Lecture (1)

ATELECTASIS (COLLAPSE)

Atelectasis, also known as collapse, **is loss of lung volume caused by *inadequate expansion of air spaces***. It results in shunting of inadequately oxygenated blood from pulmonary arteries into veins, thus giving rise to a ventilation perfusion imbalance and hypoxia. On the basis of the underlying mechanism or the distribution of alveolar collapse, atelectasis is classified into **three forms** (Fig.).

- ***Resorption atelectasis***. Resorption atelectasis occurs when an obstruction prevents air from reaching distal airways. The air already present gradually becomes absorbed, and alveolar collapse follows. Depending on the level of airway obstruction, an entire lung, a complete lobe, or one or more segments may be involved. The most common cause of resorption collapse is obstruction of a bronchus by a mucous or mucopurulent plug. This frequently occurs postoperatively but also may complicate bronchial asthma, bronchiectasis, chronic bronchitis, tumor, or foreign body aspiration, particularly in children.

- ***Compression atelectasis***. Compression atelectasis (sometimes called *passive* or *relaxation atelectasis*) is usually associated with accumulation of fluid, blood, or air within the pleural cavity, which mechanically collapses the adjacent lung. This is a frequent occurrence with pleural effusion, caused most commonly by congestive heart failure (CHF). Leakage of air into the pleural cavity (pneumothorax) also leads to compression atelectasis. Basal atelectasis resulting from the elevated

position of the diaphragm commonly occurs in bedridden patients, in patients with ascites, and during and after surgery.

• ***Contraction atelectasis***. Contraction (or *cicatrization*) atelectasis occurs when either local or generalized fibrotic changes in the lung or pleura hamper expansion and increase elastic recoil during expiration.

Atelectasis (except when caused by contraction) is potentially reversible and should be treated promptly to prevent hypoxemia and superimposed infection of the collapsed lung.

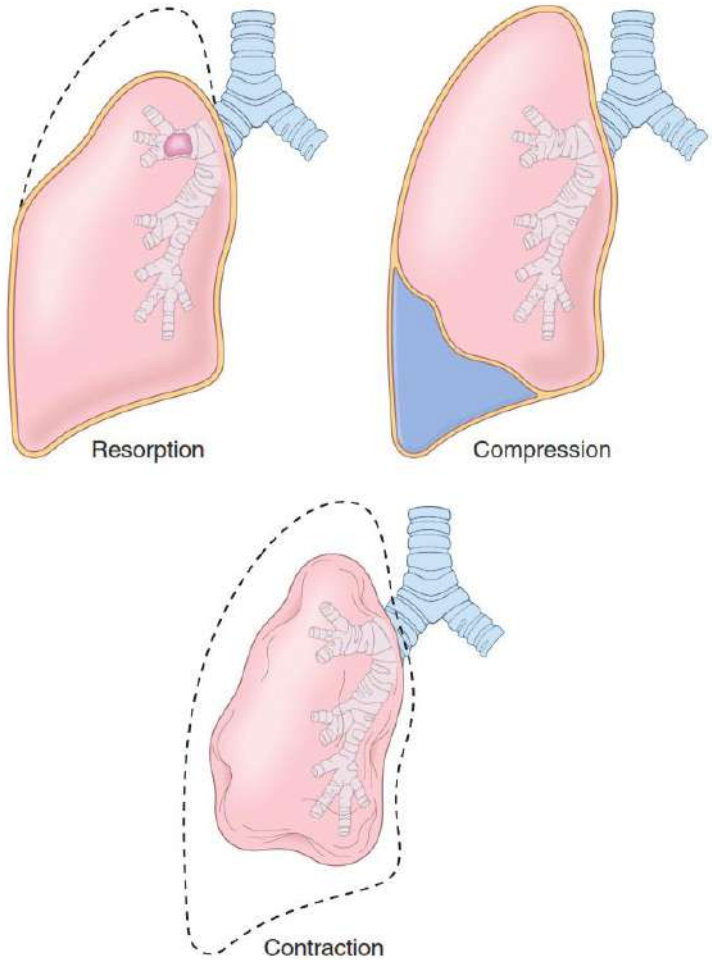


Figure Various forms of acquired atelectasis.

Reference: Robbins Basic Pathology (10th edition) .2018

What are the symptoms?

The symptoms of atelectasis range from nonexistent to very serious, depending on how much of your lung is affected and how fast it develops. If only a few alveoli are involved or it happens slowly, you might not have any symptoms.

When atelectasis involves a lot of alveoli or comes on quickly, it's hard to get enough oxygen to your blood. Having low blood oxygen can lead to:

- trouble breathing
- sharp chest pain, especially when taking a deep breath or coughing
- rapid breathing
- increased heart rate
- blue-colored skin, lips, fingernails, or toenails

Sometimes, pneumonia develops in the affected part of your lung. When this happens, you can have the typical symptoms of pneumonia, such as a productive cough, fever, and chest pain.

What causes it?

Many things can cause atelectasis. Depending on the cause, atelectasis is categorized as either **obstructive or non-obstructive**.

Causes of obstructive atelectasis

Obstructive atelectasis happens when a blockage develops in one of your airways. This prevents air from getting to your alveoli, so they collapse. Things that can block your airway include:

- inhalation of a foreign object, such as a small toy or small pieces of food, in an airway
- mucus plug (buildup of mucus) in an airway
- tumor growing within an airway
- tumor in the lung tissue that presses on the airway

Causes of non-obstructive atelectasis

Non-obstructive atelectasis refers to any type of atelectasis that isn't caused by some kind of blockage in your airways.

Common causes of non-obstructive atelectasis include:

- *Surgery*
- *Pleural effusion*
- *Pneumothorax*
- *Lung scarring*
- *Chest tumor*
- *Surfactant deficiency*

How is it diagnosed?

To diagnose atelectasis, your doctor starts by reviewing your medical history. They look for any previous lung conditions you've had or any recent surgeries.

Next, they try to get a better idea of how well your lungs are working. To do this, they might:

- **check your blood oxygen level** with an oximeter, a small device that fits on the end of your finger
- **take blood from an artery,** usually in your wrist, and check its oxygen, carbon dioxide levels, and blood chemistry with a blood gas test
- **order a chest X-ray**
- **order a CT scan** to check for infections or blockages, such as a tumor in your lung or airway
- **perform a bronchoscopy**, which involves inserting a camera, located on the end of a thin, flexible tube, through your nose or mouth and into your lungs

Lecture (2)

Acute Lung injury

An **acute lung injury (ALI)** is a condition in which the lungs are not able to provide the body with sufficient amounts of oxygen, resulting in **hypoexmia** (low levels of oxygen in the blood). ALI can occur at any age and is usually the result of **pneumonia** (lung inflammation caused by bacterial or viral infection, in which the air sacs fill with pus and may become solid.

Inflammation may affect

a- Both lungs (double pneumonia),
b- One lung (single pneumonia), or
c- Only certain lobes (lobar pneumonia)

Sepsis (widespread infection in the body), **direct trauma to the lungs**, **burns**, **near drowning**, and or any other situation that can cause inflammation or damage to the lungs.

Damage to the lungs can result in inflammation, and this inflammation can spread to the **alveoli**, decreasing the lung's ability to provide oxygen to the body and resulting in ALI. As ALI progresses, it can develop into **acute respiratory distress syndrome (ARDS)**, which is very similar to ALI but is associated with greater difficulty breathing and a lower concentration of oxygen in the blood.

The term ***acute lung injury*** encompasses a spectrum of pulmonary lesions (endothelial and epithelial), which can be initiated by numerous conditions.

Clinically, acute lung injury manifests as:

1. The acute onset of dyspnea (difficult breathing),
2. Decreased arterial oxygen pressure (hypoxemia) an abnormally low concentration of oxygen in the blood.
3. Development of bilateral pulmonary infiltrates on radiographs, all in the absence of clinical evidence of primary left-sided heart failure.

Diagnosis

Diagnosis of ALI is accomplished by using a couple different diagnostic techniques. Since ALI is associated with decreased levels of oxygen in the blood, measuring oxygen levels in the blood can help diagnose this condition. For example, the oxygenation of the blood can be measured by calculating the ratio of partial pressure of the oxygen in the arteries to the concentration of inhaled oxygen (PaO2/FiO2). The ratio is usually around 500 for healthy lungs, and a ratio of less than 300 is associated with ALI.

CT scans, x-rays, and ultrasound images of the lungs can also help diagnose ALI. ALI often results in fluid accumulating in the lungs, and this accumulation of fluid usually shows up as opaque in CT scans, x-rays, and ultrasounds.

CLINICAL AND PATHOLOGIC OVERVIEW OF HISTOLOGIC PATTERNS ASSOCIATED WITH ALI/ARDS

1- **Diffuse Alveolar Damage**: Diffuse alveolar damage is the classic histologic manifestation of ALI/ARDS. Clinically, patients present with severe hypoxemia and typically require mechanical ventilation. Histologically, DAD is typically divided into 2 phases: the acute/exudative phase and the organizing/proliferative phase. Hyaline membranes are composed of cellular and proteinaceous debris and appear as dense, glassy eosinophilic membranes lining the alveolar ducts and alveolar spaces (Fig.1)

2- **Acute Fibrinous and Organizing Pneumonia**: A histologic pattern associated with acute lung injury in which the alveolar spaces are filled with organizing fibrin balls, in contrast to the true hyaline membranes found in DAD. The process may be patchy or relatively diffuse. The alveolar septa may show mild interstitial widening or lymphocytic infiltrates, but significant eosinophils or neutrophils should not be seen (Fig. 2).

3- **Eosinophilic Pneumonia**.
Eosinophilic pneumonia in general is characterized by intra-alveolar fibrin and macrophages in variable proportions, admixed with numerous eosinophils. Eosinophils may also be present in the interstitial tissue and eosinophilic microabscess formation may be observed. In some cases, eosinophils may infiltrate blood vessel walls. In AEP, these features may be present to varying degrees with the additional finding of hyaline membrane formation identical to that seen in the acute phase of DAD (Figure 3).

4- **Diffuse Alveolar Hemorrhage With Capillaritis** : (Diffuse alveolar hemorrhage (DAH) refers to a clinical syndrome resulting from injury to the alveolar capillaries, arterioles, and venules leading to red blood cell accumulation in the distal air spaces).
Capillaritis is evidenced by neutrophils within the alveolar septa with resultant vascular necrosis (Figure 4).

5- **Organizing Pneumonia**: Organizing pneumonia (OP) is an interstitial lung disease, and OP patients present with characteristic clinical, radiological, and histological findings. Histopathologically, there are buds of granulation tissue, which are called Masson bodies and consist of exudative materials including connective tissue components, fibrin, and fibroblasts, in the alveolar ducts and alveoli). (Figure 5).

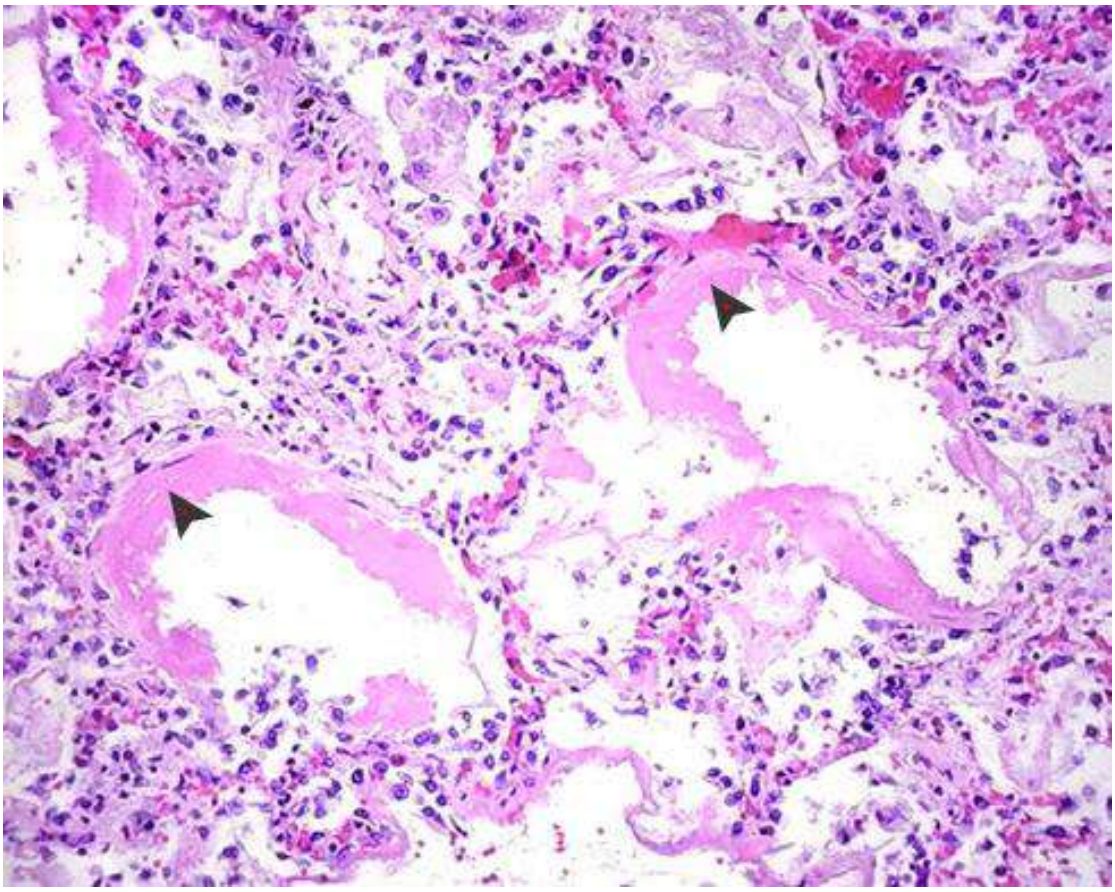


Fig. 1. Diffuse alveolar damage in acute lung injury and acute respiratory distress syndrome. Some alveoli are collapsed; others are distended. Many are lined by bright pink hyaline membranes *(arrow).*

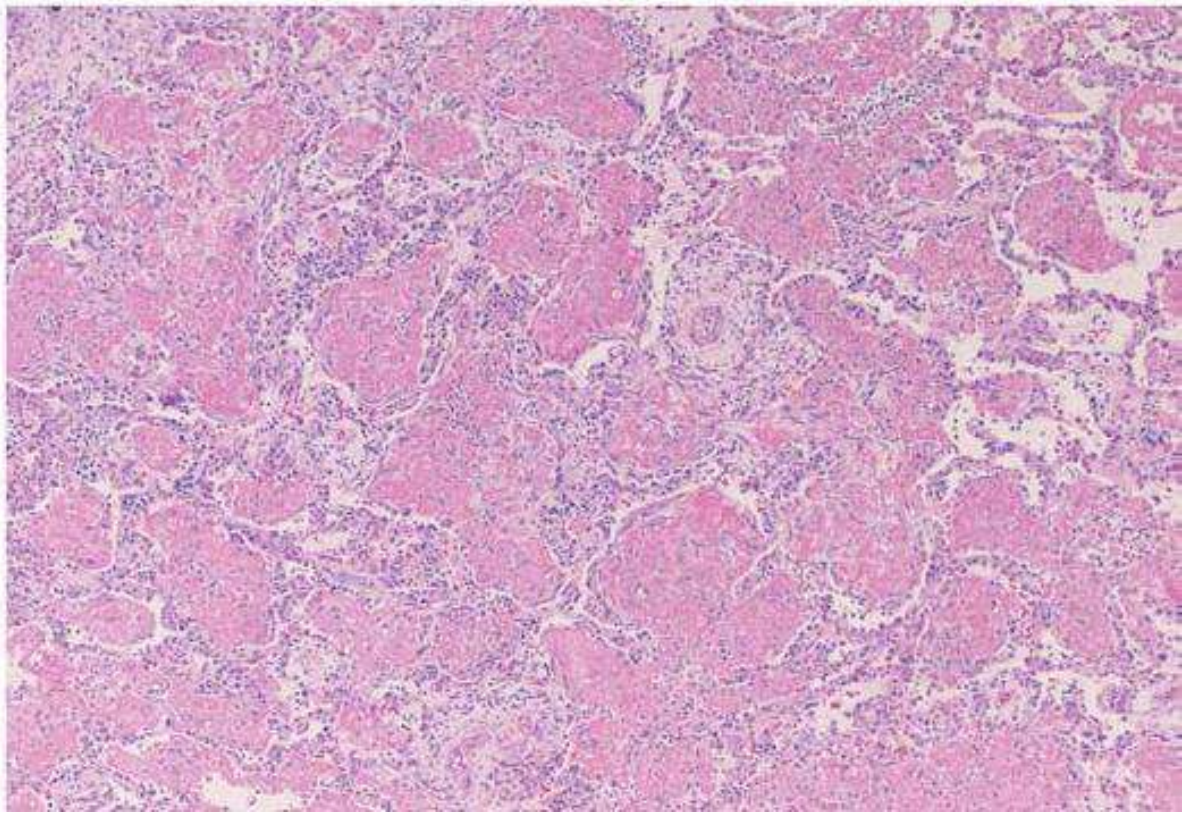


Fig. 2. Acute fibrinous and organizing pneumonia is characterized by intra-alveolar fibrin balls in contrast to classic hyaline membranes

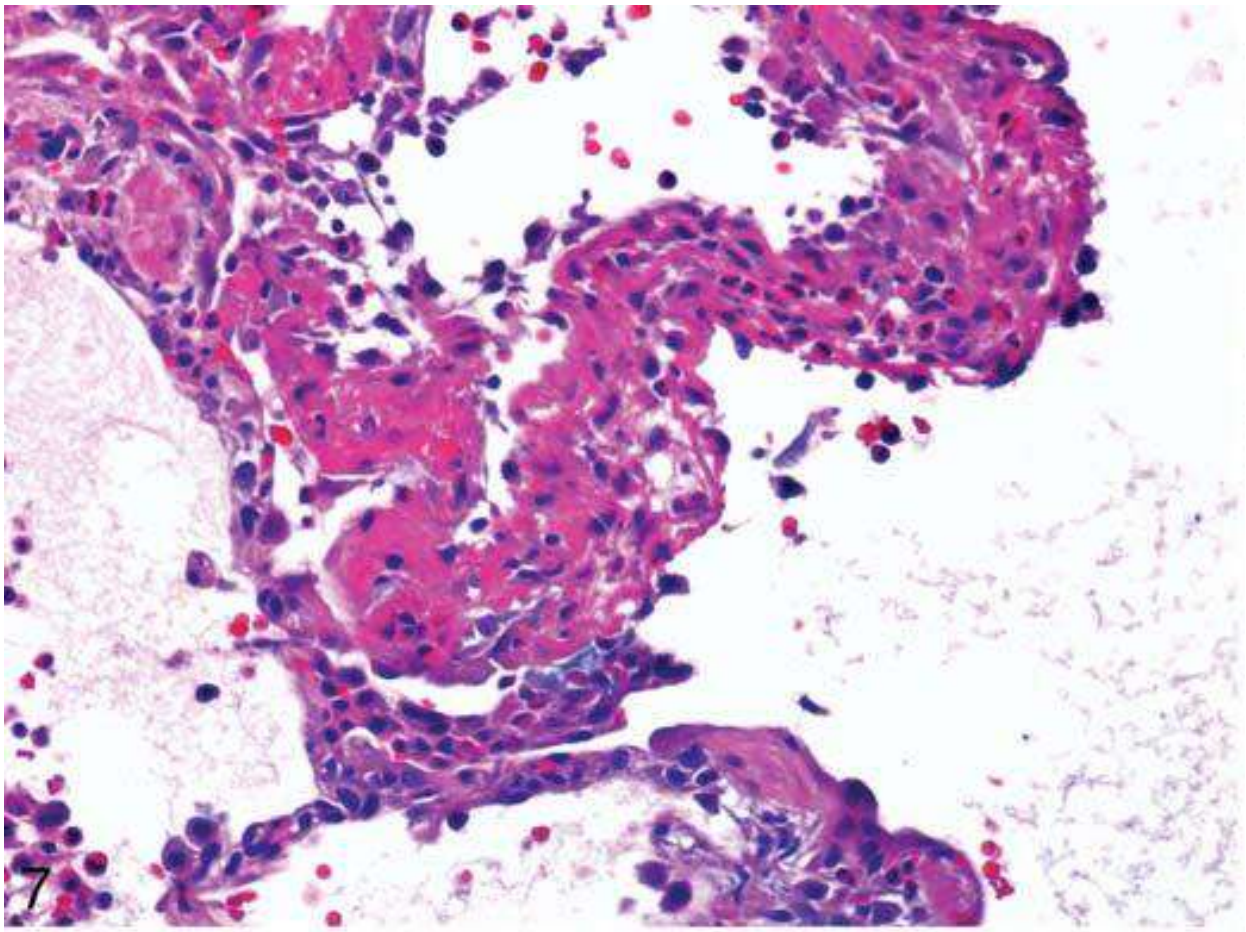


Fig. 3. Acute eosinophilic pneumonia. Hyaline membranes, essentially identical to those seen in diffuse alveolar damage, are present but contain numerous eosinophils on closer inspection.

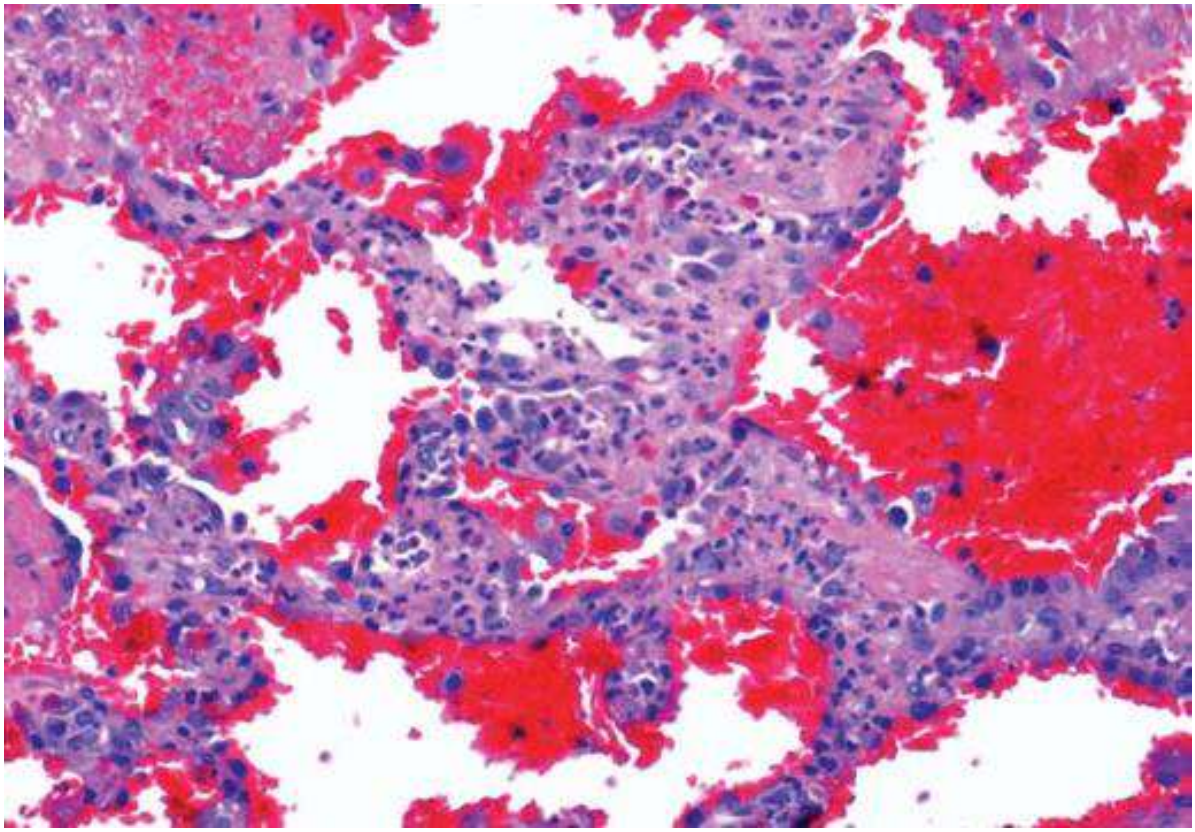


Fig. 4. Neutrophilic capillaritis is characterized by prominent neutrophils within the alveolar septa. Necrosis of the capillary may be difficult to visualize, but neutrophilic debris, as seen here, or fibrin thrombi suggest underlying vascular damage

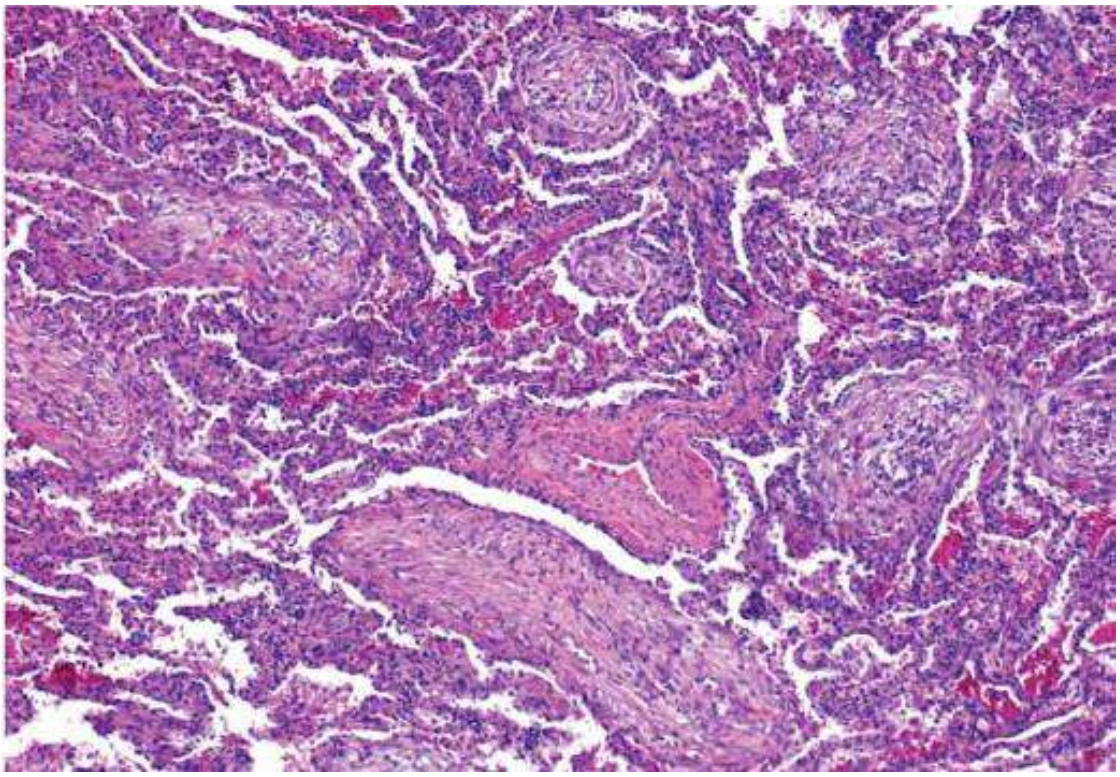


Fig.5. Organizing pneumonia is characterized by patchy intra-alveolar organizing fibroblastic tissue. The surrounding alveolar septa contain mild lymphocytic infiltrates

Lecture (3)

Chronic bronchitis and Pulmonary Embolism

Chronic bronchitis is common among cigarette smokers and urban dwellers in smog-ridden cities; some studies indicate that 20% to 25% of men in the 40- to 65-year-old age group have the disease. The diagnosis of chronic bronchitis is made on clinical grounds: it is defined by ***the presence of a persistent productive cough for at least 3 consecutive months in at least 2 consecutive years.*** In early stages of the disease, the productive cough raises mucoid sputum, but airflow is not obstructed. Some patients with chronic bronchitis may demonstrate hyperresponsive airways with intermittent bronchospasm and wheezing. A subset of bronchitic patients, especially heavy smokers, develop chronic outflow obstruction, usually with associated emphysema.

PATHOGENESIS:

The distinctive feature of chronic bronchitis is **hypersecretion of mucus,** beginning in the large airways. Although the single most important cause is cigarette smoking, other air pollutants, such as sulfur dioxide and nitrogen dioxide, may contribute. These environmental irritants induce **hypertrophy of mucous glands** in the **trachea and main bronchi**, leading to a marked increase in mucin-secreting goblet cells in the surface epithelium of smaller bronchi and bronchioles.

In addition, these irritants cause inflammation with infiltration of CD8+ lymphocytes, macrophages, and neutrophils. In contrast with asthma, **there are no eosinophils in chronic bronchitis**.

MORPHOLOGY

The mucosal lining of the larger airways usually is **hyperemic (**is the increase of blood flow to different tissues in the body) **and swollen** by edema fluid. It often is covered by a layer of mucinous **secretions.** The smaller bronchi and bronchioles also may be filled with similar secretions.

On histologic examination, the diagnostic feature of chronic bronchitis in the trachea and larger bronchi is **enlargement of the mucus-secreting glands** (Fig. 1).

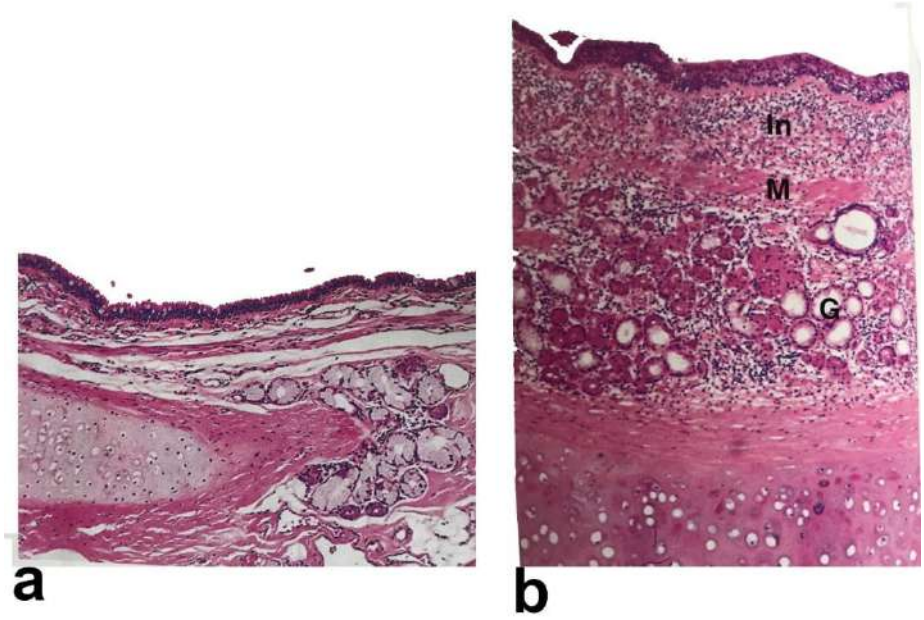


Figure 1. (a).Normal bronchial wall, (b). Bronchial wall in chronic bronchitis

Three factors contribute to the increased thickness of the bronchial wall:

1. Infiltration of the submucosa by chronic inflammatory cells (**In**).
2. Marked hypertrophy of mucosal smooth muscle (**M**).
3. Marked hyperplasia of the mucous glands (**G**). with production mucus.

The magnitude of the increase in size is assessed by the ratio of the thickness of the submucosal gland layer to that of the bronchial wall (the **Reid index** normally 0.4). Inflammatory cells, largely mononuclear but sometimes admixed with neutrophils, are frequently present in variable density in the bronchial mucosa.

"The Reid Index is a mathematical relationship that exists in a human bronchus section observed under the microscope. It is defined as ratio between the thickness of the submucosal mucus secreting glands and the thickness between the epithelium and cartilage that covers the bronchi."

Chronic bronchiolitis (small airway disease),

Characterized by goblet cell metaplasia, mucous plugging, inflammation, and fibrosis, is also present. In the most severe cases, there may be complete obliteration of the lumen as a consequence of fibrosis (bronchiolitis obliterans). It is the submucosal fibrosis that leads to

luminal narrowing and airway obstruction. Changes of emphysema often co-exist.

Pulmonary Embolism, Hemorrhage, and Infarction:

When a blood clot gets caught in one of the arteries that go from the heart to the lungs, it's called a pulmonary embolism (PE). The clot blocks the normal flow of blood.

This blockage can cause serious problems, like damage to your lungs and low oxygen levels in your blood. The lack of oxygen can harm other organs in your body, too. If the clot is big or the artery is clogged by many smaller clots, a pulmonary embolism can be fatal.

Pulmonary embolisms usually travel to the lungs from a deep vein in the legs (deep vein thrombosis DVT). These clots develop when the blood can't flow freely through the legs because r body is still for a long time, during a long flight or drive. It might also happen if patient on bed rest after surgery or illness.

Clinical Features

The clinical consequences of pulmonary thromboembolism are summarized as follows:

- Most pulmonary emboli (60% to 80%) are clinically silent because they are small; the embolic mass is rapidly removed by fibrinolytic activity, and the bronchial circulation sustains the viability of the affected lung parenchyma until this is accomplished.
- In 5% of cases, sudden death, acute right-sided heart failure, or cardiovascular collapse (shock) may occur typically when more than 60% of the total pulmonary vasculature is obstructed by a large embolus or multiple simultaneous small emboli.
- Obstruction of relatively small to medium pulmonary branches (10% to 15% of cases) that behave as end arteries causes pulmonary infarction when some element of circulatory insufficiency is present. Typically, persons who sustain such infarction manifest dyspnea.
- In a small but significant subset of patients (accounting for less than 3% of cases), recurrent multiple emboli lead to pulmonary hypertension, chronic right-sided heart strain and, in time, pulmonary vascular sclerosis with progressively worsening dyspnea.

Lecture (4)

Lung Tumors

Although lungs frequently are the site of metastases from cancers arising in extrathoracic organs, primary lung cancer is also a common disease. Roughly 95% of primary lung tumors are carcinomas; the remaining 5% constitute a miscellaneous group that includes carcinoids, mesenchymal malignancies (e.g., fibrosarcomas, leiomyomas), lymphomas, and a few benign lesions.

The most common benign tumor is a spherical, small (3 to 4 cm), discrete "hamartoma" that often shows up as a so-called coin lesion on chest radiographs. It consists mainly of mature cartilage, but this is often admixed with fat, fibrous tissue, and blood vessels in various proportions. Clonal cytogenic abnormalities have been demonstrated, indicating that it is a benign neoplasm, although still commonly referred to as hamartoma.

Carcinomas:

Carcinoma of the lung (also known as "lung cancer") is without doubt the single most important cause of cancer related deaths in industrialized countries. It has long held this position among males in the United States, accounting for about one third of cancer deaths in men, and has become the leading cause of cancer deaths in women as well.

Histologic Classification of Malignant Epithelial Lung Tumors

1. Adenocarcinoma
   Acinar, papillary, micropapillary, solid, lepidic predominant, mucinous subtypes
2. Squamous cell carcinoma
3. Large cell carcinoma
   Large cell neuroendocrine carcinoma
4. Small cell carcinoma
   Combined small cell carcinoma
5. Adenosquamous carcinoma
6. Carcinomas with pleomorphic, sarcomatoid, or sarcomatous elements
   Spindle cell carcinoma
   Giant cell carcinoma
7. Carcinoid tumor
   Typical, atypical
8. Carcinomas of salivary gland type
9. Unclassified carcinoma

The four major histologic types of carcinomas of the lung are adenocarcinoma, squamous cell carcinoma, small cell carcinoma, and large cell carcinoma. In some cases there is a combination of histologic patterns (e.g., small cell carcinoma and adenocarcinoma). Of these, squamous cell and small cell carcinomas show the strongest association with smoking.

Morphology

Carcinomas of the lung begin as small mucosal lesions that typically are firm and gray-white. They may arise as intraluminal masses, invade the bronchial mucosa, or form large bulky masses pushing into adjacent lung parenchyma. Some large masses undergo cavitation secondary to central necrosis or develop focal areas of hemorrhage. Finally, these tumors may extend to the pleura, invade the pleural cavity and chest wall, and spread to adjacent intrathoracic structures. More distant spread can occur by way of the lymphatics or the hematogenous route.

Clinical Course

Carcinomas of the lung are silent, insidious lesions that in many cases have spread so as to be unrespectable before they produce symptoms. In some instances, chronic cough and expectoration call attention to still localized, respectable disease. By the time hoarseness, chest pain, superior vena cava syndrome, pericardial or pleural effusion, or persistent segmental atelectasis or pneumonitis makes its appearance, the prognosis is grim. Too often, the tumor presents with symptoms emanating from metastatic spread to the brain (mental or neurologic changes), liver (hepatomegaly), or bones (pain). Although the adrenals may be nearly obliterated by metastatic disease, adrenal insufficiency (Addison disease) is uncommon, because islands of cortical cells sufficient to maintain adrenal function usually persist.

Lecture (5)

Disorders of the kidney

Disorders of the kidney arise from a wide range of pathological causes, many of which are common in other organ systems (e.g. infections, tumors, drug reactions, vascular disorders). However, the kidney is unusual in that it is much more prone to immunological disorders than most other organs and is of the greatest importance in the progress of the common metabolic disease, diabetes mellitus. Vascular diseases such as hypertension and vasculitis may also have profound effects on renal function. Disorders of the kidney can be conveniently divided into categories according to which structural component of the kidney is primarily affected:

- **Glomerulus Disorders**
- **Tubules and interstitium Disorders**
- **Blood vessels Disorders**

GLOMERULAR Structure

Disorders affecting the glomerulus encompass a clinically important category of renal disease. The glomerulus consists of an anastomosing network of capillaries invested by two layers of epithelium. The visceral epithelium (composed of podocytes) is an intrinsic part of the capillary wall, whereas the parietal epithelium lines Bowman space (urinary space), the cavity in which plasma ultrafiltrate first collects. The glomerular capillary wall is the filtration unit and consists of the following structures (Figs. 1 and 2):

- A thin layer of fenestrated *endothelial cells,* each fenestra being 70 to 100 nm in diameter.
- A *glomerular basement membrane* (GBM) with a thick, electron-dense central layer, the ***lamina densa,*** and thinner, electron-lucent peripheral layers, the ***lamina rara interna*** and ***lamina rara externa***. The GBM consists of collagen (mostly type IV), laminin, polyanionic proteoglycans, fibronectin, and several other glycoproteins
- *Podocytes,* which are structurally complex cells that possess interdigitating processes embedded in and adherent to the lamina rara externa of the basement membrane. Adjacent *foot processes* are separated by 20- to 30-nm-wide *filtration*

slits, which are bridged by a thin slit diaphragm composed in large part of nephrin.

- The glomerular tuft is supported by *mesangial cells* lying between the capillaries. Basement membrane–like mesangial matrix forms a meshwork through which the mesangial cells are scattered. These cells, of mesenchymal origin, are contractile and are capable of proliferation, of laying down collagen and other matrix components, and of secreting a number of biologically active mediators.

Glomerular function

Normally, the glomerular filtration system is extraordinarily permeable to water and small solutes and almost completely impermeable to molecules of the size and molecular charge of albumin (a 70,000-kDa protein). This selective permeability, called glomerular barrier function, discriminates among protein molecules according to their size (the larger, the less permeable), their charge (the more cationic, the more permeable), and their configuration. The characteristics of the normal barrier depend on the complex structure of the capillary wall, the integrity of the GBM, and the many anionic molecules present within the wall, including the acidic proteoglycans of the GBM and the sialoglycoproteins of epithelial and endothelial cell coats.

The podocyte is also crucial to the maintenance of glomerular barrier function. Podocyte slit diaphragms are important diffusion barriers for plasma proteins, and podocytes are also largely responsible for synthesis of GBM components.

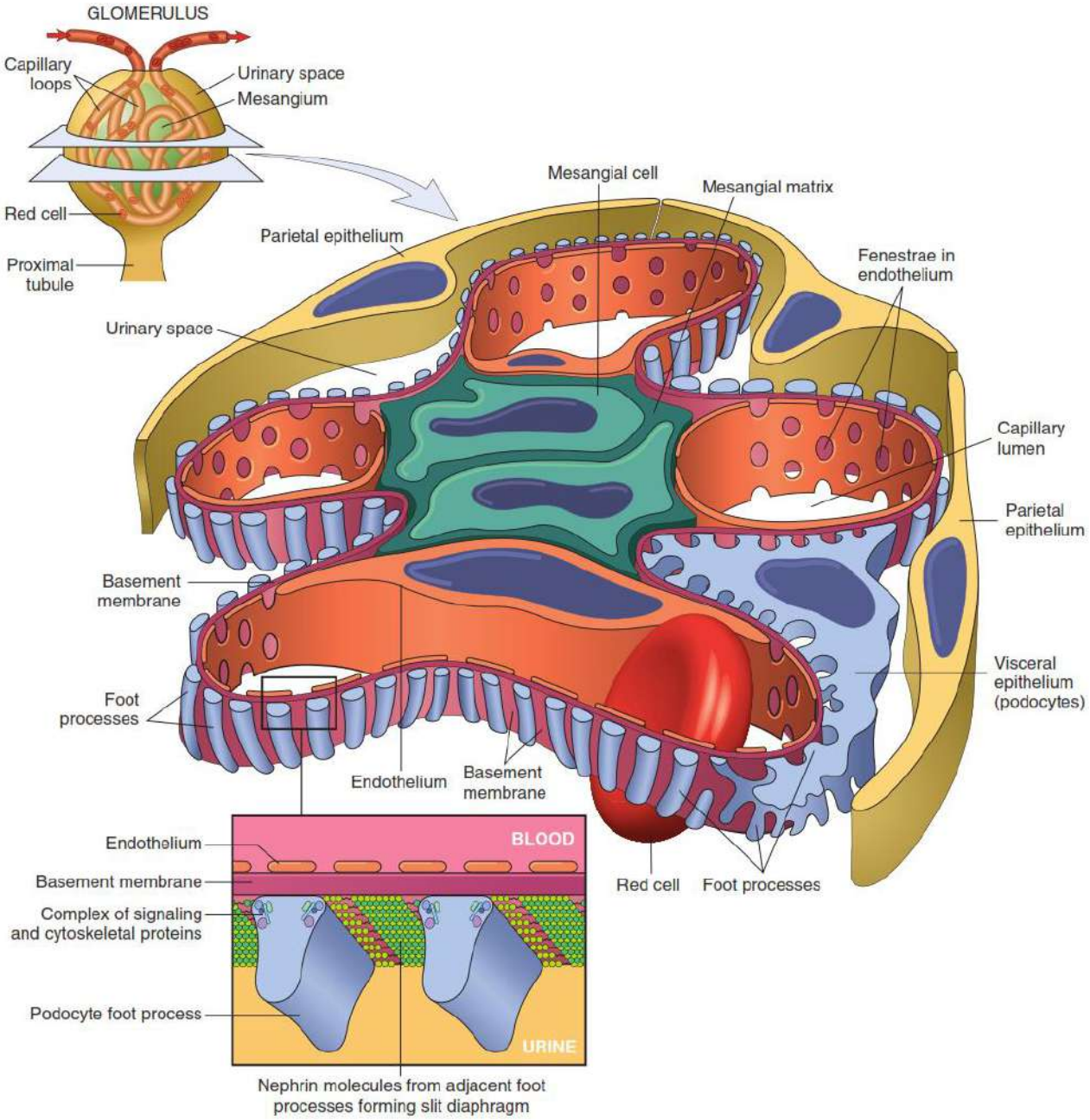


Figure 1 Schematic diagram of a lobe of a normal glomerulus.

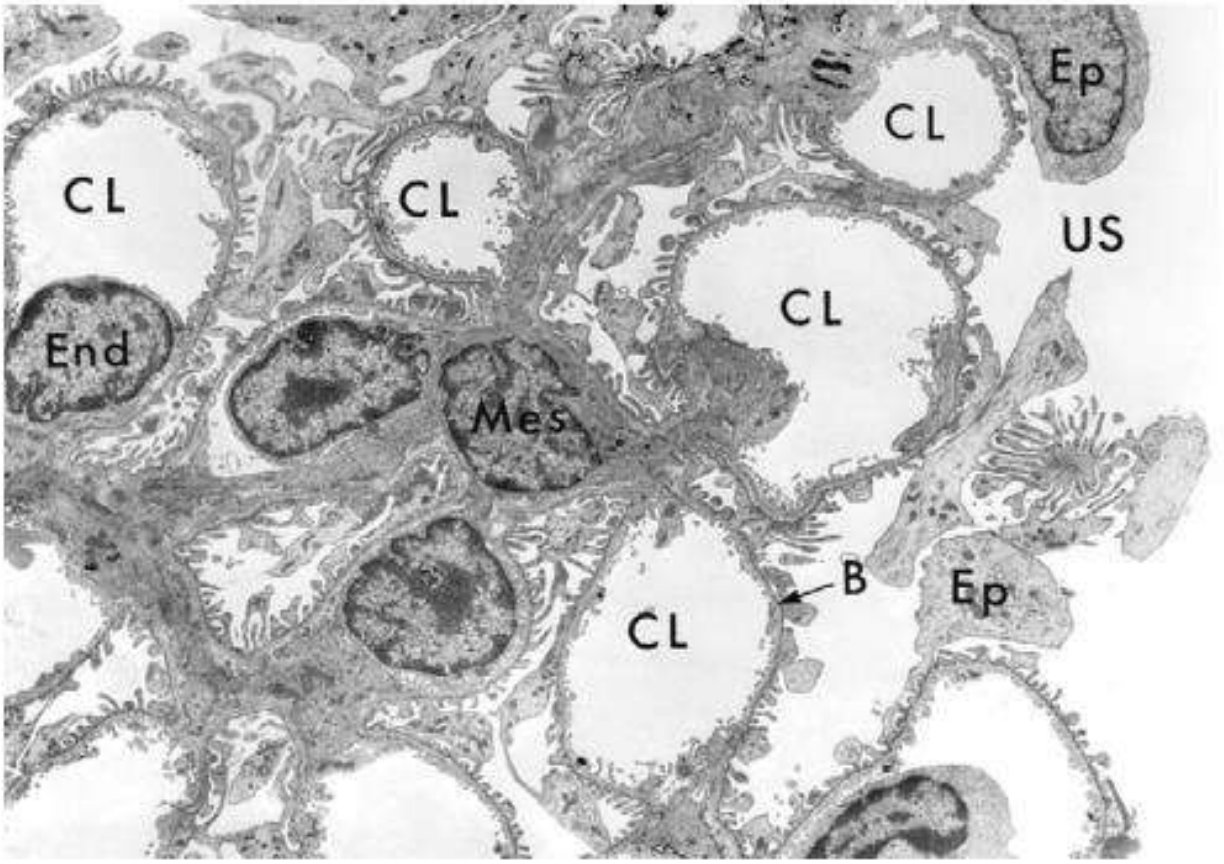


Figure 2 Low-power electron micrograph of rat glomerulus. B, basement membrane; CL, capillary lumen; End, endothelium; Ep, visceral epithelial cells (podocytes) with foot processes; Mes, mesangium; US, urinary space.

GLOMERULAR DISEASES

Glomeruli may be injured by diverse mechanisms and in the course of a number of systemic diseases. Immunologically mediated diseases such as systemic lupus erythematosus, vascular disorders such as hypertension and hemolytic uremic syndrome, metabolic diseases such as diabetes mellitus, and some purely hereditary conditions such as **Alport syndrome** often affect the glomerulus. These are termed **secondary glomerular diseases** to differentiate them from those in which the kidney is the only or predominant organ involved. The latter constitute the various types of **primary glomerular diseases**.

Table 1 Glomerular Diseases

Primary glomerular diseases
Minimal-change disease
Focal segmental glomerulosclerosis
Membranous nephropathy
Acute post infectious GN
Membranoproliferative GN
IgA nephropathy
Glomerulopathies Secondary to Systemic Diseases
Lupus nephritis (systemic lupus erythematosus)
Diabetic nephropathy
Amyloidosis
GN secondary to multiple myeloma
Goodpasture syndrome
Microscopic polyangiitis
Wegener granulomatosis
Henoch-Schonlein purpura
Bacterial endocarditis–related GN
Thrombotic microangiopathy
Hereditary Disorders
Alport syndrome
Fabry disease
Podocyte/slit-diaphragm protein mutations

Mechanisms of Glomerular Injury and Disease

Although little is known about the etiologic agents or triggering events, it is clear that immune mechanisms underlie most types of primary glomerular diseases and many of the secondary glomerular diseases. Under experimental conditions, glomerulonephritis (GN) can be readily induced by antibodies, and deposits of immunoglobulins, often with various components of complement, are found frequently in patients with GN. Cell-mediated immune mechanisms may also play a role in certain glomerular diseases.

Two forms of antibody-associated injury have been established:

1. Injury resulting from deposition of soluble circulating antigen-antibody complexes in the glomerulus and

2. Injury by antibodies reacting in situ within the glomerulus, either with insoluble fixed (intrinsic) glomerular antigens or with molecules planted within the glomerulus. In addition, antibodies directed against glomerular cell components may cause glomerular injury. These pathways are not mutually exclusive, and in humans all may contribute to injury.

Symptoms of glomerular disease

The signs and symptoms of glomerular disease include

1. **Albuminuria:** large amounts of protein in the urine.
2. **Hematuria**: blood in the urine
3. **Reduced glomerular filtration rate**: inefficient filtering of wastes from the blood
4. **hypoproteinemia**: low blood protein
5. **Edema**: swelling in parts of the body

Some of these symptoms have signs, or visible manifestations

- Proteinuria may cause foamy urine
- Blood may cause the urine to be pink or cola-colored.
- Edema may be obvious in hands and ankles, especially at the end of the day, or around the eyes when awakening in the morning, for example.

Lecture (6)

Nephrotic and Nephritic Syndromes

According to glomerular structure, we discussed in the previous lecture, we can reviewed the following:

Any molecule that has to inter the tubules, it needs to pass through the:

- ❑ Charge barrier
- ❑ Physical(size)barrier

I. **<4nm: all charged molecules pass**
II. **4-8nm: only Positive charge pass**
III. **>8nm: no filtration**

Glomeronephritis classified as:

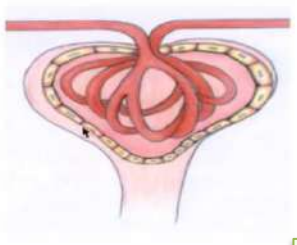
- Hereditary (e.g Alport's and Fabry's syndromes)
- Primary (most common): disease process originates from glomerulus.
- Secondary to systemic diseases e.g Diabetes mellitus , bacterial endocarditis

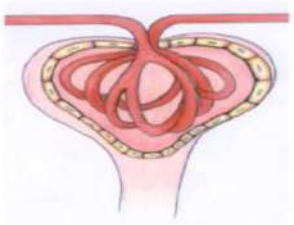
If the patient develop Glomeronephritis, it presents:

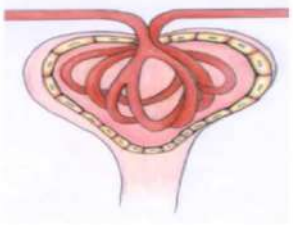
- ❖ Asymptomatic Proteinuria
- ❖ Asymptomatic haematouria
- ❖ Nephrotic Syndrome
- ❖ Nephritic Syndrome
- ❖ Rapidly progressive GN
- ❖ Chronic Kidney disease(CKD

Proteinuria

Mild GN injury **Moderate GN injury** **Sever GN injury**







Selective Albuminuria

Non-Selective Proteinuria (Albumin, globulin), Less than 3.5g/day **(Sub-nephrotic range)**

Non-Selective Proteinuria more than 3.5g/day **(Nephrotic range)**

Proteinuria clinical notes

- **Types:**
  a) Selective : only albumin
  b) Non-selective: albumin and globulin.
     i. sub-nephrotic range: <3.5 nm/day
     ii. nephrotic range: >3.5 nm/day

- Patients complain of frothy urine because of high protein level
- Other symptoms appear

Nephrotic Syndrome: is clinic-pathological condition which develops when there is significant damage to the glomeruli leading to proteinuria >3.5g/day

Nephrotic Syndrome define as clinic-pathological conditions which develop when there is significant damage to the glomeruli which is leading to heavy proteinuria (>3.5mg/day) and that is associated with **Hypoproteinemia**, Generalized **Edema and even Lipiduria.**

The nephrotic syndrome refers to a clinical complex that includes

- ***Massive proteinuria,*** with daily protein loss in the urine of 3.5 g or more in adults.
- ***Hypoalbuminemia,*** with plasma albumin levels less than 3 g/dL.
- ***Generalized edema,*** the most obvious clinical manifestation
- ***Hyperlipidemia*** *and* ***lipiduria****.*

The nephrotic syndrome has diverse causes that share a common pathophysiology (Table 1). In all there is a derangement in the capillary walls of the glomeruli that results in increased permeability to plasma proteins. Any increased permeability resulting from either structural or physicochemical alterations in the GBM allows protein to escape from the plasma into the glomerular filtrate.

Table (1) Causes of Nephrotic Syndrome

Cause	Prevalence (100%)	
	Children	Adult
Primary Glomerular Disease		
Membranous nephropathy	*5*	30
Minimal-change disease	*65*	10
Focal segmental glomerulosclerosis	10	35
Membranoproliferative glomerulonephritis	10	10
IgA nephropathy and others	10	15
Systemic Diseases with Renal Manifestations		
Diabetes mellitus		
Amyloidosis		
Systemic lupus erythematosus		
Ingestion of drugs (gold, penicillamine, “street heroin”)		
Infections (malaria, syphilis, hepatitis B, HIV infection)		
Malignancy (carcinoma, melanoma)		
Miscellaneous (bee sting allergy, hereditary nephritis		

With long-standing or extremely heavy proteinuria, serum albumin is decreased, resulting in hypoalbuminemia and a drop in plasma colloid osmotic pressure.

The resulting decrease in intravascular volume and renal blood flow triggers increased release of renin from renal juxtaglomerular cells. Renin in turn stimulates the angiotensin-aldosterone axis, which promotes the retention of salt and water by the kidney. This tendency is exacerbated by

reductions in the cardiac secretion of natriuretic factors. In the face of continuing proteinuria, these alterations further aggravate the edema and if unchecked may lead to the development of generalized edema (termed ***anasarca***). At the onset, there is little or no **azotemia**, **hematuria**, or **hypertension**.

The genesis of the hyperlipidemia is more obscure. Pre uretic factors. In the face of continuing proteinuria, these alterations further aggravate the edema and if unchecked may lead to the development of generalized edema (termed *anasarca*). At the onset, there is little or no azotemia, hematuria, or hypertension.

The genesis of the hyperlipidemia is more obscure. Presumably, hypoalbuminemia triggers increased synthesis of lipoproteins in the liver or massive proteinuria causes loss of an inhibitor of their synthesis. There is also abnormal transport of circulating lipid particles and impairment of peripheral breakdown of lipoproteins. The lipiduria, in turn, reflects the increased permeability of the GBM to lipoproteins.

The most important of the primary glomerular lesions that characteristically lead to the nephrotic syndrome are focal segmental glomerulosclerosis and minimal-change disease. The latter is more important in children; the former is more important in adults.

The nephrotic syndrome is also commonly seen in two other primary kidney diseases, membranous nephropathy and membranoproliferative glomerulonephritis, and as a complication of the systemic disease diabetes mellitus.

By contrast, *nephritic syndrome* is characterized by the following:

- *Hematuria* (red cells and red cell casts in urine)
- *Proteinuria* (usually in the subnephrotic range) with or without edema
- *Azotemia*
- *Hypertension*
- Asymptomatic hematuria
- *Acute kidney injury*
- Rapidly progressive glomerulonephritis (RPGN)
- *Chronic kidney disease*
- End-stage renal disease (ESRD)
- Urinary tract infection (UTI)
- *Nephrolithiasis*

The nephritic syndrome usually has an acute onset and is caused by inflammatory lesions of glomeruli.

The lesions that cause the nephritic syndrome have in common proliferation of the cells within the glomeruli, often accompanied by an infiltrate of leukocytes. The inflammatory reaction injures the capillary walls, permitting blood to pass into the urine, and induces hemodynamic changes that lead to a reduction in the GFR. The reduced GFR is manifested clinically by oliguria, fluid retention, and azotemia. Hypertension probably is a result of both the fluid retention and augmented renin release from the ischemic kidneys. The acute nephritic syndrome may be caused by primary glomerular diseases, such as postinfectious glomerulonephritis (GN) and various forms of crescentic GN, or as a result of systemic disorders such as systemic lupus erythematosus.

**Asymptomatic hematuria* or nonnephrotic proteinuria or a combination of the two is the typical clinical presentation of IgA nephropathy, Alport syndrome, or mild forms or early presentations of other glomerular diseases.

- *Rapidly progressive glomerulonephritis (RPGN*) results in rapid loss of renal function in a few days or weeks, typically in the setting of nephritic syndrome. The characteristic histologic finding associated with RPGN is the presence of crescents (crescentic GN). Rapidly progressive glomerulonephritis is a clinical syndrome and not a specific etiologic form of GN. If untreated, it leads to death from renal failure within a period of weeks to months.
- *Acute kidney injury* refers to abrupt onset of renal dysfunction characterized by an acute increase in serum creatinine often associated with oliguria or anuria (decreased or no urine flow). It can result from glomerular injury (such as rapidly progressive GN), interstitial injury, vascular injury (such as thrombotic microangiopathy), or acute tubular epithelial cell injury.
- *Chronic kidney disease* results from progressive scarring in the kidney of any cause. It is characterized by various metabolic and electrolyte abnormalities such as hyperphosphatemia, dyslipidemia, and metabolic acidosis. However, it is often asymptomatic until the most advanced stages, when symptoms of uremia develop.
- *End-stage renal disease (ESRD)* is irreversible loss of renal function requiring dialysis or transplantation typically due to severe progressive scarring in the kidney from any cause.

- *Urinary tract infection (UTI)* is characterized by bacteriuria and pyuria (bacteria and leukocytes in the urine). It may be symptomatic or asymptomatic, and may affect the kidney (pyelonephritis) or the bladder (cystitis) only.
- *Nephrolithiasis* refers to formation of stones in the collecting system and x is manifested by renal colic and hematuria (without red cell casts).

IgA nephropathy (Berger disease)

This condition usually affects children and young adults and begins as an episode of gross hematuria that occurs within 1 or 2 days of a nonspecific upper respiratory tract infection. Typically, the hematuria lasts several days and then subsides, only to recur every few months. It may be associated with local pain. *IgA nephropathy is one of the most common causes of recurrent microscopic or gross hematuria and is the most common glomerular disease revealed by renal biopsy worldwide.*

The hallmark of the disease is the deposition of IgA in the mesangium. Some workers have considered IgA nephropathy to be a localized variant of *Henoch-Schonlein purpura,* also characterized by IgA deposition in the mesangium. In contrast with IgA nephropathy, which is purely a renal disorder, Henoch-Schonlein purpura is a systemic syndrome involving the skin (purpuric rash), gastrointestinal tract (abdominal pain), joints (arthritis), and kidneys.

Lecture (7)

Tumors of the Kidney

Many types of benign and malignant tumors occur in the urinary tract. In general, benign tumors such as small (less than 0.5 cm in diameter) cortical papillary adenomas, which are found in 40% of adults, have no clinical significance.

The most common malignant tumor of the kidney is **renal cell carcinoma**, followed in frequency by **nephroblastoma (Wilms tumor)** and by primary tumors of the calyces and pelvis. Other types of renal cancer are rare. *Tumors of the lower urinary tract are about twice as common as renal cell carcinomas.*

Oncocytoma

Oncocytoma, a benign tumor that arises from the intercalated cells of collecting ducts, represents about 10% of renal tumors. These tumors are associated with genetic changes loss of chromosomes 1, 14, and Y—that distinguish them from other renal neoplasms. Oncocytomas are histologically characterized by a **plethora of mitochondria**, providing the basis for their tan color and their finely granular eosinophilic cytoplasm that is seen histologically. **A central stellate scar**, which is another feature of oncocytomas, provides a characteristic appearance on imaging studies.

Renal Cell Carcinoma

Renal cell carcinomas are derived from the renal tubular epithelium and hence they are located predominantly in the cortex. These tumors represent 80% to 85% of all primary malignant tumors of the kidney and 2% to 3% of all cancers in adults.

Tumors of the Kidney

Carcinomas of the kidney are most common from the sixth to seventh decades, and men are affected about twice as commonly as women. The risk of developing these tumors is higher in smokers, hypertensive or obese patients, and those who have had occupational exposure to cadmium. The risk of developing renal cell cancer is increased 30-fold in persons who acquire polycystic disease as a complication of chronic dialysis. The role of genetic factors in the causation of these cancers is discussed later on.

Renal cell cancers are classified on the basis of morphology and growth patterns. However, recent advances in the understanding of the genetic basis of renal carcinomas have led to a new classification that takes into account the molecular origins of these tumors. The three most common forms, discussed next, are clear cell carcinoma, papillary renal cell carcinoma, and chromophobe renal carcinoma.

Clear Cell Carcinomas

Clear cell carcinomas are the most common type, accounting for 65% of renal cell cancers. Histologically, they are composed of cells with clear cytoplasm. Although most are sporadic, they also occur in familial forms or in association with von Hippel-Lindau (VHL) disease.

VHL disease is inherited as an autosomal dominant trait and is characterized by predisposition to a variety of neoplasms, but particularly to hemangioblastomas of the cerebellum and retina. Hundreds of bilateral renal cysts and bilateral, often multiple, clear cell carcinomas develop in 40% to 60% of affected persons. Those with VHL syndrome inherit a germline mutation of the *VHL* gene on chromosomal band 3p25 and lose the second allele by somatic mutation. Thus, the loss of both copies of this tumor suppressor gene is a key step in the development of

clear cell carcinoma. The *VHL* gene is also involved in the majority of sporadic clear cell carcinomas.

Papillary Renal Cell Carcinomas

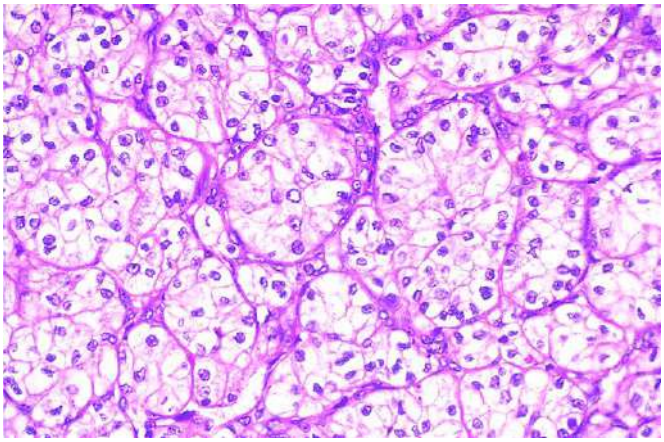
Papillary renal cell carcinomas account for 10% to 15% of all renal cancers. As the name indicates, they show a papillary growth pattern. These tumors are frequently multifocal and bilateral and appear as early-stage tumors.

Like clear cell carcinomas, they occur in familial and sporadic forms, but unlike these tumors, papillary renal cancers are not associated with abnormalities of chromosome 3.

Chromophobe Renal Carcinomas

Chromophobe renal carcinomas are the least common, representing 5% of all renal cell carcinomas. They arise from intercalated cells of collecting ducts. Their name derives from the observation that the tumor cells stain more darkly (i.e., they are less clear) than cells in clear cell carcinomas.

These tumors are unique in having multiple losses of entire chromosomes, including chromosomes 1, 2, 6, 10, 13, 17, and 21. Thus, they show extreme hypodiploidy. Because of multiple losses, the “critical hit” has not been determined. In general, chromophobe renal cancers have a good prognosis.



High-power detail of the clear cell pattern of renal cell carcinoma.

***Wilms Tumor* (*nephroblastoma*)**

Although Wilms tumor occurs infrequently in adults, it is the third most common organ cancer in children younger than 10 years of age. These tumors contain a variety of cell and tissue components, all derived from the mesoderm. Wilms tumor, like retinoblastoma, may arise sporadically or be familial, with the susceptibility to tumorigenesis inherited as an autosomal dominant trait.

Lecture (8)

Cancer of the Oral Cavity and Tongue

The mouth and associated structures may be involved in a wide variety of disease states that may be loosely divided **into three categories**.

First, many systemic diseases, particularly dermatological conditions, exhibit oral manifestations (e.g. *lichen planus, syphilis*).

Second, all oral tissues may be subject to acute or chronic inflammatory states, the most common being dental caries and its sequel periapical abscess formation, and periodontal disease (i.e. inflammation of the gums). Of more general histopathological interest is inflammation of the salivary glands leading to *chronic sialadenitis*.

Third, many benign and malignant tumors may arise in the oral tissues, the most common being **squamous cell carcinomas** of the lips, oral mucosa and tongue. Salivary tumors, both benign and malignant, can arise in both major and minor salivary glands.

Squamous Cell Carcinomas:

Approximately 95% of cancers of the oral cavity are squamous cell carcinomas, with the remainder largely consisting of adenocarcinomas of salivary glands. Squamous cell carcinoma, an aggressive epithelial malignancy, is the sixth most common neoplasm in the world today. Despite numerous advances in treatment, the overall long-term survival rate has remained less than 50% for the past 50 years. This dismal outlook is due to several factors, in large part because oral cancer often is diagnosed at an advanced stage.

Squamous cancers of the oropharynx arise through two distinct pathogenic pathways, one involving exposure to carcinogens, and the other related to infection with high risk variants of human papilloma virus (HPV). Squamous cell carcinoma may arise anywhere in the oral cavity. However, the most common locations are the ventral surface of the tongue, floor of the mouth, lower lip , soft palate, and gingiva.

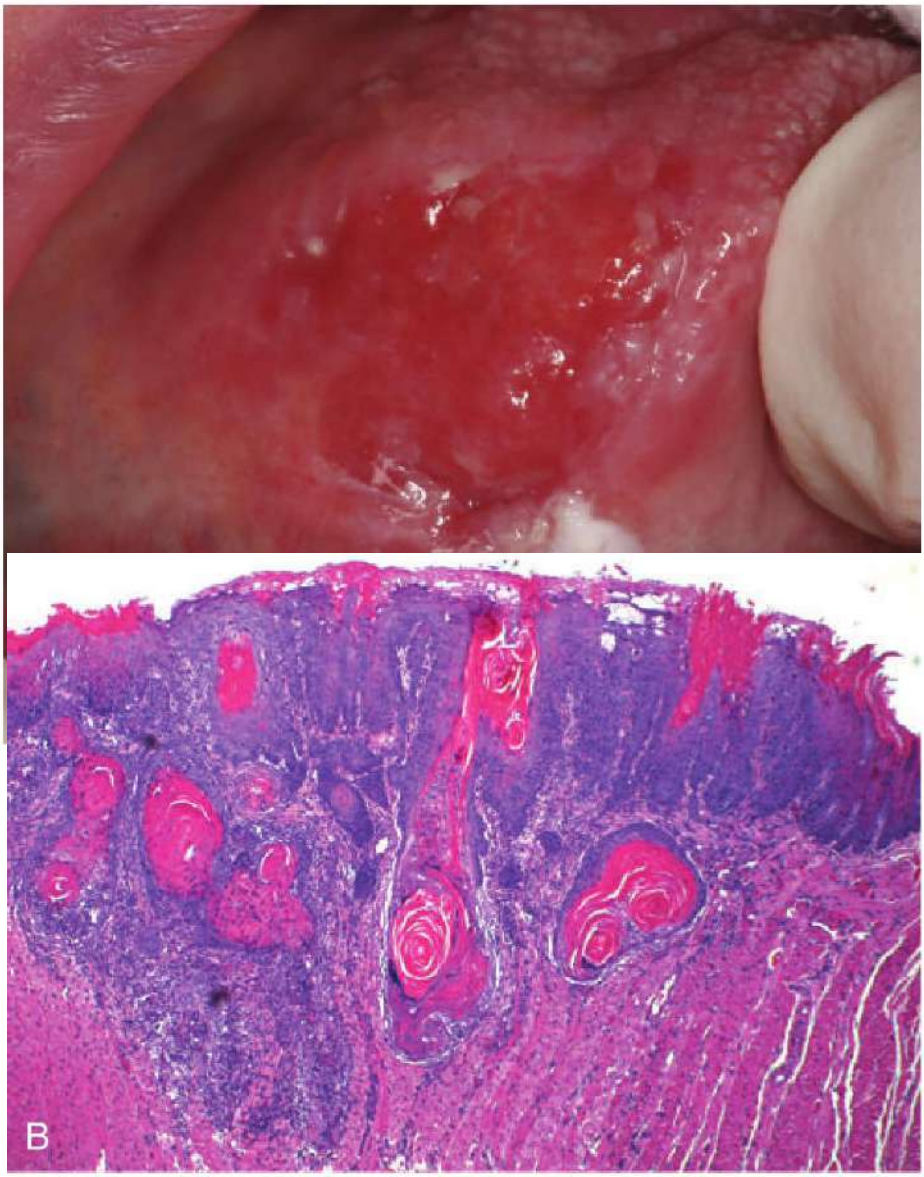


Fig. (1) Oral squamous cell carcinoma.

(A) Gross appearance demonstrating ulceration and induration of the oral mucosa. (B) Histologic appearance demonstrating numerous nests and islands of malignant keratinocytes invading the underlying connective tissue stroma.

Salivary Gland Tumors

Despite their relatively simple morphology, the salivary glands give rise to at least 30 histologically distinct tumors (Table 1). A small number of these neoplasms account for more than 90% of tumors. Overall, salivary gland tumors are relatively uncommon and represent less than 2% of all human tumors. Approximately 65% to 80% arise within the

parotid, 10% in the submandibular gland, and the remainder in the minor salivary glands, including the sublingual glands. Approximately 15% to 30% of tumors in the parotid glands are malignant. By contrast, approximately 40% of submandibular, 50% of minor salivary gland, and 70% to 90% of sublingual tumors are cancerous. Thus, the likelihood that a salivary gland tumor is malignant is inversely proportional, roughly, to the size of the gland.

Salivary gland tumors usually occur in adults, with a slight female predominance, but about 5% occur in children younger than 16 years of age. Whatever the histologic pattern, parotid gland neoplasms produce swelling in front of and below the ear. Benign tumors may be present for months to several years before coming to clinical attention, while cancers more often come to attention promptly, probably because of their more rapid growth. However, there are no reliable criteria to differentiate benign from malignant lesions on clinical grounds, and histopathologic evaluation is essential.

Table 1 Histopathologic Classification and Prevalence of the Most Common Benign and Malignant Salivary Gland Tumors

Benign	Malignant
Pleomorphic adenoma (50%)	Mucoepidermoid carcinoma (15%)
Warthin tumor (5%)	Acinic cell carcinoma (6%)
Oncocytoma (2%)	Adenocarcinoma NOS (6%)
Cystadenoma (2%)	Adenoid cystic carcinoma (4%)
Basal cell adenoma (2%)	Malignant mixed tumor (3%)

Pleomorphic Adenoma

Pleomorphic adenomas are benign tumors that consist of a mixture of ductal (epithelial) and myoepithelial cells, so they exhibit both epithelial and mesenchymal differentiation

Pleomorphic adenomas typically manifest as rounded, well demarcated masses rarely exceeding 6 cm in the

greatest dimension. Although they are encapsulated, in some locations (particularly the palate), the capsule is not fully developed, and expansile growth produces protrusions into the surrounding tissues.

Mucoepidermoid carcinoma

Mucoepidermoid carcinomas are composed of variable mixtures of squamous cells, mucus-secreting cells, and intermediate cells.

Mucoepidermoid carcinomas can grow as large as 8 cm in diameter and, although they are apparently circumscribed, they lack well-defined capsules and often are infiltrative.

Adenocystic carcinoma (MP)

The most common malignant tumor of salivary tissue is the *adenocystic* or *adenoid cystic carcinoma.* This tumor is uncommon in the parotid glands but is seen in the other major glands and in the minor salivary glands. Histologically, it has a characteristic cribriform (sieve-like) appearance owing to the presence of small spaces S in a mass of tightly packed tumor cells. The tumor cells are arranged in clumps and cords separated by a fibrous stroma F which may exhibit a marked degree of hyalinization.

As well as occurring in the major salivary glands, adenocystic carcinomas can arise in the minor or accessory salivary glands of the palate. These tumors are locally invasive and prone to recurrence following surgical excision. Spread to regional lymph nodes is frequent and wide local spread is common, although the rate of growth is often slow. Perineural invasion, which is often extremely painful, is a common feature of this tumor.

Lecture (9)

Esophagus

The esophagus develops from the cranial portion of the foregut. It is a hollow, highly distensible muscular tube that extends from the epiglottis to the gastroesophageal junction, located just above the diaphragm. Acquired diseases of the esophagus run the gamut from lethal cancers to the persistent "heartburn" of gastroesophageal reflux that may be chronic and incapacitating or merely an occasional annoyance.

OBSTRUCTIVE AND VASCULAR DISEASES

Mechanical Obstruction

Atresia, fistulas, and duplications may occur in any part of the gastrointestinal tract. When they involve the esophagus, they are discovered shortly after birth, usually because of regurgitation during feeding. Prompt surgical repair is required. Absence, or agenesis, of the esophagus is extremely rare. Atresia, in which a thin, noncanalized cord replaces a segment of esophagus, is more common.

It occurs most frequently at or near the tracheal bifurcation and usually is associated with a fistula connecting the upper or lower esophageal pouches to a bronchus or the trachea. This abnormal connection can result in aspiration, suffocation, pneumonia, or severe fluid and electrolyte imbalances.

Esophageal stenosis may be congenital or more com monly acquired. When acquired the narrowing generally is caused by fibrous thickening of the submucosa and atrophy of the muscularis propria. Stenosis due to inflammation and scarring may be caused by chronic gastroesophageal reflux, irradiation, ingestion of caustic agents, or other forms of severe injury. Stenosis-associated dysphagia usually is progressive; difficulty eating solids typically occurs long before problems with liquids.

Functional Obstruction

Efficient delivery of food and fluids to the stomach requires coordinated waves of peristaltic contractions. *Esophageal dysmotility* interferes with this process and can take several forms, all of which are characterized by discoordinated contraction or spasm of the muscularis. Because it increases esophageal wall stress, spasm also can cause small diverticula to form. Esophageal dysmotility can be separated into several forms depending on the character of the contractile abnormalities.

Achalasia is characterized by the triad of incomplete lower esophageal sphincter (LES) relaxation, increased LES tone, and esophageal aperistalsis.

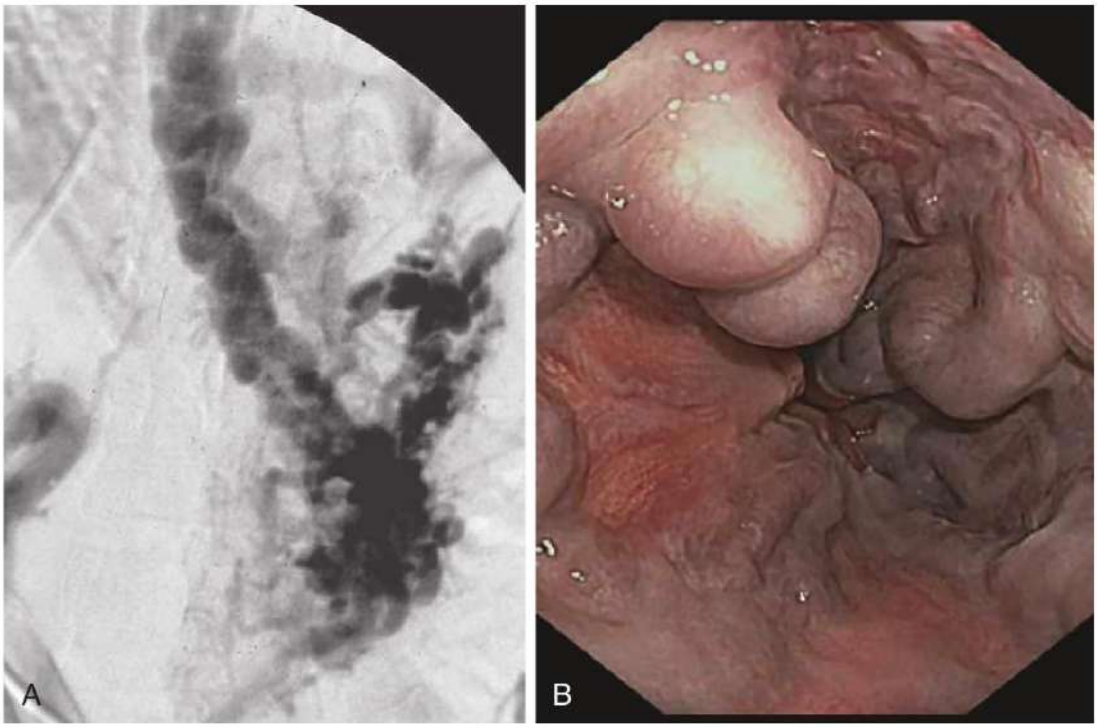
Ectopia

Ectopic tissues (developmental rests) are common in the gastrointestinal tract. The most frequent site of ectopic gastric mucosa is the upper third of the esophagus, where it is referred to as an *inlet patch.*

Esophageal Varices

Instead of returning directly to the heart, venous blood from the gastrointestinal tract is delivered to the liver via the portal vein before reaching the inferior vena cava. This circulatory pattern is responsible for the first-pass effect, in which drugs and other materials absorbed in the intestines are processed by the liver before entering the systemic circulation. Diseases that impede portal blood flow cause portal hypertension, which can lead to the development of esophageal varices, an important cause of massive and frequently life-threatening bleeding.

Varices can be detected by angiography, but are most commonly detected during endoscopy (Fig.1, A &B), and appear as tortuous dilated veins within the submucosa of the distal esophagus and proximal stomach (Fig.1, C &D). The overlying mucosa can be intact or ulcerated and necrotic, particularly if rupture has occurred.



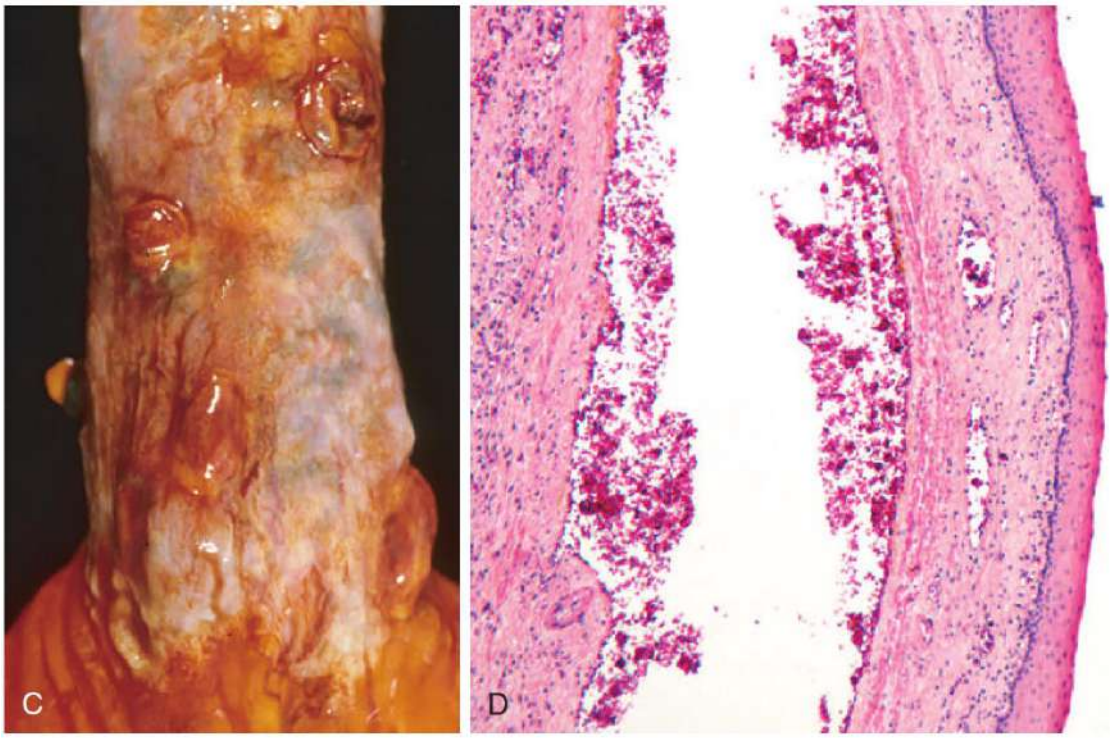


Fig. 1 Esophageal varices. (A) Angiogram showing several tortuous esophageal varices. (B) Although the angiogram is striking, endoscopy is more commonly used to identify varices. (C) Collapsed varices are present in this postmortem specimen corresponding to the angiogram in (A). The polypoid areas are sites of variceal hemorrhage that were ligated with bands. (D) Dilated varices beneath intact squamous mucosa.

Esophageal Lacerations

The most common esophageal lacerations are **Mallory Weiss tears**, which are often induced by severe retching or vomiting. Normally, a reflex relaxation of the gastroesophageal musculature precedes the anti-peristaltic contractile wave associated with vomiting. This relaxation may fail during prolonged vomiting, with the result that refluxing gastric contents cause the esophageal wall to stretch and tear. Patients usually present with hematemesis.

The roughly linear lacerations of Mallory-Weiss syndrome are longitudinally oriented and usually cross the gastroesophageal junction (Fig. 2A). These superficial tears generally heal quickly without surgical intervention. By contrast, severe, transmural esophageal tears (Boerhaave syndrome) result in mediastinitis, are catastrophic, and require prompt surgical intervention.

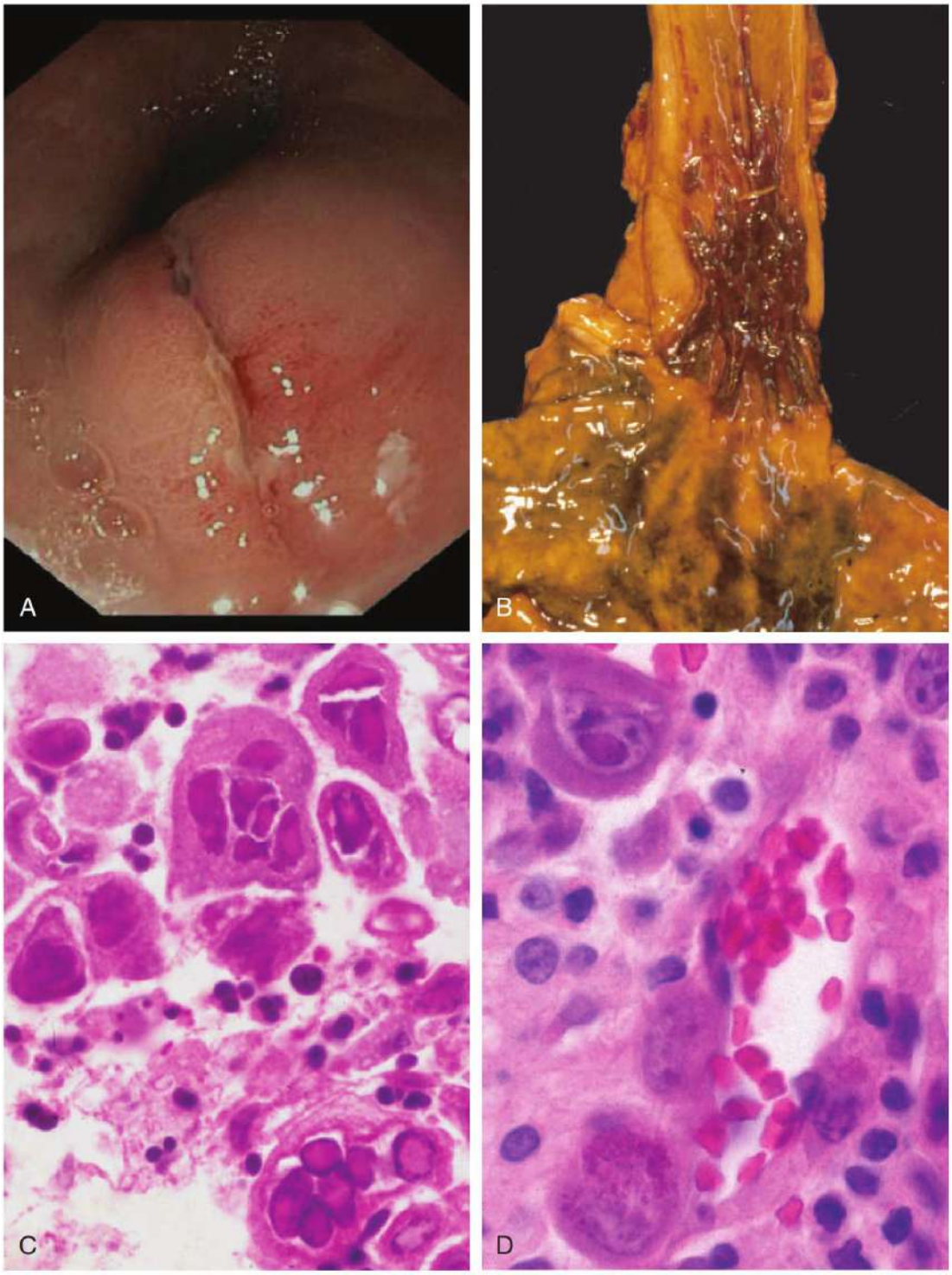


Fig. 2 Traumatic and viral esophagitis. (A) Endoscopic view of a longitudinally-oriented Mallory-Weiss tear. These superficial lacerations can range from millimeters to several centimeters in length. (B) Postmortem specimen with multiple herpetic ulcers in the distal esophagus. (C) Multinucleate squamous cells containing herpesvirus nuclear inclusions. (D) Cytomegalovirus-infected endothelial cells with nuclear and cytoplasmic inclusions.

ESOPHAGEAL TUMORS

Two morphologic variants account for a majority of esophageal cancers: adenocarcinoma and squamous cell carcinoma.

Worldwide, squamous cell carcinoma is more common, but adenocarcinoma is on the rise. Other rare tumors are not discussed here.

Adenocarcinoma

Esophageal adenocarcinoma typically arises in a background of Barrett esophagus and long-standing GERD. Risk for development of adenocarcinoma is greater in patients with documented dysplasia and in those who use tobacco, are obese, or who have had previous radiation therapy.

Morphology

Esophageal adenocarcinoma usually occurs in the distal third of the esophagus and may invade the adjacent gastric cardia (Fig. 3A). While early lesions may appear as flat or raised patches in otherwise intact mucosa, later tumors may form large exophytic masses, infiltrate diffusely, or ulcerate and invade deeply.

On microscopic examination, Barrett esophagus frequently is present adjacent to the tumor. Tumors typically produce mucin and form glands (Fig. 3B).

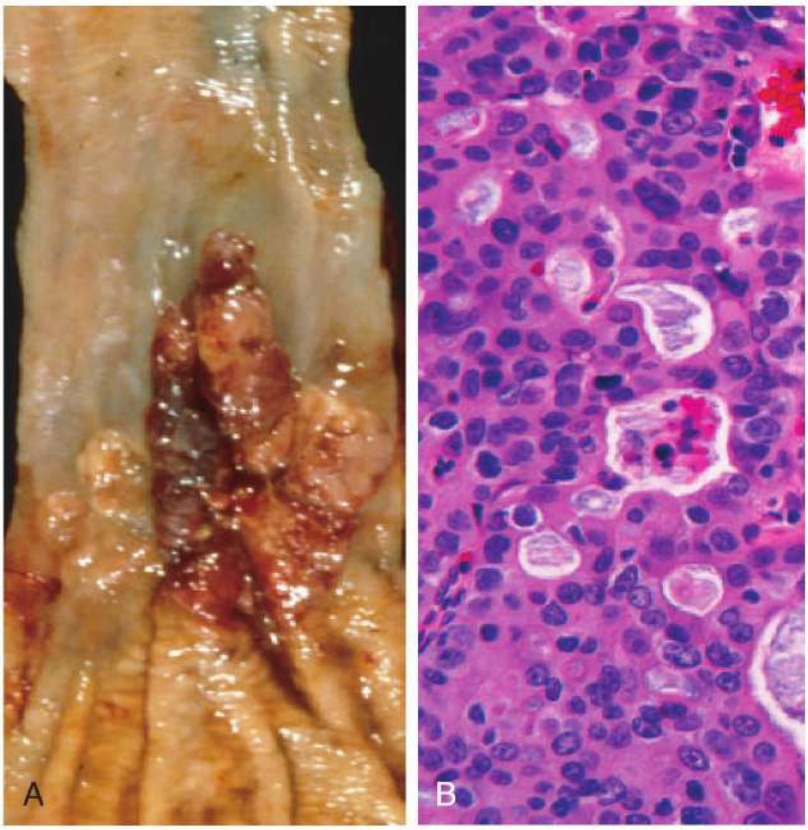


Fig. (3) Esophageal adenocarcinoma. (A) Adenocarcinoma usually occurs distally and, as in this case, often involves the gastric cardia.
(B) Esophageal adenocarcinoma growing as back-to-back glands.

Clinical Features

Patients most commonly present with pain or difficulty in swallowing, progressive weight loss, chest pain, or vomiting. By the time signs and symptoms appear, the tumor usually has invaded submucosal lymphatic vessels.

Squamous Cell Carcinoma

Risk factors include alcohol and tobacco use, poverty, caustic esophageal injury, achalasia, Plummer-Vinson syndrome, frequent consumption of very hot beverages, and previous radiation therapy to the mediastinum.

Pathogenesis

A majority of esophageal squamous cell carcinomas are at least partially related to the use of alcohol and tobacco, the effects of which synergize to increase risk. Nutritional deficiencies, as well as exposure to polycyclic hydrocarbons, nitrosamines, and other mutagenic compounds, such as those found in fungus-contaminated foods, are suspected to be the risk factors. HPV infection also has been implicated in esophageal squamous cell carcinoma in high-risk but not in low-risk regions. The molecular pathogenesis of esophageal squamous cell carcinoma remains incompletely defined.

MORPHOLOGY

In contrast to the distal location of most adenocarcinomas, half of squamous cell carcinomas occur in the middle third of the esophagus (fig.4 **A**).

Squamous cell carcinoma begins as an in situ lesion in the form of squamous dysplasia. Early lesions appear as small, gray-white plaque like thickenings. Over months to years, they grow into tumor masses that may be polypoid and protrude into and obstruct the lumen. Other tumors are either ulcerated or diffusely infiltrative lesions that spread within the esophageal wall, where they can cause thickening, rigidity and luminal narrowing.

These cancers may invade surrounding structures including the respiratory tree, causing catastrophic exsanguination; or the mediastinum and pericardium.

Most squamous cell carcinomas are moderately to well differentiate (**fig.4 B**).

Clinical Features

Clinical manifestations of squamous cell carcinoma of the esophagus begin insidiously and include dysphagia, odynophagia (pain on swallowing), and obstruction. As with other forms of esophageal obstruction, patients may unwittingly adjust to the progressively increasing obstruction by altering their diet from solid to liquid foods. Extreme weight loss and debilitation may occur as consequences of both impaired nutrition and tumor-associated cachexia. As with adenocarcinoma, hemorrhage and sepsis may accompany tumor ulceration. Occasionally, squamous cell carcinomas of the upper and mid esophagus present with symptoms caused by aspiration of food via a tracheoesophageal fistula.

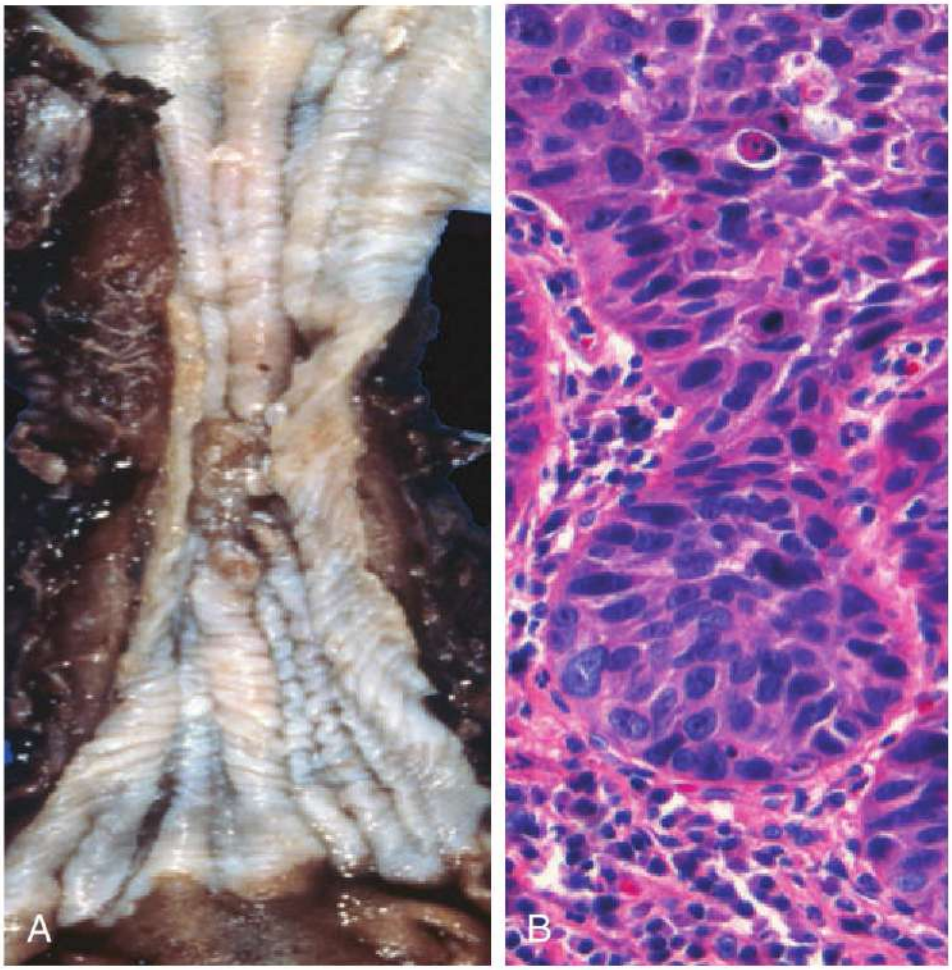


Fig. 4 Esophageal squamous cell carcinoma. (A) Squamous cell carcinoma most frequently is found in the mid-esophagus, where it commonly causes strictures. (B) Squamous cell carcinoma composed of nests of malignant cells that partially recapitulate the stratified organization of squamous epithelium.

Lecture (11 & 12)

Stomach (Gastritis, Ulcer, Carcinoma)

Disorders of the stomach are a frequent cause of clinical disease, with inflammatory and neoplastic lesions being particularly common.

The stomach is divided into four major anatomic regions: the cardia, fundus, body, and antrum. The cardia is lined mainly by mucin-secreting *foveolar cells* that form shallow glands. The antral glands are similar but also contain endocrine cells, such as *G cells,* that release gastrin to stimulate luminal acid secretion by *parietal cells* within the gastric fundus and body. The well-developed glands of the body and fundus also contain *chief cells* that produce and secrete digestive enzymes such as pepsin.

GASTROPATHY AND ACUTE GASTRITIS

Gastritis results from mucosal injury. When neutrophils are present, the lesion is referred to as *acute gastritis*. When cell injury and regeneration are present but inflammatory cells are rare or absent, the term *gastropathy* is applied.

Agents that cause gastropathy include nonsteroidal anti-inflammatory drugs, alcohol, bile, and stress-induced injury. Acute mucosal erosion or hemorrhage, such as Curling ulcers or lesions following disruption of gastric blood flow, for example, in portal hypertension, can also cause gastropathy that typically progresses to gastritis. The term *hypertrophic gastropathy* is applied to a specific group of diseases exemplified by Ménétrier disease and Zollinger Ellison syndrome.

Both gastropathy and acute gastritis may be asymptomatic or cause variable degrees of epigastric pain, nausea, and vomiting. In more severe cases, there may be mucosal erosion, ulceration, hemorrhage, hematemesis, melena, or, rarely, massive blood loss.

Pathogenesis

The gastric lumen is strongly acidic, with a pH close to 1—more than 1 million times more acidic than the blood. This harsh environment contributes to digestion but also has the potential to damage the mucosa. Multiple mechanisms have evolved to protect the gastric mucosa (Fig.1)

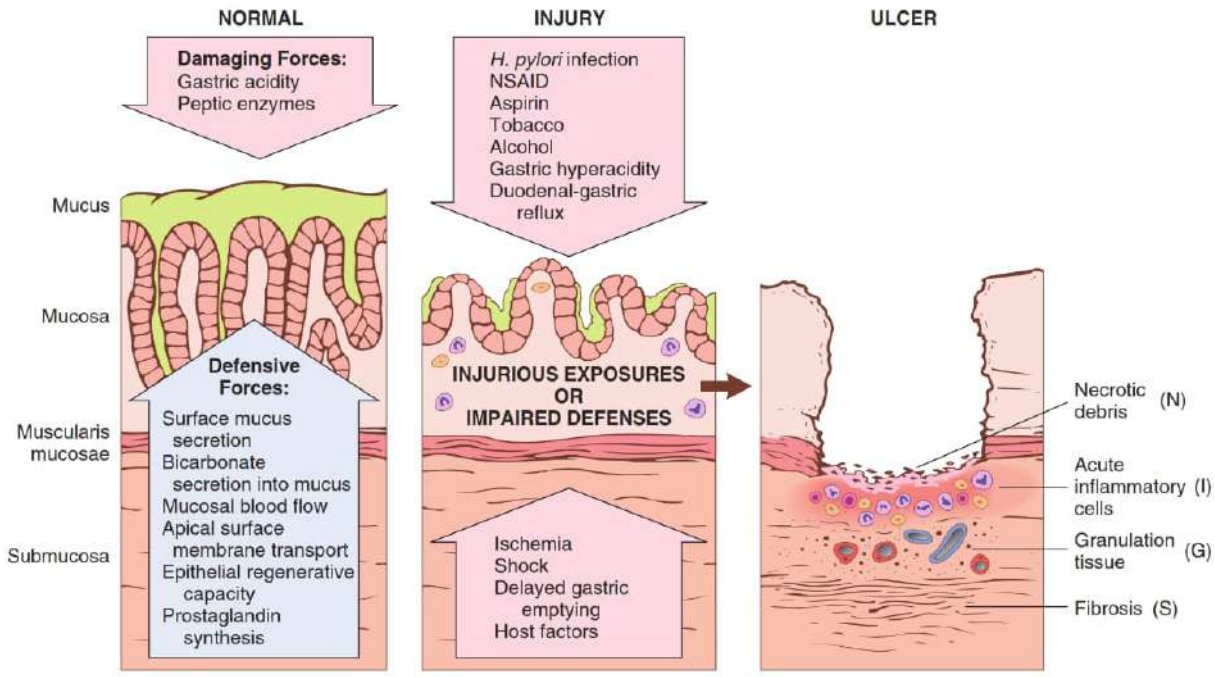


Fig. (1) Mechanisms of gastric injury and protection.

This diagram illustrates the progression from mild forms of injury to ulceration that may occur with acute or chronic gastritis. Ulcers include layers of necrotic debris (N), inflammation (I), and granulation tissue (G); scarring (S), which develops over time, is present only in chronic lesions.

Mucin secreted by surface foveolar cells forms a thin layer of mucus that prevents large food particles from directly touching the epithelium. The mucus layer also promotes formation of an "unstirred" layer of fluid over the epithelium that protects the mucosa; it has a neutral pH as a result of secretion of bicarbonate ions by surface epithelial cells. Finally, the rich blood supply of the gastric mucosa efficiently buffers and removes protons that back diffuse into the lamina propria.

Gastropathy, acute gastritis, and chronic gastritis can occur after disruption of any of these protective mechanisms.

The main causes include:

1. Nonsteroidal anti-inflammatory drugs (NSAIDs)
2. The gastric injury that occurs in uremic patients and those infected with urease-secreting *H. pylori* may be due to

inhibition of gastric bicarbonate transporters by ammonium ions.

3. Reduced mucin and bicarbonate secretion.
4. Hypoxemia and decreased oxygen delivery.
5. Ingestion of harsh chemicals, particularly acids or bases.
6. Direct cellular damage also contributes to gastritis induced by excessive alcohol consumption.
7. Radiation therapy. Agents that inhibit DNA synthesis or the mitotic apparatus, including those used in cancer chemotherapy, may cause generalized mucosal damage due to insufficient epithelial renewal

CHRONIC GASTRITIS

The most common cause of chronic gastritis is infection with the bacillus *Helicobacter pylori. Autoimmune gastritis,* typically associated with gastric atrophy, represents less than 10% of cases of chronic gastritis but is the most common cause in patients without *H. pylori* infection. Chronic NSAID use is a third important cause of gastritis in some populations. Less common causes include radiation injury and chronic bile reflux.

The *signs and symptoms* associated with chronic gastritis typically are less severe but more persistent than those of acute gastritis. Nausea and upper-abdominal discomfort may occur, sometimes with vomiting, but hematemesis is uncommon.

COMPLICATIONS OF CHRONIC GASTRITIS

Here are three important complications of chronic gastritis:

1. Peptic ulcer disease,
2. Mucosal atrophy and intestinal metaplasia, and
3. Dysplasia.

Each of these is discussed shortly.

Peptic Ulcer Disease

Peptic ulcer disease (PUD) most often is associated with *H. pylori* infection or NSAID use. The imbalances of mucosal defenses and damaging forces that cause chronic gastritis are also responsible for PUD. (Fig. 1)

PUD may occur in any portion of the gastro intestinal tract exposed to acidic gastric juices but is most common in the gastric antrum and first portion of the duodenum. Peptic (acid-induced) injury may occur in the esophagus as a result of acid reflux (GERD) or acid secretion by ectopic gastric mucosa. Peptic injury in the small intestine may also be associated with gastric heterotopia, including that within a Meckel diverticulum.

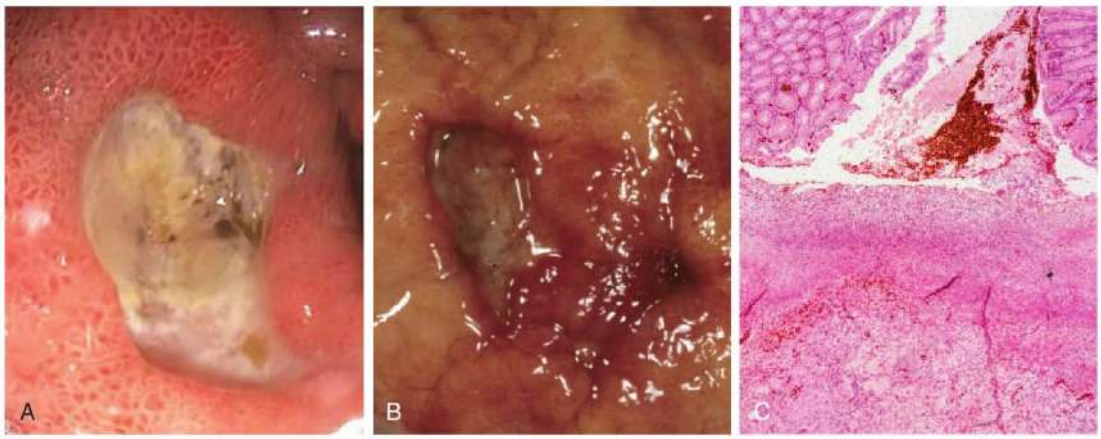


Fig. 1 Peptic ulcer disease.

(A) Endoscopic view of typical antral ulcer associated with NSAID use. (B) Gross view of a similar ulcer that was resected due to gastric perforation, presenting as free air under the diaphragm. Note the clean edges. (C) The necrotic ulcer base is composed of granulation tissue overlaid by degraded blood.

GASTRIC POLYPS AND TUMORS

Polyps are nodules or masses that project above the level of the surrounding mucosa. They are identified in up to 5% of upper gastrointestinal tract endoscopies. Polyps may develop as a result of epithelial or stromal cell hyperplasia, inflammation, ectopia, or neoplasia. Although many different types of polyps can occur in the stomach, the most common are:

- *Inflammatory and Hyperplastic Polyps*
- *Fundic Gland Polyps*
- *Gastric Adenoma*

Gastric Adenocarcinoma

Adenocarcinoma is the most common malignancy of the stomach, comprising more than 90% of all gastric cancers.

Early symptoms resemble those of chronic gastritis, including:

1. Dyspepsia,
2. Dysphagia, and

3. Nausea.

As a result, the cancer is often diagnosed at advanced stages when clinical manifestations such as weight loss, anorexia, altered bowel habits, anemia, and hemorrhage trigger diagnostic evaluation.

Pathogenesis

1) *Mutations.* While the majority of gastric cancers are not hereditary, mutations identified in familial gastric cancer have provided important insights into the mechanisms of carcinogenesis in sporadic cases.
2) *H. pylori.* Chronic gastritis, most commonly due to *H. pylori* infection, promotes the development and progression of cancers that may be induced by diverse genetic alterations.
3) *Epstein-Barr virus (EBV).* While *H. pylori* is most commonly associated with gastric cancer, approximately 10% of gastric adenocarcinomas are associated with Epstein-Barr virus (EBV) infection.

Lymphoma

Although extra-nodal lymphomas can arise in virtually any tissue, they do so most commonly in the gastrointestinal tract, particularly the stomach. Nearly 5% of all gastric malignancies are primary lymphomas

Neuroendocrine (Carcinoid) Tumor

Neuroendocrine tumors, also referred to as *carcinoid tumors,* arise from neuroendocrine organs (e.g., the endocrine pancreas) and neuroendocrine-differentiated gastrointestinal epithelia (e.g., G cells). A majority of these tumors are found in the gastrointestinal tract, and more than 40% occur in the small intestine.

Gastrointestinal Stromal Tumor

Gastrointestinal stromal tumor (GIST) is the most common mesenchymal tumor of the abdomen, and more than half of these tumors occur in the stomach. A wide variety of other mesenchymal neoplasms may arise in the stomach. Many are named according to the cell type they most resemble; for example, smooth muscle tumors are called *leiomyomas* or *leiomyosarcomas,* nerve sheath tumors are termed *schwannomas,* and those resembling glomus bodies in the nail beds and at other sites are termed *glomus tumors.* These tumors are all rare.

Lecture (13)

Crohn Disease

Crohn disease, also known as *regional enteritis*, may occur in any area of the gastrointestinal tract but the most common sites involved at presentation are the **terminal ileum, ileocecal valve,** and **cecum.** Disease is limited to the small intestine alone in about 40% of cases; the small intestine and the colon both are involved in 30% of patients; and the remainder of cases are characterized by colonic involvement only. Infrequently, Crohn disease may involve the esophagus or stomach. The presence of multiple, separate, sharply delineated areas of disease, resulting in **skip lesions,** is characteristic of Crohn disease and may help in differentiation from ulcerative colitis. Strictures are common (Fig. A).

The earliest lesion, the **aphthous ulcer,** may progress, and multiple lesions often coalesce into elongated, serpentine ulcers oriented along the axis of the bowel.

Edema and loss of normal mucosal folds are common. Sparing of interspersed mucosa results in a coarsely textured, **cobblestone** appearance in which diseased tissue is depressed below the level of normal mucosa (Fig.B).

Fissures frequently develop between mucosal folds and may extend deeply to become sites of perforation or fistula tracts. The intestinal wall is thickened as a consequence of trans mural edema, inflammation, submucosal fibrosis, and

hypertrophy of the muscularis propria, all of which contribute to stricture formation. In cases with extensive transmural disease, mesenteric fat frequently extends around the serosal surface **(creeping fat)** (Fig C).

The microscopic features of active Crohn disease include abundant neutrophils that infiltrate and damage crypt epithe ium. Clusters of neutrophils within a crypt are referred to as a **crypt abscess** and often are associated with crypt destruction. Ulceration is common in Crohn disease, and there may be an abrupt transition between ulcerated and normal mucosa.

Repeated cycles of crypt destruction and regeneration lead to **distortion of mucosal architecture;** the normally straight and parallel crypts take on bizarre branching shapes and unusual orientations to one another (Fig A). Epithelial metaplasia, another consequence of chronic relapsing injury, often takes the form of gastric antral-appearing glands (pseudopyloric metaplasia). **Paneth cell metaplasia** may occur in the left colon, where Paneth cells are normally absent. These architec tural and metaplastic changes may persist, even when active inflammation has resolved. Mucosal atrophy, with loss of crypts, may follow years of disease. **Noncaseating granulomas** (Fig. 15. B), a hallmark of Crohn disease, are found in approximately 35% of cases and may arise in areas of active disease or uninvolved regions in any layer of the intestinal wall (Fig. C). Granulomas also may be found in mesenteric lymph nodes. Cutaneous granulomas form nodules that

are referred to (misleadingly) as **metastatic Crohn disease. The absence of granulomas does not preclude a diagnosis of Crohn disease.**

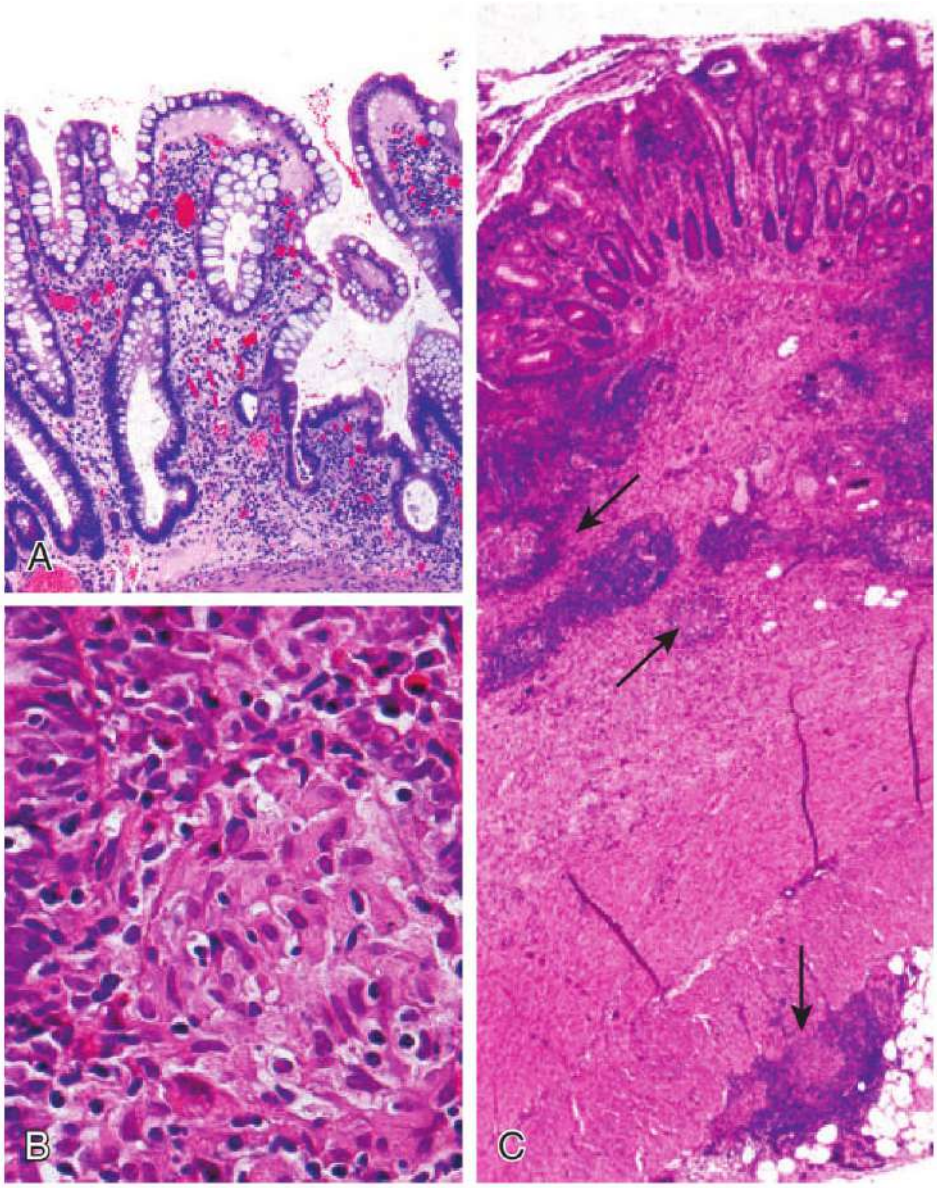


Fig. 15.29 Microscopic pathology of Crohn disease. (A) Haphazard crypt organization results from repeated injury and regeneration. (B) Noncaseating granuloma. (C) Transmural Crohn disease with submucosal and serosal granulomas *(arrows).*

Clinical Features

The clinical manifestations of Crohn disease are extremely variable. In most patients, disease begins with intermittent attacks of relatively mild diarrhea, fever, and abdominal pain. Approximately 20% of patients present acutely with right lower-quadrant pain and fever, which may mimic acute appendicitis or bowel perforation. Patients with colonic involvement may present with bloody diarrhea and abdominal pain, creating a differential diagnosis with some colonic infections. Periods of disease activity typically are interrupted by asymptomatic intervals that last for weeks to many months. Disease reactivation can be associated with a variety of external triggers, including physical or emotional stress, specific dietary items, NSAID use, and cigarette smoking.

Iron-deficiency anemia may develop in individuals with colonic disease, while extensive small-bowel disease may result in serum protein loss and hypoalbuminemia, generalized nutrient malabsorption, or malabsorption of vitamin B and bile salts. Fibrosing strictures, particularly of the terminal ileum, are common and require surgical resection.

Disease often recurs at the site of anastomosis, and as many as 40% of patients require additional resections within 10 years. Fistulas develop between loops of bowel and may also involve the urinary bladder, vagina, and abdominal or perianal skin. Perforations and peritoneal abscesses can also occur.

Extraintestinal manifestations of Crohn disease include uveitis, migratory polyarthritis, sacroiliitis, ankylosing spondylitis, erythema nodosum, and clubbing of the fingertips, any of which may develop before intestinal disease is recognized.

Pericholangitis and primary sclerosing cholangitis may occur in Crohn disease but are more common in ulcerative colitis. As discussed

later, the risk for development of colonic adenocarcinoma is increased in patients with long-standing colonic Crohn disease.

Lecture (14)

Large intestine (Hemorrhoids, Malabsorption Syndrome)

Hemorrhoids

Hemorrhoids are dilated anal and perianal collateral vessels that connect the portal and caval venous systems to relieve elevated venous pressure within the hemorrhoid plexus. Thus, although hemorrhoids are less serious than esophageal varices, the pathogenesis of these lesions is similar. They are common, affecting about 5% of the general population.

Common predisposing factors include constipation and associated straining, which increase intraabdominal and venous pressures, venous stasis of pregnancy, and portal hypertension.

Collateral vessels within the inferior hemorrhoidal plexus are located below the anorectal line and are termed external hemorrhoids, while those that result from dilation of the superior hemorrhoidal plexus within the distal rectum are referred to as internal hemorrhoids.

On histologic examination, hemorrhoids consist of thin-walled, dilated, submucosal vessels beneath anal or rectal mucosa. These vessels are subject to trauma, which leads to rectal bleeding. In addition, they can become thrombosed and inflamed.

Hemorrhoids often manifest with pain and rectal bleed- ing, particularly bright red blood seen on toilet tissue.

Hemorrhoids also may develop as a result of portal hyper tension, where the implications are more ominous. Hemorrhoidal bleeding generally is not a medical emergency; treatment options include sclerotherapy, rubber band ligation, and infrared coagulation. In severe cases, hemorrhoids may be removed surgically by *hemorrhoidectomy.*

Malabsorptive Diarrhea

Malabsorption manifests most commonly as *chronic diarrhea* and is characterized by defective absorption of fats, fat- and water-soluble vitamins, proteins, carbohydrates, electrolytes, minerals, and water. Chronic malabsorption causes weight loss, anorexia, abdominal distention, borborygmi, and muscle wasting. A hallmark of malabsorption is *steatorrhea,* characterized by excessive fecal fat and bulky, frothy, greasy, yellow, or clay-colored stools.

Malabsorption results from disturbance in at least one of the four phases of nutrient absorption:

- *Intraluminal digestion,* in which proteins, carbohydrates, and fats are broken down into absorbable forms
- *Terminal digestion,* which involves the hydrolysis of carbohydrates and peptides by disaccharidases and peptidases, respectively, in the brush border of the small-intestinal mucosa
- *Transepithelial transport,* in which nutrients, fluid, and electrolytes are transported across and processed within the small-intestinal epithelium
- *Lymphatic transport* of absorbed lipids

In many malabsorptive disorders, a defect in one of these processes predominates, but more than one usually contributes. As a result, malabsorption syndromes resemble each other more than they differ.

Signs and symptoms include diarrhea (from nutrient malabsorption and excessive intestinal secretion), flatus, abdominal pain, and weight loss. Inadequate absorption of vitamins and minerals can result in anemia and mucositis due to pyridoxine, folate, or vitamin B_{12} deficiency; bleeding due to vitamin K deficiency; osteopenia and tetany due to calcium, magnesium, or vitamin D deficiency; or neuropathy due to vitamin A or B_{12} deficiency. A variety of endocrine and skin disturbances may also occur. Mycobacterial infection, which can be led to lymphatic transport defects.