape. The chromatin has a fine, even texture and is pale in color compared to the dysplastic cells in HSIL. Small dense nucleoli are visible in many of the cells (*arrow*).

❖ **Invasive Squamous Cell Carcinoma**

- Features include
  - Deep keratinization
  - Large nucleoli
  - Blurred or sawtooth interface between epithelium and stroma
  - Loss of the regular palisading basal layer
  - Desmoplastic response within stroma
- Specific instructions for measurement of the DOI exist, but not mentioned on pathoutlines in the way mentioned in Molavi
  - Pathology Outlines - HPV associated cervical squamous cell carcinoma

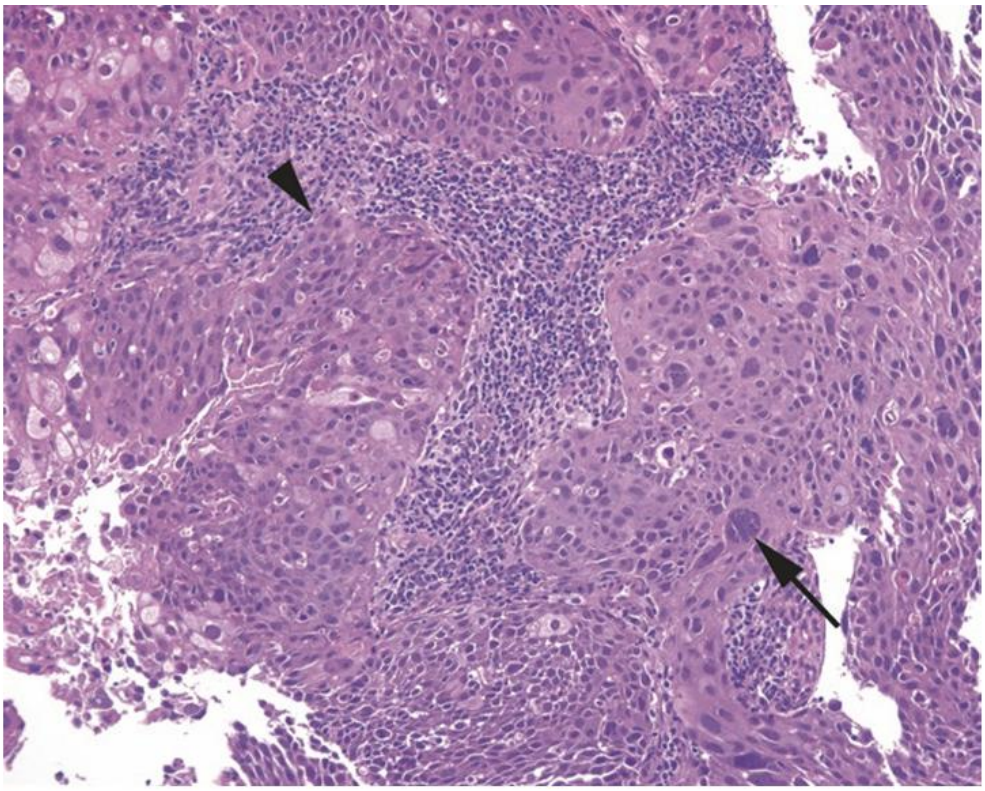


FIGURE 16.7. Invasive squamous cell carcinoma. Broad fronts of cells push into the stroma of the cervix, and at the leading edge, there is a ragged border with individual infiltrating cells (*arrowhead*). Occasional huge and pleomorphic cells are visible (*arrow*).

- DDx for Invasion:
  - Pseudoepitheliomatous hyperplasia
  - Glandular involvement by HSIL
    - HSIL tends to grow down into endocervical glands
      - Clues include remnants of columnar epithelium, a smooth rounded contour to the gland, lack of individual cells in the stroma
  - Placental site nodule
    - Remnant of pregnancy
    - A large, dark, smudgey nuclei without nucleoli
    - Can mimic ISCC
    - Unlike ISCC, nuclear membrane is not irregular
    - Unlike HSIL, chromatin is not chunky

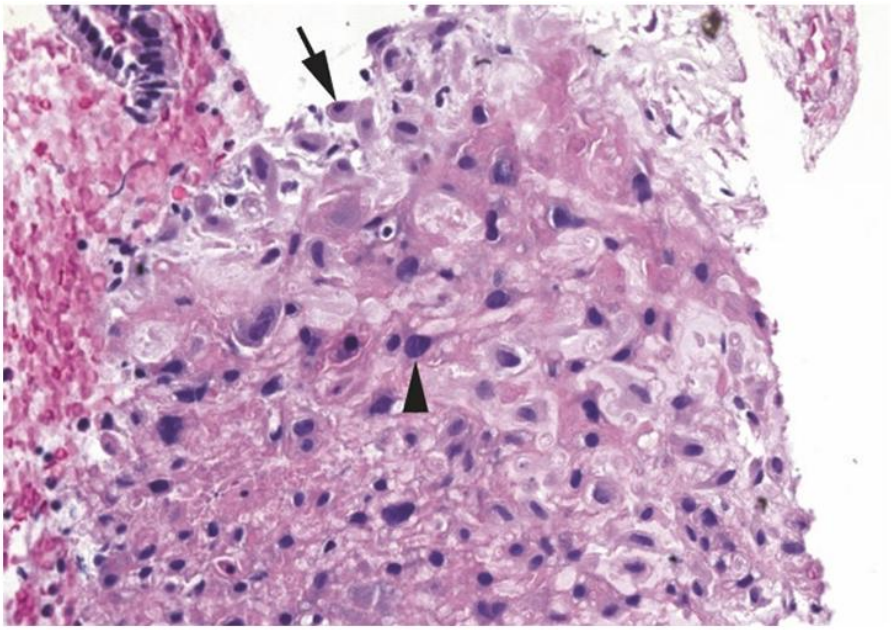


FIGURE 16.8. Placental site nodule, cervix. Although the dark nuclei and pink cytoplasm are concerning for squamous cell carcinoma, the nuclei are predominantly small and oval, with a few large nuclei visible (*arrowhead*). These large cells have dark but smudgy (blurred or indistinct) chromatin, without the chunky texture seen in HSIL (see Figure 16.6), and do not have the nuclear membrane irregularity of invasive squamous cell carcinoma (see Figure 16.7). The final clue is what appears to be a decidualized cell at the periphery (*arrow*).

Glandular Lesions

- **Microglandular Hyperplasia**
  - Proliferation of small back to back glands lined with cuboidal or mucinous columnar cells with squamous cells
  - Associated with OCP
  - Glands are pale, unlike AIS (dark)
  - Is Benign

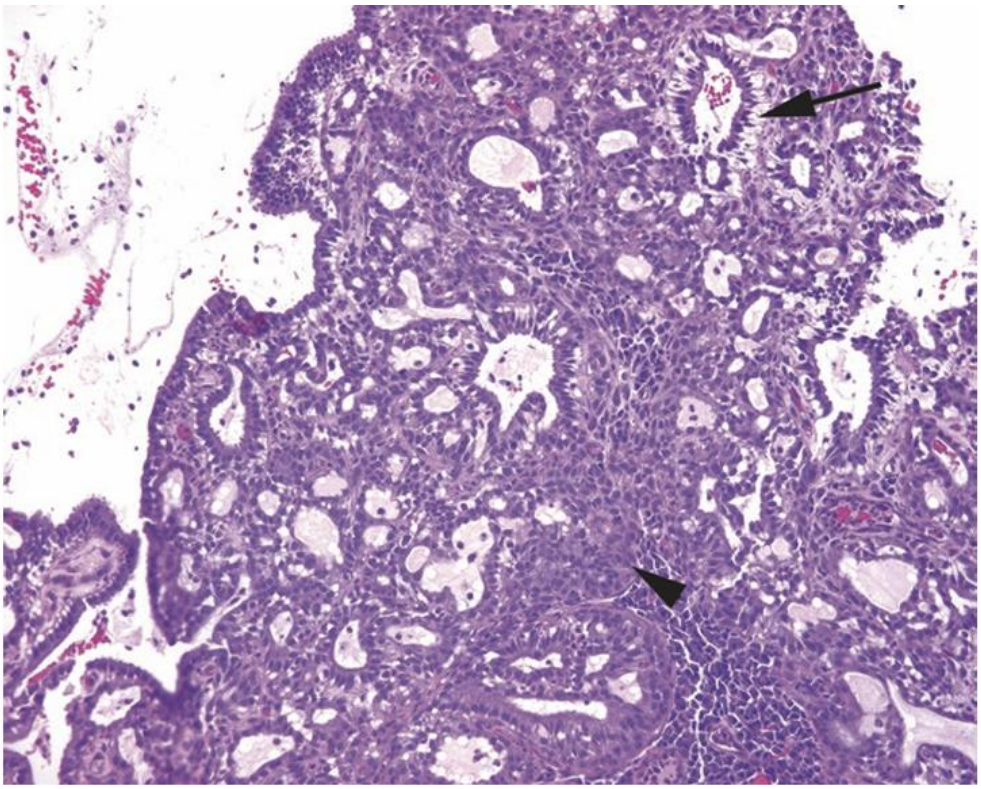


FIGURE 16.9. Microglandular hyperplasia. These endocervical glands show a very cellular proliferation composed of mucinous cells (*arrow*) and squamous metaplasia (*arrowhead*) and a cribriform pattern of lumens. This is benign.

- This is benign.

❖ **Endometriosis**

- Dense blue palisaded columnar glands surrounded by endometrial stroma
  - Stroma is key to the diagnosis

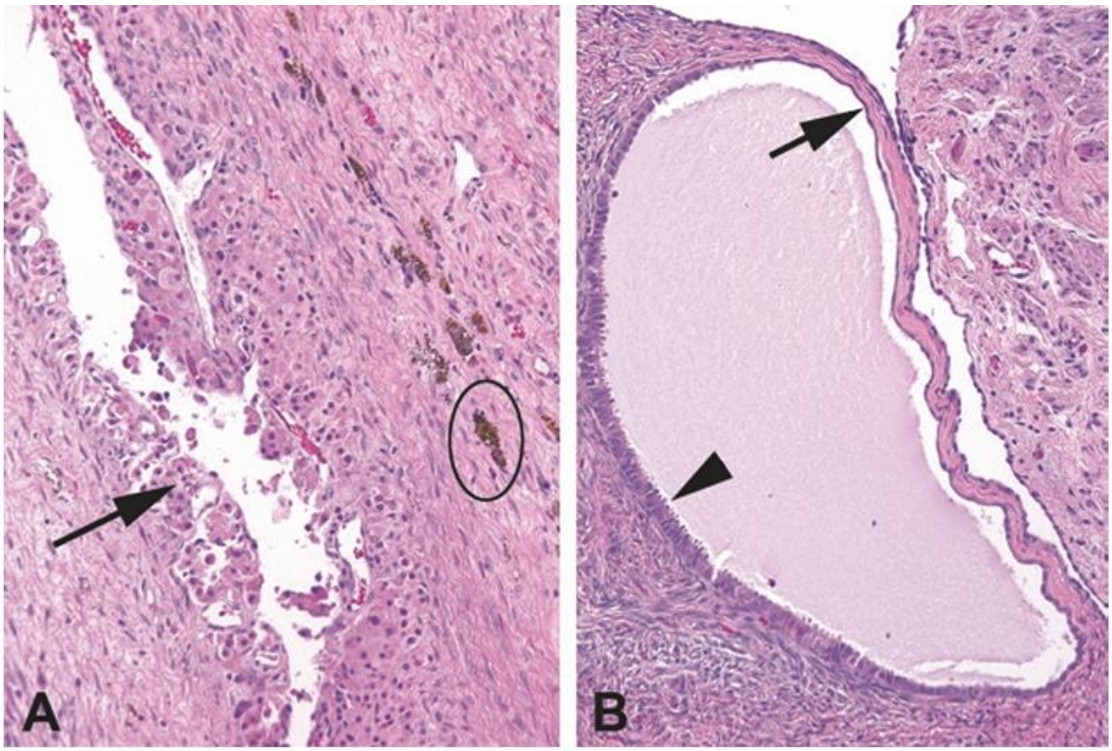


FIGURE 15.4. Follicular cyst versus inclusion cyst. (**a**) A follicle cyst is lined by luteinized cells, similar to those seen in the corpus luteum (*arrow*). There is adjacent hemosiderin (*oval*). (**b**) An inclusion cyst may be lined by an attenuated epithelium, similar to the surface epithelium (*arrow*), or may show tubal metaplasia (*arrowhead*).

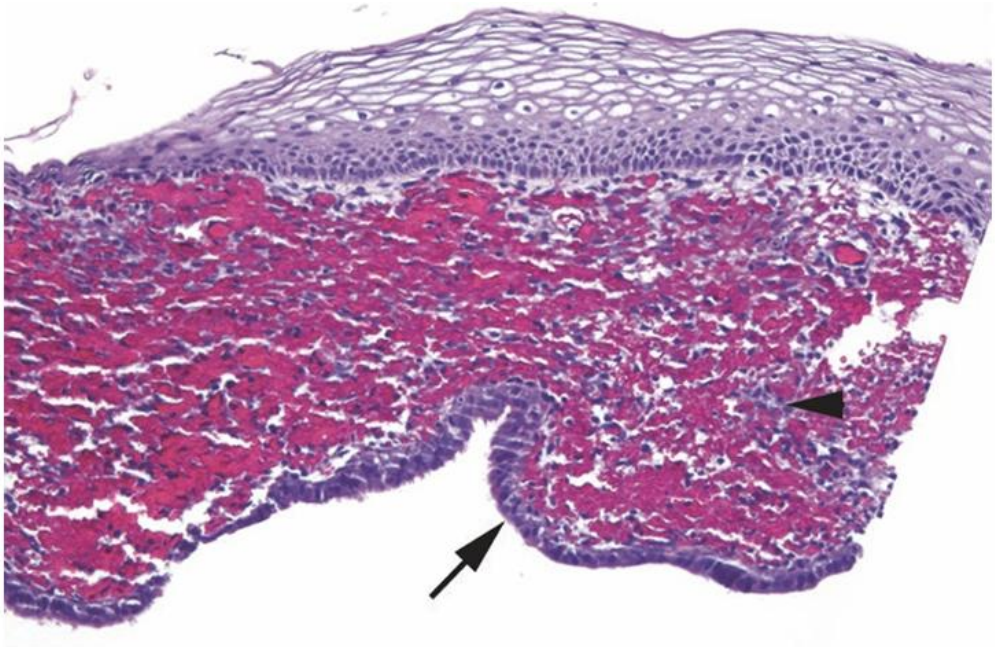


FIGURE 16.10. Endometriosis. This cervical biopsy specimen shows a squamous epithelium overlying stroma with hemorrhage. At the bottom of the fragment, there is a dark cuboidal lining (*arrow*) resembling endometrial epithelium. The telltale endometrial stroma (*arrowhead*) is mostly obscured by blood.

- **Endocervical Adenocarcinoma in Situ**
  - Close clusters of glands that may resemble colonic TAs
  - Nuclei
    - Rall and pseudostratified

- Large
- Hyperchromatic
- Nucleoli may be present

- Mitoses / apoptotic bodies common
- Papillary or cribriform architecture possible, and if it is, should raise the possibility of stromal invasion
- Mucin vacuoles / goblet cells possible
- p16 diffusely +ve (however p16 also +ve in tubal metaplasia. To differentiate, look for the ciliated cells in tubal metaplasia

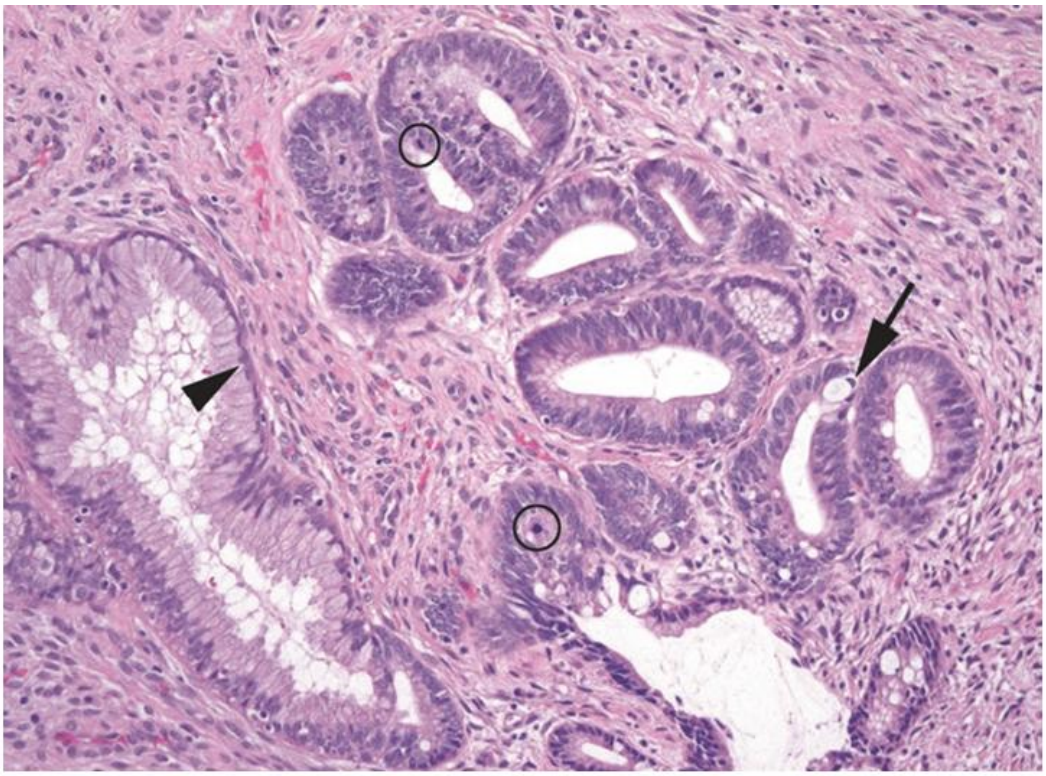


FIGURE 16.11. Adenocarcinoma in situ (AIS). This field shows some residual normal endocervical glands (*arrowhead*) adjacent to a very abnormal population with dark, elongated, crowded, and stratified nuclei representing AIS. Occasional intestinal-type goblet cells (*arrow*) and mitoses (*circles*) are present.

- ❖ **Invasive Endocervical Adenocarcinoma**
  - Glands that are too close (like AIS) with cribriform or back-to-back glands
  - Cell clusters diving off into the stroma
  - Desmoplastic response
  - Glands that are significantly deeper into he stroma than the benign glands (on perpendicular section)
  - p16 +ve, use this feature to distinguish endocervical adenoCA from endometrial adenoCA which is usually p16 -ve and ER/PR +ve
- ❖ **Minimal Deviation Adenocarcinoma**
  - p16 -ve
  - well differentiated adenocarcinoma
  - No desmoplasia

- No obvious changes from normal beside that the glands invade deeper than normal endocervical glands

Vulvar Epithelium

- **Lichen Sclerosus**
  - Bland, pale swaths of dermal collagen – early finding
  - Thin epidermis
  - Loss of rete ridges

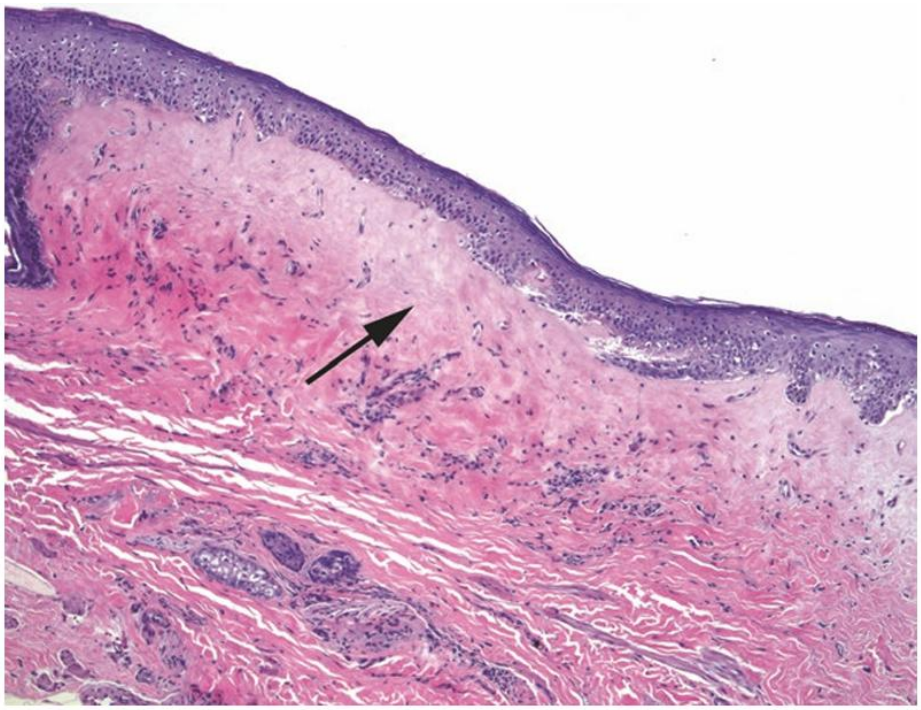


FIGURE 16.14. Lichen sclerosus. The epithelium is thin and atrophic, and the collagen underneath is pale, dense, and homogenized in texture (*arrow*). The dermal–epidermal junction is flattened, with an absence of rete.

- **Lichen Simplex Chronicus**
  - Thick epidermis
  - Hyperkeratosis
  - Chronically inflamed dermis
  - Dx of exclusion
  - Due to chronic spongiotic dermatitis
- **Extramammary Paget's Disease**
  - Large atypical (carcinomatous) cells percolating through epidermis
  - Analogous to mammary Paget's
  - Differentiate from melanoma with a panel

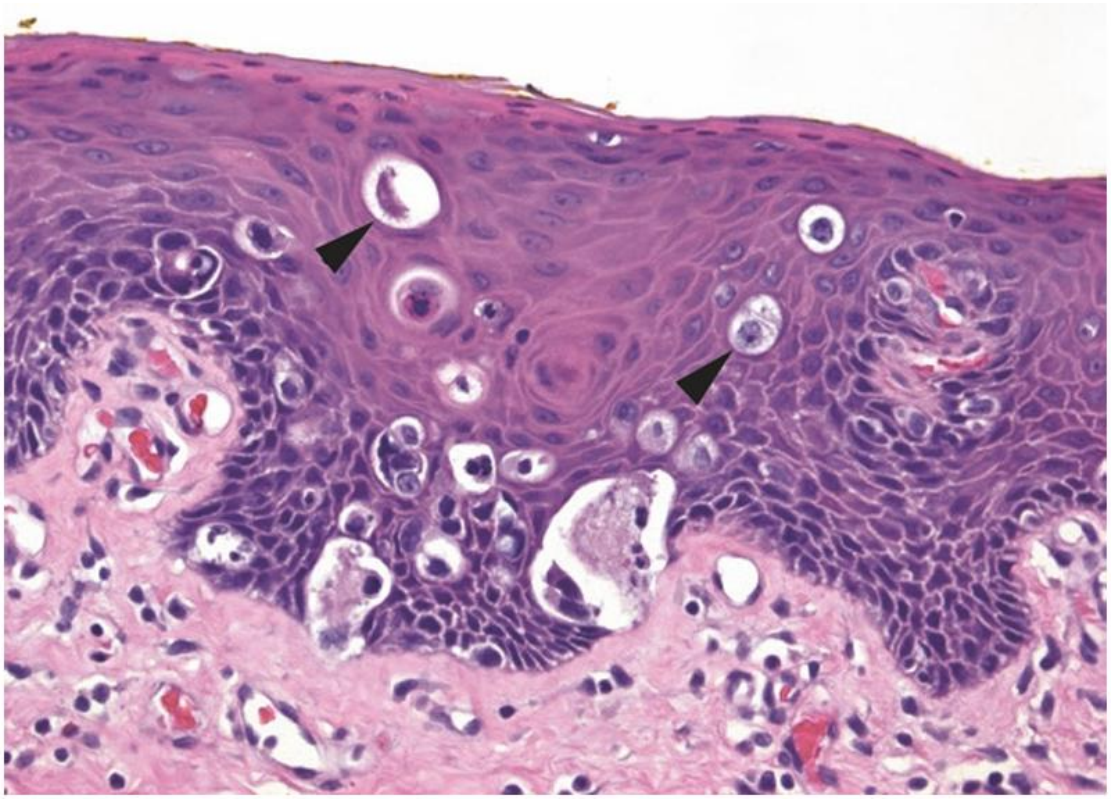


FIGURE 16.15. Paget's disease. Several nonsquamous cells (*arrowheads*) are visible within the squamous epithelium.

- Squamous Carcinoma of the Vulva
  - Has a variety of patterns (keratinizing, non-keratinizing, basaloid)
    - Watch for the Differentiated VIN, which has nuclear atypia limited to the lower half of the epithelium, but is severe
  - Vulva is keratinized unlike cervix so it manifests differently
    - HSIL is more subtle
      - Nuclear atypia is not as bad, but
      - Thicken epithelium with dark appearance at low power
      - Mitotic activity high in the epithelium

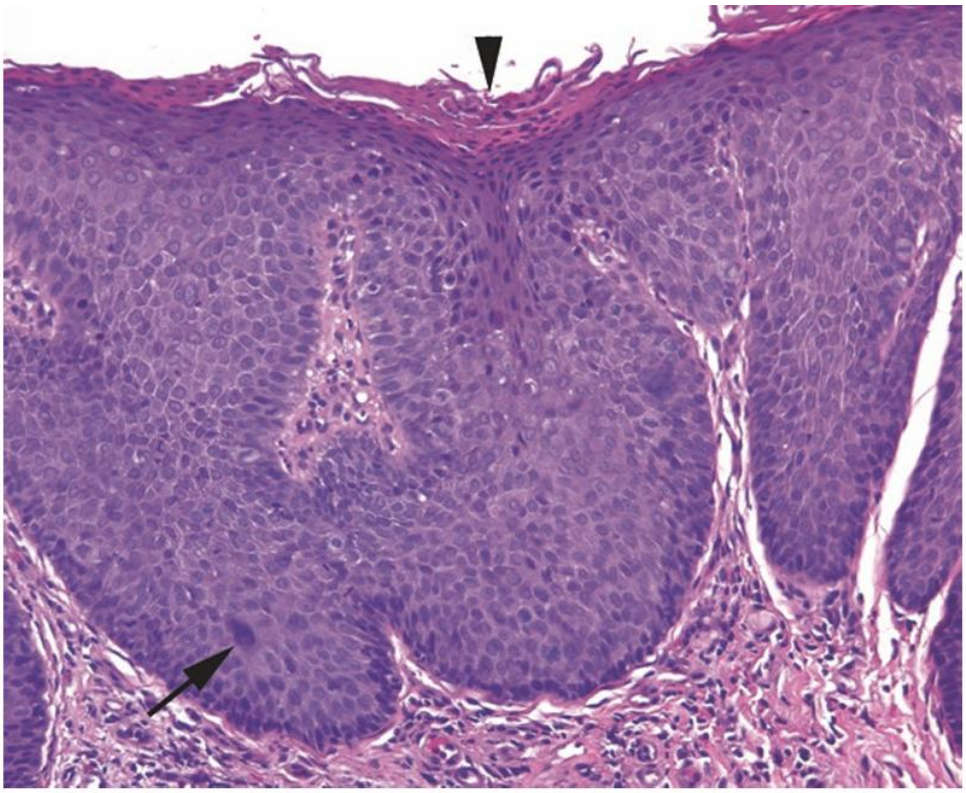


FIGURE 16.12. Vulvar HSIL (VIN3). This biopsy specimen shows hyperkeratosis and parakeratosis (arrowhead) overlying a very blue squamous epithelium. Although the nuclear changes are not as obvious as in high-grade cervical lesions, there is loss of polarity and high N/C ratios in the superficial epithelium. Occasional large atypical cells (*arrow*) are visible.

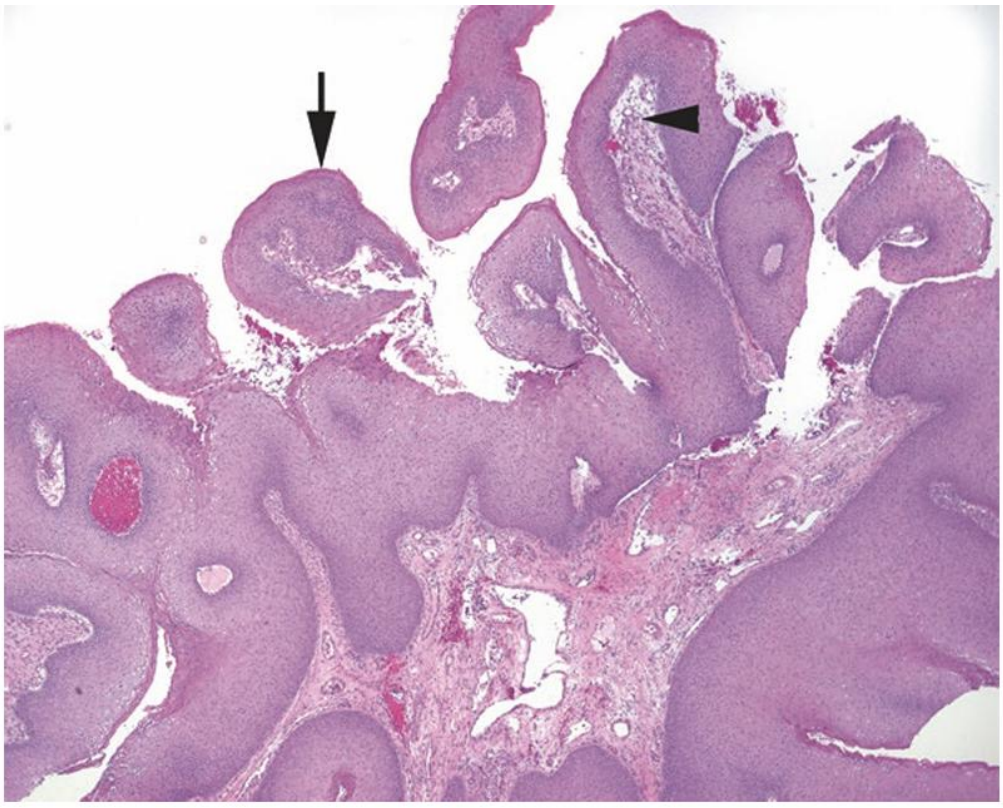


FIGURE 16.13. Condyloma. This exophytic lesion has prominent fibrovascular cores (*arrowhead*) underlying a thickened and hyperkeratotic squamous epithelium (*arrow*). Koilocytic or LSIL-type changes are not always obvious in condylomas.

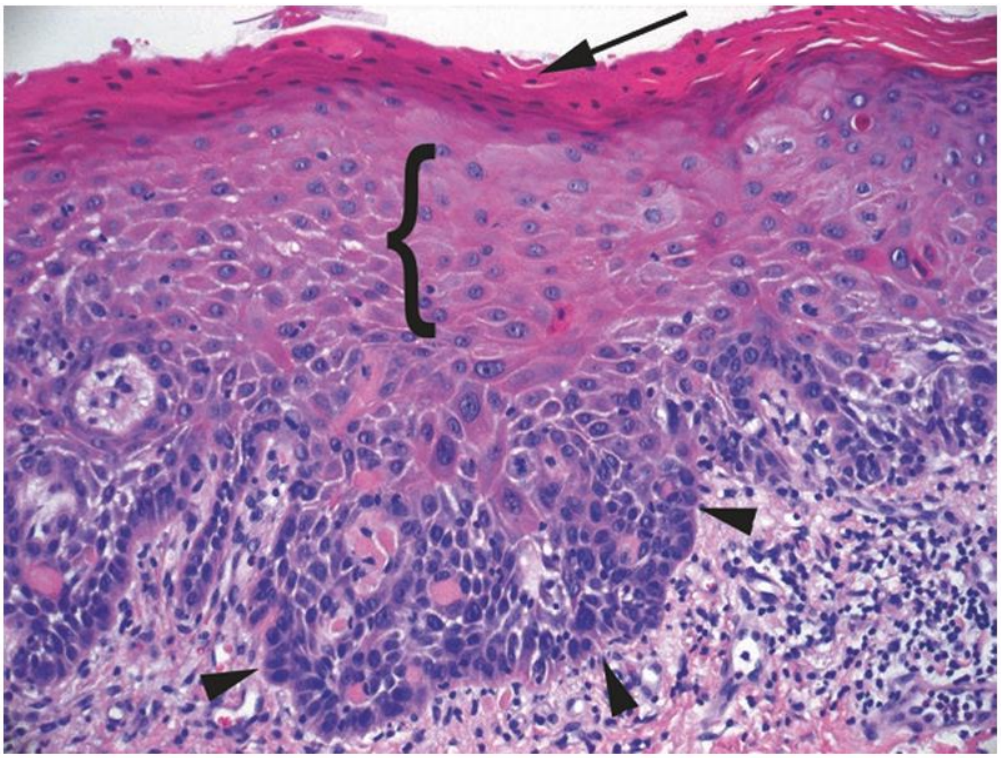


FIGURE 16.16. Differentiated VIN. In this type of dysplasia, there are misshapen and atypical nuclei clustered along the base (*arrowheads*), but the overlying cells appear to be maturing (*bracket*), and the upper nuclei are small, round, and regular. There is parakeratosis on the surface (*arrow*).

***Chapter 17* – Uterus**

Dating the Endometrium

Atrophic	- Low gland:stroma ratio - Comes off as hairpins on biopsy - Responsible for 50% of all cases of postmenopausal bleeding
Proliferative	- 1:1 gland:stroma - Fuller, blue look - Glands are simple tubular structures, "blue donuts" - Columnar epithelium with mostly basally located nuclei - **Mitoses should be readily visible**
Inactive	Like proliferative but ***no mitoses***
Secretory	- Prominent spiral arteries - Edematous stroma (variable) (looks like naked nuclei floating in water) - No mitoses
Secretory, **early** (days 16-18)	- **Cytoplasmic vacuoles** - **Secretions in lumens start**
Secretory, **mid** (days 19-23)	- Supranuclear-to-exhausted vacuoles - Peak secretions in the lumen - Ragged luminal border - Stromal edema
Secretory, **late** (days 24-28)	- **Decidualized stroma (pink cytoplasm), especially periarteriolar** - **Glands lose their vacuoles** - **Ragged luminal shapes** - **Tortuous glands**
Progestin Treated	- Very decidualized stroma paired with flattened gland epithelium

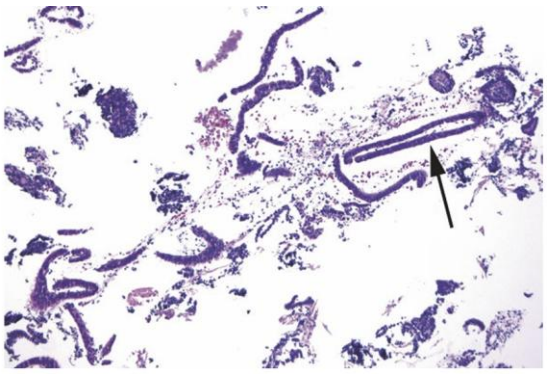


FIGURE 17.1. Atrophic endometrium. When curetted, the epithelium typically comes off in thin strips resembling hairpins (*arrow*). The specimen is also scant.

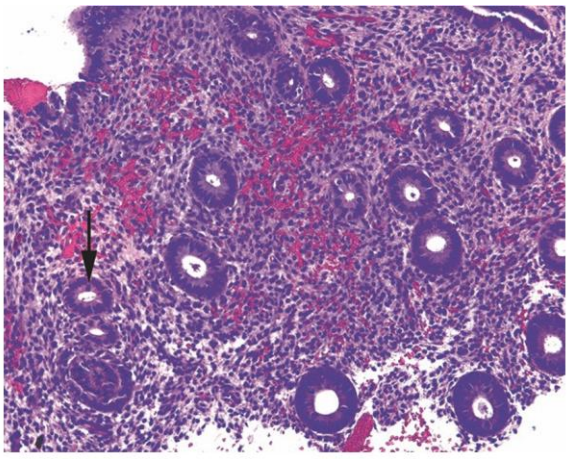


FIGURE 17.2. Proliferative endometrium. Multiple donut-shaped glands are visible, with dark oblong nuclei and frequent mitoses (*arrow*).

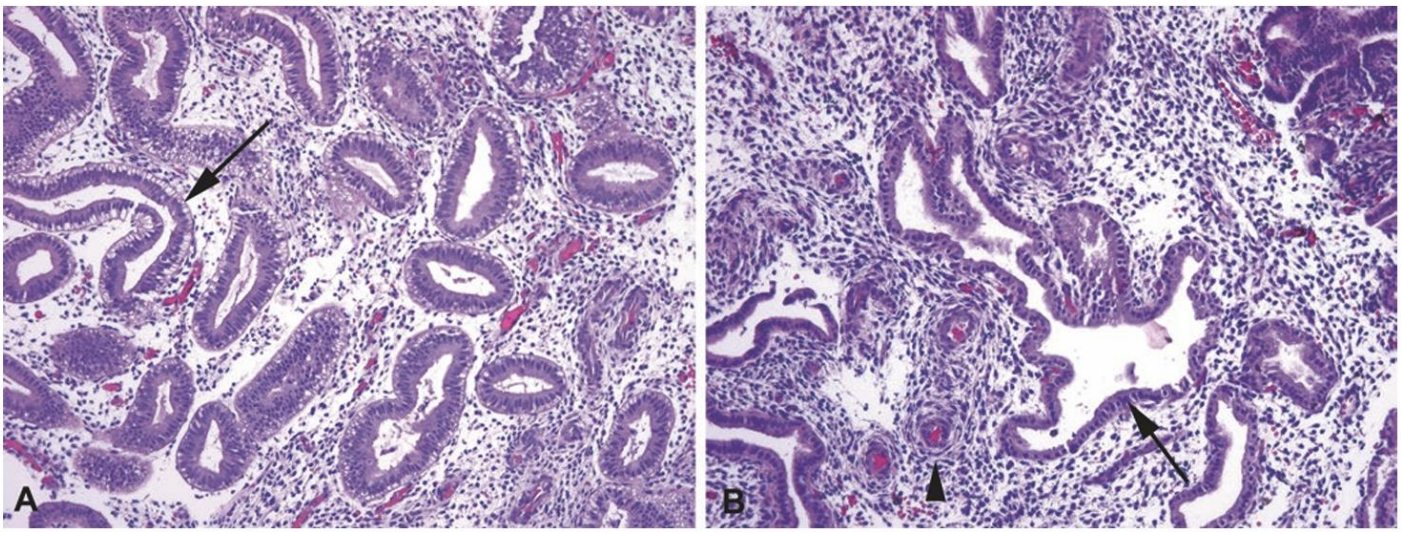


FIGURE 17.3. Secretory endometrium, various phases. (**a**) In early secretory endometrium, the glands have become tortuous in shape, and prominent cytoplasmic vacuoles are present (subnuclear, in this example; *arrow*). (**b**) Later in the secretory phase, the cytoplasmic vacuoles are gone, and the epithelium is more cuboidal in shape, with small round nuclei (*arrow*). The stroma is edematous, and early decidualization (accumulation of pink cytoplasm) is beginning around the spiral arteries (*arrowhead*).

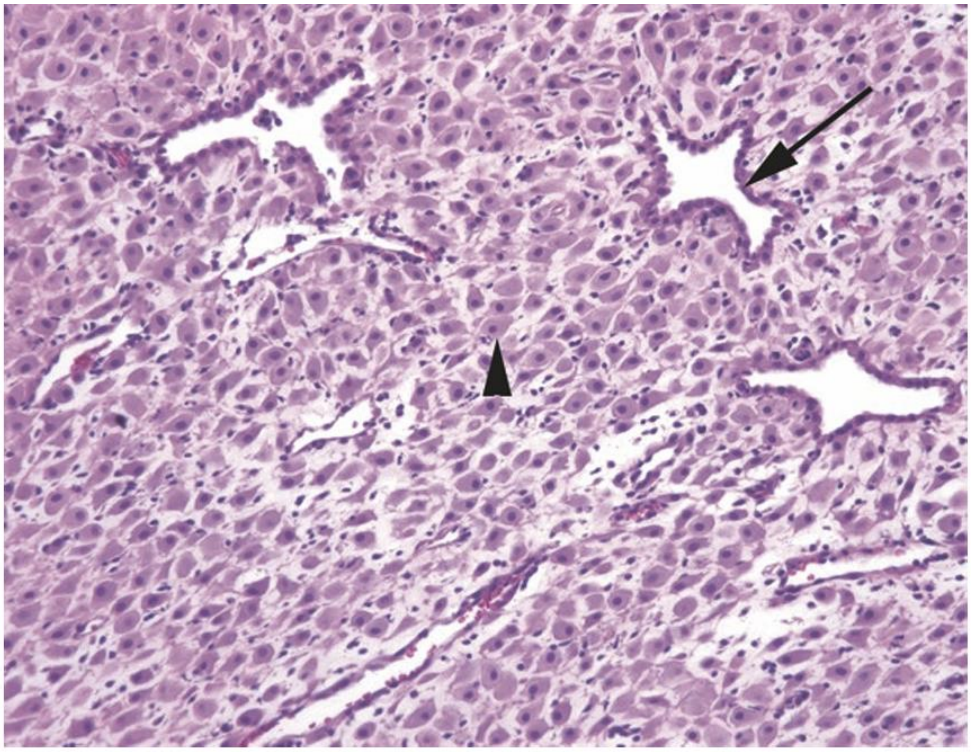


FIGURE 17.4. Progestin-treated endometrium. The glands are still tortuous in shape, like secretory endometrium, but the epithelium is markedly thinned (*arrow*). The stromal cells are decidualized (*arrowhead*), which means they have plump pink cytoplasm and distinct cell borders.

- ❖ Benign Endometrial Polyp
  - Thick walled vessels
  - Fibrotic stroma
  - Atrophic or cystically dilated glands

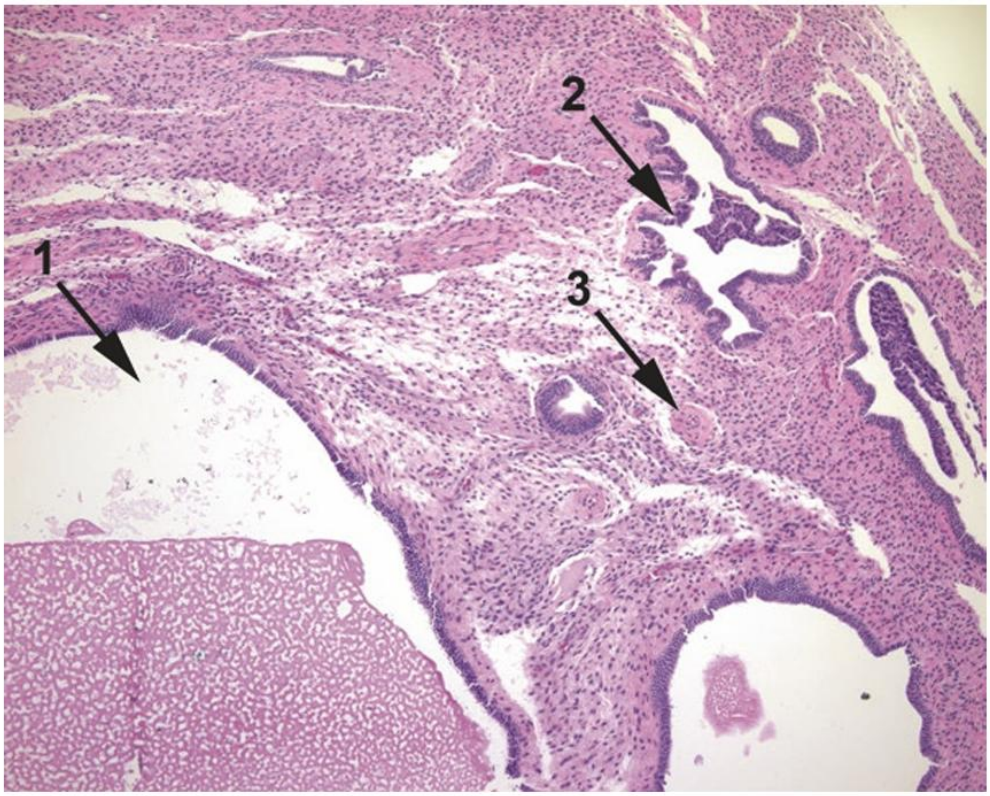


FIGURE 17.5. Benign endometrial polyp. This polyp shows cystic dilation of glands (*1*), secretory-type epithelium (*2*), and thickened arteries (*3*). The stroma is also pink, indicating a high collagen content.

- Endometrial Stromal Breakdown
  - Blue stroma
  - Eosinophilic surface metaplasia
  - ± thrombi in vessels
    - Neutrophils

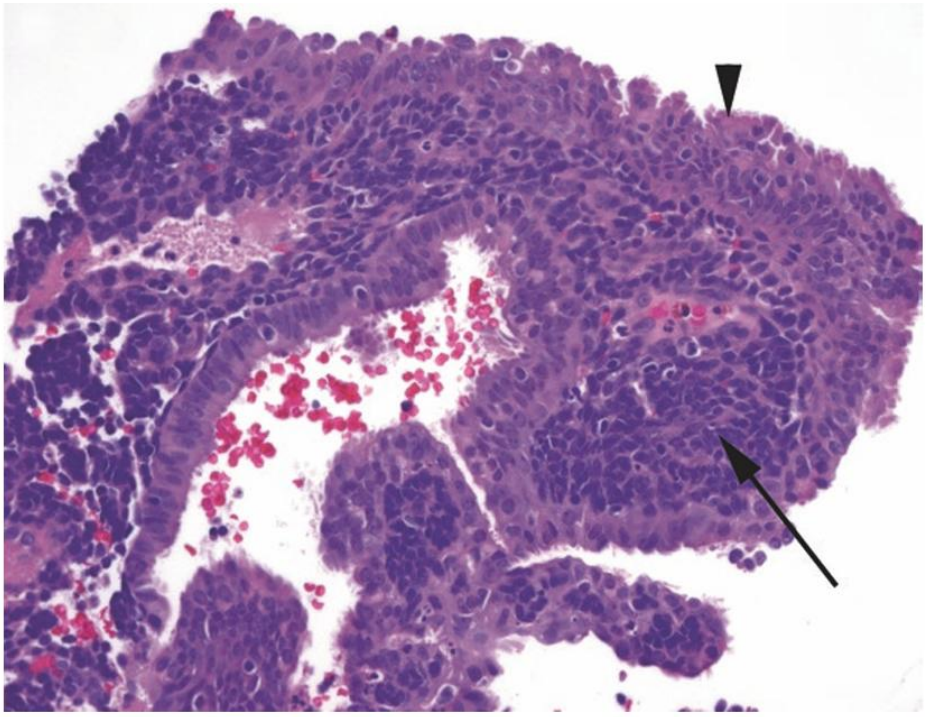


FIGURE 17.6. Endometrial stromal breakdown. The stroma is condensed into an extremely blue mass of tightly packed cells (*arrow*). The overlying epithelium is expanded into papillary tufts of pink cells, some with cilia, which is a metaplastic change (*arrowhead*).

- Endometritis
  - Acute
    - Diagnosis requires
      - Microabsecesses
      - Epithelial breakdown
    - PMNs are part of normal breakdown
  - Chronic
    - Dx by Plasma cells
    - Stroma looks more blue and spindly, with lymphocytes

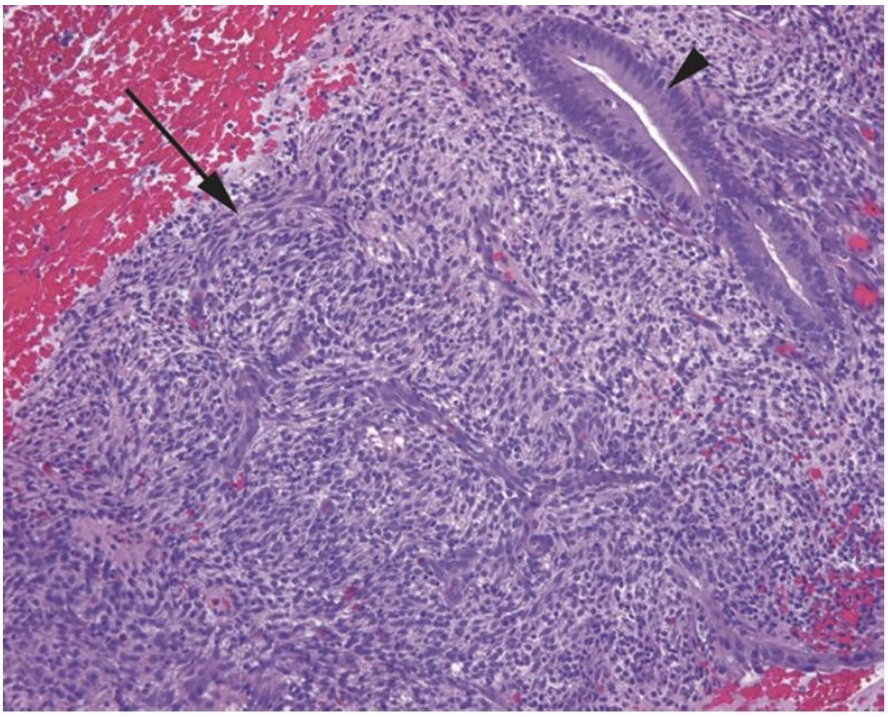


FIGURE 17.7. Chronic endometritis. At low power, the diagnostic plasma cells are not visible, but the spindly, swirling blue stroma (*arrow*) should be a clue to look more closely. The epithelium here is proliferative (*arrowhead*).

- Disordered Proliferative Endometrium
  - Resembles hyperplasia but not quite there
    - Glands crowded
    - Mix of cystically dilated, budding and tubular glands

Hyperplasia

- *with atypia*, and, *without atypia* varieties
- atypia is quite different in the endometrium from other organs
    - Normal endometrium = Hyperchromatic, pseudostratified, elongated nuclei and frequent mitoses. Stroma to gland ratio > 1

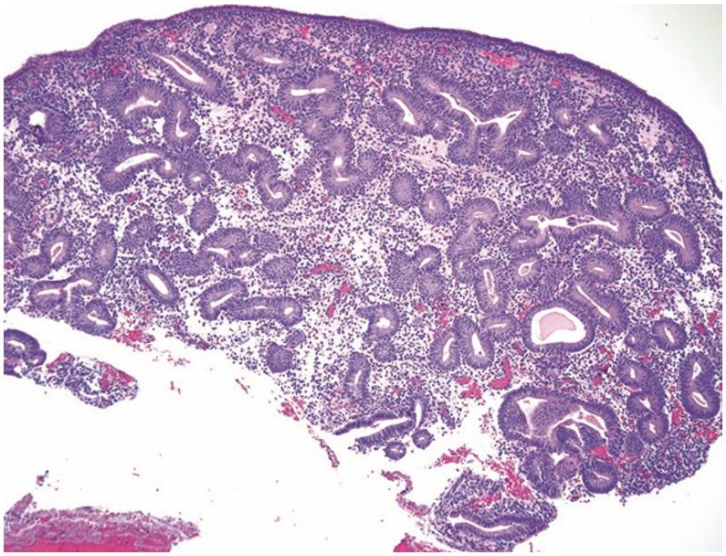


FIGURE 17.8. Hyperplasia without atypia. In this biopsy specimen, the glands appear proliferative and are too crowded (the gland-to-stroma ratio is greater than 1). The cells resemble normal endometrium and are not atypical.

- **<u>Atypical Endometrium (EIN)</u>**
  - aka Endometrial intraepithelial neoplasia (EIN)
  - nuclei become round and pale or vesicular because of the chromatin clumping up and migrating to the nuclear membrane
  - nucleoli may be prominent
  - nuclei lose polarity and are seen at all levels of the epithelium
  - nuclear larger in show increased variability in size and shape
  - cytoplasm becomes more eosinophilic. This makes it look more pale
    - ♦ distinguishes it from background
  - architectural complexity bumps this up to endometroid adenocarcinoma

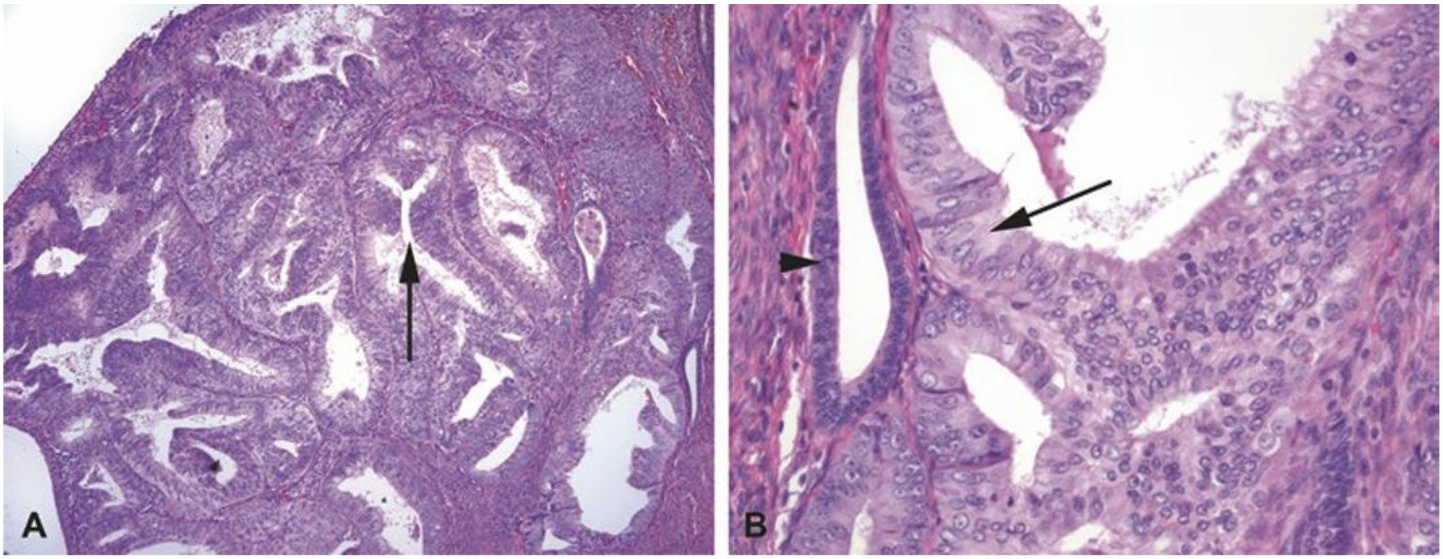


FIGURE 17.9. Atypical hyperplasia. (**a**) At low power, the glands are very crowded, even back to back, and the gland lumens have become branching and irregular (*arrow*). (**b**) At high power, comparing the hyperplastic epithelium (*arrow*) with normal residual glands (*arrowhead*), the hyperplastic cells have round nuclei and pale, vesicular chromatin with prominent nucleoli, diagnostic of atypia.

❖ Pitfalls
- ➢ Artifactual crowding
  - When glands are scraped out of the uterine cavity, they may clump together and look crowded. You need to find an intact piece of endometrium to evaluate the gland:stroma ratio.
  - Beware of diagnosing hyperplasia in the setting of endometrial polyp as they're often crowded

❖ Pregnancy associated changes
  - Is a solid sheet of decidua (Decidual cells are plump polygonal cells with pink to lavender cytoplasm and small oval nuclei)
  - Epithelium can become almost papillary with hypersecretory appearance
- ➢ Arias-Stella Reaction
  - Well-formed glands with ballooning, cleared out cytoplasm, and very pleomorphic nuclei
  - Normal change of pregnancy
- ➢ Can look like clear cell carcinoma but this lacks mitoses. (Also Clear cell happens in old people not child-bearing age women)
- ➢ May see placental site nodules

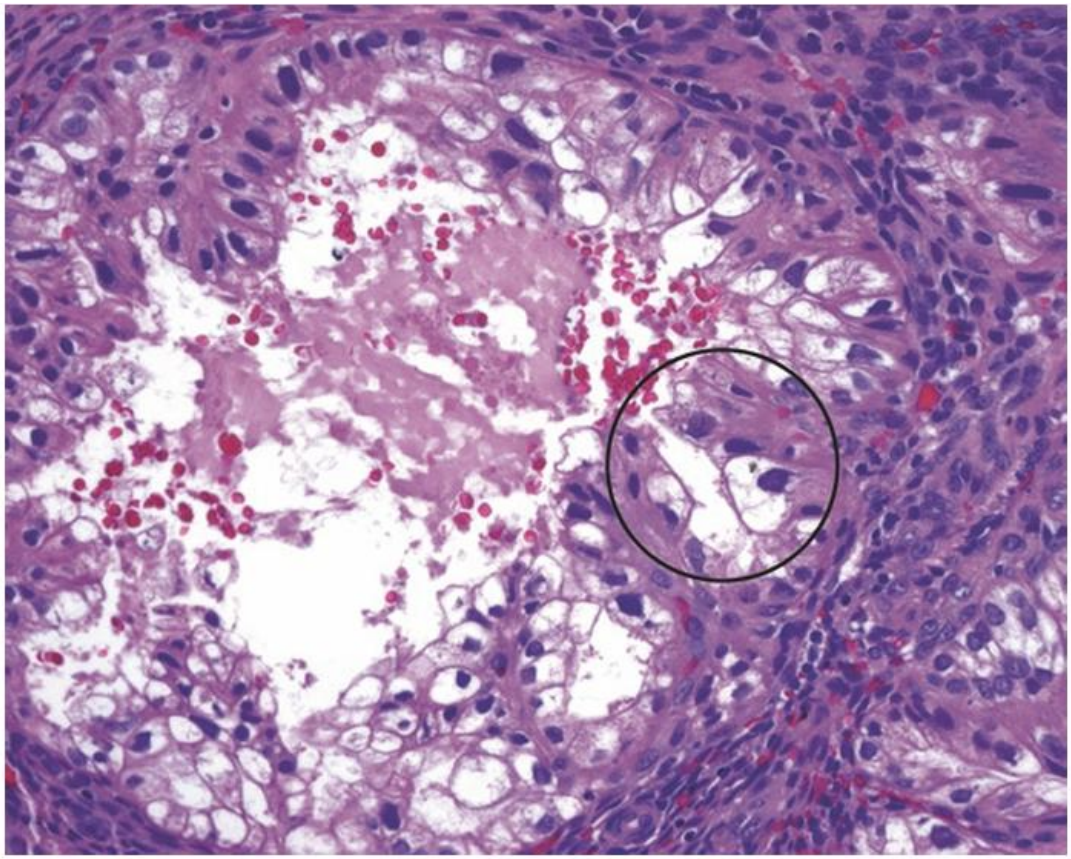


FIGURE 17.10. Arias-Stella reaction. Glands in the gestational endometrium can show bizarre cytology, including cleared-out cytoplasm and large hyperchromatic irregular nuclei (*circle*).

Types of Endometrial Metaplasia

- Tubal Metaplasia
  - Luminal cilia in an epithelium that looks slightly plumped up and cleared out
  - (don't overlook the cilia of the nuclei may worry you)
- Squamous metaplasia
  - Swirling islands of immature squamous cells
  - Rare keratinization
- Mucinous metaplasia
  - Mucinous, endocervical type cells
- Eosinophilic metaplasia
  - Increased eosinophilic cytoplasm
  - Bland nuclei
  - Gland proliferation possible tot eh point of looking papillary

Endometrial Malignancies

- Endometrial Carcinoma
  - Most common endometrial cancer
  - usually old women
  - precursor lesion is Atypical Hyperplasia
  - fused and complex clans possibly cribriform or villoglandular

- Clear cytoplasm is possible, so can distinguish clear cell endometrial Ca and clear variant of endometrial carcinoma with p53
- The clear variant of endometrial carcinoma would also lack true CC features such as hobnailing and significant nuclear atypia

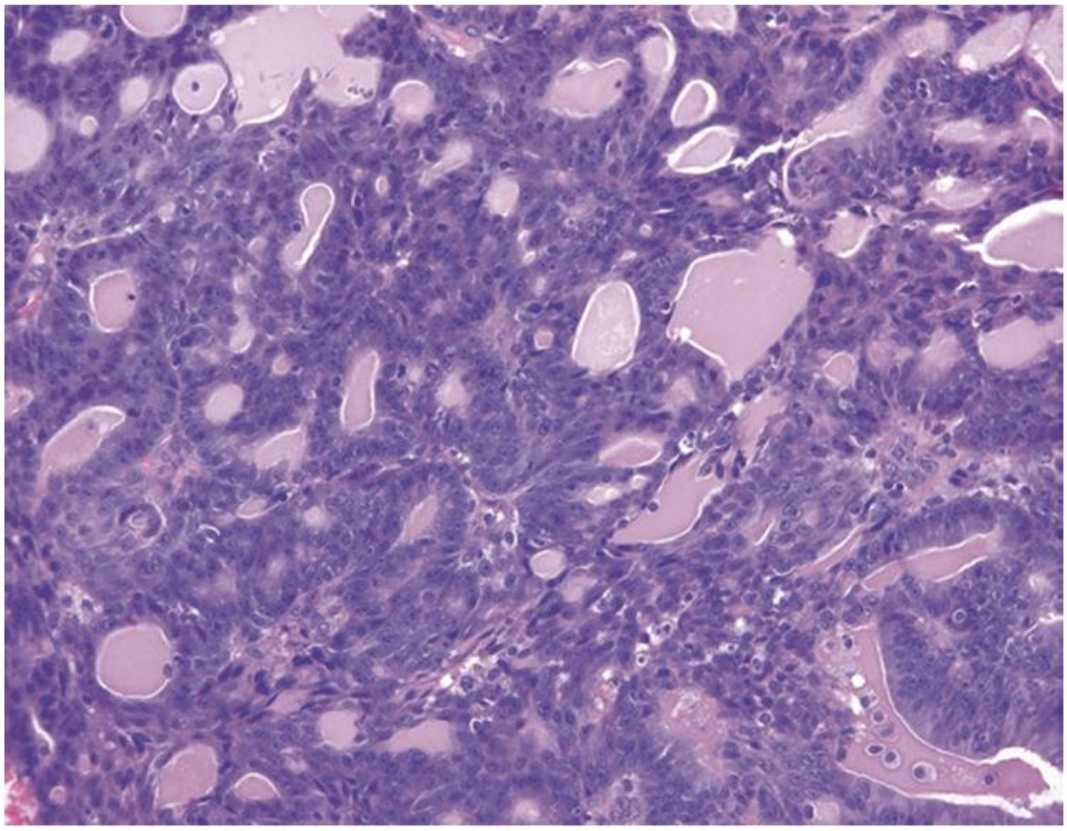


FIGURE 17.11. Endometrioid adenocarcinoma. Foci of well-differentiated endometrioid adenocarcinoma can be difficult to distinguish from atypical hyperplasia. However, the complicated proliferation of fused and cribriform glands in this biopsy specimen is diagnostic of carcinoma. The nuclei in this example resemble those of atypical hyperplasia.

❖ Serous Carcinoma
- Not graded, is high-grade by definition
- Resembles serous carcinoma of the ovary
- Hallmark: papillary architecture
  - ♦ may have *Solid growth with slit like spaces*
- Extreme atypia
  - "cherry red nuclei"
  - Bizarre mitoses
  - Multinucleated cells
- p53 positive, or dead negative due to mutation
- precursor is Serous EIC

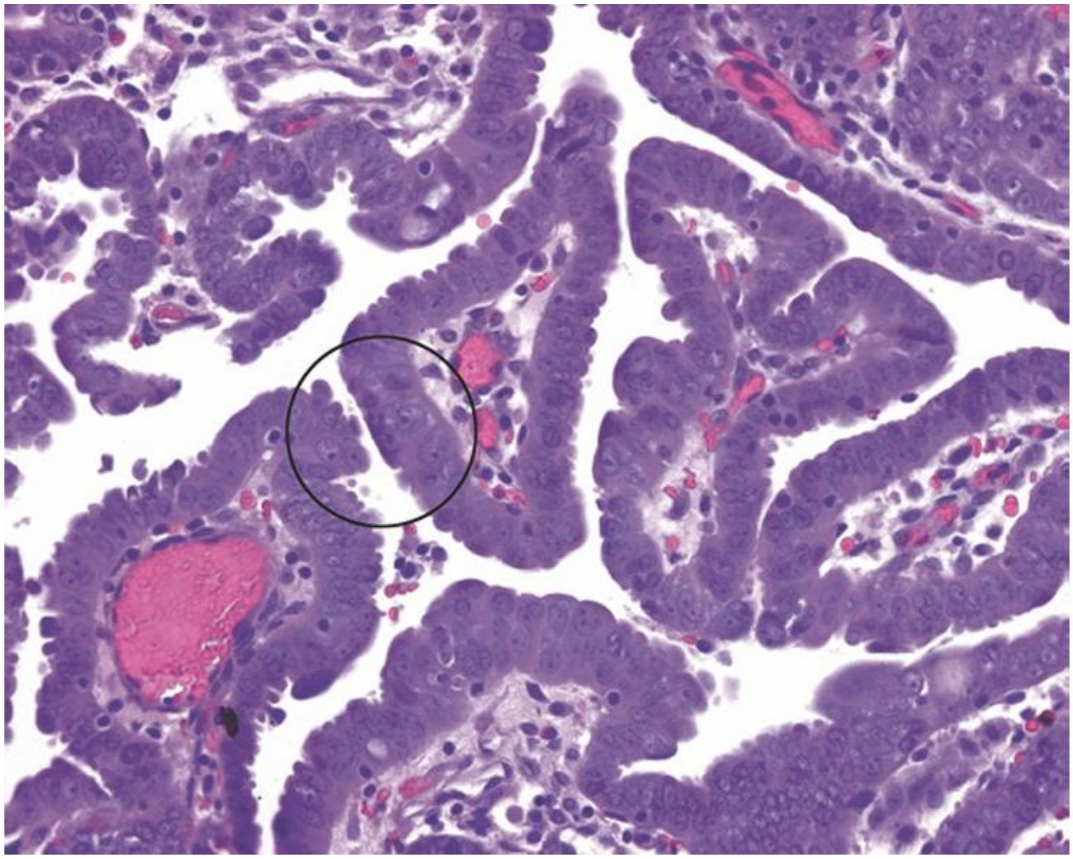


FIGURE 17.12. Serous carcinoma. Papillary structures are lined by atypical nuclei with prominent nucleoli (*circle*).

- Serous Endometrial Intraepithelial carcinoma (Serous EIC)
  - Metastatic potential in of itself
  - Abrupt transition point from benign atrophic endothelium to pleomorphic, enlarged, atypical mitotically active cells

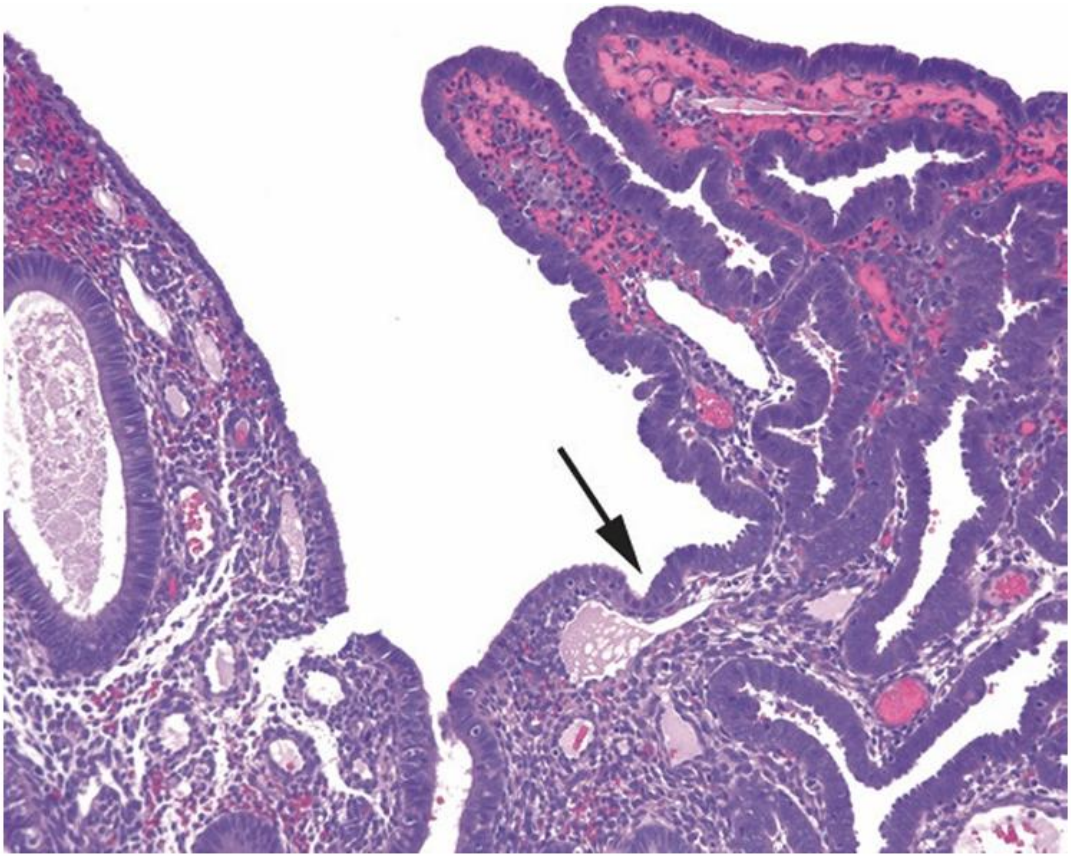


FIGURE 17.13. Serous endometrial intraepithelial carcinoma. There is an abrupt transition (*arrow*) from normal surface epithelium (*left*) to malignant cells (*right*). The cells resemble those of serous carcinoma.

- Clear Cell Endometrial Carcinoma
  - Old women
  - Not related to hormones
  - Hobhailing
  - Significant nuclear atypia
  - HG by definition
  - Looks like cc-RCC
  - Architectures
    - Tubular
    - Papillary
    - Solid
- Endometrial Stromal Nodule
  - Like LGESS but not infiltrative
  - Is a circumscribed nodule of endometrial stroma w/o glands
- Endometrial Stromal sarcoma
  - Low-grade (LGESS) and high-grade (HGESS)
  - Rare
  - Minimal atypia & few mitoses
  - Vascular proliferation
- Malignant Mullerian Mixed Tumour

- Malignant epithelium & stroma
- Appears

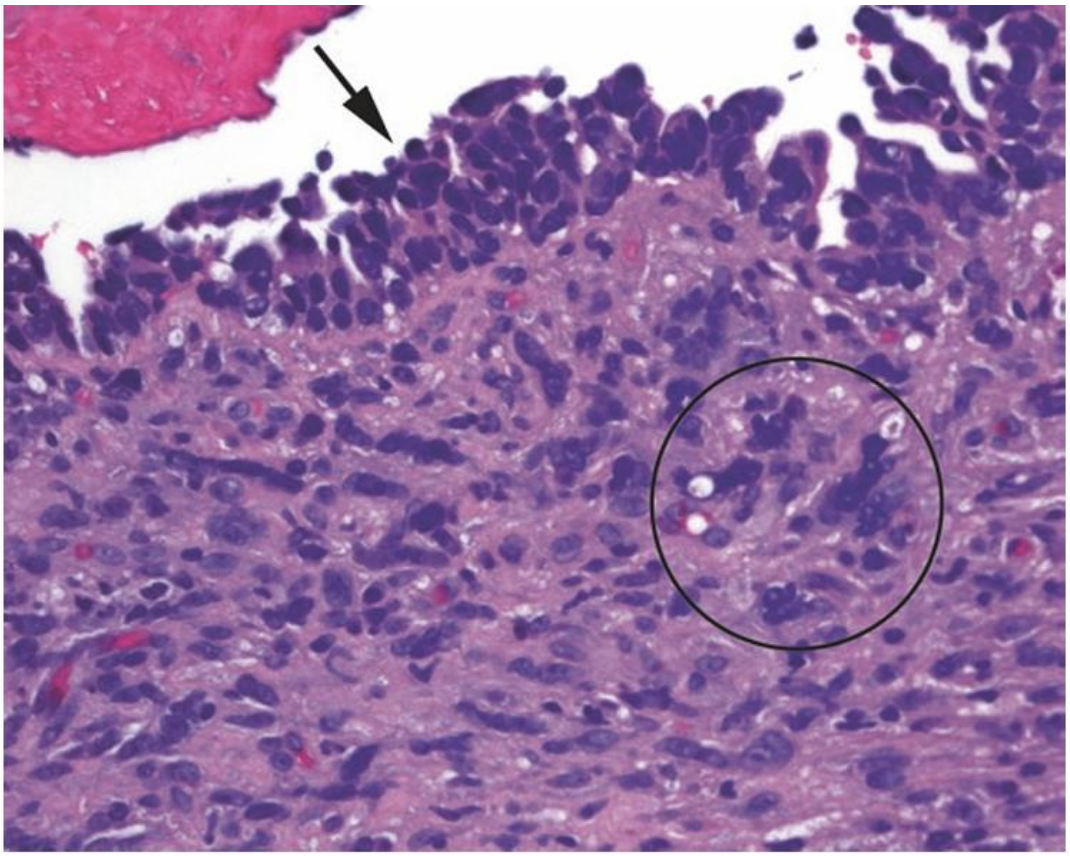


FIGURE 17.14. Malignant Mullerian mixed tumor. This tumor is defined by the presence of carcinomatous cells in the epithelium (*arrow*) and sarcomatous cells in the stroma (*circle*). The carcinoma cells are hyperchromatic and crowded; elsewhere in this biopsy specimen, there were malignant glands. The sarcomatous cells are hyperchromatic, large, and irregular in shape, similar to those found in other sarcomas (see Chapter 29).

❖ Adenosarcoma
- Malignant stroma and benign glands

❖ Adenofibroma
- Benign glands and benign stroma

❖ Leiomyoma
- Spindle cell lesion
- Fascicles @ right angles
- Dog poop nuclei (Long thin w fine pale chromatin)
- Doesn't progress

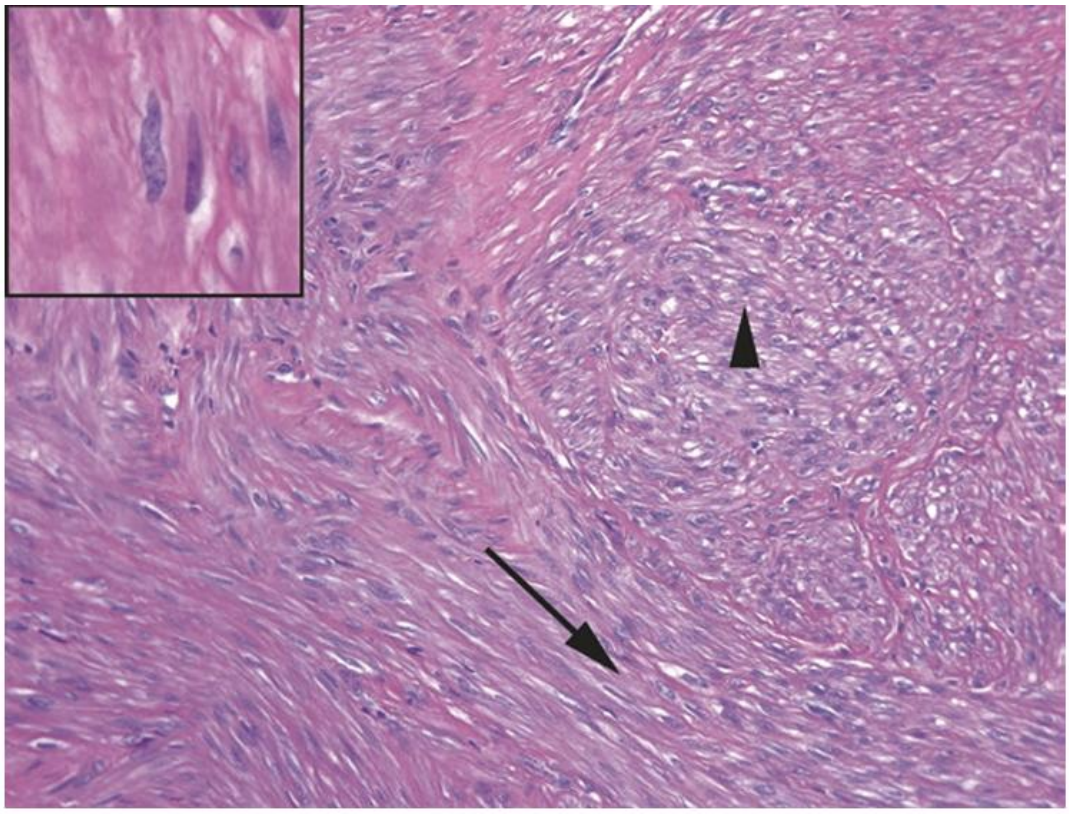


FIGURE 17.15. Leiomyoma. The low-power impression is that of fascicles or bundles of cells, some parallel to the slide (*arrow*) and some coming out at right angles (*arrowhead*). *Inset*: The nuclei are tapered and pale, with occasional paranuclear vacuoles, and sometimes show "corkscrew" morphology, as though the nucleus was twisted longitudinally. (Dog owners may liken this lumpy shape to something else).

- Leiomyosarcoma
  - Looks like fibroid but prominent mitoses (> 10/10 HPF)
  - Atypia
    - Large, hyperchromatic nuclei
    - Irregular nuclear shape, usually no nucleoli
    - Tumour necrosis

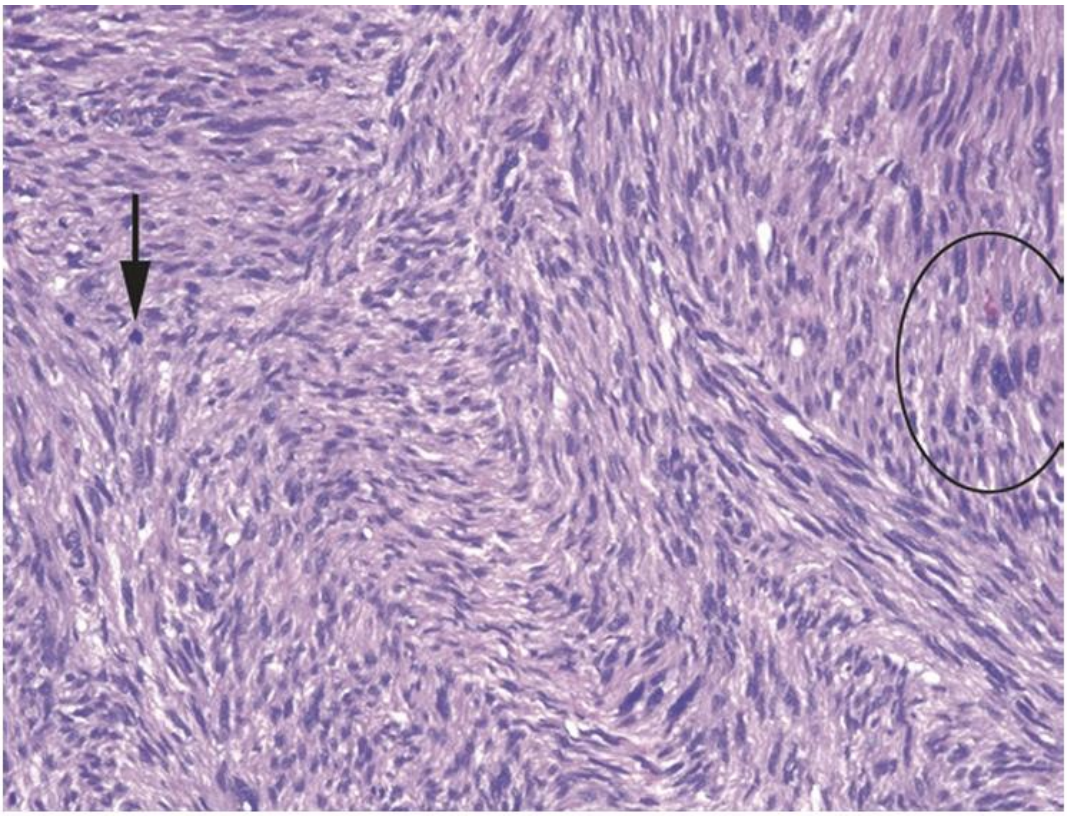


FIGURE 17.16. Leiomyosarcoma. The threshold for diagnosing leiomyosarcoma in the uterus is high. This lesion should be much more cellular than the leiomyoma, with mitoses (*arrow*), atypical and pleomorphic cells (*circle*), and necrosis (not seen here).

***Chapter 18* – Placenta**

❖ General

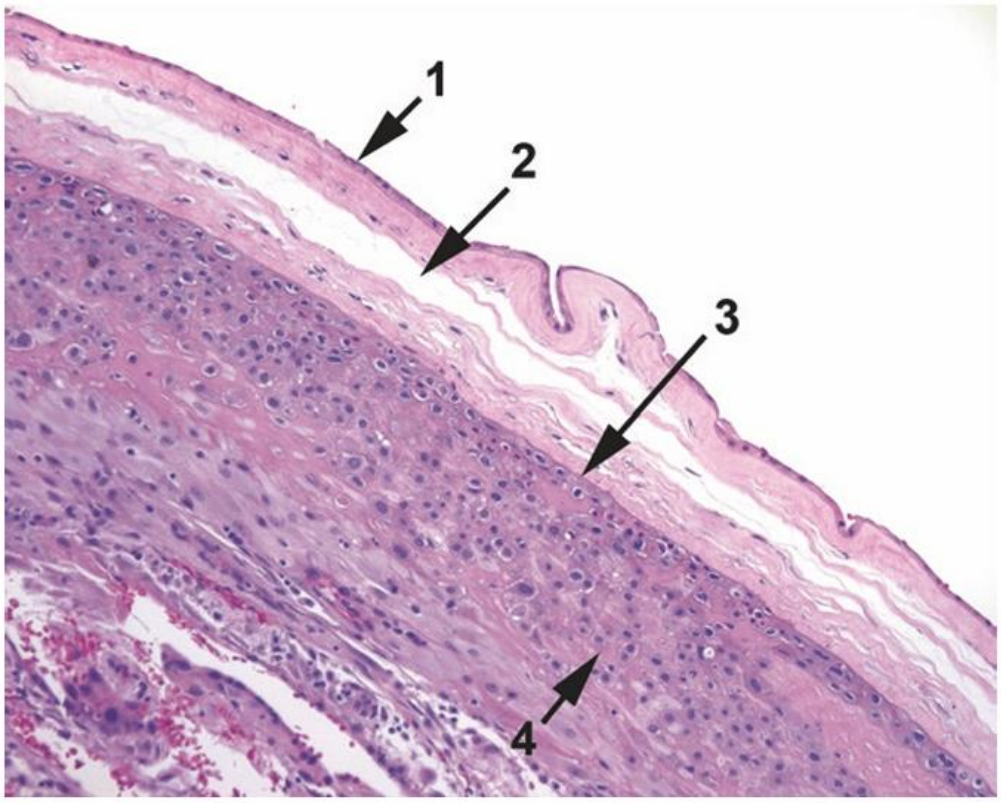


FIGURE 18.1. Placental membranes. In the membrane section, you can see amnion (*1*), an artifactual space (*2*) between amnion and chorion (*3*), and underlying decidua (*4*).

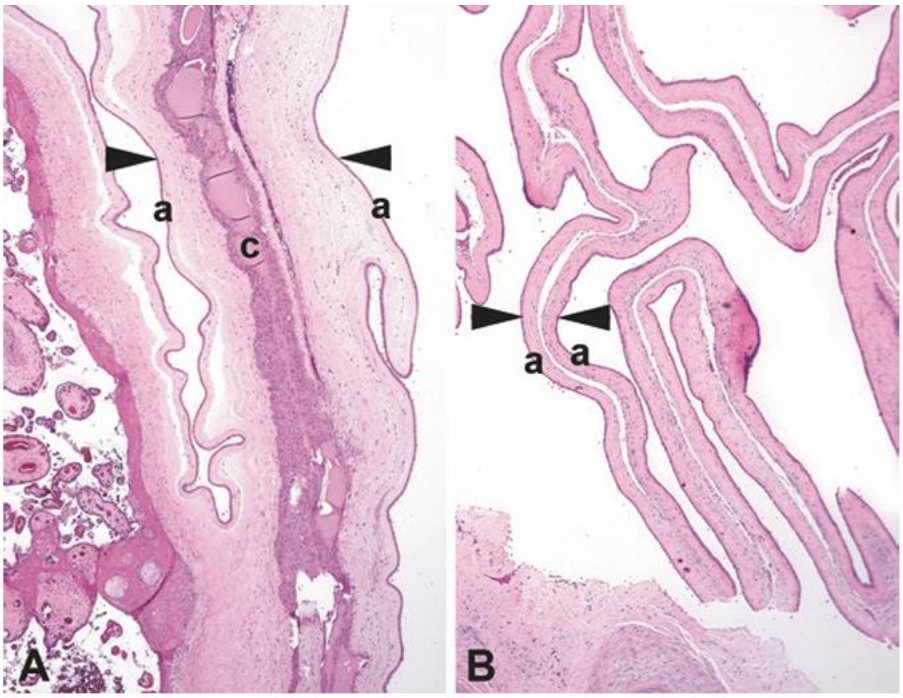


FIGURE 18.3. Twin placentas. (**a**) In a diamnionic–dichorionic placenta, the dividing membrane is captured here between the arrowheads. Amnion is seen on both surfaces (*a*), and a double layer of chorion is sandwiched in the middle (*c*). **b** In a diamnionic–monochorionic placenta, no chorion is present between the layers (*arrowheads*) of amnion (*a*).

➢ Immature Villi

- Open and pale appearance
- Large compared to terminal vili of a full term placenta (when surface area is most required)
- Lined by
  - Outer syncytiotrophoblast layer
  - Inner cytotrophoblast layer
- May have a large heaped up trophoblastic proliferation if it is a very early rely
- Circumference show proliferation of trophoblasts is suspicious for hydatidiform mole

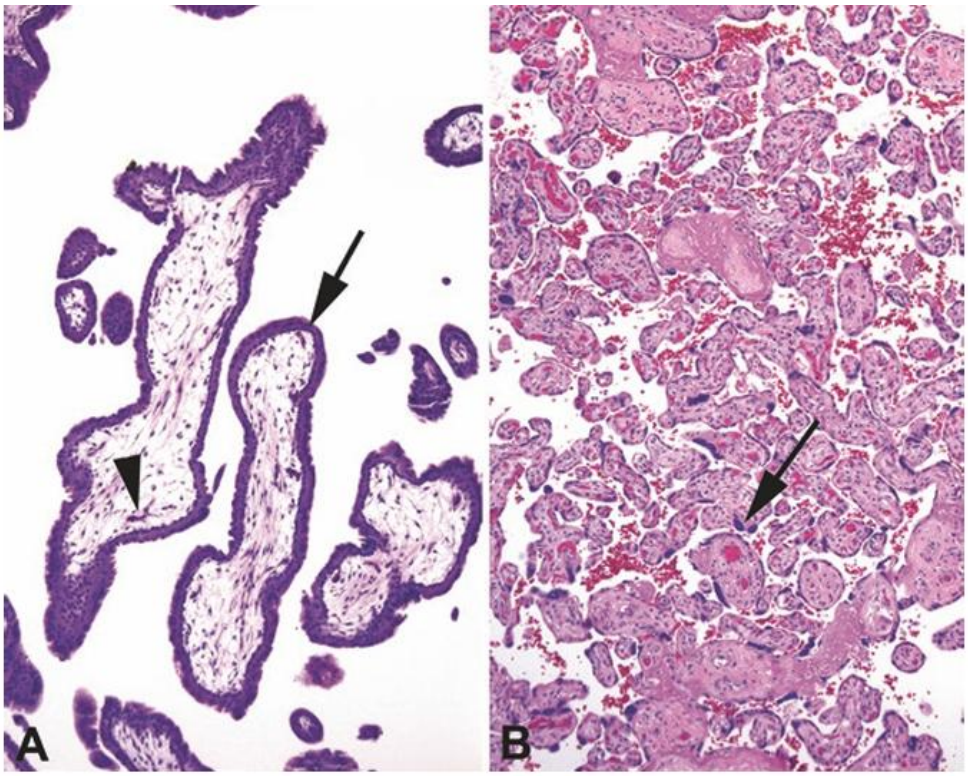


FIGURE 18.2. Immature villi versus terminal villi. (**a**) Villi at around 8–10 weeks are large in diameter and have a double layer of cells lining the surface (*arrow*). Tiny fetal capillaries have nucleated red blood cells inside (*arrowhead*). (**b**) Taken at the same magnification as A, this shows mature villi at approximately 38 weeks. The villi are much smaller, the fetal capillaries are more prominent, and the cytotrophoblasts have pulled away from the gas-exchange surface into syncytial knots (*arrow*). Maternal blood and fibrin are visible between villi.

➢

❖ Approach to Placenta Slides

➢ Umbilical Cord

- Funisitis
  - Vessels have PMNs infiltrating their walls (umbilical phlebitis)
    - ♦ Mild → umbilical vein
    - ♦ Moderate →umbilical arteries
    - ♦ Severe → Wharton's Jelly

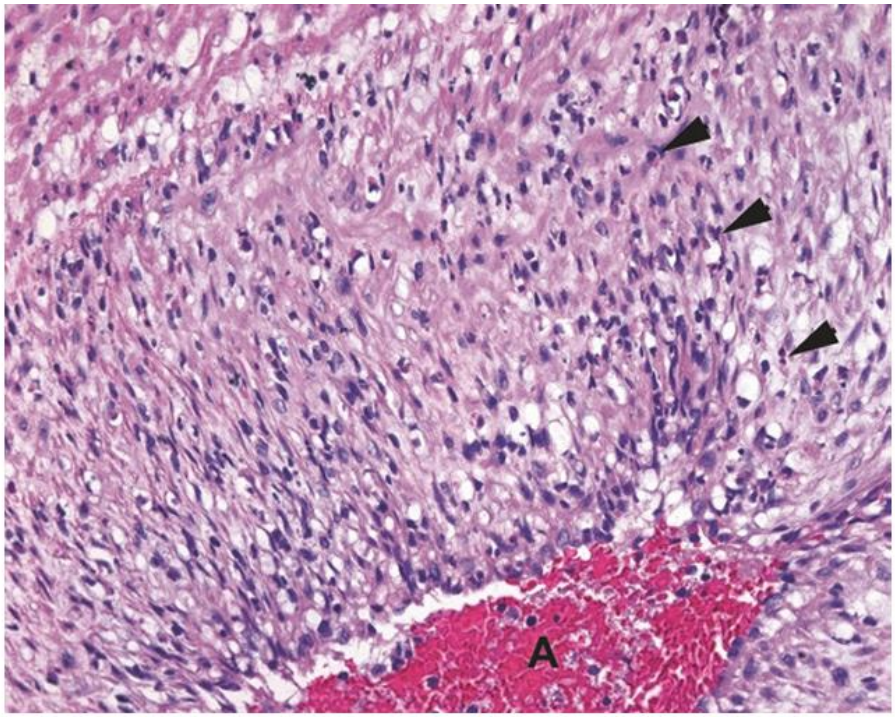


FIGURE 18.5. Funisitis. Neutrophils (*arrowheads*) can be seen squeezing through the muscular layer of an umbilical artery (*A*). This migration is a fetal response to infection.

- Membrane Roll
  - Chorioamnionitis: PMNs invading chorion & amnion but PMNs in the decidua are OK

TABLE 18.1. Criteria for staging of acute chorioamnionitis and funisitis.

Stage	Maternal response	Fetal response (funisitis)
1	Subchorionitis and chorionitis: *maternal neutrophils* line up beneath the chorionic surface of either the chorionic plate or membranes	Chorionic plate vasculitis and umbilical phlebitis: *fetal neutrophils* marginate through the vessel wall
2	Chorioamnionitis: neutrophils cross the basement membrane into the connective tissue between chorion and amnion	Umbilical arteritis: neutrophils in the arterial wall
3	Necrotizing chorioamnionitis: sheets of neutrophils below the amnion, reactive or necrotic amnion, thickened amniotic basement membrane	Umbilical perivasculitis: neutrophils spread out from the vessels into Wharton's jelly

Grade 1 focal disease, *grade 2* extensive disease

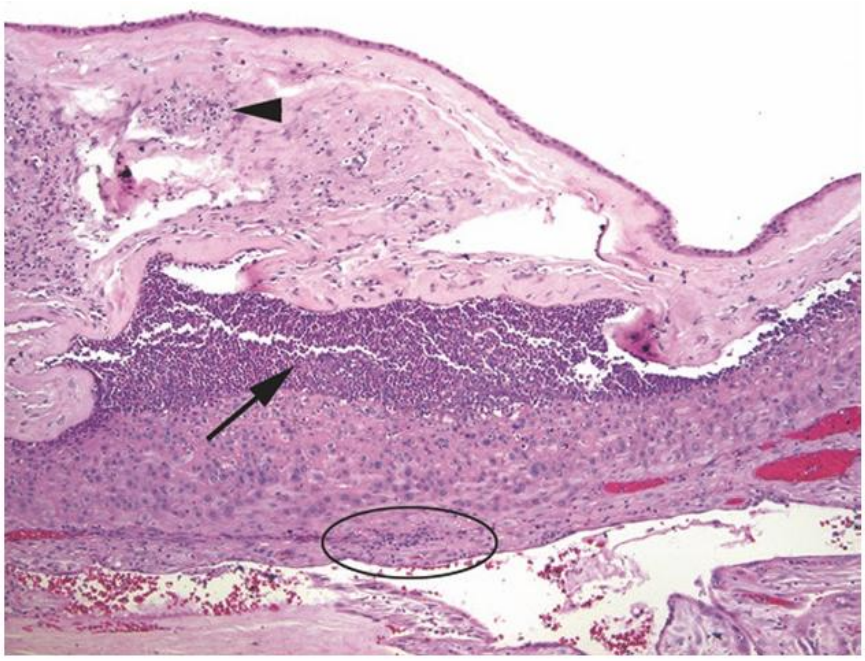


FIGURE 18.6. Chorioamnionitis. A collection of neutrophils (pus) has formed between the amnion and chorion (*arrow*). Neutrophils can also be seen beneath the amnion (*arrowhead*). Inflammation in the decidua (*oval*) may be physiologic and is not sufficient to diagnose chorioamnionitis. This is a maternal response to infection.

- Decidual Vasculopathy (Preeclampsia / Eclampsia)
  - Fibrinoid necrosis in the maternal vessels in the decidua of the membrane roll is suggestive for preeclampsia
  - Persistence of spiral arteries on the maternal surface

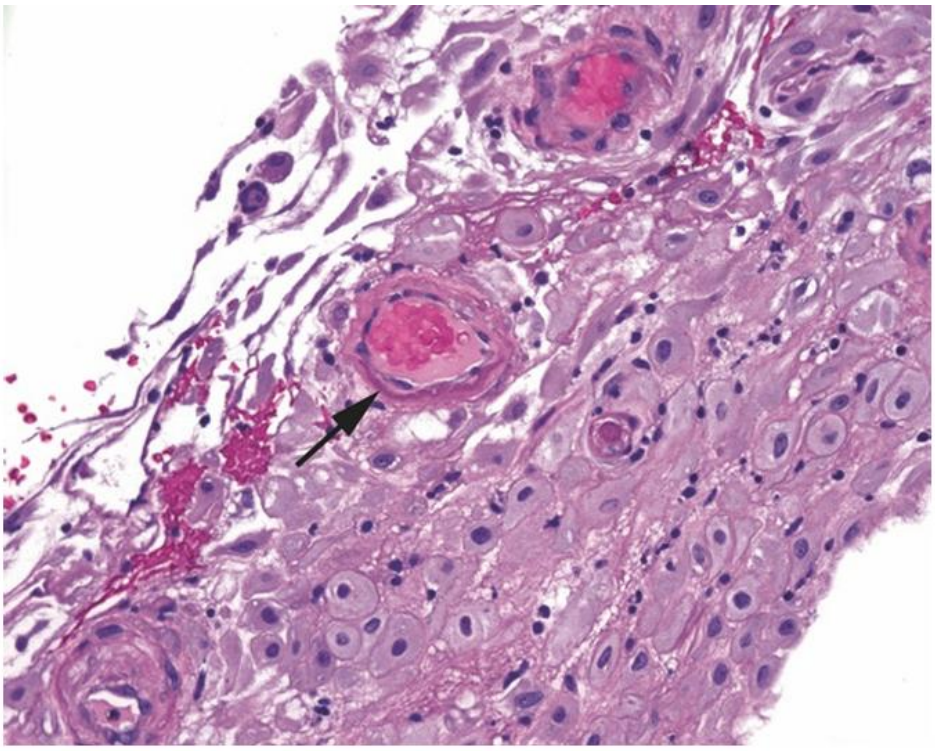


FIGURE 18.8. Fibrinoid necrosis. The dark pink condensation of the wall of this small artery (*arrow*) is an early sign of fibrinoid necrosis, which may be seen in preeclampsia.

- Meconium Staining

        - low power autolyzed amnion appearance
        - edema between amnion & chorion
        - look for meconium laden macrophages (they look granular and gold-brown)
- Fetal Vasculitis
    - The vessels that become the umbilical vessels arborize on the fetal surface are sandwiched between the amnion and chorion.
    - (Another place to look for fetal inflammatory response)
- Hydatidiform Mole
    - Circumferential proliferation of villi **(?????????????)**
    - Partial moles
        - Triploid, 1 maternal and 2 paternal genomes
        - Has a fetus *(definition of partial)*
        - Abnormal and normal villi
    - Complete moles
        - Diploid, 2 Paternal genomes
        - Has no fetus *(definition of complete)*
        - Large abnormal villi only
    - Abnormal villi
        - Large, swollen
        - No internal fetal vessels
        - Central cisterns of proteinaceous fluids
        - Circumferential & atypical trophoblast proliferation
        - Scalloped outline

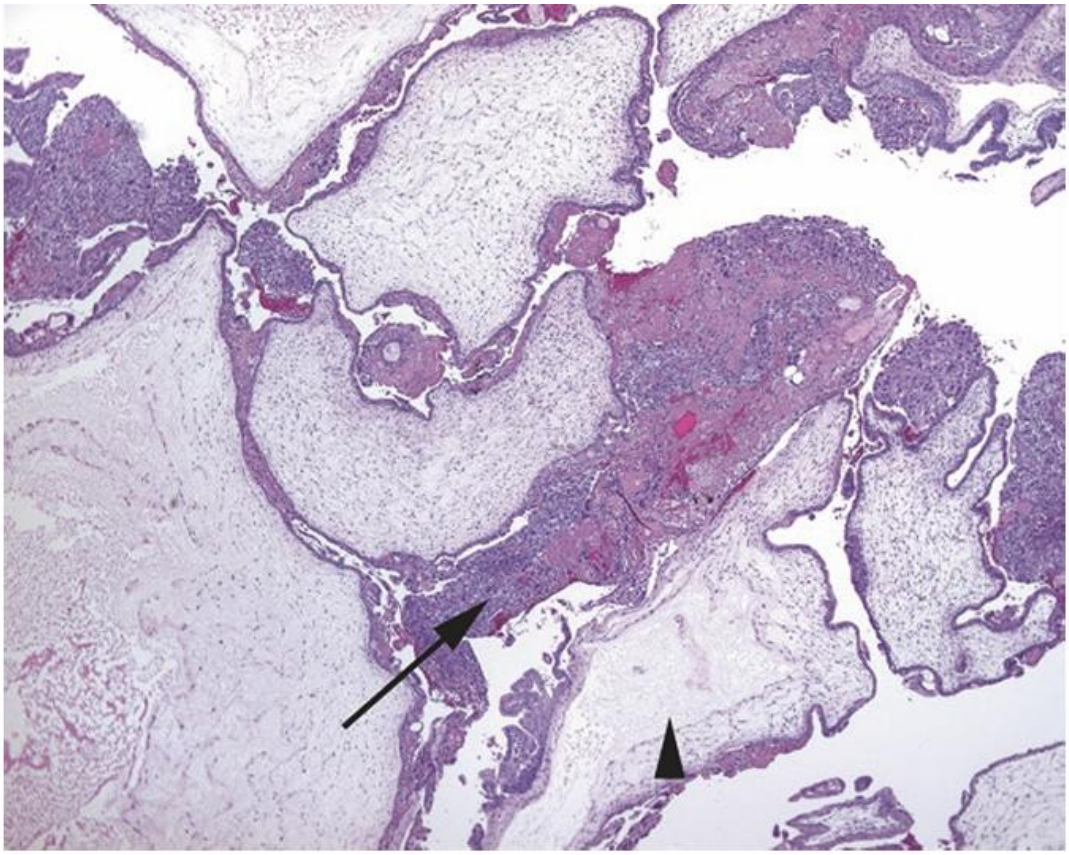


FIGURE 18.10. Molar villi. The villi are markedly enlarged, some with central cavities or cisterns (*arrowhead*). Dense trophoblastic proliferation is visible (*arrow*); on higher power, the cells may be very pleomorphic. This is a complete mole, so there are no fetal capillaries within the villi. Note the irregular coastline-like outlines of the villi.

- Mature Placenta (Evaluate for all the following)
  - Maturity of villi
    - Mature villi should be full of capillaries & lined by syncytial knots
    - Mature villi on a placenta <32 weeks may indicate ischemia
  - Fibrin around villi "previllous fibrin"
    - Looks like hyaline membranes outlining the villi
  - Villitis / Inter-villositis
    - Can be acute/chronic/granulomatous
    - May indicate viral or a syphilis infection
  - Infarct
    - Mummified villi touching each other
    - Loss of good nuclear detail

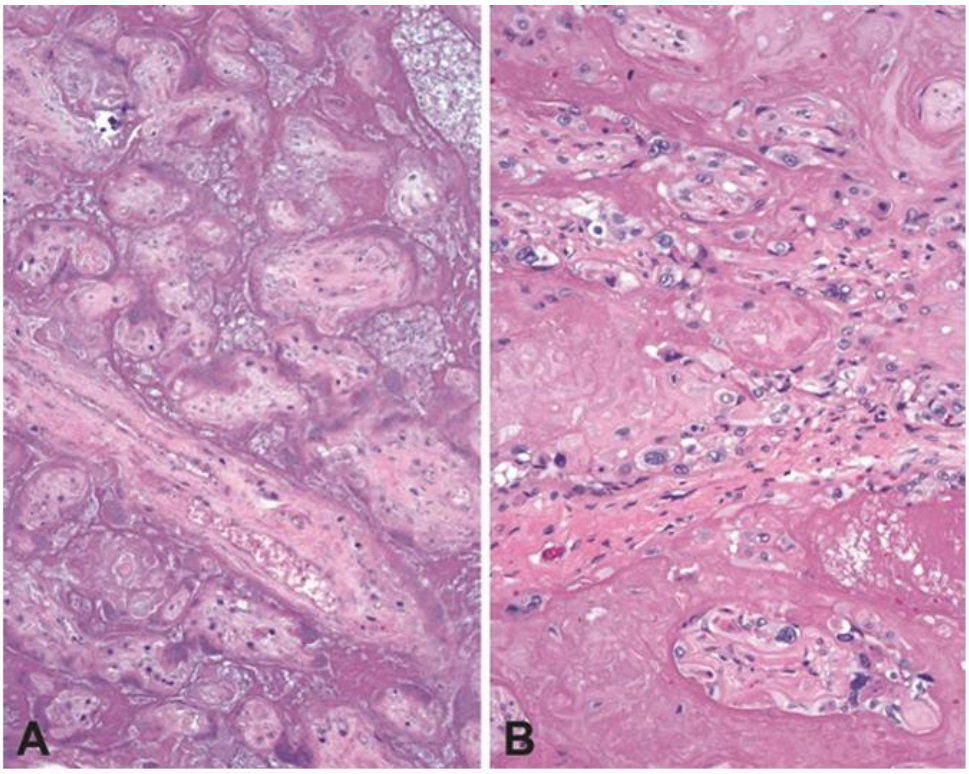


FIGURE 18.11. Infarct versus perivillous fibrin. (**a**) In an infarct, there is loss of basophilia and cellular detail with residual apoptotic bodies, as in coagulative necrosis elsewhere. (**b**) In a mass of perivillous fibrin, while the low-power impression is a sheet of consolidated pink, on high power you can see the villi remain viable, with good nuclear detail.

- Hematoma
- Fetal Capillaries
  - Collapse, avascular fetal capillareis may indicate fetal death
- Subchorionic Fibrin (normal, not to be mistaken for infarct)

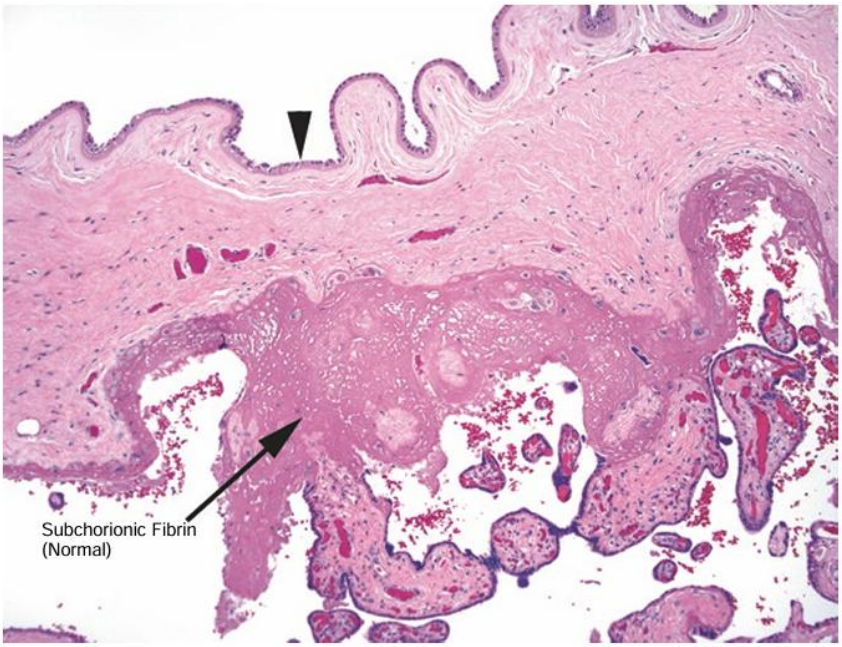


FIGURE 18.9. Fibrin, subchorionic. Subchorionic deposits of fibrin (*arrow*) are normal in a term placenta and should not be mistaken for infarct. The amnion lies atop the fetal surface (*arrowhead*).

- Maternal Floor Infarct (dense rind of fibrin encasing all of the villi along the maternal surface)

- Placenta Accreta
  - Placental villi very close to smooth muscle without intervening stroma

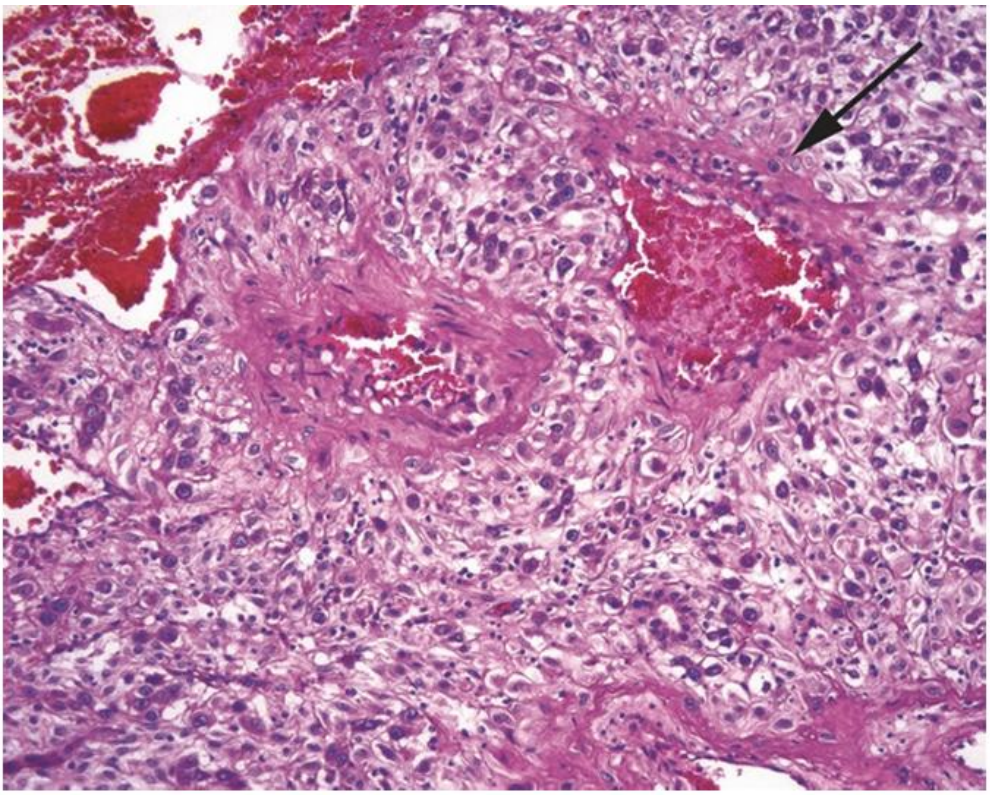


FIGURE 18.12. Trophoblasts in vessels. Intermediate trophoblasts (*arrow*) invading the wall of the maternal arteries. This is a normal process, opening firehoses of blood to supply the placenta.

Chapter 19 **– Breast**

Normal

- Children and males have breast ducts but no lobules
- Normal layering
  - Basement membrane
  - Myoepithelial (outer layer)
  - Inner epithelial (luminal layer)
- Two types of calcifications
- classic purple calcifications
- Calcium oxalate = clear refractile crystals

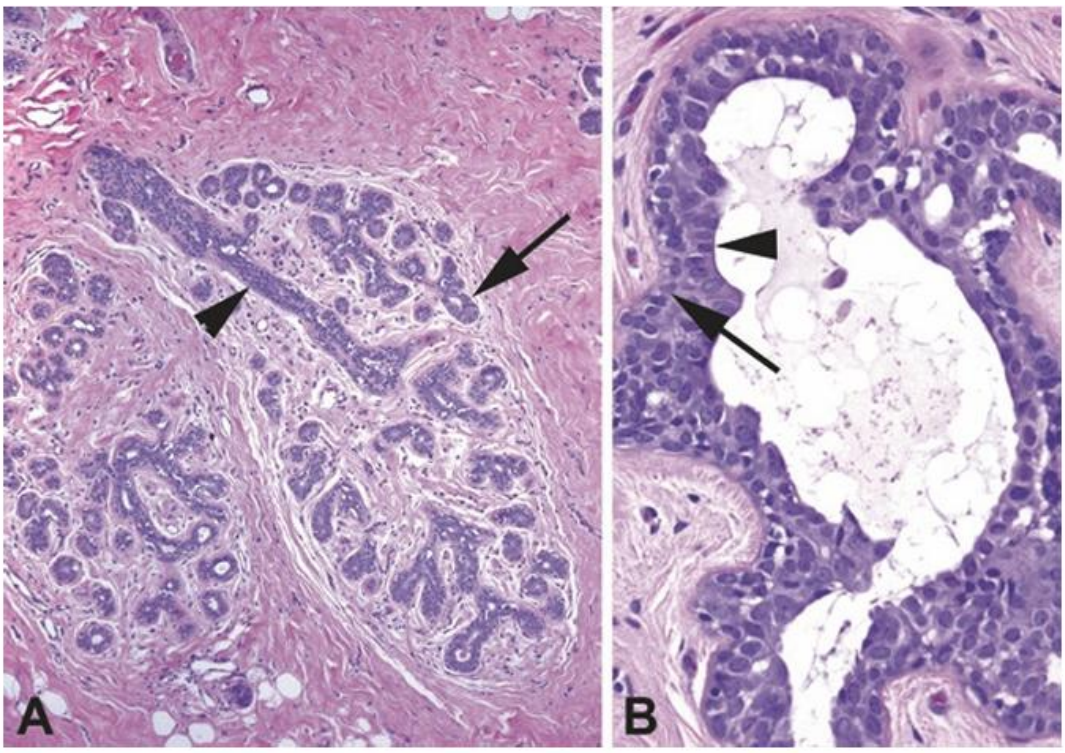


FIGURE 19.1. Normal breast. (**a**) The terminal duct lobular unit (*TDLU*) is arranged like a cluster of grapes, with the duct (*arrowhead*) as the stem and secretory lobules (*arrow*) as the grapes. The rounded and circumscribed border of the TDLU is a key feature of noninvasive lesions. (**b**) The benign breast always has two cell layers, the outer myoepithelial cells (*arrow*) and the inner epithelial cells (*arrowhead*). In situ lesions also have two cell layers.

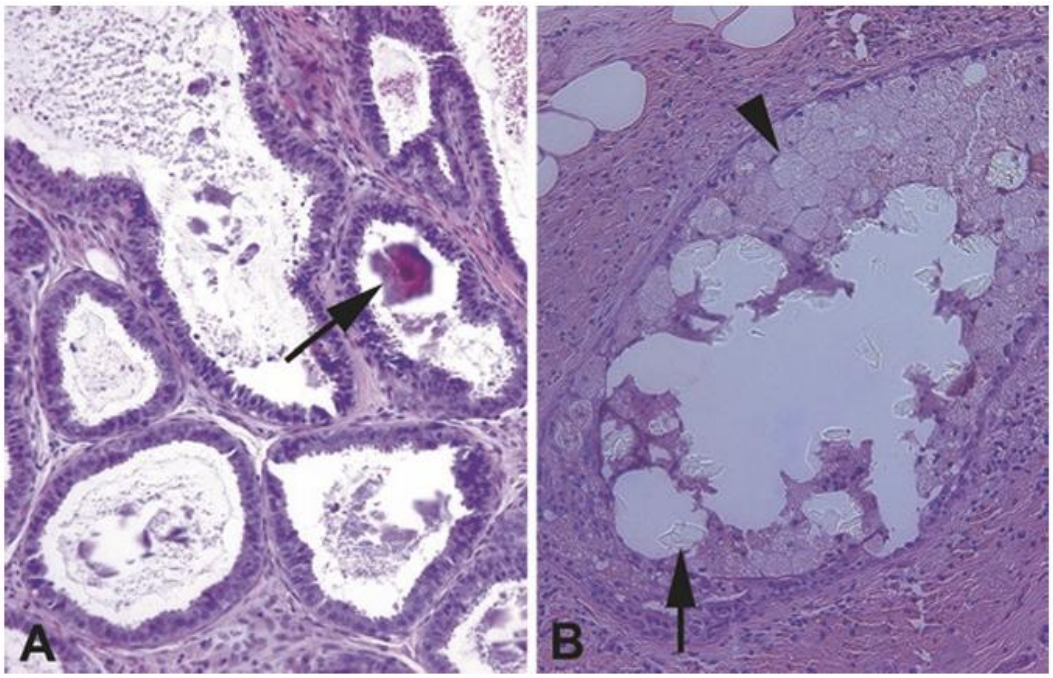


FIGURE 19.2. Calcifications. (**a**) Microcalcifications in this columnar cell lesion appear as tiny purple rocks (*arrow*), which may shatter and drag through the tissue, creating telltale scratches in the H&E stain. (**b**) Calcium oxalate does not pick up hematoxylin and therefore is only visible with a polarizer or when the condenser is flipped down, as in this photograph. The oxalate crystals (*arrow*) are seen in a duct space, surrounded by foamy macrophages (*arrowhead*).

Fibrocystic changes

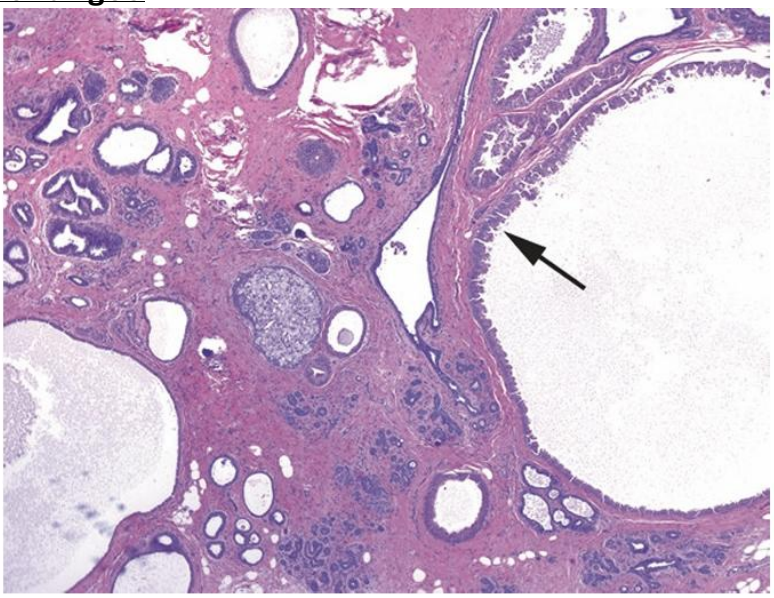


FIGURE 19.3. Fibrocystic disease. In this example, large dilated duct spaces are visible, some with a lining of apocrine metaplasia (*arrow*). The stroma is dense and fibrotic (pink).

- Fibrosis, usually among lobules
- Cysts, often visible macroscopically
- UDH
- Sclerosing Adenosis

- Lobules can look very crowded and worrisome (proliferative lobules are squeezed together by fibrosis making them look very small and infiltrative)
- Myoepithelial layer can be hard to see, but should be visible in some cells
- Has overall lobular (round and circumscribed) architecture

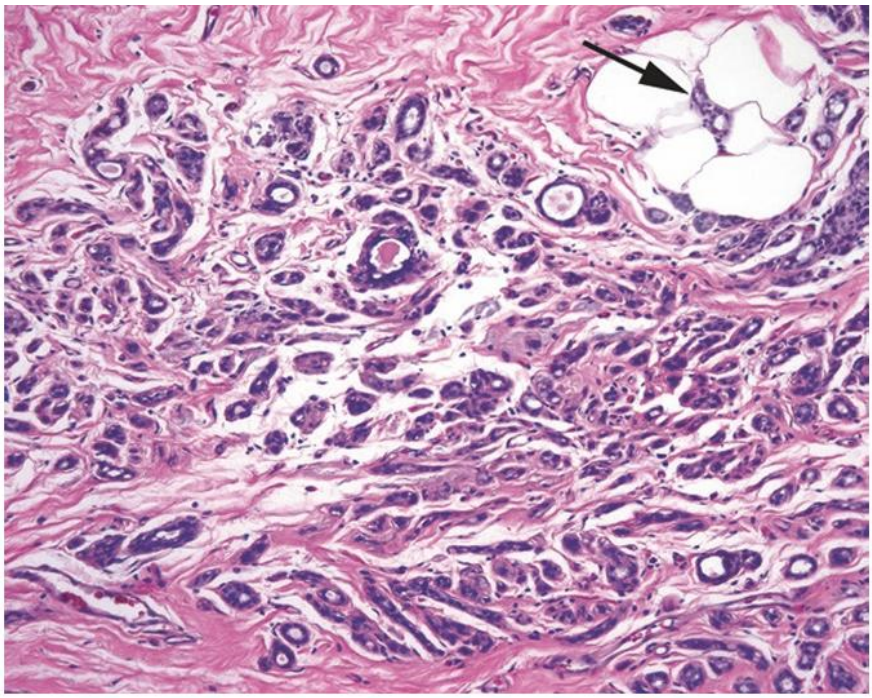


FIGURE 19.4. Sclerosing adenosis. On high power, this benign lesion looks infiltrative. Tiny tubules are entrapped in a fibrotic stroma, and some tubules are even seen among fat (*arrow*). Because of the compression, myoepithelial cells are not visible. Clues to the diagnosis include a circumscribed lesion at low power, the lack of desmoplastic reaction, and an intact myoepithelial cell layer seen on immunostains.

- Apocrine metaplasia
  - Means the cells lining the ducts have an apocrine look (bright pink cytoplasm, hobnail profile, large nuclei and prominent nucleoli)

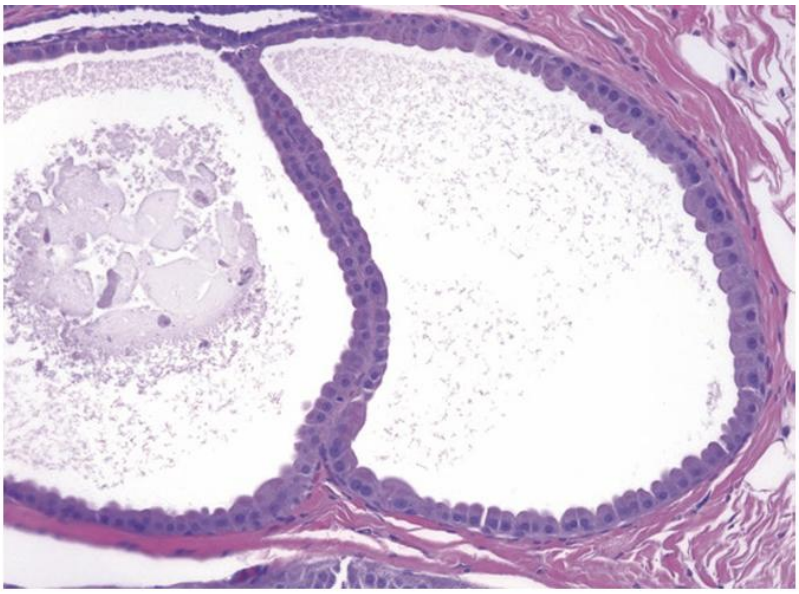


FIGURE 19.5. Apocrine metaplasia in fibrocystic disease. The epithelial cells lining the dilated duct are large and plump, with abundant dark pink cytoplasm, and round nuclei with prominent nucleoli. Secretions (the granular schmutz in the lumen) are common.

- Fibroadenomas
  - Myxoid pale halo around the ducts and the proliferative stroma compresses the ducts
  - May be hyalinized or calcified if old
  - Can occur without fibrocystic changes (Duh!)

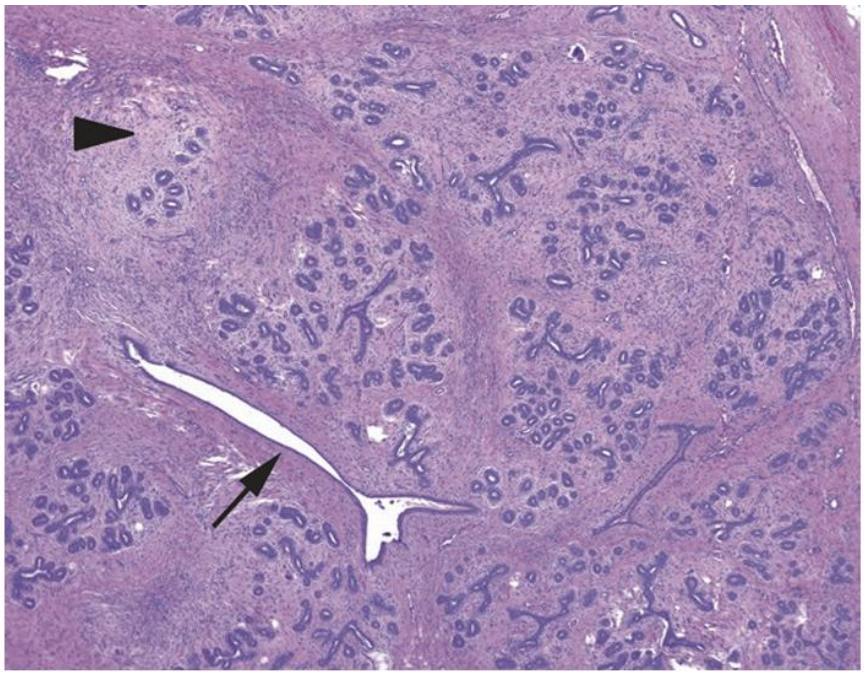


FIGURE 19.6. Fibroadenoma. At low power, the fibroadenoma is a well-circumscribed nodule (the perimeter is not shown here). Within the lesion, the secretory lobules stand out in slightly edematous (pale) stroma (*arrowhead*), and the ducts are compressed into slit-like spaces (*arrow*) by the proliferative stroma.

- Phyllodes tumour
  - Graded on stromal growth pattern
  - Can be benign or malignant
  - Much more cellular stroma than fibroadenoma

- Fat Necrosis
  - Is evidence of a prior biopsy site. Can be hard or painful or discoloured or calcified
  - Key features
    - Foamy macrophages ring each dead fat cell, digesting the lipid
    - Disrupted and irregular fat cells
    - Spaces between fat cells lined with fibrosis
    - Edema and hemosiderin
    - Acute inflammation

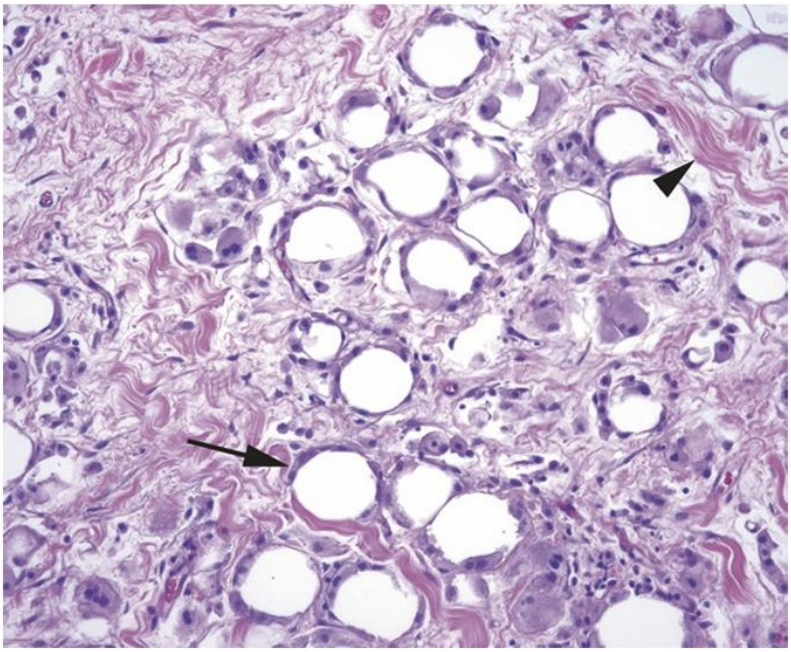


FIGURE 19.7. Fat necrosis. In an area of fat necrosis, secondary to trauma or surgery, the fat cells die but the globs of lipid remain. Foamy macrophages ring each dead fat cell (*arrow*), digesting the lipid; the spaces between the fat cells are filled in by fibrosis (*arrowhead*).

- ❖ Intraductal Papilloma
  - ➢ Not UDG can be micropapillary (but not papillary) so don't mix these up
  - ➢ Intraductal papilloma has myoepithelial cells, but papillary carcinoma does not
  - ➢ Looks like branching arbor of fibrovascular cores lined by benign secretory and myoepithelial cells

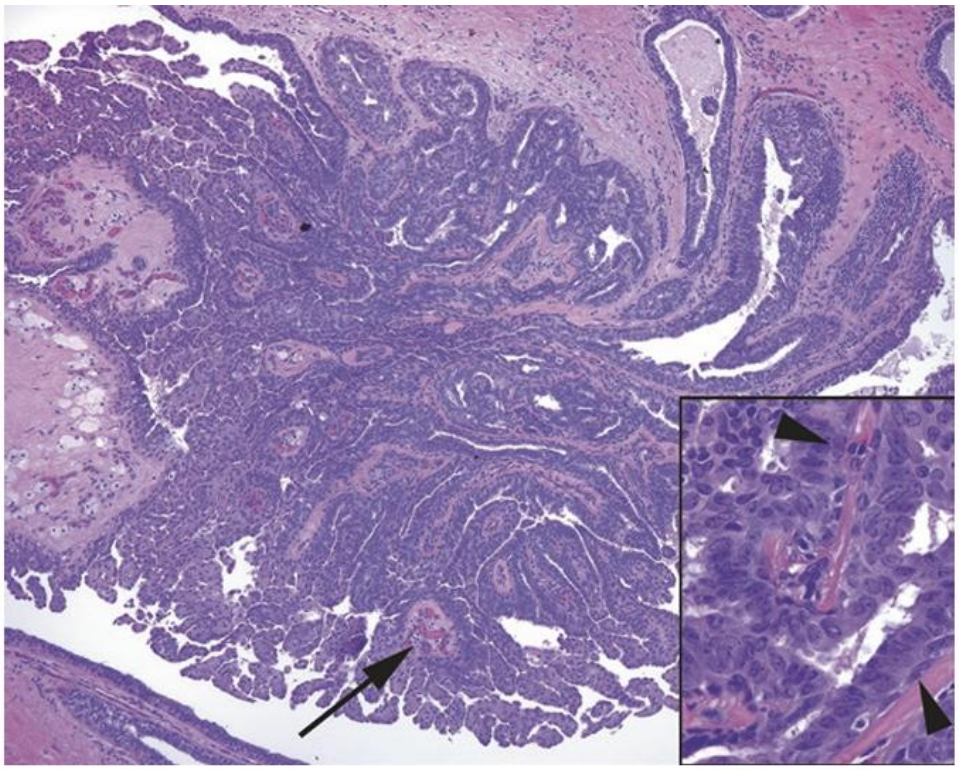


FIGURE 19.8. Intraductal papilloma. The branching structure fills a subareolar duct; smaller, more distal examples may be called micropapillomas. Although there is florid usual ductal hyperplasia, resulting in fusion of multiple branches of the papilloma, distinct fibrovascular cores are still visible (*arrow*). *Inset*: along each fibrovascular core, you should still see myoepithelial cells (*arrowheads*), which differentiates this from a papillary carcinoma.

Ductal and Lobular Proliferations

- UDH
  - A proliferation of cells within ducts
  - Several patterns of UDH
  - Cells have a streaming look, circumferentially to the lumen
  - Lumen spaces around the UDH should be slit like or irregular (not round)
  - Normochromic to pale appearing cells,
  - Jumbled overlapping or streaming cells
  - Heterogeneity present (Molavi describes a lazy artist tries to draw them all the same but they very slightly). Bland nuclei with even chromatin. Molavi specifically says heterogeneity =/= pleomorphism.

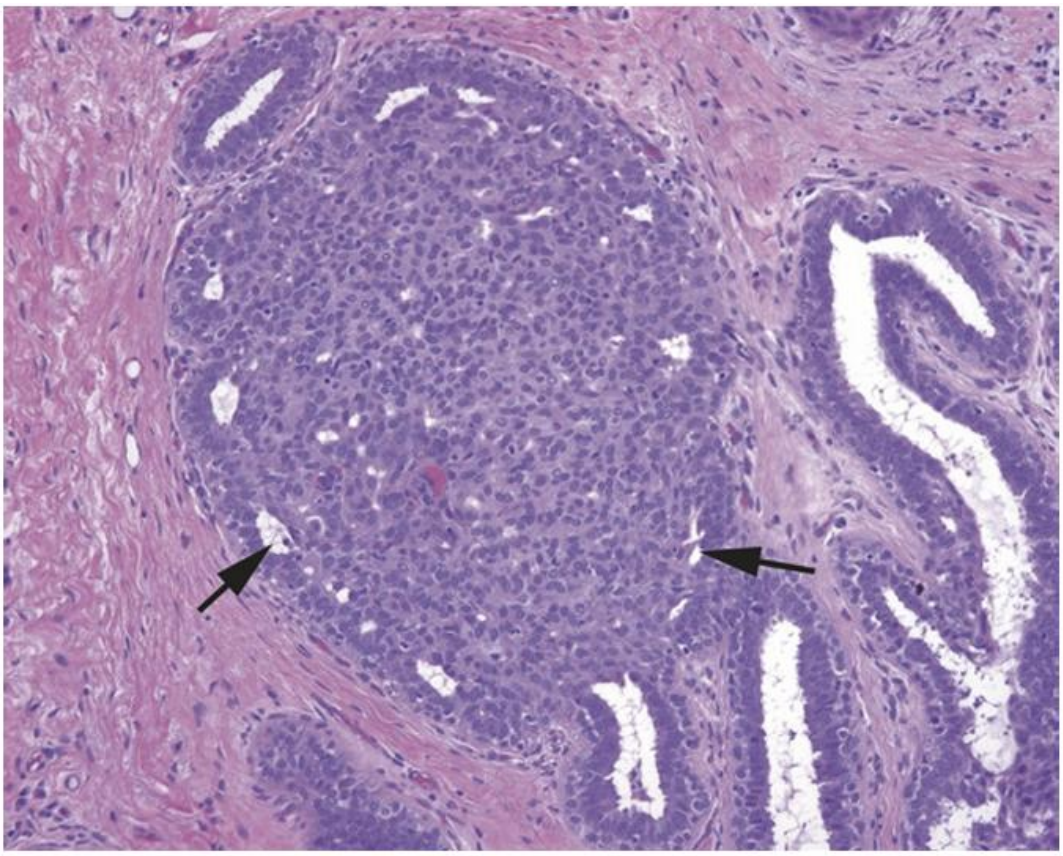


FIGURE 19.9. Florid usual ductal hyperplasia. The cellular proliferation entirely fills this duct, but the cell population is swirly and heterogeneous, with randomly overlapping nuclei. The peripheral ring of slit-like spaces (*arrows*), as though this clot of cells floated into the duct and stuck there, is classic for usual ductal hyperplasia.

- ADH
  - somewhere between UDH and DCIS
- DCIS
  - Myoepithelial cell layer and BM is intact
  - Architectural patterns include
    - Cribriform
    - Solid
    - Micropapillary
    - Flat
    - Papillary
    - Comedo
  - Grade 1 can appear MORE homogenous & regular than normal breast tissue
    - Monotonous cells with dark nuclei , no overlapping cells which polarize around tiny lumens
    - Distinct cell border
    - Monotonous cells w dark nuclei, no overlapping, cells which polarize around tiny lumens
    - Distinct cell borders
  - Grade 2/3
    - Looks very pink
    - Large nuclei

- Nucleoli
- Non-overlapping cells
- Irregular borders

➢ Nottingham grade

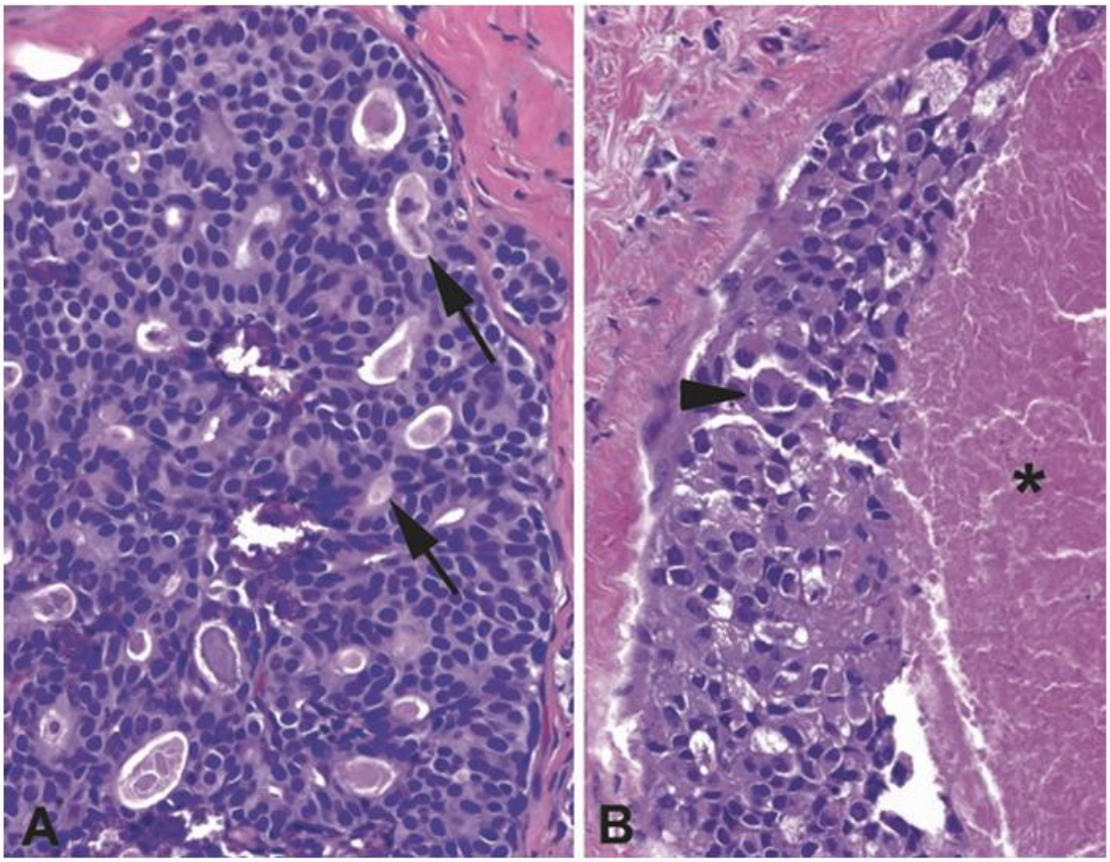


FIGURE 19.10. Ductal carcinoma in situ (*DCIS*). (**a**) In low-grade DCIS, the cells are monotonous, uniform, and largely nonoverlapping, and they form cribriform duct spaces with the cells polarized around the tiny lumens (*arrows*). (**b**) In high-grade DCIS, the cells have lost their monotony and are instead pleomorphic, some with prominent nucleoli (*arrowhead*). At the center of the dilated duct, there is necrosis (*asterisk*), indicating comedo-type DCIS.

❖ Invasive BC of NST (IDC)

➢ Cells look like DCIS cells
➢ NO myoepithelial layer
➢ Architecturally is nests radiating out in a stellate look
➢ Pleomorphic nuclei & pink cytoplasm
➢ Necrosis common therefore easy to mix up with comedo DCIS
➢ Dense desmoplasia
➢ Variants
- Tubular
  - well differentiated, cytologically bland small angular tubules. May coexist with lobular carcinoma

- Mucinous or colloid

- Medullary
  - a well circumscribed yet ugly group of cells within ducts a dense lymphocytic infiltrate
- Micropapillary
  - florets of tumour cells are seen in a cleft in the tissue, similar to micropapillary serous carcinoma of ovary or micropapillary lung adenoCA
- Adenoid cystic carcinoma (identical of salivary gland tumour of the same name)
- Metaplastic
  - tumour in which there is squamous, mesenchymal or spindle cell components such as cartilage, bone frank sarcoma, with prognosis depending on the scale

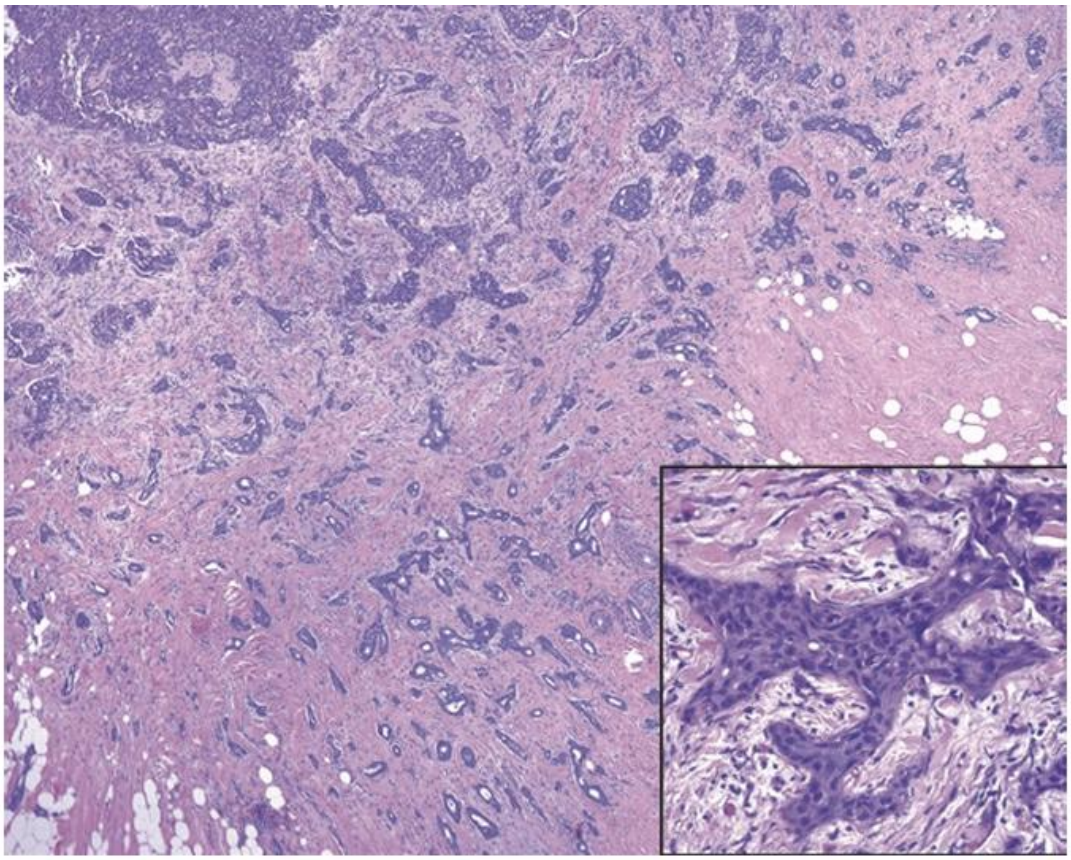


FIGURE 19.11. Infiltrating ductal carcinoma. At low power, the irregular border of the lesion is evident, with small angular tubules radiating outward into the fat. Grossly, this lesion would have a stellate appearance, and the dense stromal reaction would make the lesion very hard. *Inset*: the irregularly shaped nests of tumor cells create a desmoplastic stromal reaction, which is a combination of edema (white space) and fibrosis (pink collagen).

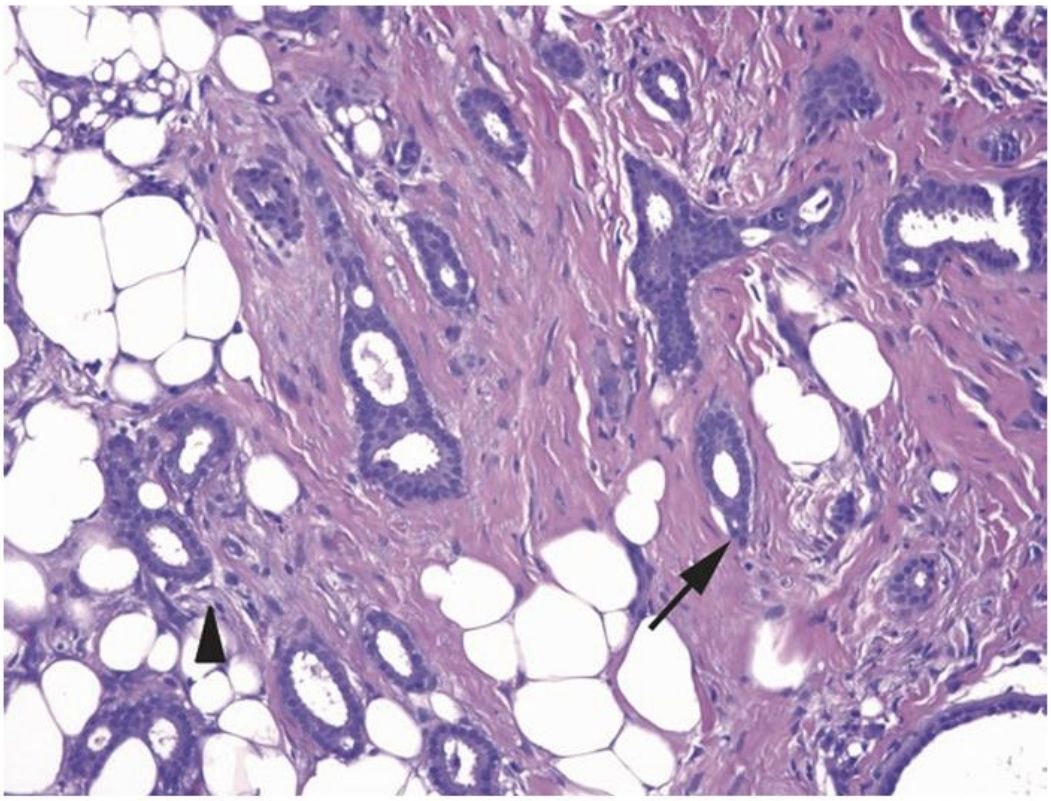


FIGURE 19.12. Tubular carcinoma. Well-formed tubules with pointed ends (*arrow*) and round, monotonous cells infiltrate through the stroma and fat. The myoepithelial layer is absent, both on H&E stain and by immunostain, and there is a subtle desmoplastic reaction around some of the tubules (*arrowhead*).

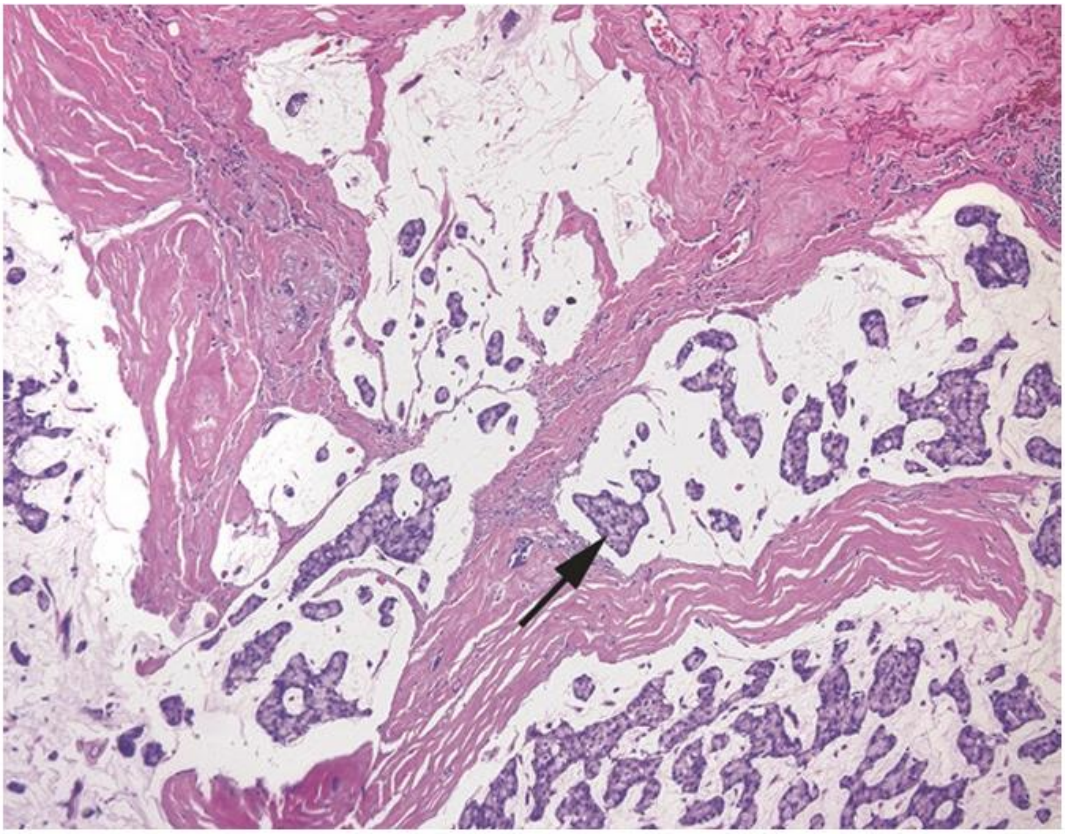


FIGURE 19.13. Mucinous carcinoma. Pools of extruded mucin dissect into the stroma. Although this can occur in benign mucocele-like lesions, the presence of floating clumps of cells (*arrow*) is diagnostic of mucinous, or colloid, carcinoma.

- LCIS
  - homogenous cells that when they begin to proliferate have a orund fried egg shape with a pale cytoplasm, discrete borders and central round nucleus
  - e cadherin negative
  - bland cytology
  - doesn't form masses
  - central round nuclei & discrete cell borders
  - pale cytoplasm
  - can have intracytoplasmic vacuoles or even signet ring cells
  - progression to cancer is not considered innevtiable or predictable so presnece at a margin is not usually noted
  - Elston grade, aka Nottingham or Bloom-Richardson

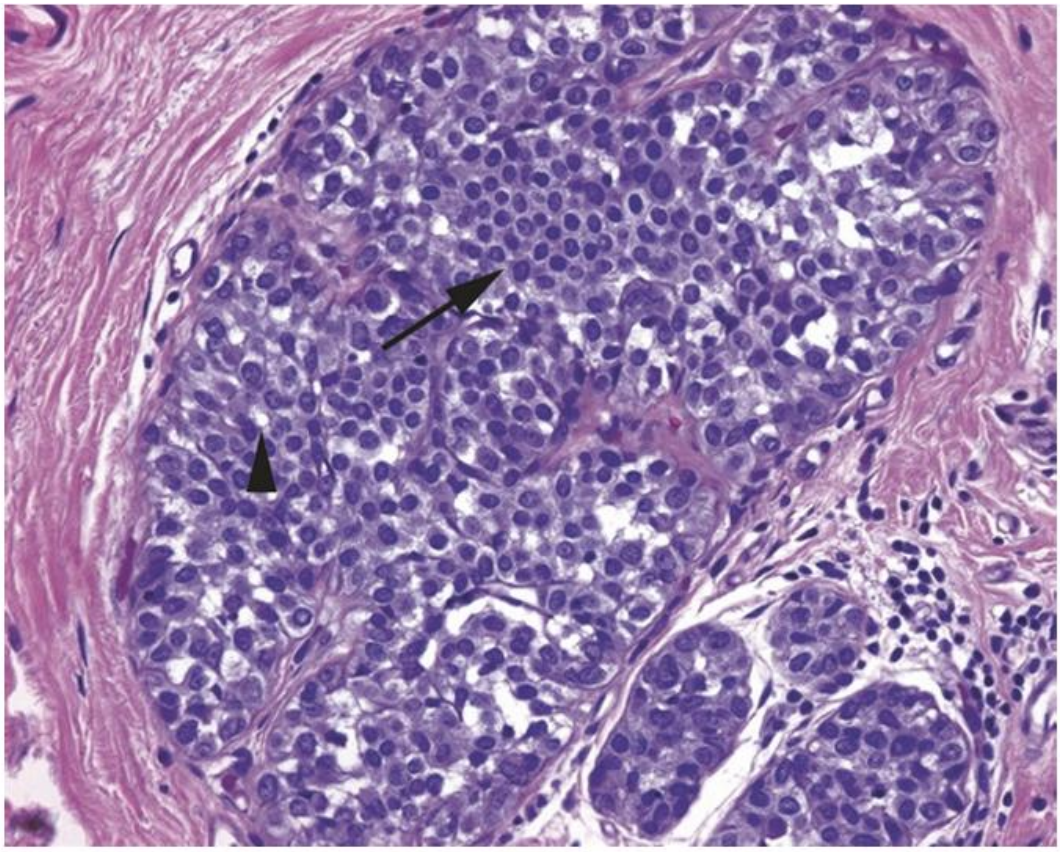


FIGURE 19.14. Lobular carcinoma in situ. The lobule is distended by a population of monotonous cells with distinct cellular borders and small round nuclei (*arrow*). As the lesion expands, the noncohesive cells will begin to fall apart. Cytoplasmic vacuoles (*arrowhead*) are typical of lobular carcinoma cells, both in situ and invasive.

- Atypical Lobular Carcinoma
  - "I'm worried about LCIS but I quite can't get there"

- Invasive Lobular Carcinoma

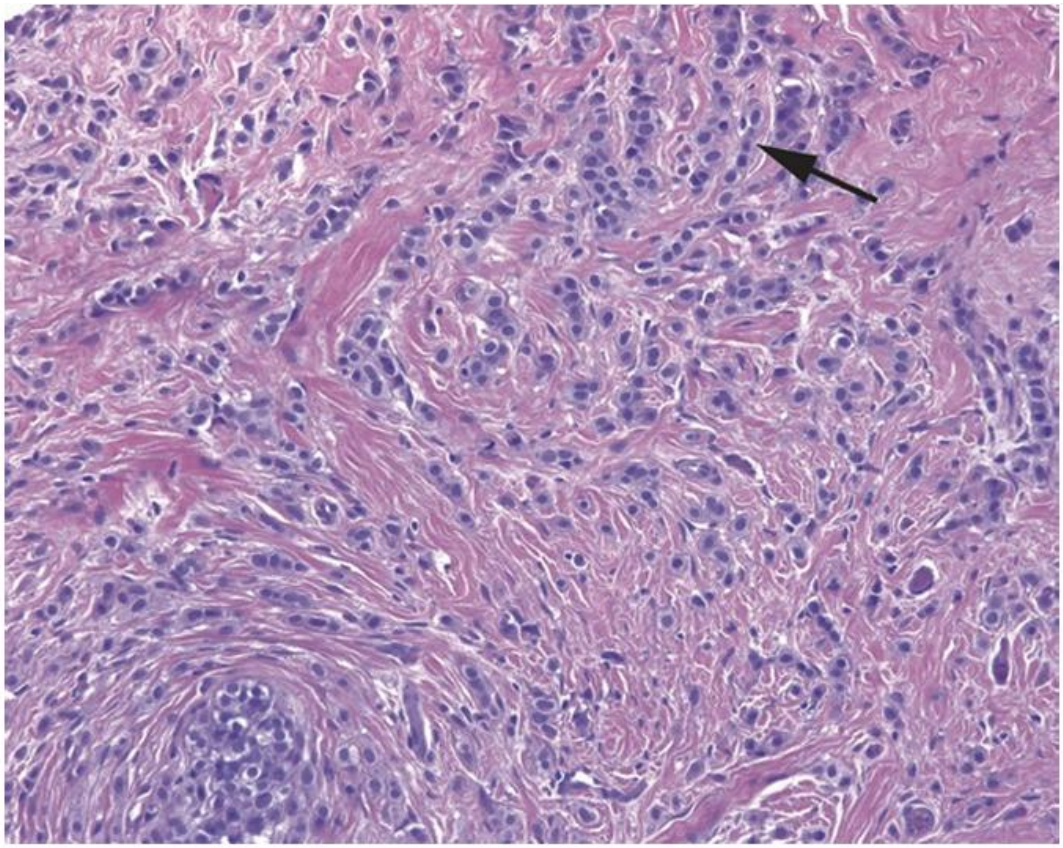


FIGURE 19.15. Invasive lobular carcinoma. The same cells as in Figure 19.14 are seen here invading through the stroma. They often form single file lines (*arrow*) but may also be seen as single cells or concentric circles around a duct. In some cases there is little to no desmoplastic stromal reaction, making the lesion difficult to palpate or detect.

Chapter 20 **– Bone marrow**

Chapter 21 **– Lymph node & Spleen**

Chapter 22 **– Lungs & Pleura**

Normal

- 4 compartments of the normal lung
  - Bronchi
    - Ciliated epithelium with scattered goblet cells
    - Goblet cell metaplasia = indication of irritation
    - Squamous metaplasia = common in smokers
  - Bronchioles
    - No cartilage
    - Respiratory epithelium but No goblet cells
  - Alveoli
    - Normally lined with near invisible Type 1 pneumocytes
    - Cuboidal epithelium indicates Type 2 hyperplasia (seen in chronic inflammation and repair)
  - Vessels
    - Pulmonary arteries
      - run with bronchioles
      - Have 2 elastic lamina
    - Veins
      - Run in the interlobular septa
      - Have one elastic lamina

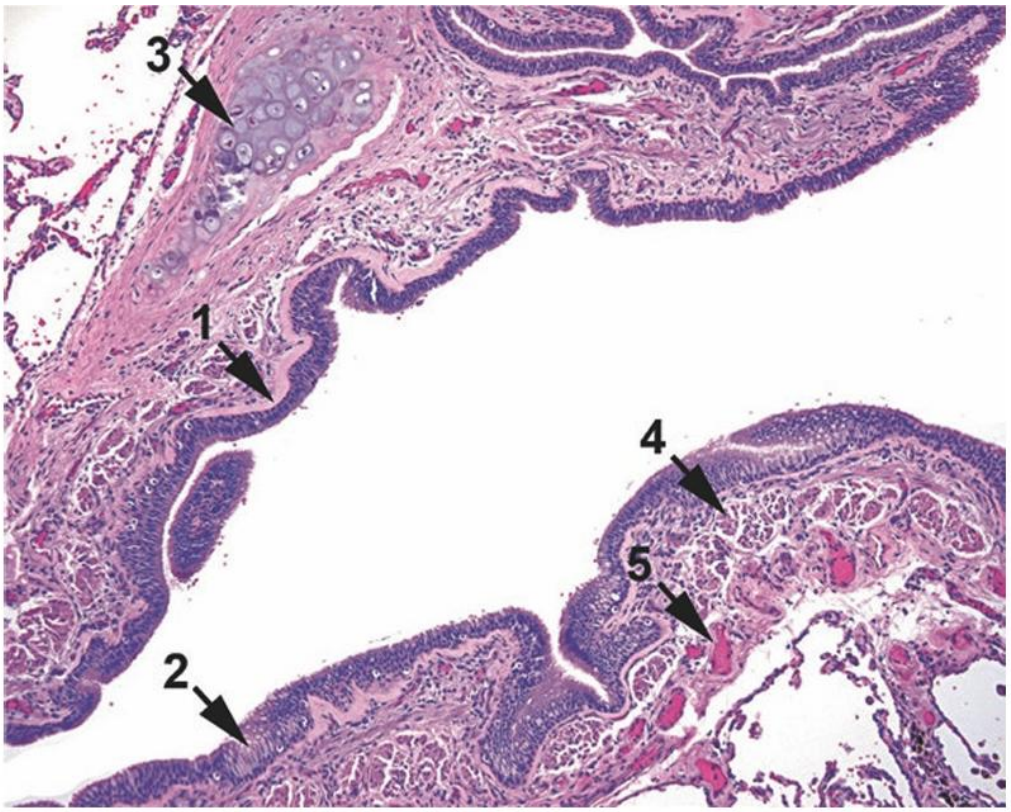


FIGURE 22.1. Normal bronchus. The bronchus is lined by ciliated columnar epithelium (*1*), foci of goblet cells (*2*), cartilage (*3*), and smooth muscle (*4*). The small arteries seen here (*5*) are branches of the bronchial artery, which carries oxygenated blood from the left ventricle.

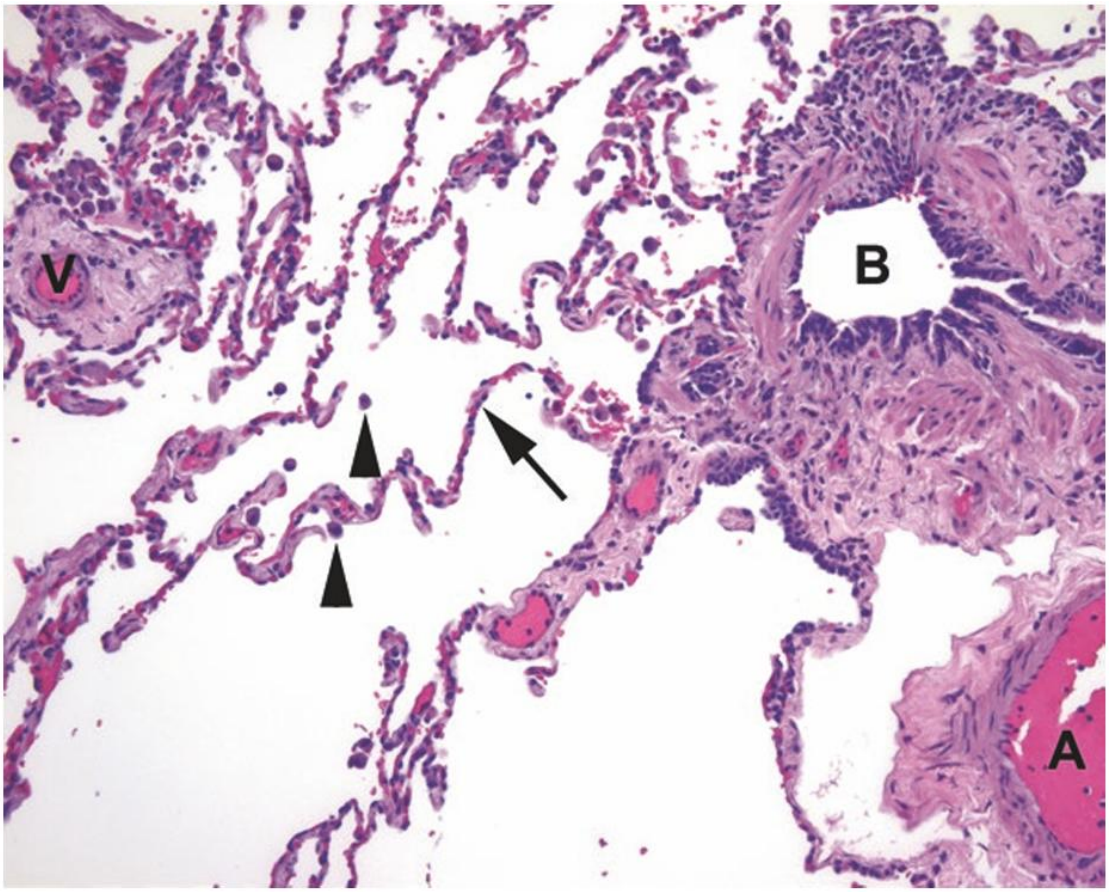


FIGURE 22.2. Bronchioles and alveoli. The small bronchiole (*B*) seen here is lined by a cuboidal epithelium and smooth muscle. The large adjacent arteriole (*A*) is a branch of the pulmonary artery. The veins or venules (*V*) run in septa. The alveolar walls (*arrow*) are normally lined with flat type I epithelium, of which only the nuclei are visible. Alveolar macrophages (*arrowheads*) are common.

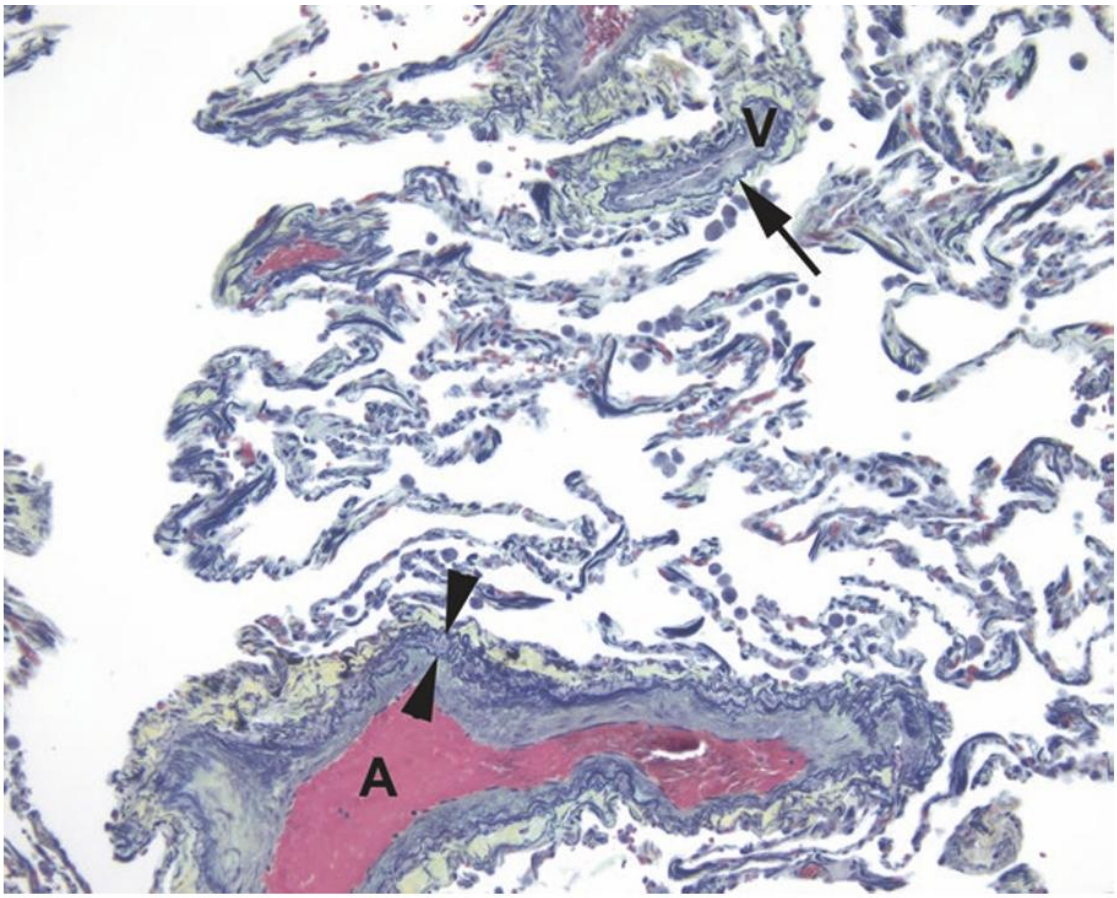


FIGURE 22.3. Movat's stain. The pulmonary arteries (*A*) have two elastic layers (*arrowheads*), while the veins (*V*) have one (*arrow*). The collagen lining the vessels is pale yellow-green in this stain.

Non-Neoplastic Lung:

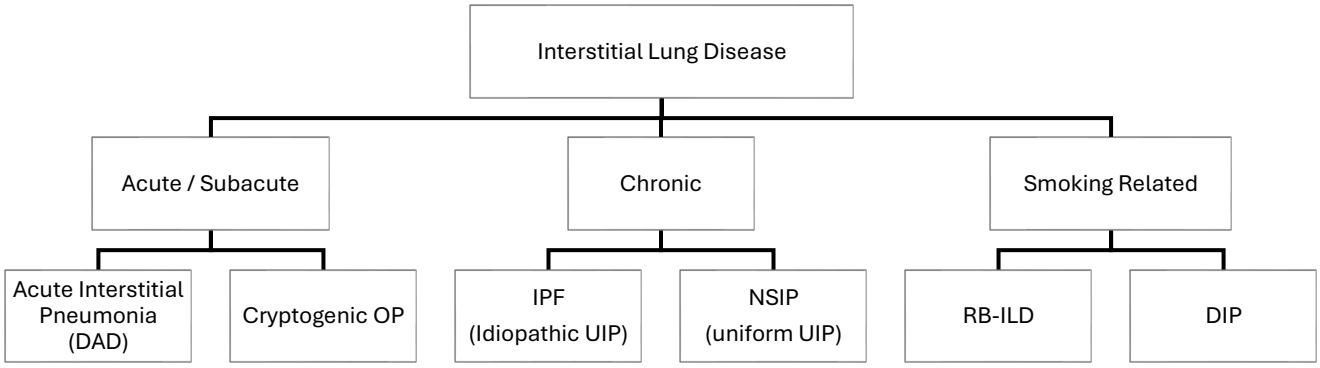
Differential Diagnosis of Non-Neoplastic Lung, by compartment

Infiltrate	Large and small airways	Alveoli	Interstitium / Septa	Vessels
Lymphocytes & mononuclear cells	Atypical/viral pneumonia CHP Respiratory bronchiolitis (macrophages)	Atypical/viral pneumonia CHP Desquamative interstitial pneumonia (macrophages)	CHP DAD LCH LIP NSIP Systemic CTD UIP	
Neutrophils	Bronchopneumonia Bronchocentric granulomatosis	Bronchopneumonia		Wegener's granulomatosis
Eosinophils	ABPA Asthma Bronchocentric granulomatosis Chronic eosinophilic pneumonia	Chronic eosinophilic pneumonia Churg-Strauss syndrome Loeffler syndrome	Chronic eosinophilic pneumonia LCH	Churg-Strauss syndrome
Granulomas	TB and fungus Bronchocentric granulomatosis	TB and fungus	CHP (poorly formed) Sarcoidosis Rheumatoid nodules	Churg-Strauss syndrome Invasive aspergillosis Sarcoidosis Wegner's granulomatosis
Fibrosis and fibroblast foci	Organizing pneumonia Constrictive bronchiolitis	Organizing pneumonia	DAD (late or organizing) DIP Pneumoconioses Sarcoidosis	Pulmonary HTN

			Systemic CTD UIP and NSIP	
Other substances (mucus, exudates, etc.)	Asthma Chronic bronchitis	Early DAD (HM) Goodpasture's syndrome Pulmonary alveolar proteinosis (exudate) *Pneumocystis* pneumonia (foamy material)	Lymphangioleimyomatosis (smooth muscle) Pneumoconiosis (refractile material)	Amyloidosis DAD (fibrin thrombi)

ABPA allergic bronchopulmonary aspergillosis
CHP chronic hypersensitivity pneumonitis
CIP chronic interstitial pneumonia
DAD diffuse alveolar damage
HM highland membrane
LCH Langerhans cell histiocytosis
LIP lymphocytic interstitial pneumonia
NSIP non specific interstitial pneumonia
UIP Usual interstitial pneumonia

"Interstitial Lung Disease" Meaning in pathology:



<u>3 phases (acute, subacute, chronic)</u>

- Acute Injury / DAD
  - Acute injury leads to Diffuse Alveolar Damage
  - Clinically, DAD correlates to ARDS
  - Histo
    - Non-specific
      - Interstitial edema
      - Hemorrhage
      - Hyaline membrane formation9
      - Type II hyperplasia
      - Fibrin thrombi
      - Fibrin extravasation into alveolar spaces
    - Uniform throughout the FOV, but may be patchy if you drive around
    - No neutrophils in the alveolar spaces

- Neutrophils in the alveolar spaces above = bronchopneumonia

❖ Acute Interstitial Pneumonia = AIP

➢ Idiopathic DAD

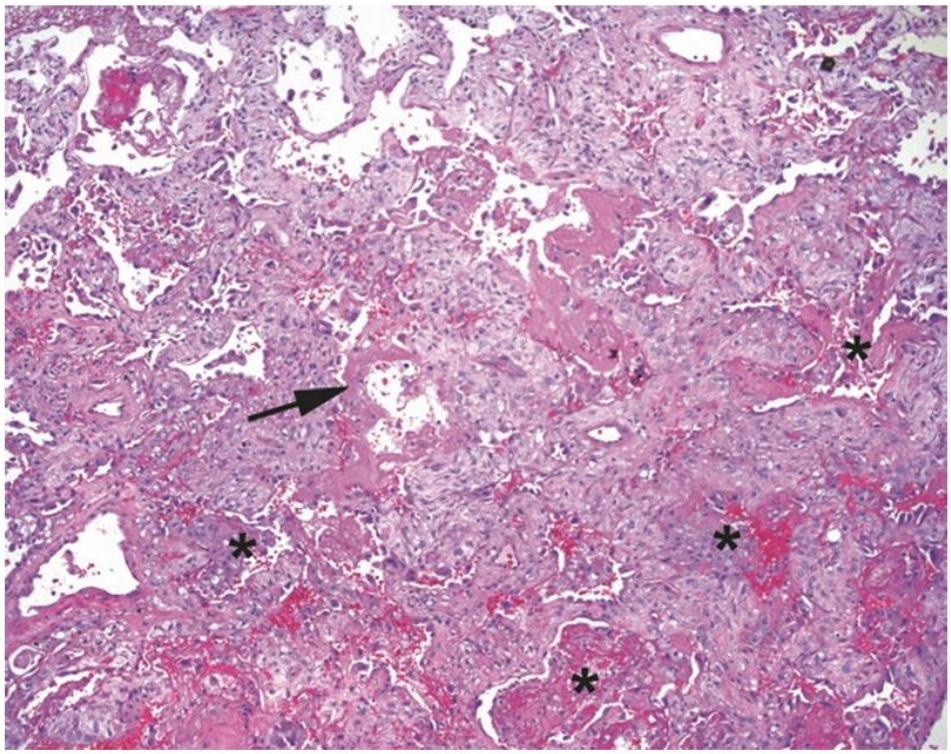


FIGURE 22.4. Diffuse alveolar damage. The alveolar spaces are full of fluid and blood (*asterisk*), which in some areas are beginning to coalesce into thick pink hyaline membranes (*arrow*). The interstitial spaces are thickened due to edema.

❖ Subacute Injury = Organizing Pneumonia

➢ OP can be seen in the healing phase of any injury

➢ Histo

- Fibroblast foci in the alveoli & bronchioles (unlike in UIP where it is interstitial)
- Swirling nodules of stellate fibroblasts
- "myxoid look of fibroblasts"

➢ Primary idiopathic OP = cryptogenic organizing pneumonia

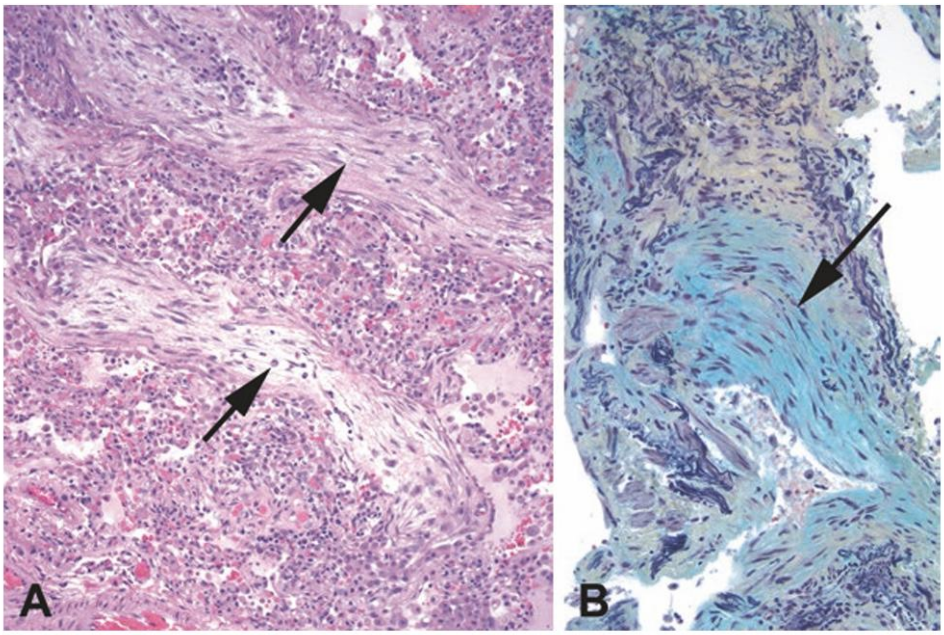


FIGURE 22.5. Fibroblast foci. (**a**) By H&E stain, these myxoid swirls of new fibroblasts are pale and streamy (*arrows*). (**b**) On Movat's stain, they are turquoise (*arrow*).

- Chronic Injury = UIP = Honeycomb Lung
  - Honeycomb Lung = gross appearance
  - Usual Interstitial Pneumonia = micro appearance
  - UIP
    - Non-specific pattern
    - Is heterogenous in time and space
      - (should see evidence of all stages of injury – acute subacute chronic)
    - Histo
      - Should see fibrosis interspersed with normal lung
      - Large and angular distorted airspaces
      - Fibroblast foci in the interstitium (unlike OP where it is alveolar & bronchiolar)
      - Airspaces lined by plump/reactive Type II pneumocytes
      - Chronic inflammation with pockets of acute inflammation
  - Idiopathic UIP = "Idiopathic Pulmonary Fibrosis"
  - Non-specific Interstitial Pneumonia = NSIP
    - Like UIP but heterogeneous in time and space

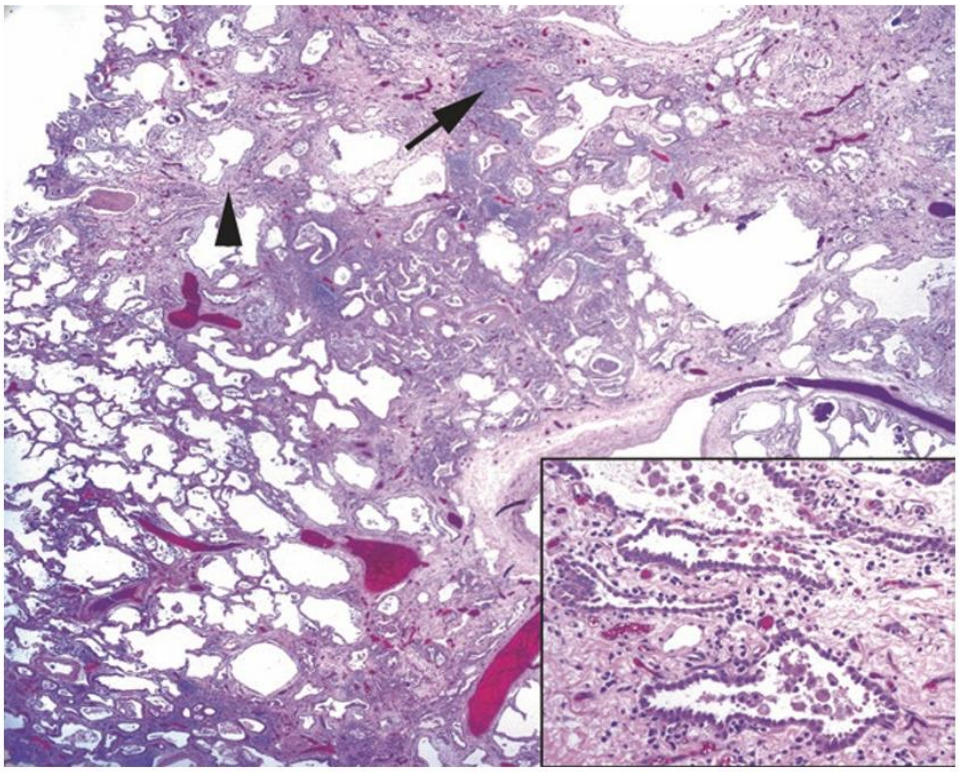


FIGURE 22.6. Usual interstitial pneumonia. The interstitial spaces are thickened and fibrotic (*arrowhead*), and there is abundant chronic inflammation (*arrow*). *Inset*: The scarred-down, irregularly shaped, residual alveolar spaces are lined with type II pneumocytes, which protrude into the lumen and may have atypical nuclei.

- Diseaseas of Smokers
  - Smokers get a range of diseases → respiratory bronchiolitis, desquamative interstitial pneumonia, Langerhans cell histiocytosis (LCH). Also COPD
  - DIP = desquamative interstitial pneumonia
    - Macrophages pack the alveoli
  - Respiratory bronchiolitis is less severe DIP
    - Macrophages in the alveoli
  - LCH
    - May have eosinophils
    - Langerhans cells – pale nuclei with folds and creases
      - Can highlight the Langerhans cells with S100 or CD1a
- Allergic Disease
  - There are 2 types of allergic responses in the lung
    - IgE-mediated
      - Asthma
      - Allergic aspergillosis
      - Bronchocentric granulomatosis
      - Eosinophilic pneumonias
    - Cell-mediated hypersensitivity reactions
      - Hypersensitivity pneumonia a.k.a. extrinsic allergic alveolitis

- Due to certain occupations (Dirty Jobs Lungs)
- Eosinophils not a component of the hypersensitivity reactions
- Triad
  - Chronic inflammation esp. peribronchiolar
  - Non-necrotizing granulomas
  - Organizing PNA

Neoplastic Lung

- Presence of cilia is a reassuring sign that all is well, even in the presence of reactive atypia

❖ Atypical Adenomatous Hyperplasia

- aka dysplasia of the lungs
  - progresses to AdenoCa in Situ
- features type 2 hyperplasia & interstitial inflammation in the absence of an inflammatory background that could explain reactive T2 hyperplasia
- <0.5cm in size

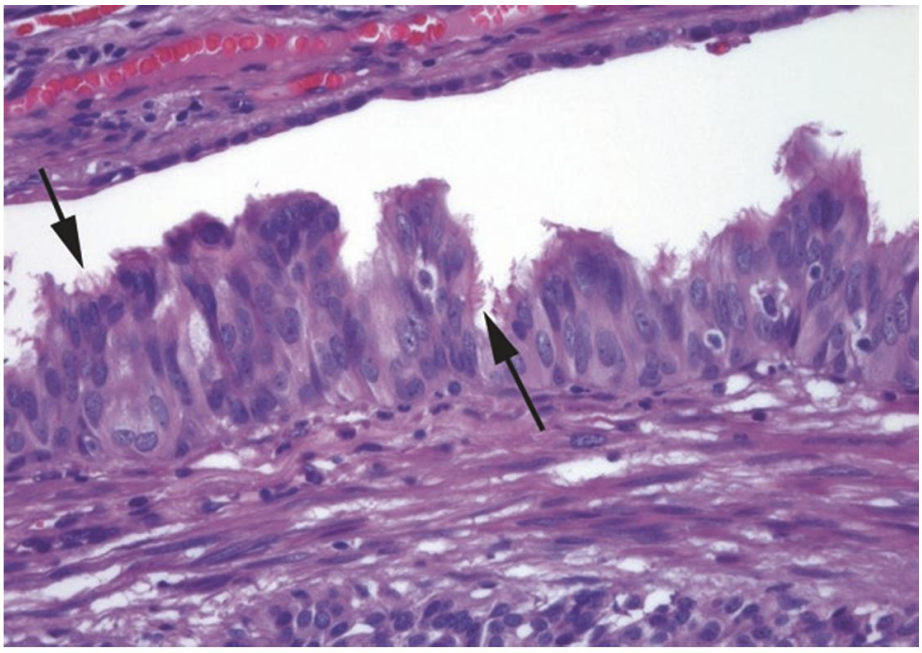


FIGURE 22.7. Reactive bronchial epithelium overlying a carcinoid tumor. Although the epithelium is very proliferative and has enlarged and crowded nuclei, the presence of cilia (*arrows*) indicates that these cells are benign.

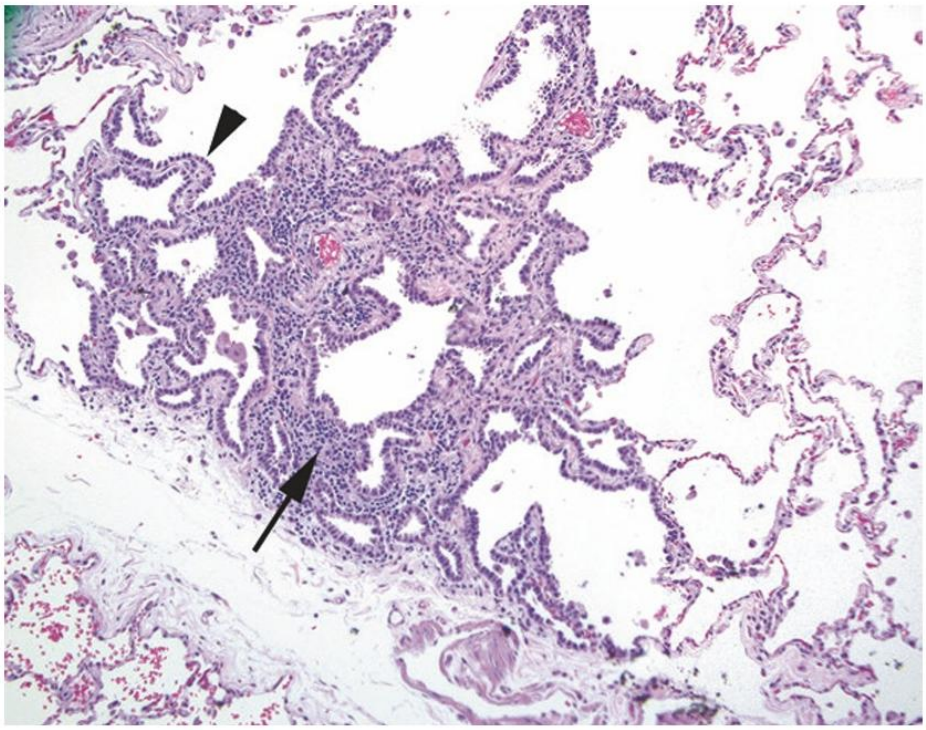


FIGURE 22.8. Atypical adenomatous hyperplasia. In this tiny, limited focus, there is interstitial inflammation (*arrow*) and prominent type II hyperplasia (*arrowhead*). The adjacent alveolar walls are unremarkable.

- Adenocarcinoma in Situ
  - Histo
    - Cuboidal/columnar eosiniophilic cells growing in lepidic pattern
    - Usually no mucinous cells but there can be types with mucinous cells
    - No stromal invasion (duh)
      - No irregularly shaped, back-to-back glands
      - No desmoplasia
    - Often found surrounding invasive tumour so careful calling this on biopsy
  - Natural progression is AdenoCa in situ → minimally invasive Adeno → Invasive Adeno

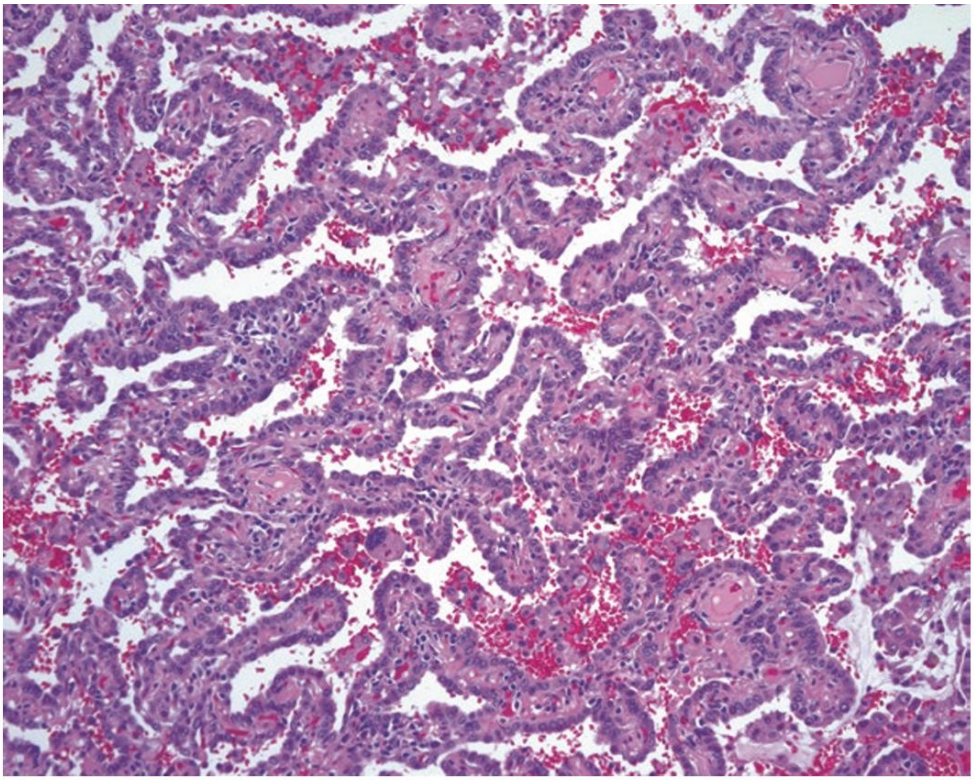


FIGURE 22.9. Adenocarcinoma in situ. The malignant cells line the alveolar walls but do not invade the stroma.

- Minimally Invasive Adenocarcinoma
  - TTF1 +ve, p40-ve
  - < 3cm in size
  - Allowed to invade up to 5mm (not inclusive)
- Invasive Adenocarcinoma
  - TTF1 +ve, p40-ve
  - Patterns include
    - Acinar
    - Solid
    - Lepidic
    - Papillary
    - Micropapillary
  - Often presents as a mix of the above patterns
  - Plane jane adeno can have intracytoplasmic mucin BUT

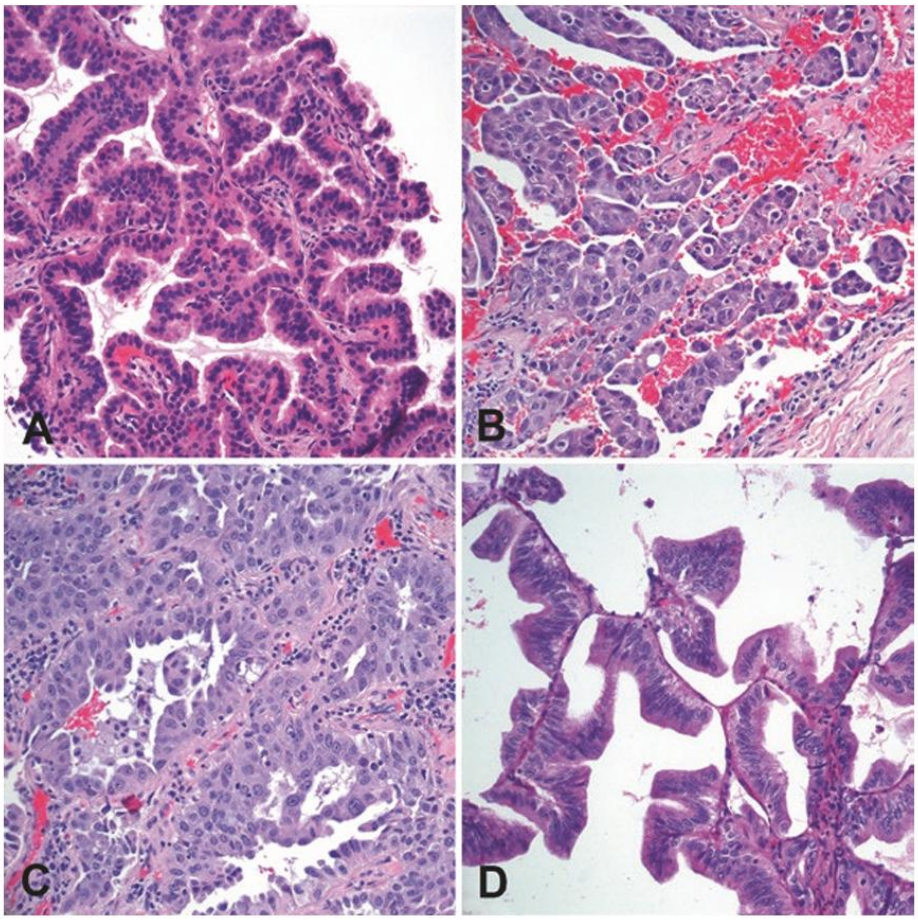


FIGURE 22.11. Adenocarcinoma. Patterns include (**a**) papillary (tumor cells on fibrovascular cores), (**b**) micropapillary (rounded fingers and florets of tumor without fibrovascular cores), (**c**) acinar (gland forming), (**d**) lepidic (growing along alveolar walls), and solid (not shown).

- Mucinous Adenocarcinoma
  - Tumour filled with mostly mucin filled goblet cells

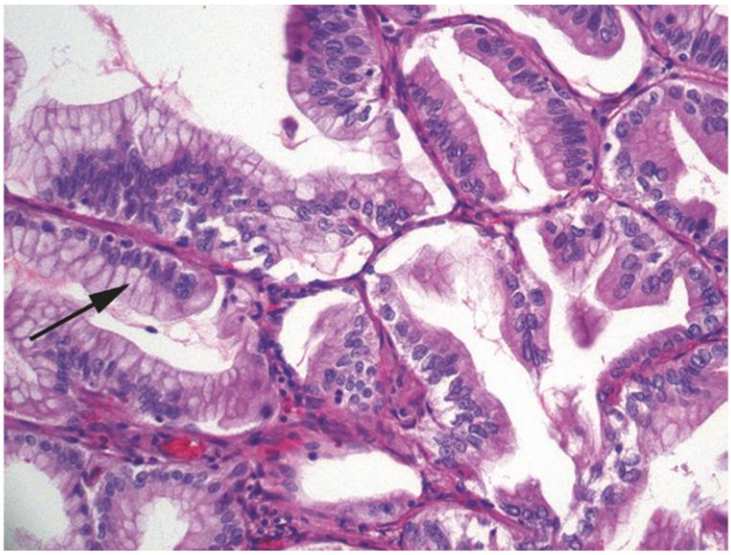


FIGURE 22.12. Mucinous adenocarcinoma. The tumor cells resemble goblet cells, with uniform basal nuclei and fat drops of mucin at the apical surface (*arrow*). This field also shows a lepidic pattern.

- Colloid Carcinoma
  - Tumour of pools of mucin with floating tumour cells

- Lung SqCC
  - Often central 2/2 arising often in bronchi
  - Comes as
    - Keratinizing
    - Non-keratinizing
    - Basaloid (non-keratinizing, mimics HPV associated SCC of the head and neck)
    - All 3 are p40 +ve, TTF1 -ve

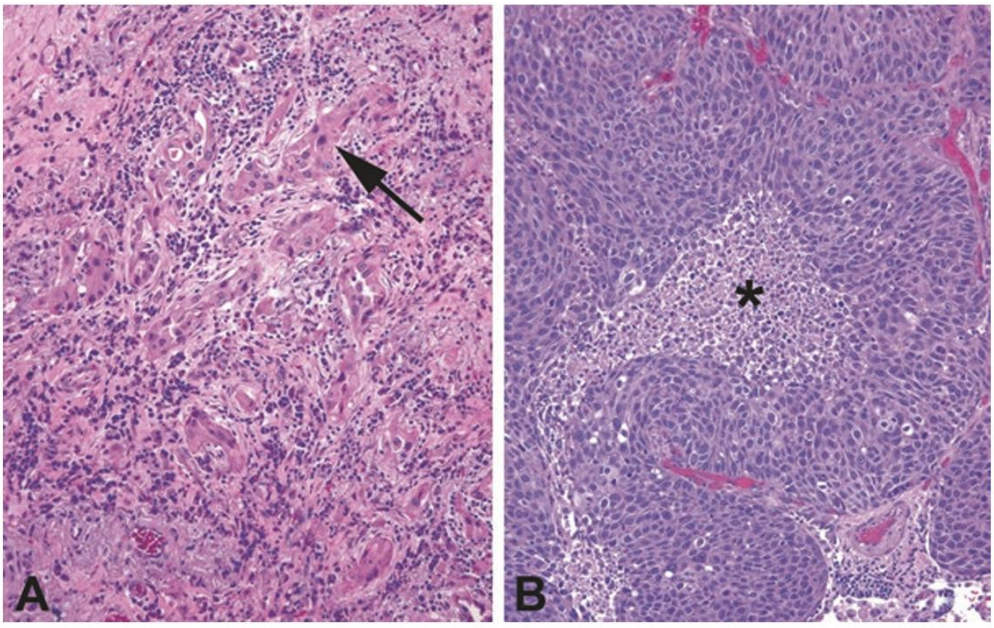


FIGURE 22.10. Squamous cell carcinoma. (**a**) Moderately differentiated squamous cell carcinoma, with irregular nests of cells with highly pleomorphic nuclei and bright pink, dense cytoplasm (*arrow*). Keratin pearls may also be seen in more well-differentiated tumors. (**b**) Basaloid squamous cell carcinoma, with rounded nests of very blue tumor cells with high N/C ratio and a high mitotic rate. Central necrosis (*asterisk*) is common.

- Large Cell Carcinoma
  - No recognizable glandular or squamous features, aka its not a small cell but not an AdenoCa or an SqCC
  - Not the same as a large cell N.E.C.
- Sarcomatoid Lung Cancer
  - Mimics a sarcoma but is keratin positive (even if focal or weak)
  - Sheets of spindle cells
  - Prominent nucleoli which sarcomas do not have
  - A carcinosarcoma is a biphasic tumour with mixed epithelial and sarcoma components

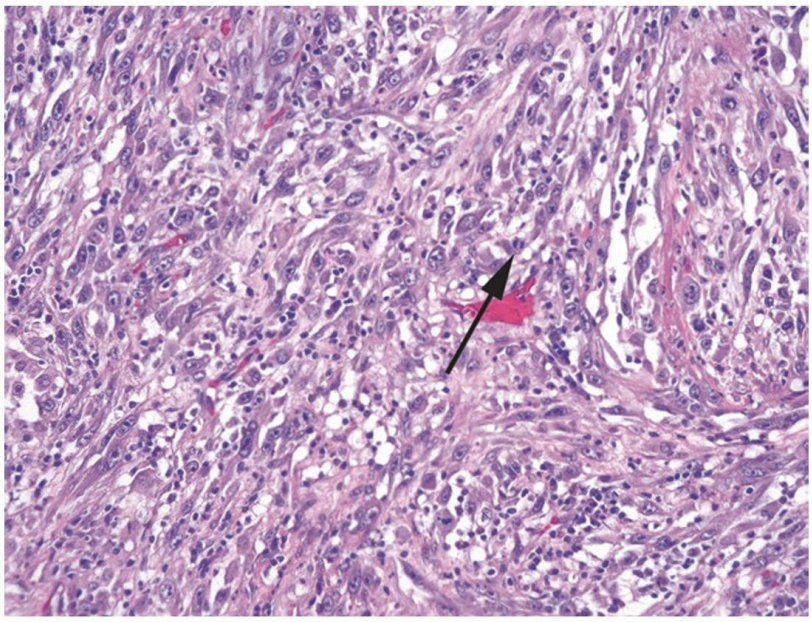


FIGURE 22.13. Sarcomatoid carcinoma. Sheets of spindled cells with large nuclei and prominent nucleoli are visible. Mitoses (*arrow*) are common. These cells should be positive for cytokeratin stains, confirming their epithelial origin.

- Carcinosarcoma
  - Epithelial component + Sarcoma component (usually osteosarcoma or chondrosarcoma)
- Pleomorphic Carcinoma
  - Adeno ***or*** Squamous carcinoma + spindle cell or giant cell component

Neuroendocrine Tumours

- Typical Carcinoid
  - Finally speckled chromatin, low mitotic rate, no nucleoli
- Atypical Carcinoid
  - aka Intermediate grade NET
  - Carcinoid with (2-10 mitoses / $2mm^2$) or necrosis
  - more aggressive than a well-differentiated NET
- Small Cell Carcinoma
  - High grade NE neoplasm with small cell morphology
    - Hyperchromatic, dense blue nuclei w/o nucleoli
    - Nuclear molding
    - Necrosis/mitoses common
    - Streaming crush artifact

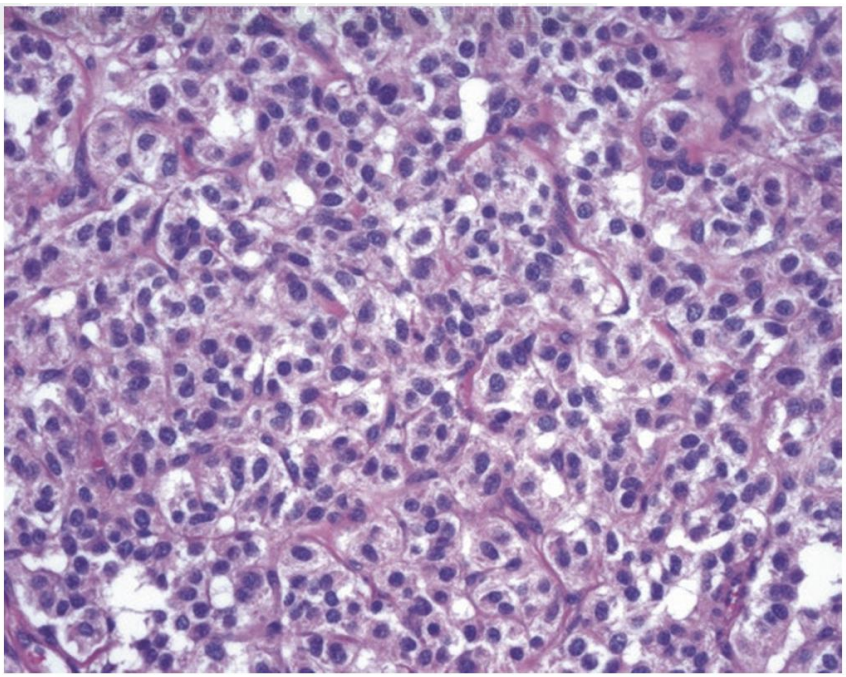


FIGURE 22.14. Carcinoid. This high-power view of an intrabronchial carcinoid shows a nested and trabecular pattern of cells with oval nuclei and typical "neuroendocrine" chromatin, meaning finely textured and speckled, without nucleoli or prominent nuclear membranes.

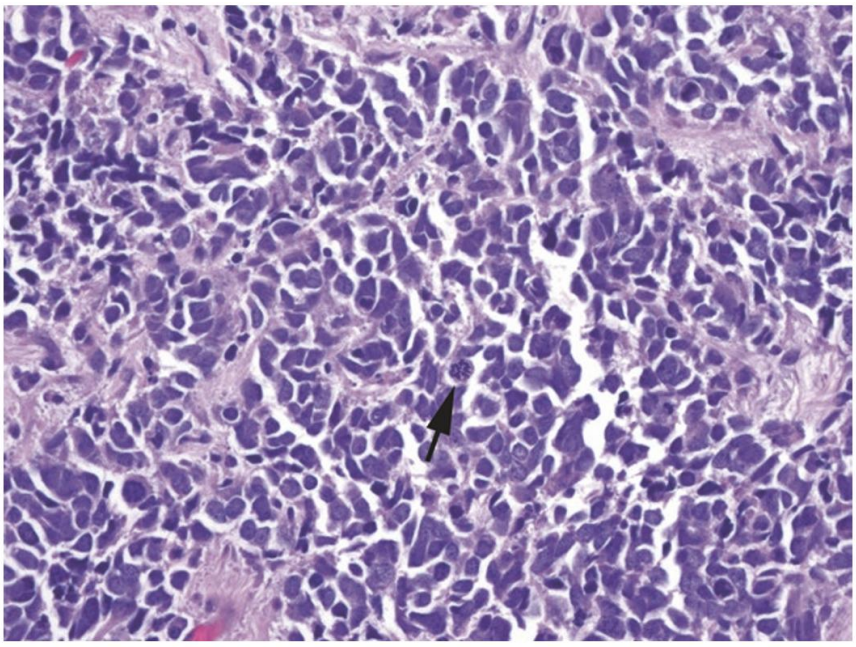


FIGURE 22.15. Small cell carcinoma. Sheets of nuclei appear molded together with interlocking shapes due to the near absence of cytoplasm. The dense chromatin is uniform and lacks nucleoli. Necrosis and mitoses (*arrow*) are common.

- Large Cell N.E.C.
  - A high grade NEC
    - Large ≠ the cells are large
    - Large = cells with cytoplasm or nucleoli
- Mesothelioma
  - Epitheliod
  - Patterns

- Tubules
- Papillary
- Solid

➢ Can have sarcomatoid differentiation

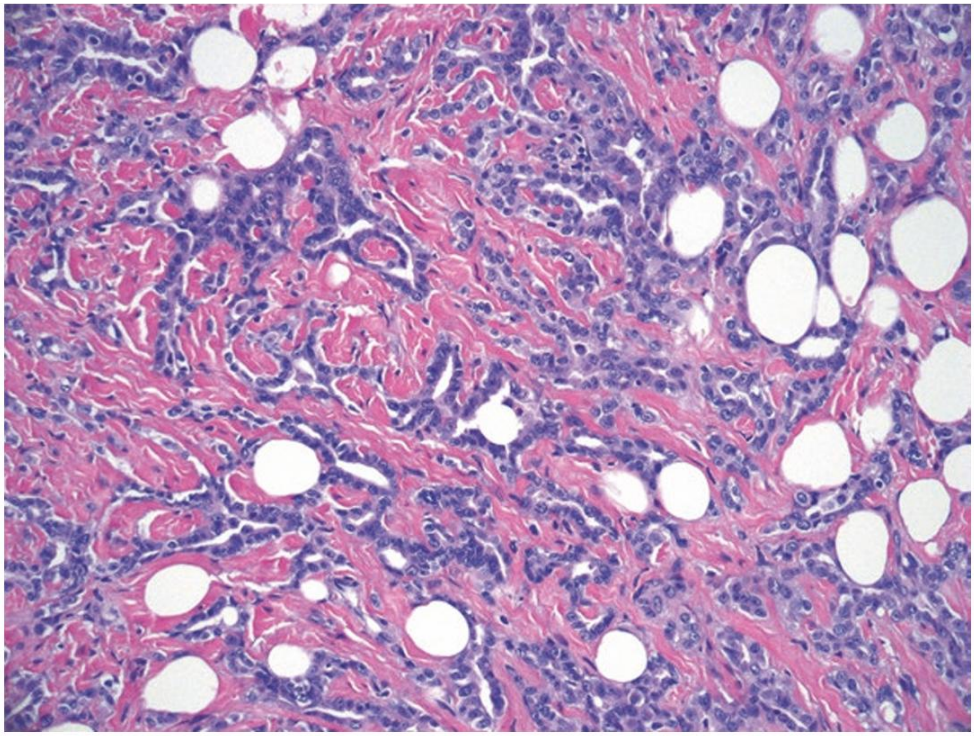


FIGURE 22.16. Mesothelioma. Small angular tubules are seen invading fat and fibrous tissue. The nuclei, however, are smaller and more uniform than a typical adenocarcinoma.

More notes on Non-neoplastic Lung (not sure where these came from, Boss Man Adam?)

1. DAD with organizing pattern ≠ organizing pneumonia
2. DAD features
    a. Has hyaline membrane around alveoli
        i. Hyaline membrane is actually fibrin in the alveolar wall. The fibrin is deposited in two patterns, in lines (hyaline) or in balls
    b. Type 2 hyperplasia (hobnailing) at alveolar lumen
    c. DAD with organising pattern tends to have fibroblast foci both in the walls of alveoli and in alveolar void whereas OP is fibroblast foci in the ?

    Per above: DAD = fibroblast foci in alveoli and bronchioles, UIP = fibroblast foci in the interstitium
3. Organizing pneumonia can progress from DAD but can be spontaneous
4. UIP is lower lobe predominant
   UIP is worse at periphery
   } what is meant by heterogenous in time and space

Chapter 23 – Thymus & Mediastinum

Chapter 24 **– Thyroid**

Normal

- Follicular epithelium is low cuboidal
- Stroma is scant but highly vascular

❖ Two cell types

- Follicular Epithelial cells
  - Positive: TTF-1, PAX8, thyroglobulin
- C-Cells
  - Positive: TTF-1, neuroendocrine markers, calcitonin
  - Negative: thyroglobulin

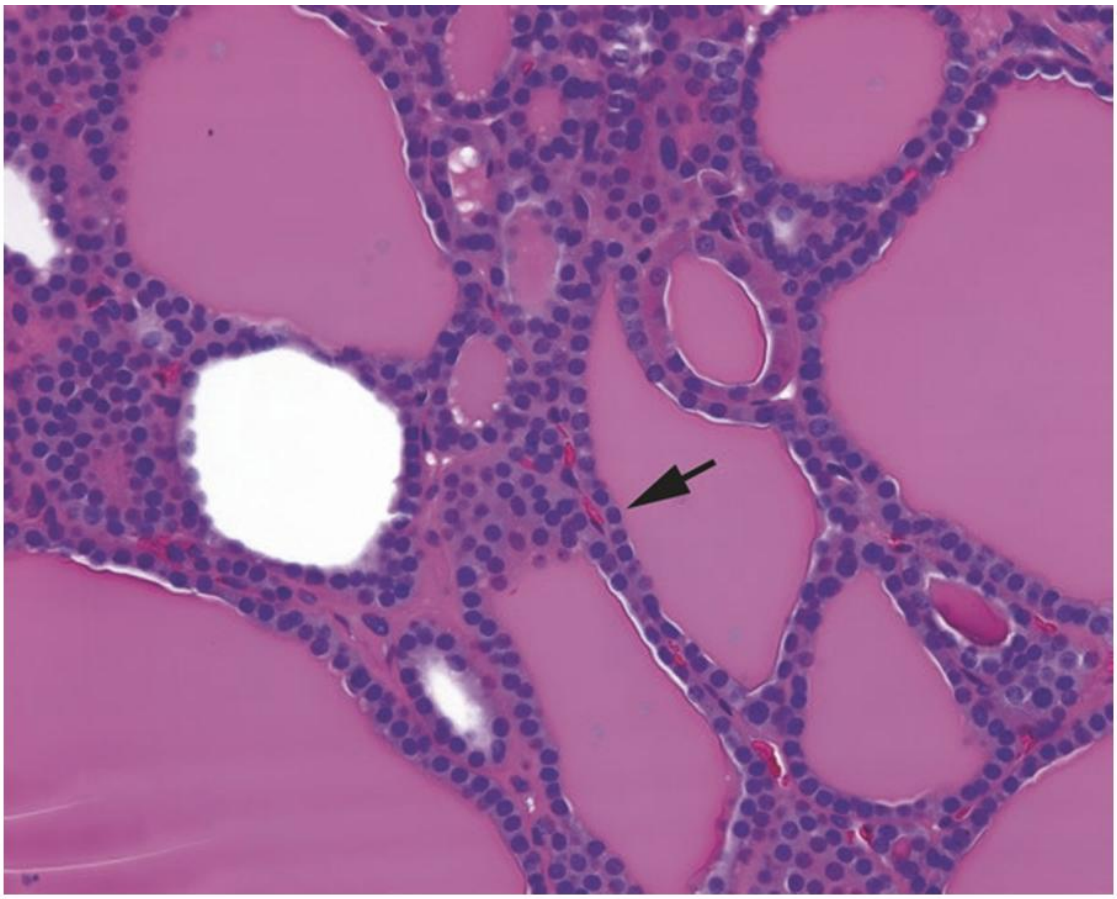


FIGURE 24.3. Follicular cells. Normal follicular epithelium has round uniform nuclei that tend not to overlap or crowd each other (*arrow*). This field is a combination of large and small follicles full of colloid and could represent normal thyroid, nodular hyperplasia, or a follicular neoplasm.

Inflammatory Thyroidites

❖ Acute thyroiditis

- Usually infectious
- Histo - Acute inflammation and necrosis

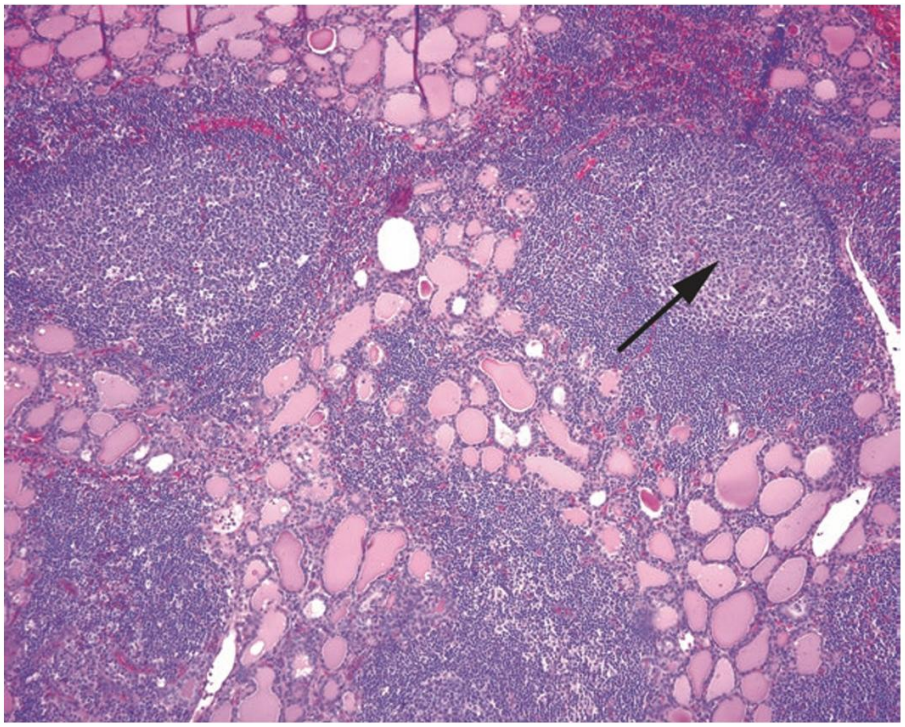
❖ Granulomatous/Subacute thyroiditis

- Histo
  - Foreign body giant cells, histiocytes, and lymphocytes
  - Diffuse

❖ Palpation thyroiditis

- Histo
  - Histiocytes, lymphocytes and rare giant cells
  - Focal
- Is a reaction to physical trauma

❖ Lymphocytic thyroiditis / Hashimoto's Thyroiditis
- Lymphocytic thyroiditis is a general term.
- Histo
  - Lymphocytic infiltrate with germinal centres
  - Hashimoto's will have small atrophic follicles with Hurtle cell change
  - Scattered atypia possible
  - Large, hyperchromatic Hurtle cell nuclei
  - Nuclear clearing possible
  - Nuclear pleomorphism possible



24.1. Hashimoto thyroiditis. The thyroid follicles are displaced by germinal centers (*arrow*).

❖ Fibrosing thyroiditis
  - Histo - Dense fibrosis and chronic inflammation
  - Aka Riedel thyroiditis, an IgG-4 related sclerosing disease

Graves
- Histo
  - Untreated: Highly cellular with minimal colloid
  - If treated: Large and distended follicles with prominent papillary infoldings

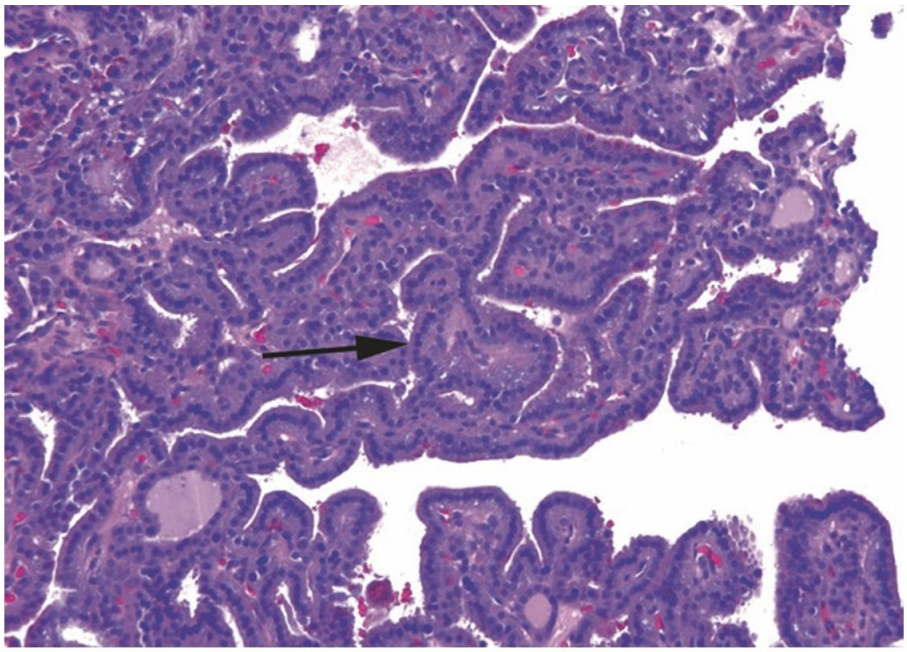


FIGURE 24.2. Graves disease with papillary hyperplasia. These papillary formations are due to hyperplasia of the follicular epithelium. The follicular cells are round and fairly evenly spaced and have dark uniform chromatin (*arrow*), similar to normal follicles.

Summary of Thyroid Lesions:

TABLE 24.1. Summary matrix of architectural and cytologic features of thyroid neoplasms.

Cytology	Macro- or normofollicular nodule	Microfollicular nodule	Papillary pattern	Solid or nested growth
"Follicular" nuclei	Hyperplastic nodule or follicular adenoma	Follicular adenoma/ carcinoma	Graves disease	Follicular carcinoma
Hürthle cells	Hürthle cell adenoma	Hürthle cell adenoma/ carcinoma	Oncocytic variant of papillary carcinoma	Hürthle cell adenoma/ carcinoma
"Papillary" nuclei	Follicular variant of papillary carcinoma	Follicular variant of papillary carcinoma	Papillary carcinoma	Hyalinizing trabecular tumor
Pleomorphic or squamoid cells				Anaplastic carcinoma
Neuroendocrine nuclei				Medullary carcinoma

Follicular-Type Lesions

- In general
  - Uniform cells
  - Nuclei tend to be rounded monotonous, but can be enlarged in neoplasms
  - No crowded overlapping or irregular nuclei
  - Chromatin is smooth and even (not vesicular)
- There is a spectrum of follicular lesion.
  - Colloid nodule → adenomatoid nodule → follicular adenoma
  - All describe a nodular cluster of follicular epithelium ± capsule

- **Colloid nodule** – large, distended nodules with high colloid:cell ratio
- **Adenomatoid nodule** – features of follicular adenoma but lacks a proper capsule
- **Follicular adenoma** –
    - ➢ Solitary encapsulated nodule composed of small microfollicles with low colloid:cell ratio.
    - ➢ Usually compresses normal thyroid.
    - ➢ Called follicular neoplasm on FNA as cannot differentiate it from follicular carcinoma without seeing the full "capsule" (has Thick fibrous capsule)

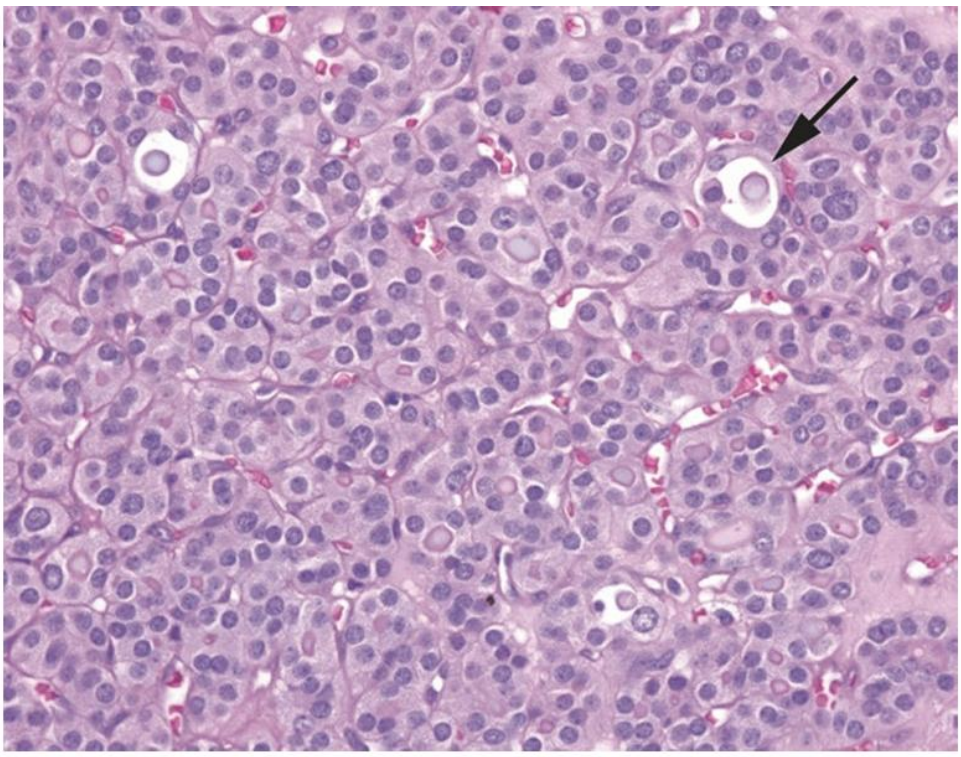


FIGURE 24.4. Follicular adenoma. This field shows a microfollicular pattern in a follicular adenoma. The capsule is not seen here. The neoplasm is composed of tightly packed small follicles (*arrow*) with round nuclei that, like normal follicular epithelium (compared to Figure 24.3), tend not to overlap or crowd. There are scattered enlarged nuclei, some with pale chromatin that should not be mistaken for true nuclear clearing.

❖ Follicular Carcinoma

- Histologically similar to follicular adenoma BUT
- Distinguished with capsular or vascular invasion
    - Vascular invasion must be within or outside the capsule
    - Tumour deposits must be visibly attached to the vessel wall
- Necrosis and or cellular atypia is *insufficient* to make the diagnosis

➢ Comes in *microinvasive* and *widely invasive* patterns

- Widely invasive
    - ♦ No capsule left. Have to peel it off adherent neck structures
- Minimally invasive
    - ♦ >5 vessels invaded is a worse prognostic factor
    - ♦ Likes to spread to lung and bone

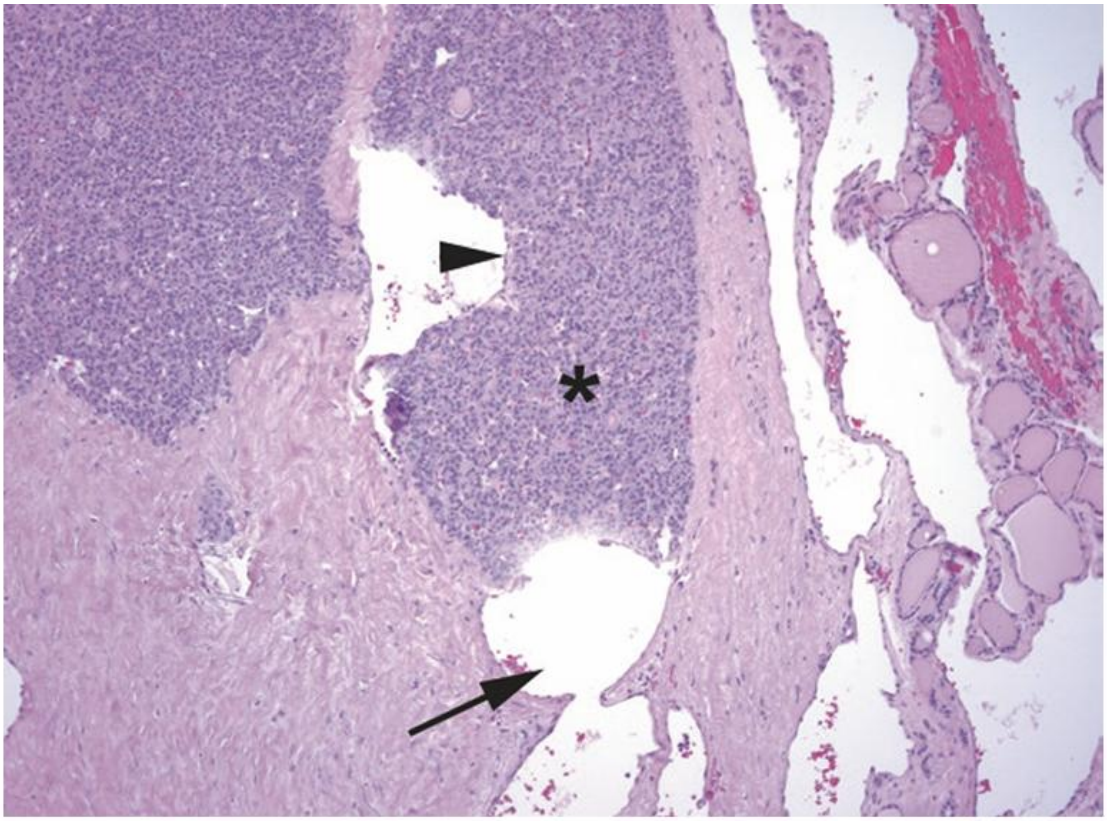
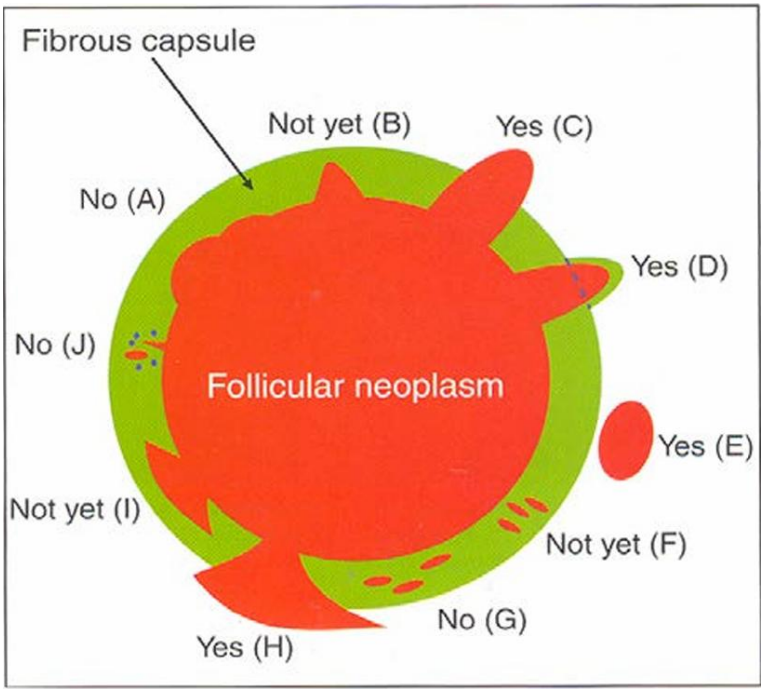


FIGURE 24.6. Follicular carcinoma. The neoplasm here resembles a follicular adenoma at low power, with a dense microfollicular pattern and a thick capsule. However, there is vascular invasion in the capsule, diagnostic of follicular carcinoma. A tumor plug (*asterisk*) is seen in the lumen of a large vessel (*arrow*). The surface of the tumor plug becomes endothelialized (*arrowhead*).



CAP Cancer Protocol Thyroid Gland

- Hurthle Cell Adenoma
  - Similar in concept to follicular adenoma BUT
  - The cells are large, pink oncocytes (Hurthle cell change)

- Nuclei may be: Prominent, Large, or Irregular

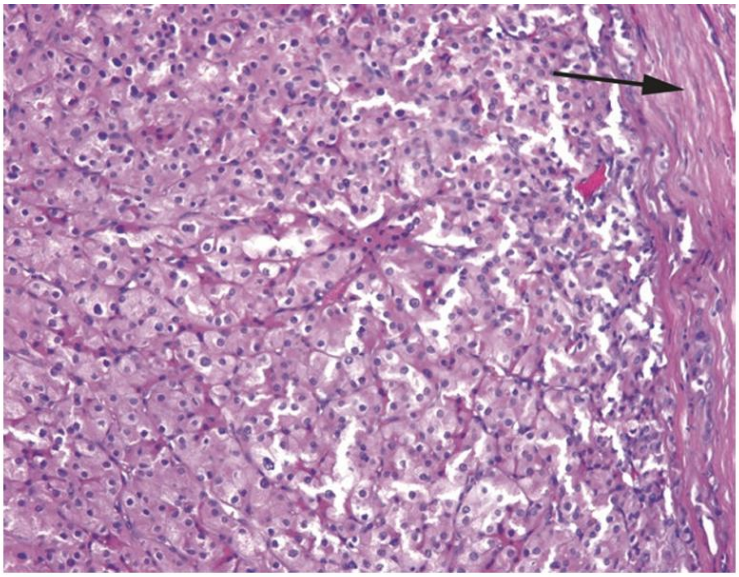


FIGURE 24.5. Hürthle cell adenoma. Like follicular adenomas, there is a thick fibrous capsule surrounding the neoplasm (*arrow*). In a Hürthle cell adenoma, the cells have abundant pink cytoplasm, and although the nuclei are still overall round and nonoverlapping, there is increased nuclear atypia in the form of some prominent nucleoli and irregular nuclear shapes.

❖ Poorly Differentiated Thyroid Carcinoma

- Cells resemble follicular carcinoma cells but the architecture is complex (sheets, nests, cords)
- Notably more aggressive than follicular carcinoma but not anaplastic carcinoma

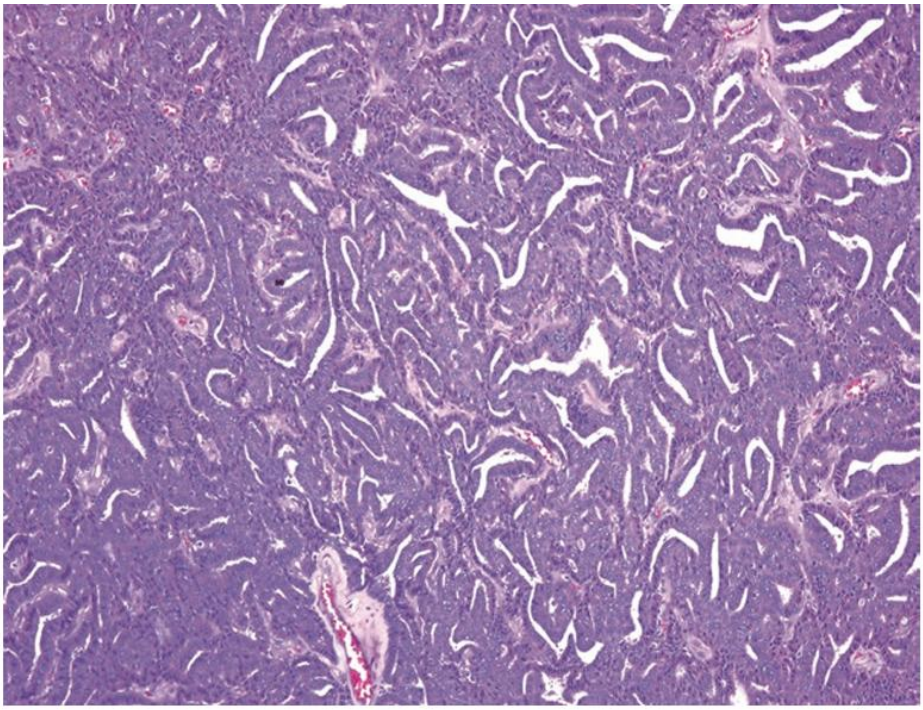


FIGURE 24.7. Poorly differentiated carcinoma. Instead of microfollicles, the tumor has acquired a pattern of ribbons, cords, and slit-like spaces.

<u>Papillary Thyroid Carcinoma</u>

- There is no papillary adenoma

❖ Classic PTC

➢ Associated with radiation & thyroiditis

- Spreads to lymph nodes unlike follicular carcinoma
- Age is most important prognosticator
- Histo
  - Chromatin I cleared out (Orphan Annie nuclei). This is an artifact of formalin, so it is **NOT** seen at frozen section or cytology
  - Nuclei are overlapping /crowded
  - Nuclei pleomorphic
  - Nuclear grooves
  - Nuclear pseudoinclusion (EINCI as Bacani calls them) which are indentations of cytoplasm from the nuclear grooves
- Psammoma bodies = ONLY in Papillary pattern PTC
  - Dark purple, ringed like a tree

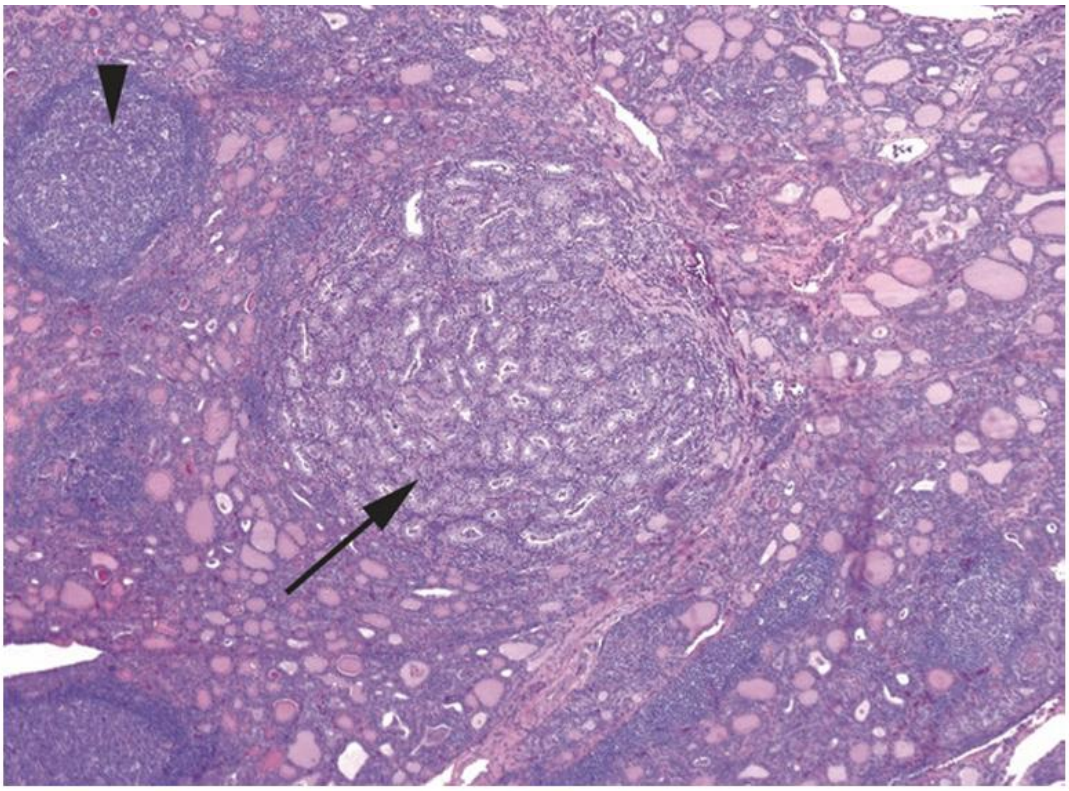


FIGURE 24.8. Papillary carcinoma, low power. The nuclear features of papillary carcinoma are eye-catching even at low power, as the clear nuclei give a translucent or glassy appearance to the tumor nodule (*arrow*). This is an example of an incidental microcarcinoma, arising in Hashimoto thyroiditis (note germinal centers, *arrowhead*).

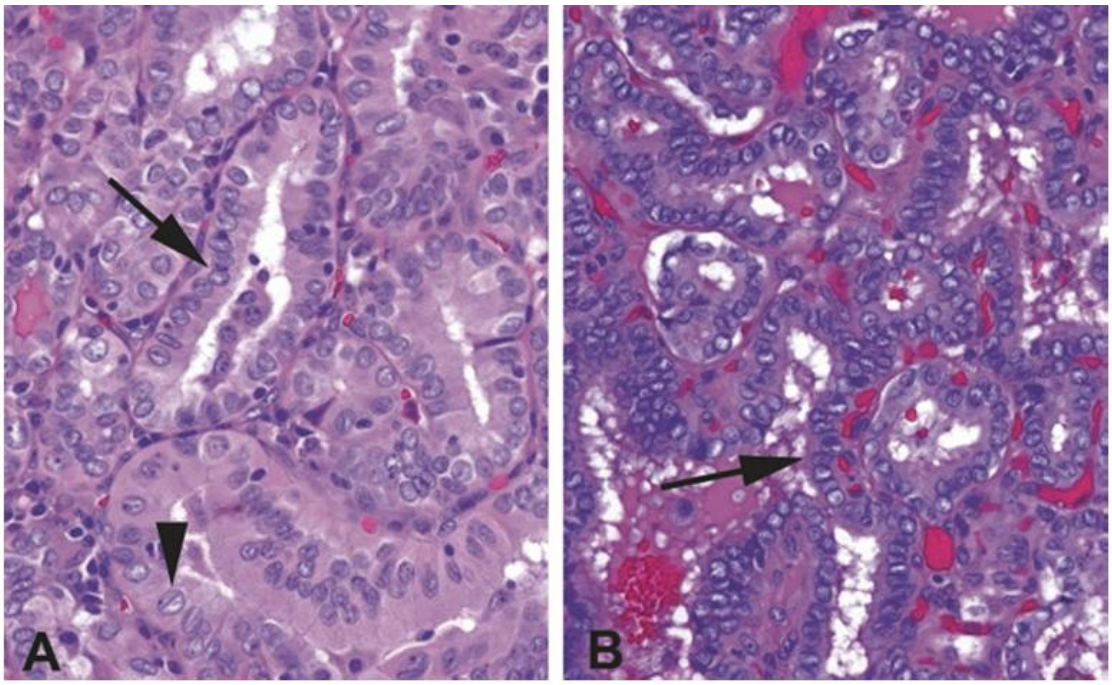


FIGURE 24.9. Papillary nuclei. (**a**) In this example, although the nuclear clearing is not striking, the presence of oval nuclei crowded into a row (*arrow*) suggests papillary carcinoma, as does the presence of nuclear grooves (*arrowhead*). Compare these nuclei to those of follicular epithelium; see Figure 24.3. (**b**) In this lesion the nuclear clearing is much more evident. However, the nuclei are still oval in shape and crammed together such that they mold to each other, popping up and out of their crowded rows (*arrow*).

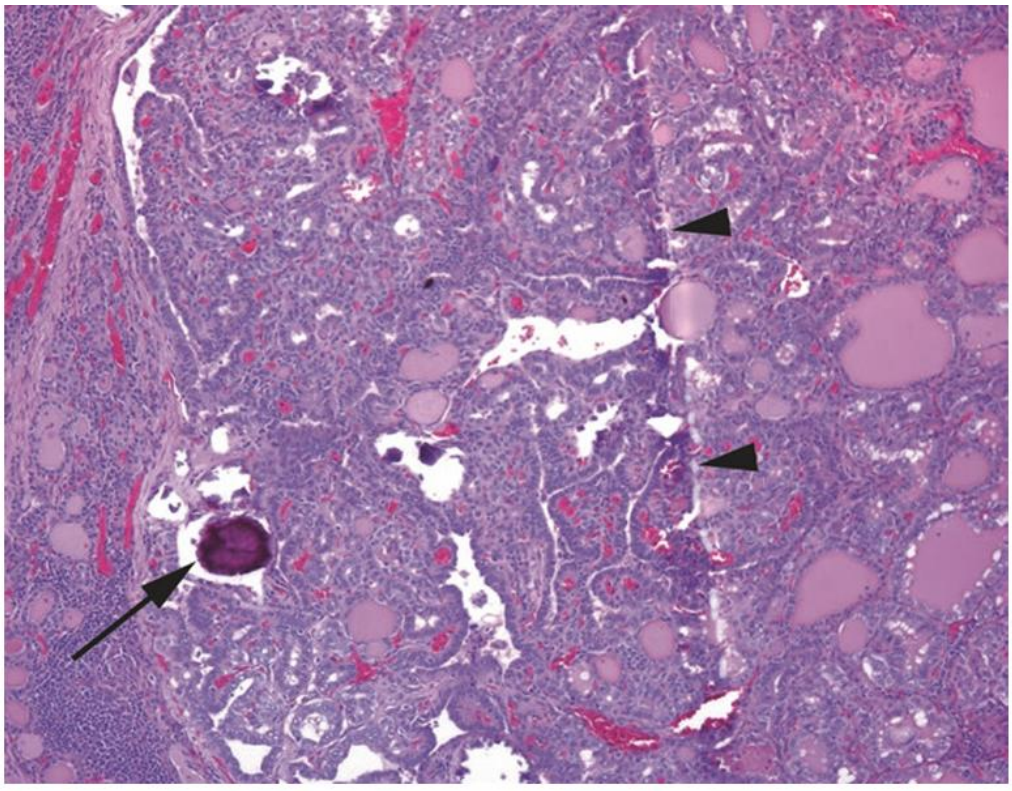


FIGURE 24.10. Psammoma body. This dense purple laminated calcification (*arrow*) is virtually diagnostic of papillary thyroid carcinoma in the thyroid or in a neck lymph node. Telltale scratches in the tissue section (*arrowheads*) often show where a psammoma body was dragged across the block during sectioning.

- Follicular Variant PTC
  - Follicular architecture but PTC nuclear features
  - IF....
    - ... unencapsulated and infiltrative, classified/acts like papillary carcinoma
    - ... encapsulated but invades capsule, classified/acts like follicular carcinoma
    - ... has an intact capsule, call it NIFTP

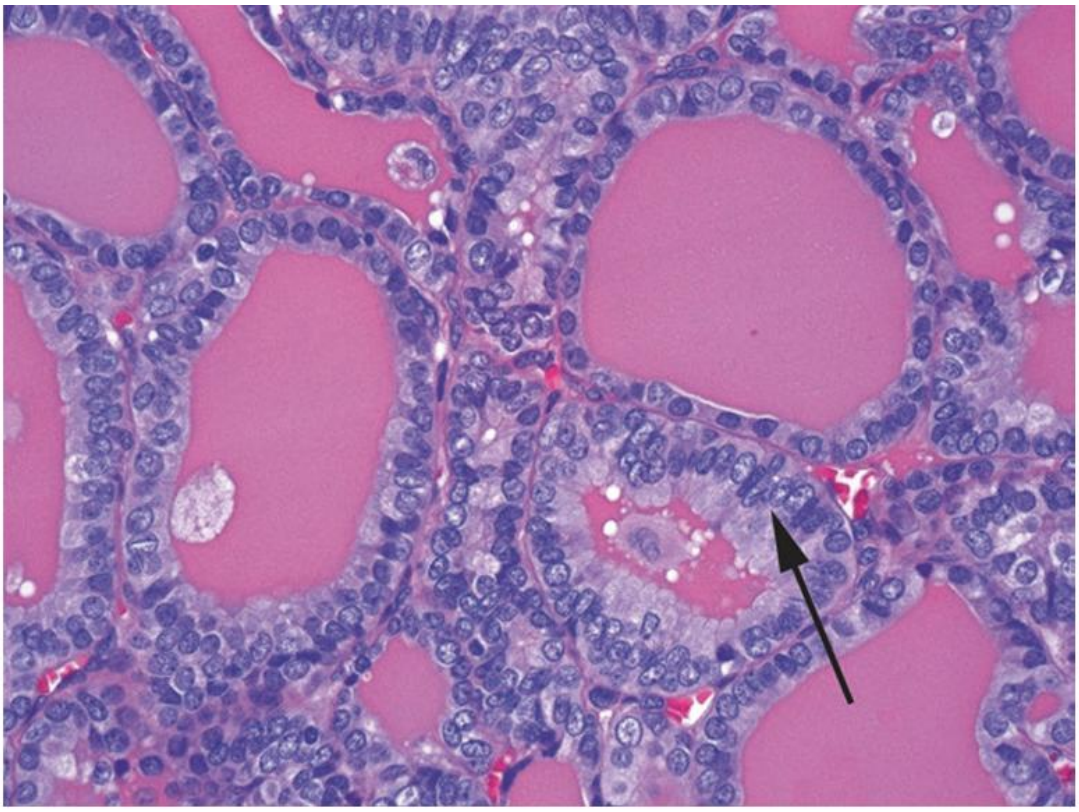


FIGURE 24.11. Follicular variant of papillary carcinoma. The architecture is that of a follicular adenoma, but the nuclei, oval in shape and crowded together (*arrow*), are those of papillary carcinoma. The presence or absence of a capsule, and invasion, determines how this lesion would be classified.

- Diffuse Sclerosing variant
  - Rare
  - Worse prognosis, more aggressive
  - Widely infiltrative, but not discrete or mass forming
  - Histo
    - Desmoplasia
    - Squamous metaplasia
    - +++ Psammoma bodies
    - Dense lymphocytic infiltrate
    - Lymphovascular invasion
- Tall Cell PTC
  - Cells at least 2x tall as they are wide
  - Oncocytic cytoplasm

- Bad prognosis

❖ Other Variants
- Oncocytic
- Clear cell
- Cribriform-morular
- Columnar
- Solid

❖ Anaplastic
- Histo
  - Sheet of pleomorphic cells, truly undifferentiated
    - Can be squamoid differentiation or sarcomatoid
  - Usually lose TTF-1 and thyroglobulin marker

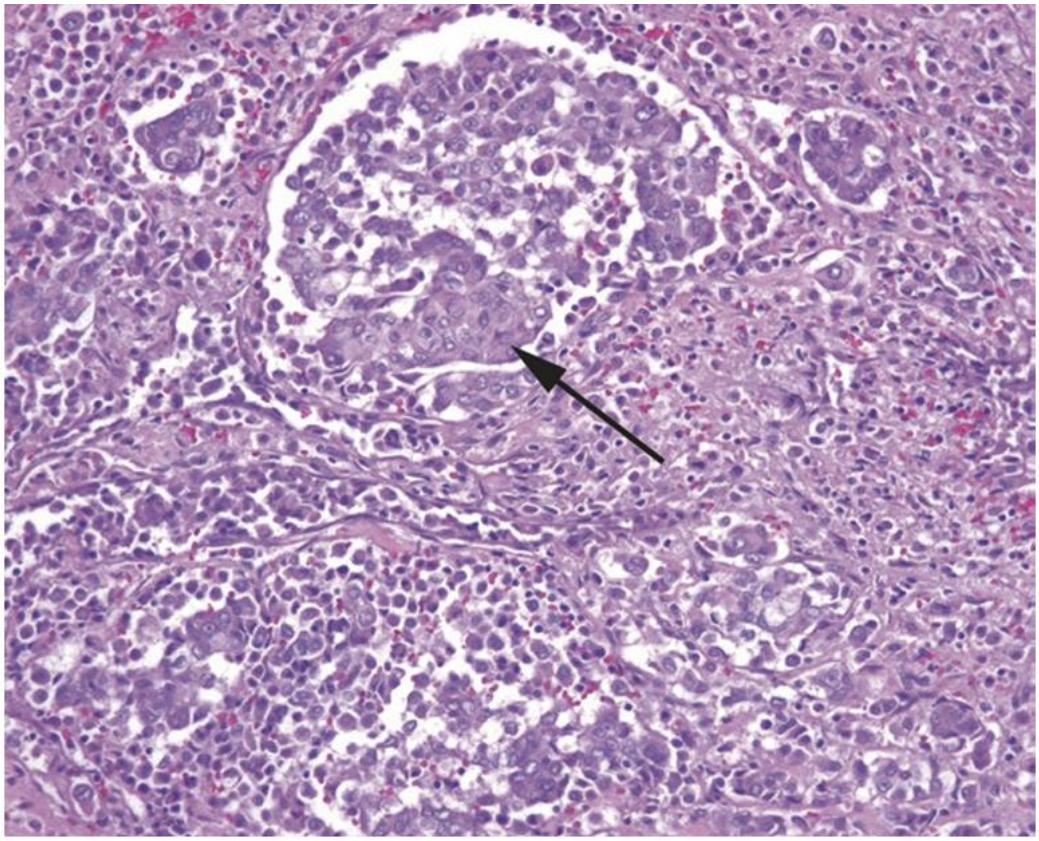


FIGURE 24.12. Anaplastic carcinoma. Nests and sheets of poorly differentiated carcinoma, some areas with a squamoid appearance (*arrow*).

❖ Hyalinizing trabecular tumour
- Benign
- Histo
  - Papillary nuclei (beautiful grooves and inclusions)
  - Architecture of medullary carcinoma
    - Well-circumscribed nodule
    - Trabecular
    - Dense pink stroma (hyalinized)

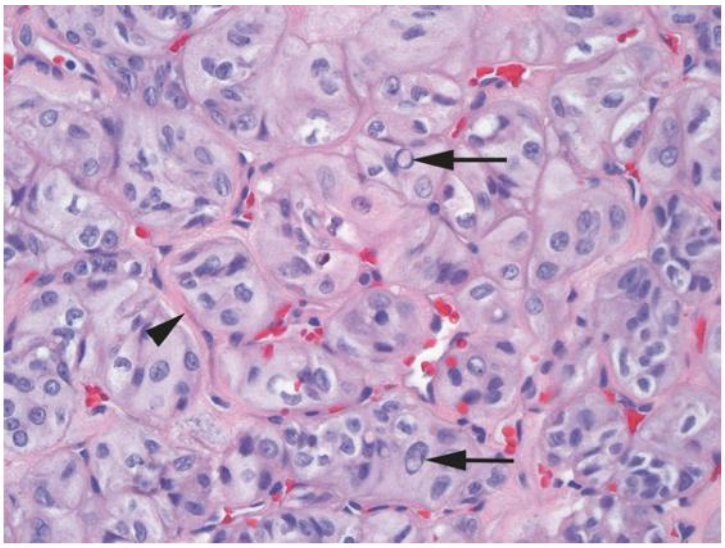


FIGURE 24.13. Hyalinizing trabecular tumor. This tumor shows nests and cords of pale, sometimes spindly cells with a background of dense pink amyloid-like stroma (*arrowhead*). The nuclei may be mistaken for papillary carcinoma, as grooves and nuclear inclusions are prominent (*arrows*).

Neuroendocrine Lesions / Medullary Carcinoma

- Histo
  - Makes amyloid
  - NET nuclei / chromatin
  - Calcitonin +ve (which follicular is not)
  - NET marker +ve
  - Hyperchromasia may hide speckled chromatin
  - Forms islands
  - Eccentric nuclei are common (plasmacytoid)

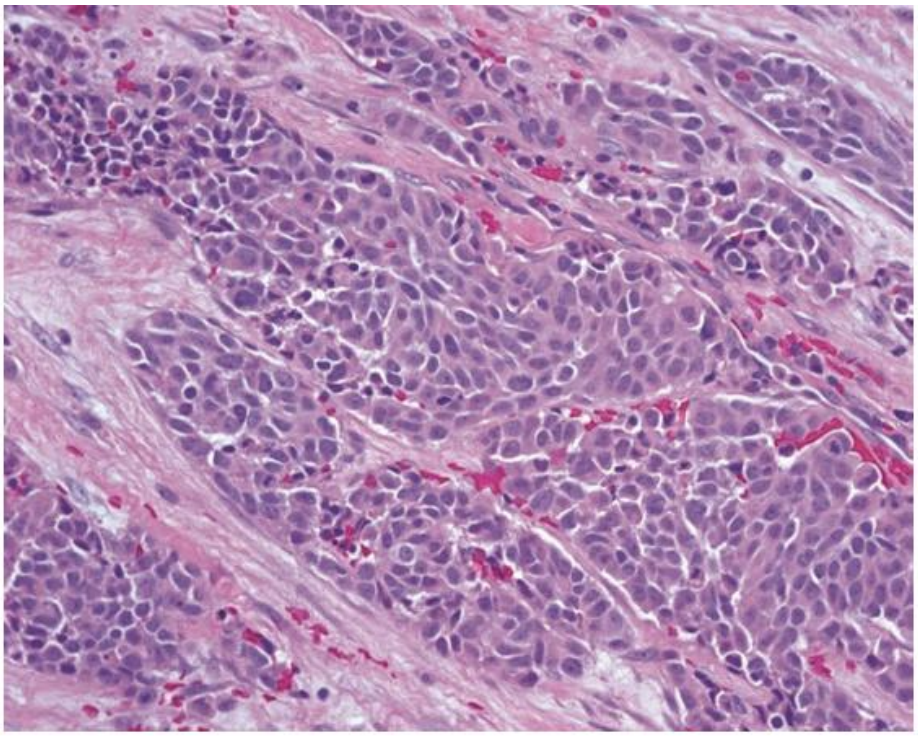


FIGURE 24.14. Medullary carcinoma. Although the pattern of infiltrative nests of cells may resemble anaplastic carcinoma, the nuclei are much more bland, with pale, finely speckled, neuroendocrine-type chromatin.

Chapter 25 **– Salivary Gland**

- Biopsies of salivary gland often done to diagnose Sjoren Syndrome
- Inflammatory lesions
  - Can create a mass, eg.
    - Chronic sialadenitis
    - Lymphoepithelial cyst
- Necrotizing Sialometaplasia
  - Known pitfall
  - Reactive condition with
    - intense inflammation, squamous metaplasia, reactive atypia in the ducts
  - may form a mass

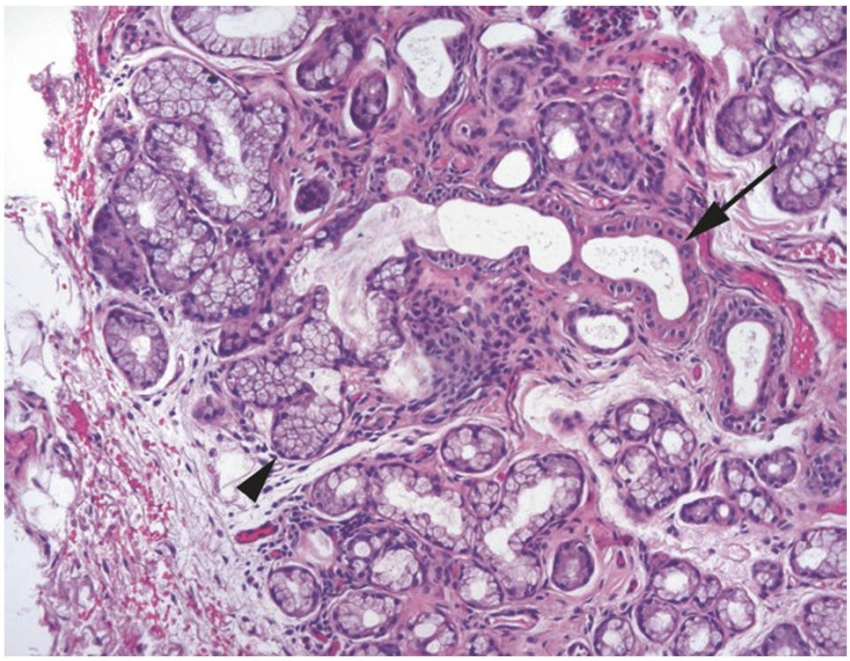


FIGURE 25.1. Normal salivary gland. In this example of mucinous salivary gland, the columnar secretory cells (*arrowhead*) form acini arranged around salivary ducts (*arrow*). Myoepithelial cells are not particularly visible on H&E stain.

Histology

- 3 Major glands and innumerable small glands
  - in general, the smaller the gland, the more likely to be malignant
    - parotid = mostly serous
    - submandibular = mixed
    - sublingual = mostly mucinous
- 3 Major Cell Lines
  - Secretory Cell (serous or mucinous)
    - Serous Cells
      - Wedge shaped
      - Arranged in acini around ducts
      - Full of blue to purple granules
    - Mucinous Cells
      - Basal nuclei and apical mucin

        - Arranged in acinar formations
- Duct Cells (derived tumours resemble duct of origin)
    - Intercalated (terminal) ducts
        - “Small profiles” with low cuboidal epithelium, similar to bile ductules
    - Striated ducts
        - Intermediate sized, larger than intercalated
        - Pink columnar cells (full of mitochondria)
        - Striated basal borders
    - Interlobular ducts
        - Pseudostratified columnar epithelium +/- goblet cell and squamous metaplasia
- Myoepithelial Cell
    - Surround acini and ducts
    - Pale stellate cells with small nuclei
    - 4 different forms (and hence tumour lineages)
        - Spindled
        - Plasmacytoid
        - Epithelioid
        - Clear

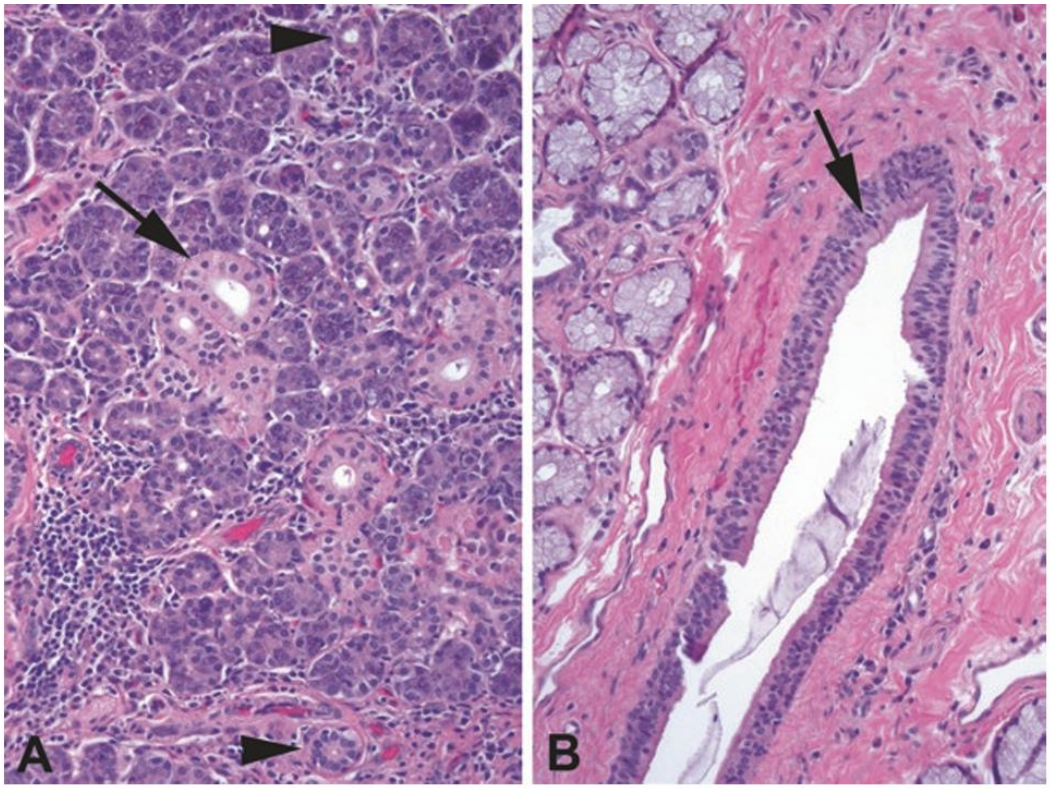


FIGURE 25.2. Types of ducts. (**a**) In the parotid, which has mainly serous glands, the terminal or intercalated ducts are visible as small tubules lined by cuboidal epithelium (*arrowheads*). The medium-sized striated ducts are more oncocytic in appearance, with abundant pink cytoplasm (*arrow*). (**b**) The large interlobular ducts have pseudostratified columnar epithelium (*arrow*), with occasional goblet cells, and become squamous at their junction with the gingival mucosa.

TABLE 25.1. Basic categories of the most common neoplasms.

Common neoplasms	Probable cells of origin
Benign adenomas	
Pleomorphic adenoma (mixed tumor) and its end-of-the-spectrum variant, myoepithelioma	Epithelial–myoepithelial
Basal cell adenoma	Epithelial–myoepithelial
Warthin tumor and oncocytoma	Striated duct cells
Low grade, malignant	
Mucoepidermoid carcinoma (low grade)	Interlobular duct cells, translocation related
Polymorphous adenocarcinoma	Epithelial–myoepithelial
Acinic cell carcinoma	Serous acinar cells
Secretory carcinoma	Terminal duct cells, translocation related
Intermediate to high grade, malignant	
Mucoepidermoid carcinoma (intermediate to high grade)	Interlobular duct cells, translocation related
Adenoid cystic carcinoma	Epithelial–myoepithelial
Salivary duct carcinoma	Striated duct cells
Adenocarcinoma not otherwise specified (wastebasket of those adenocarcinomas that do not show specific differentiation)	Ducts

In general, encapsulated lesions are benign in the salivary glans and malignant tumours are infiltrative.
*Acinic Cell Carcinoma and Mucoepidermoid carcinoma can be well-circumscribed

The tumours listed next are in order of decreasing prevalence.

Pleomorphic Adenoma

- Pleomorphic adenoma: Benign Mixed Tumour
  - Common in parotid gland
    - If it is an encapsulated solid lesion in the parotid, it probably fits into this category somehow
  - Encapsulated and circumscribed
  - Stromal component in background
    - Myxoid
    - Chondroid ….(or even osseous)
  - Epithelial component is highly variable (can be any of the four myoepithelial cell patterns)
  - Invasive equivalent of the PA is the Polymorphous Adenocarcinoma
    - but this is almost exclusive to the minor salivary glands & is rare in parotid
    - Salivary duct carcinoma is the most common carcinoma to arise from a pleomorphic adenoma but Carcinoma Ex-pleomorphic Adenoma & Polymorphous Adenocarcinoma are histologically more similar (so easy to mix up)
- Myoepithelioma
  - One end of the PA spectrum
    - Very little stromal component, no ductular differentiation
    - Should be encapsulated and circumscribed
  - IHC stains will help: S100, cytokeratin, GFAP, actin +ve

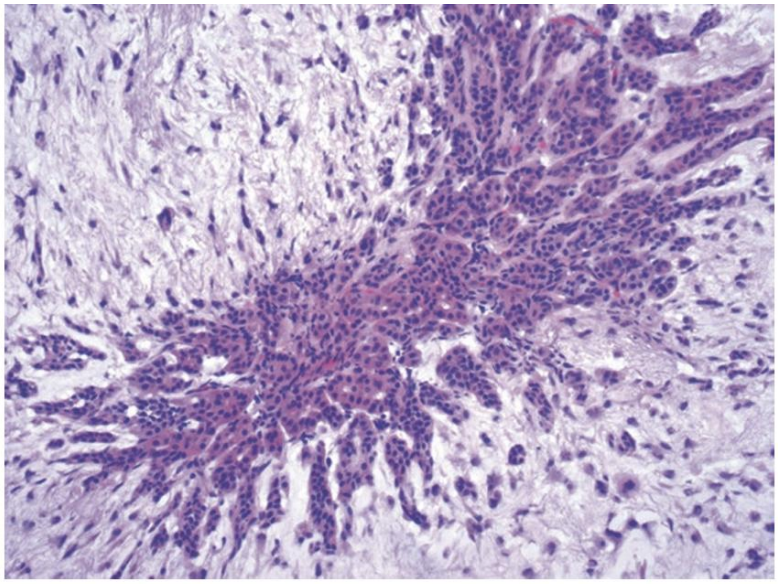


FIGURE 25.3. Pleomorphic adenoma. A cluster of cells is visible within the bluish myxoid stroma of a pleomorphic adenoma. The epithelial cells are small and cytologically benign, and they appear as small cords and tubules set within the stroma. The proportion of epithelial cells to stroma can vary widely.

Non-PA Salivary Tumours

- Warthin tumour
  - Cysts or Papillae lined by a double layer of oncocytic cells On top of a prominent lymphoid infiltrate
  - Only in the parotid
  - May arise from striated ducts passing through intra parotid lymph nodes
    - (Remember striated ducts are mitochondrial rich which explains the oncocytic colour)
  - DDX:
    - lymphoepithelial cyst (affects HIV patients)
      - Lining is thin and ragged
      - Lining is not oncocytic

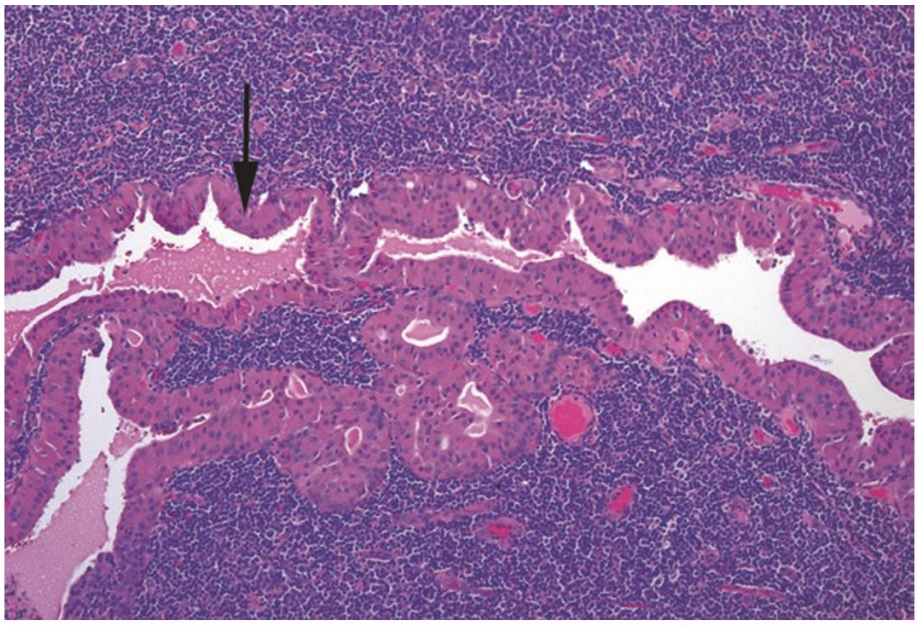


FIGURE 25.4. Warthin tumor. This cyst is lined by a double layer of oncocytic cells (*arrow*) overlying a dense lymphoid infiltrate.

❖ Mucoepidermoid Carcinoma
- ➢ The third most common salivary tumor overall, but the *most common malignant* salivary tumor
- ➢ Periphery should be infiltrative, not encapsulated, but low-grade can be well circumscribed
- ➢ Recognizing intracellular mucin is key to the diagnosis
  - so use PAS stain
  - Has a mix of cell types but often one predominates which may trick you into thinking Mucoepidermoid Carcinoma is SCC or Clear Cell Carcinoma
- ➢ Low- vs High-grade distinguished on 5 factors
  1. Percentage of cystic component
  2. tumor necrosis
  3. mitoses
  4. anaplasia
  5. neural invasion
- ➢ Low-grade Pitfalls
  - Interlobular duct derived
    - Inflamed or metaplastic duct can mimic Mucoepidermoid Carcinoma
  - Staining salary duct cyst can mimic Mucoepidermoid Carcinoma
  - surprisingly can be fairly well circumscribed

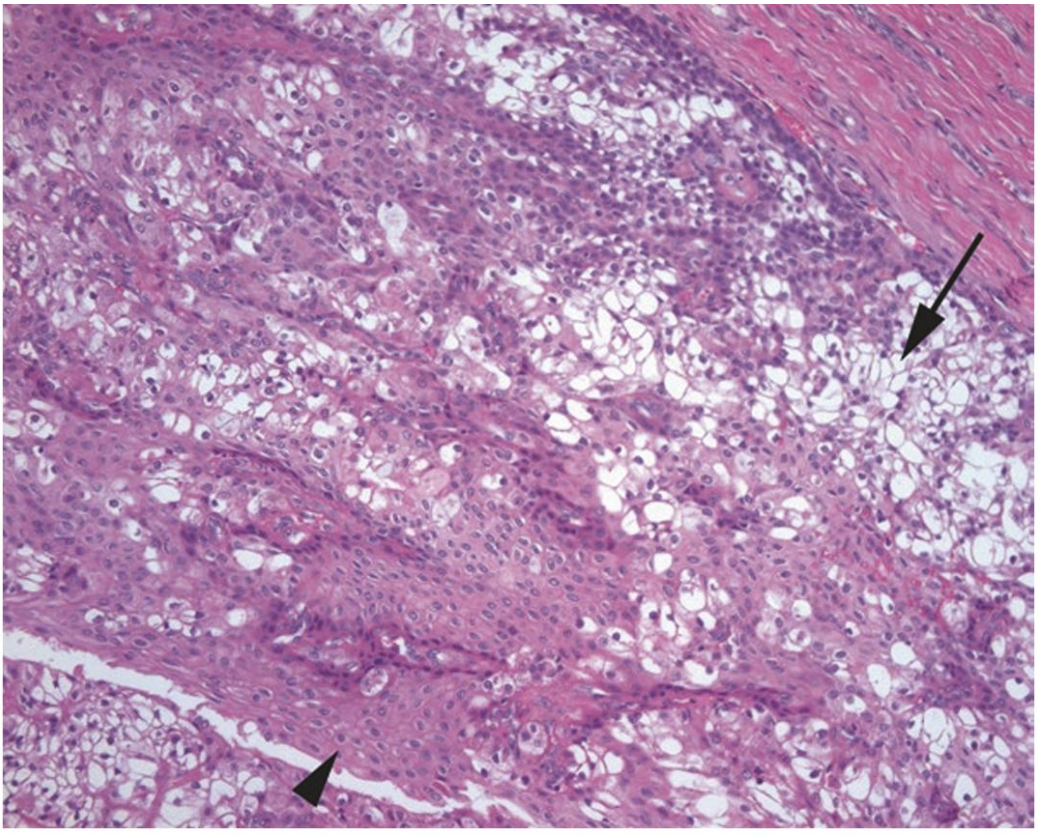


FIGURE 25.5. Mucoepidermoid carcinoma, low grade. This tumor resembles the metaplastic epithelium within an interlobular duct and is composed predominantly of clear goblet-like mucinous cells (*arrow*) and squamous cells (*arrowhead*).

- Adenoid Cystic Carcinoma
  - Prototype cribriform tumor (but can be solid/tubular)
  - very blue, very cellular, high NCR, dense angulated nuclei
  - classically has hyaline material in the lumens of the punched-out spaces
  - 2 cell types: myoepithelial cells (which predominate) & ducts
  - "Loves nerves"
  - Resembles cylindroma of the skin
  - Should not be encapsulated or well circumscribed
    - If so, maybe and myoepithelioma or other adenoma
  - Presence of squamous areas favor a SCC diagnosis

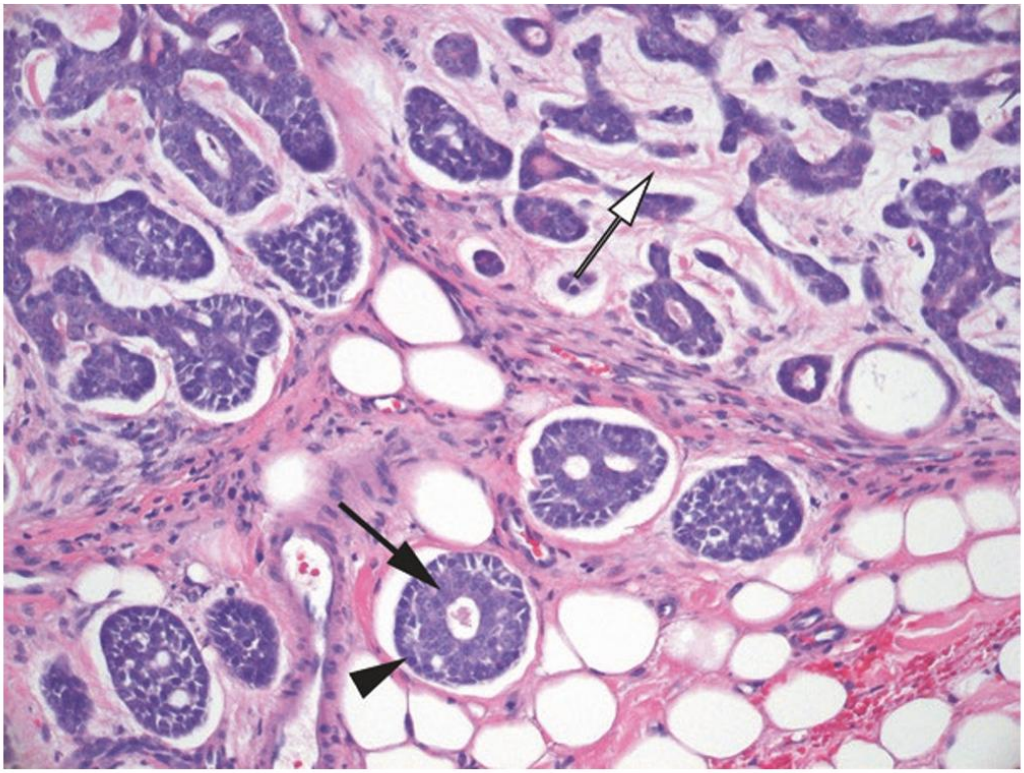


FIGURE 25.6. Adenoid cystic carcinoma. Although the nuclei are small, the nuclear to cytoplasmic ratio is high, making the tumor appear blue at low power. The architecture is classically cribriform, with sharply punched-out spaces full of pink secretions. There are actually two cell populations, the ductal cells (*black arrow*) and the slightly darker myoepithelial cells (*arrowhead*). The pink basement membrane material is visible between cell nests (*white arrow*).

- Acinic Cell Carcinoma
  - Similar to normal product without ducks
  - Is a tumor of solid blue serrous acinar cells
  - hallmark: cytoplasmic blue granules
  - subtypes: cystic, microcystic, solid
  - invasive with pushing borders (not cells)

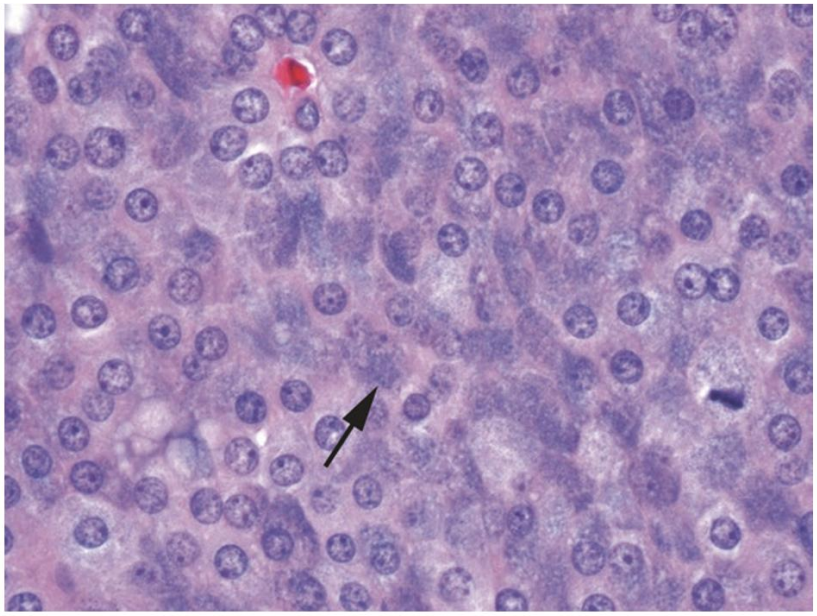


FIGURE 25.7. Acinic cell, solid pattern. The cells in acinic cell carcinoma replicate those of serous acini, with blue granular cytoplasm (*arrow*).

Breast Like Cancers of the Salivary Gland

- Secretory Carcinoma
  - Very similar to secretory carcinoma of the breast
  - Microcystic pattern …kinda looks like thyroid to me
  - Mammaglobin and S100 +ve (which is unique)
  - Should not have cytoplasmic mucin (unlike mucoepidermoid carcinoma)
  - Nuclei are uniform and well spaced

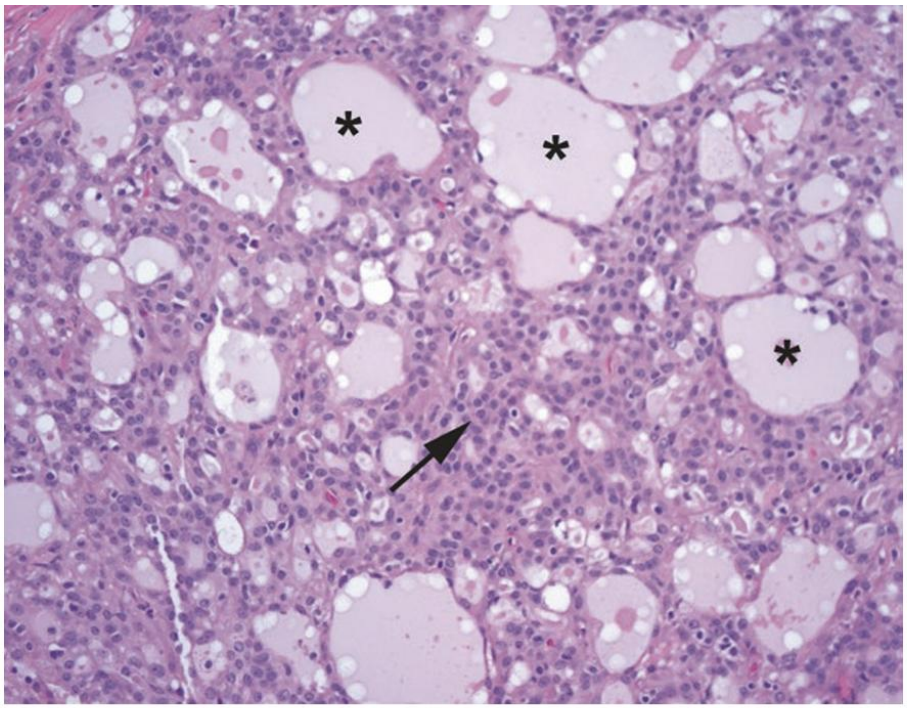


FIGURE 25.8. Secretory carcinoma. The cells are pink (*arrow*) and lack the telltale blue granules of acinic cell. The microcystic pattern, in which cells appear to be pushed apart by expanding pockets of fluid (*asterisks*), is typical. Compare these microcysts to the sharp cribriform spaces in adenoid cystic carcinoma (see Figure 25.6).

- Salivary Duct Carcinoma
  - Aggressive
  - Usually in males
  - Androgen positive IHC
  - Mimics DCIS if intraductal
    - cribriform or comedo forms
  - Arises from pleomorphic adenoma

Polymorphous AdenoCarcinoma

- Polymorphous AdenoCarcinoma
  - Almost exclusive to intraoral, minor salivary glands (lip and palate)
  - Looks like an infiltrative pleomorphic adenoma
    - Infiltration can be in spiralling tendrils or like in ILC
  - Can be cribriform, like Adenoid cystic carcinoma, but only 1 cell type

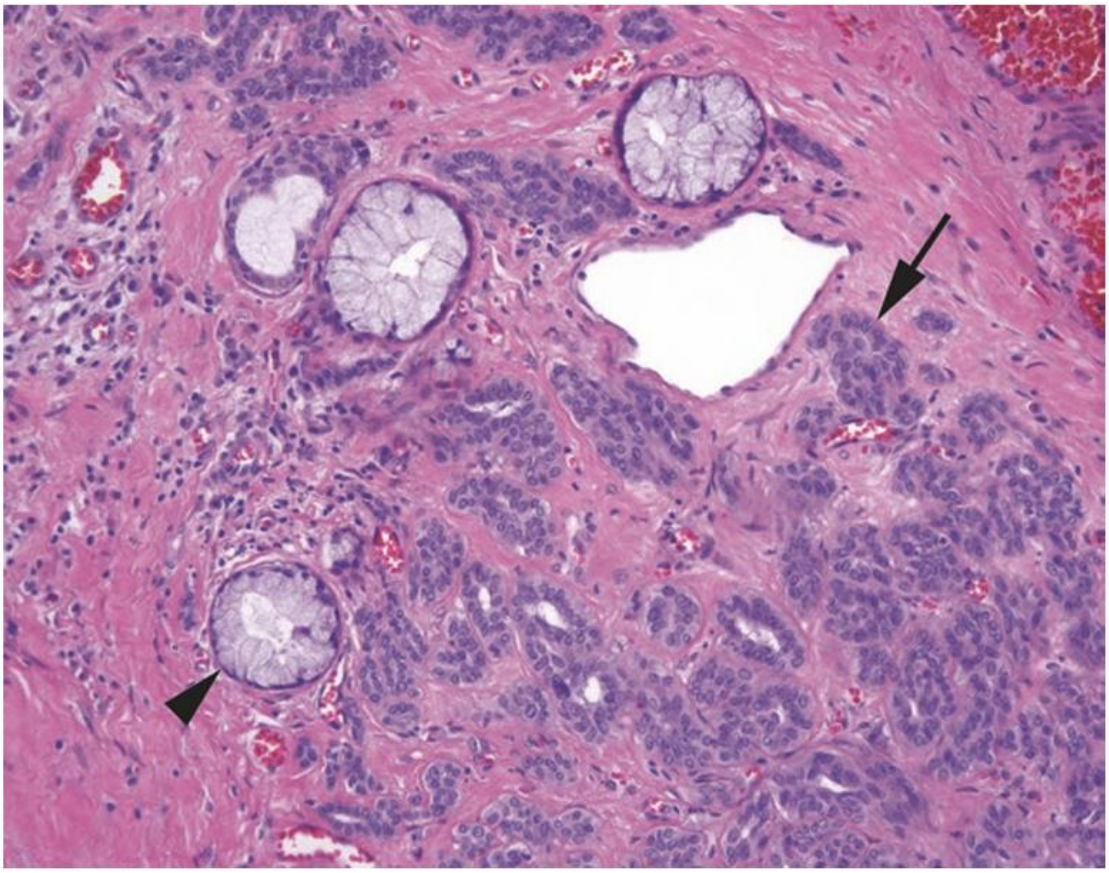


FIGURE 25.9. Polymorphous adenocarcinoma. Small tubules of bland cells (*arrow*) creep between benign mucinous glands (*arrowhead*). On high power, these infiltrative cells resemble those of the pleomorphic adenoma, but unlike that benign tumor, the polymorphous adenocarcinoma infiltrates surrounding tissues. It may also invade as single-file lines, like lobular breast carcinoma.

Chapter 26 **– Neuroendocrine Neoplasms**

Neuro → because they neuroendocrine cells store their secretory products in granules which resemble synaptic vesicles. (not they have no structural processes)
Endocrine → because they secrete things (albeit, paracrine not by synapse)
Neuroendocrine Markers → chromogranin, synaptophysin, CD56 (neural cell adhesion molecule) and maybe INSM1

TABLE 26.1. Major neuroendocrine cell types and corresponding neoplasms.

Location	Neuroendocrine cell type (secreted product)	Corresponding neoplasm	Cytokeratin expression
Intestine and appendix	EC cell (serotonin); D, L cells; others	WD-NET	Positive
Gastric fundus	ECL cell (histamine)	WD-NET	Positive
Gastric antrum, duodenum	G cell (gastrin)	WD-NET	Positive
Lung	Kulchitsky cell	Carcinoid	Positive
Pancreatic islets of Langerhans	α-Cell (insulin) β-Cell (glucagon) δ-Cell (somatostatin)	WD-NET	Positive
Thyroid	C cell (calcitonin)	Medullary carcinoma	Positive
Skin	Merkel cell	Merkel cell carcinoma	Positive
Anterior pituitary	Acidophil (PRL, GH) Basophil (ACTH, TSH, FSH/LH)	Pituitary neoplasms	Positive
Parathyroid	Parathyroid cells (PTH)	Parathyroid neoplasms	Positive
Adrenal medulla and paraganglia	Sympathetic neural cells (epinephrine, norepinephrine)	Pheochromocytoma Paraganglioma	Negative
Adrenal medulla and other sites	Neuroblast (catecholamines, variable)	Neuroblastoma	Negative

ACTH adrenocorticotropic hormone, *EC* enterochromaffin, *ECL* enterochromaffin-like, *FSH* follicle-stimulating hormone, *GH* growth hormone, *LH* luteinizing hormone, *PRL* prolactin, *PTH* parathyroid hormone, *WD-NET* well-differentiated neuroendocrine tumor (carcinoid)

Expression of various hormones in neuroendocrine tumors is not site specific for the origin of the hormone(s). ie "*just because it makes glucagon doesn't mean its from pancreas"*

Neuroendocrine Morphology

- Neuroendocrine Cytology
  - Nuclear monotony/uniformity
  - Finely speckled chromatin, "S&P", without prominent nucleoli
  - Cytoplasmic granularity (neurosecretory granules) which are variably present/absent
- Neuroendocrine Architecture
  - Prominent vasculature
  - Formation of
    - Nests (→ Normal in Adrenal medulla. nesting is called Organoid pattern)

- Rosettes (→ Normal in developing neural tube)
- Ribbons/trabeculae (→ normal in the islets of Langerhans)

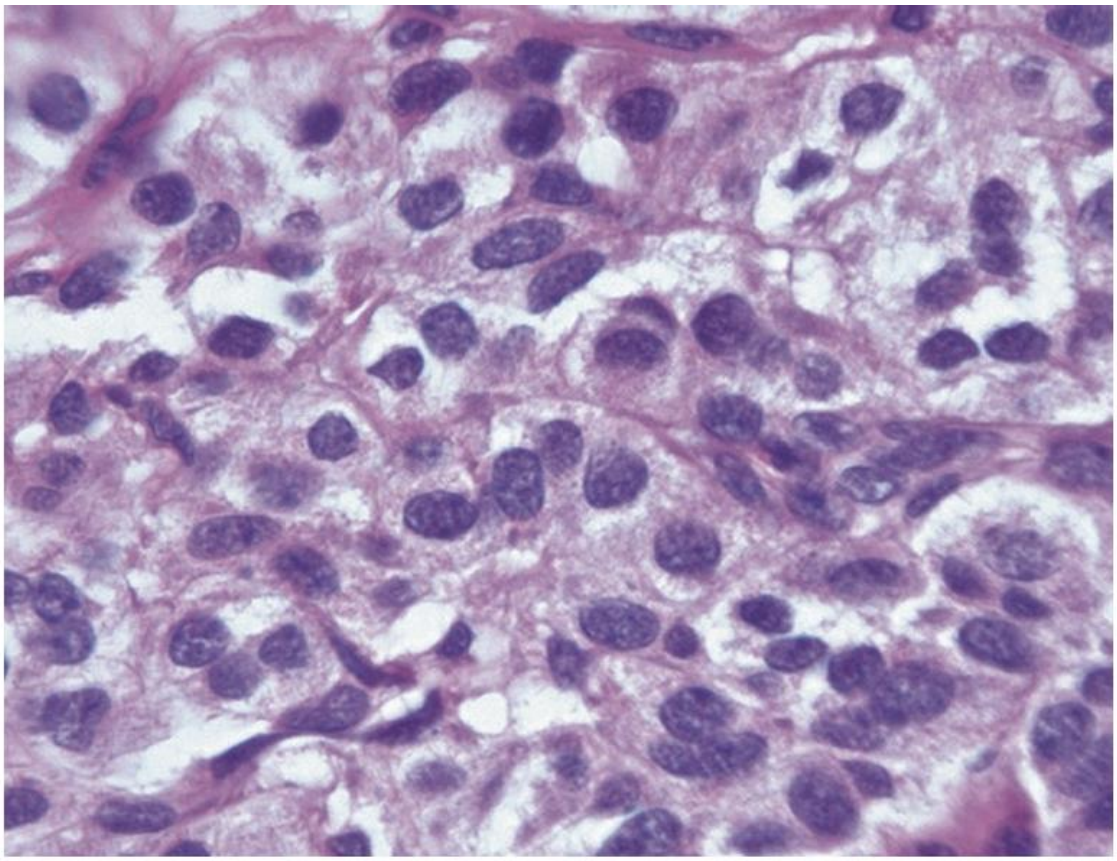


FIGURE 26.1. Classic neuroendocrine nuclei, with smooth *oval* nuclear borders, chromatin that is finely speckled throughout ("salt and pepper"), and no nucleoli.

Terminology & Grading

- NENs = NETs + NECs
- NETs comprise two groups, The "truly neural" group and the endoderm derived "epithelial" group.
  - Respectively, the (pheochromocytomas/paragangliomas) group and (carcinoid, pancreatic NET, small cell, others) group
  - Truly neural → cytokeratin negative
  - Epithelial → positive for cytokeratin except in ~20% of lung carcinoids
- Grading
  - Small- and Large-cell Neuroendocrine Carcinomas are graded as grade 3 by definition
  - Highly proliferative WD-NET is graded as grade 3 as well
  - WD-NETs do NOT progress to NECs
    - Inclusion of WD-NETs and NECs in the same grading system is misleading as they are completely separate diseases and one does not progress to the other

Table 26.2. Corresponding categories and grading criteria for thoracic vs. gastro-entero-pancreatic neuroendocrine neoplasms.

Grade	Gastro-entero-pancreatic	Lung and thymus
Low	WD-NET, grade 1 <2 mits/10 HPF and <3% Ki67	Typical carcinoid <2 mits/10 HPF and no necrosis
Intermediate	WD-NET, grade 2 2–20 mits/10 HPF and/or 3–20% Ki67	Atypical carcinoid 2–10 mits/10 HPF and/or necrosis
High	WD-NET, grade 3[a] >20 mits/HPF and/or >20% Ki67 Small cell and large cell neuroendocrine carcinoma	Stay tuned (category of carcinoids with elevated proliferation rate is starting to emerge) Small cell and large cell neuroendocrine carcinoma

HPF high-power fields, *WD-NET* well-differentiated neuroendocrine tumor

[a]Note: Poorly differentiated neuroendocrine carcinomas (small cell and large cell) are always grade 3

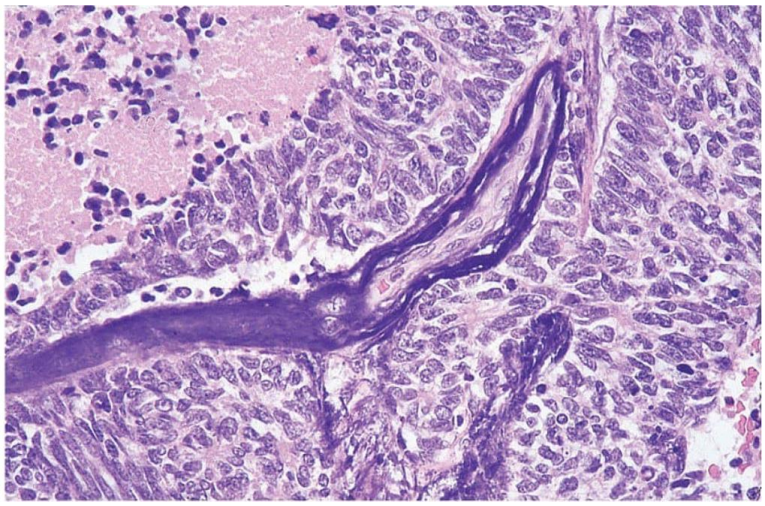
➢

Well-Differentiated Neuroendocrine Tumours (eg Lung Carcinoid)

- ➢ Examples
  - Formerly named bowel carcinoids,
  - Formerly named pancreatic endocrine neoplasms
  - Lung Carcinoids
- ➢ WD-NET family
  - Have all these cytologic features of neuroendocrine tumors mentioned above along with plasmacytoid cytology
  - Architecture can be nests, rosettes, ribbons or trabeculae
  - may occasionally develop pleomorphism or random nuclear atypia (aka *neuroendocrine-type atypia*)
- ➢ Neuroendocrine-type atypia
  - Large nuclei with bizarre shapes
  - smudgy chromatin
  - This atypia is degenerative in nature, likely due to slow growth rate, and is not a feature of high-grade malignancy

Poorly-Differentiated Neuroendocrine tumours (eg Small Cell Carcinoma)

- ❖ Small cell carcinoma
  - Diagnosis not based purely on size, but nuclei for SCC generally are ≤3 lymphocytes in size
  - Fine speckled chromatin
  - Chromatin is very dark, may obscure S&P look
  - No prominent nucleoli
  - Nuclear molding
  - high NCR
  - Numerous mitosis and apoptotic bodies



- Azzopardi effect
- Nests, trabeculae, rosettes focal in resections
- Sometimes Small CC can stain negative for chromogranin and synaptophysin
- Teaching is if the H&E is required these are not required for the DX, provided you exclude the mimics of
    - Lymphoma
    - Basaloid SCC
    - SRBCT

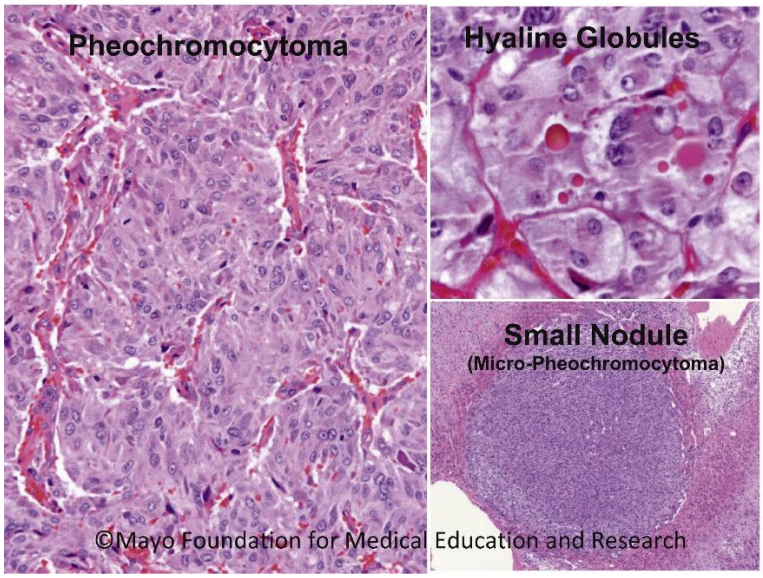
Select Other Neuroendocrine Neoplasms

- Merkel Cell Carcinoma of the Skin
    - Mimic small cell carcinoma
        - nuclear molding, crush artifact, necrosis, numerous mitosis and apoptotic bodies
    - need IHC to distinguish from Small Cell
        - +ve: CK20, Merkel cell viral protein, narrow filament
        - -ve: TTF-1
            - Small cell is opposite staining
- Medullary Carcinoma of Thyroid
    - Hyperchromasia may hide speckled chromatin
    - Amyloid
    - forms large cellular islands
    - common to see plasmacytoid morphology (eccentric nuclei)
    - Calcitonin positive (follicular adenoma is not)
- Large Cell Neuroendocrine Carcinoma
    - doesn't have the usual nuclear features, instead has is vesicular chromatin with prominent nucleoli
    - neuroendocrine Casa fication isn't due to the architecture (rosettes, nesting, nuclear palisading) and expression of neuroendocrine IHC
    - most common in the lung but can occur anywhere
- Pheochromocytoma / Paraganglioma
    - Nuclei
        - Some have traditional NET nuclei

- Uniform come around and finally speckled
- Others have neuron like nuclei
  - large nuclei & single prominent nucleoli
- Nuclear pseudoinclusions (cytoplasmic invaginations) are present in 30% of cases
- Random nuclear atypia is common

❖ Cytoplasm → Granular, amphophilic, abundant

➢ Hyaline globules are often present
- If present, distinguishes pheochromocytoma from other adrenal neoplasms



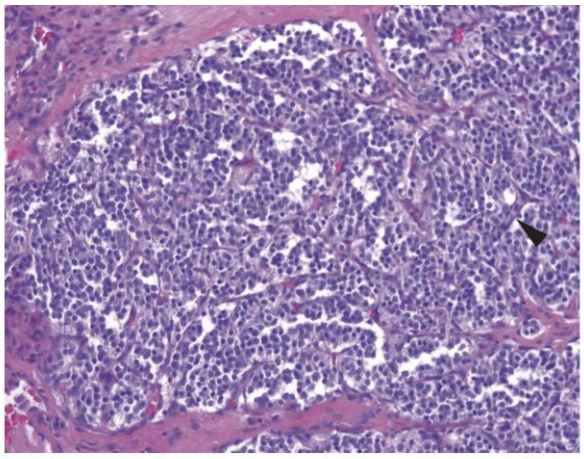


FIGURE 29.23. Paraganglioma. Fibrovascular septa (*arrowhead*) divide the neoplasm into small balls of cells (the "zellballen" pattern). The cells have small, perfectly round nuclei with neuroendocrine chromatin. Despite the paraganglioma's classification as an extra-adrenal pheochromocytoma, it resembles the carcinoid tumor more closely than the pheochromocytoma.

➢ Classic architecture is the nested pattern / "Zellballen" pattern
- Fibrovascular septa divide the neoplasm into small balls of cells "zellballen"
- Nests are surrounded by sustentacular cells which can be highlighted by S100
  - Sustentacular cells are not visible on H&E
  - ∴ S100 is positive at the periphery

➢ Always cytokeratin +ve

<u>In addition to the tumours above, you can also see Neuroendocrine differentiation in:</u>

1. Occult differentiation of a completely non-neuroendocrine tumour
2. de novo Small cell carcinoma as a component of another type of carcinoma
   a. Confers worse prognosis and has specific therapy
3. Small cell carcinoma developing from a formerly non-small cell as a result of treatment evasion
   a. Often in prostate after ADT or lung adenocarcinoma after EGFR

Chapter 27 **– Brain & Meninges**

Chapter 28 **– Skin**

Chapter 29 **– Soft tissue**

Chapter 30 **– Bone**

Chapter 31 – A Primer on Immunostains

Chapter 32 **– So You Want to Get a Job**