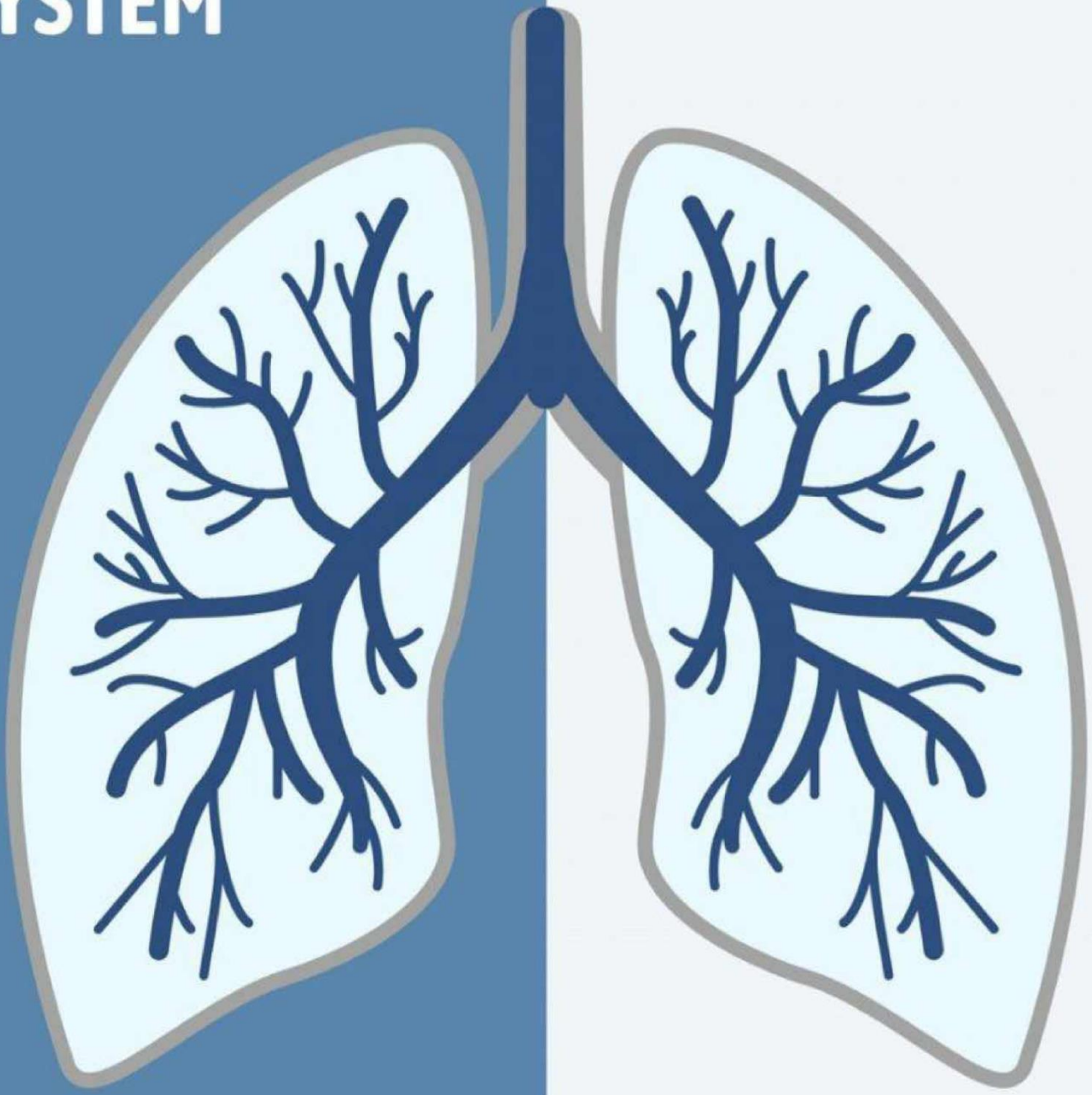
RESPIRATORY SYSTEM

PATHOLOGY



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- In this sheet we will talk about pulmonary diseases of vascular origin, including:

  1. Pulmonary embolism (liquid, gas, solid), hemorrhage and infarction
  2. Pulmonary hypertension
  3. Diffuse alveolar hemorrhage syndromes

- Regarding pulmonary embolism, it is subdivided into **Thromboembolism (95%) And Non-thrombotic pulmonary embolism (5%).**

THROMBOEMBOLISM

- Blot clots that occlude pulmonary arteries are almost always embolic in origin, and more than 95% of pulmonary emboli arise from thrombi within the large deep veinsof the legs, most often **popliteal vein, and larger veins above it (iliac vein and femoral).** It usually occurs in patients with predisposing condition that increases the tendency of bleeding (thrombophilia).

- **Risk factors** for venous thrombosis are related to Virchow triad (stasis, hypercoagulability, and vascular injury)

1. Prolonged bed rest - Especially with immobilization of the legs (resulting stasis).
2. Surgery - Particularly orthopedic surgery on the knee or hip (resulting stasis).
3. Severe trauma - As in burns, multiple fractures, or RTA (induces inflammation that leads to secretion of pro-coagulation mediators and thus hypercoagulability and stasis of blood because of immobilization.
4. Congestive heart failure (resulting stasis).
5. In women, the period around parturition (the period just before and after birth) or the use of oral contraceptive pills(OCP) with high estrogen content which induces hypercoagulability. Also, it has been shown that late months of pregnancy are associated with venous stasis.
6. Disseminated cancer (Hypercoagulability).
7. Primary disorders of hypercoagulability (like factor V Leiden or prothrombin).

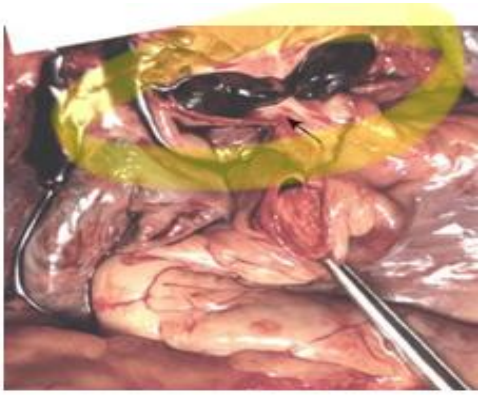
- There are 2 important **consequences** of pulmonary arterial occlusion:

  - **Increase in pulmonary artery pressure** due to the blockage of flow by the embolic occlusion as well as the induction of **vasospasm** via the release of mediators, like thromboxane A_2, and serotonin)
  - **Ischemia of the downstream pulmonary parenchyma** due to the nonperfused, although ventilated segment. This happens only in 10% of cases as the presence of dual lung circulation (bronchial, pulmonary) protects against ischemia.

- The pathophysiologic consequences **depend on 2 factors:**

1. **Size and number of the embolus** (determines the size of the occluded pulmonary artery)
   Large embolus may embed in the main pulmonary artery or its major branches or lodge at the bifurcation as a saddle embolus, while **smaller emboli** become impacted in medium-sized and small-sized pulmonary arteries.
2. The **cardiopulmonary status** of the patient. (The general state of the circulation)

- This figure shows the gross appearance of large saddle embolus from the femoral vein,lying astride the main left and right pulmonary arteries. This type of embolus usually leads to sudden death before the appearance of any gross or histological features other than the occlusion.



Morphology

The morphologic changes also depend on the size and the general circulatory status.

- As **in large embolus**, it may embed in the main pulmonary and cause death, so there is **notime for morphologic alteration.**
- **Smaller emboli** may cause alveolar hemorrhage and may occur because of ischemic damage to the endothelial cells.
- **Infarction:** the occlusion must occur peripherally at an end arteriole for it to happen.

With compromised cardiovascular status, which could occur with congestive heart failure, infarction results. The more peripheral the embolic occlusion, the higher the risk for infarction.

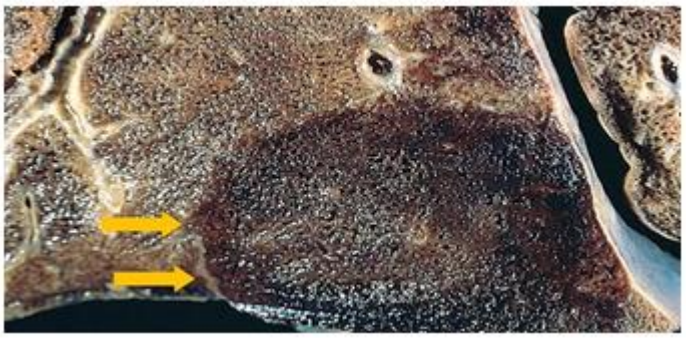
About three-fourths of all infarcts affect the lower lobes, and more than one-half are multiple.

Characteristically, they are wedge-shaped, with their base at the pleural surface and the apex pointing toward the hilus of the lung.

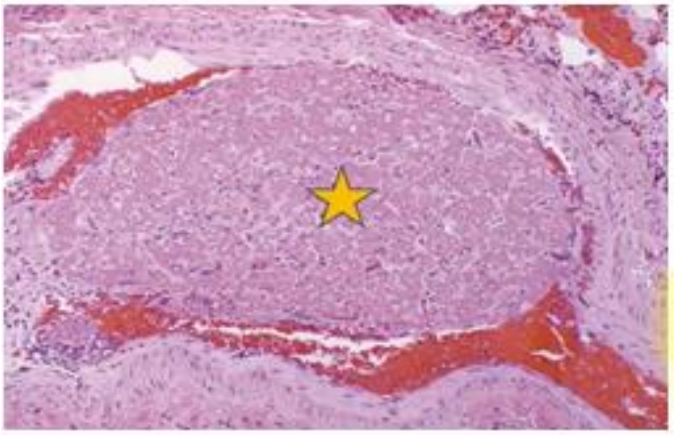
Pulmonary infarcts are typically hemorrhagic and appear as raised, red-blue areas of coagulative necrosis in the early stages. The adjacent pleural surface is often covered by a fibrinous exudate. The occluded vessel is usually located near the apex of the infarcted area.

The red cells begin to lyse within 48 hours, and the infarct gradually becomes red brown as hemosiderin is produced. In time, fibrous replacement begins at the margins as a gray-white peripheral zone which eventually converts the infarct into a scars

- This figure shows small, roughly wedge-shaped hemorrhagic pulmonary infarct of recent occurrence. Notice that is it peripherally located and is bounded by the pleural surface.



- While this figure shows a thrombo-embolism in a peripheral pulmonary arterial branch(yellow star), if there are numerous small peripheral thrombi emboli, then the vascular bed is diminished, and pulmonary hypertension may occur.



Clinical Features

- **Mostly silent (60-80%)** because they are small; the bronchial circulation sustains the viability of the affected lung parenchyma, and the embolic mass is rapidly removed by fibrinolytic activity.
- In **5% of cases, sudden death, acute right-sided heart failure, or cardiovascular collapse (shock) occurs suddenly,** as in saddle-embolism or massive pulmonary embolism which typically happen when more than 60% of the total pulmonary vasculature is obstructed by a large embolus or multiple simultaneous small emboli.
- Obstruction of small to medium pulmonary branches **(10% to 15% of cases) causes pulmonary infarction** if some element of circulatory insufficiency is also present. Typically, individuals who sustain infarctions **present with dyspnea**.
- In a small but significant subset of patients (accounting for less than 3% of cases), recurrent "showers" of emboli lead to pulmonary hypertension, chronic right-sided heart failure, and, in time, pulmonary vascular sclerosis with **progressively worsening dyspnea.**

Management (3 types of therapy)

Prophylactic therapy which may include anticoagulation, early ambulation for postoperative and postparturient patients, application of elastic stockings, intermittent pneumatic calf compression, and isometric leg exercises for bedridden patients.

Those who develop pulmonary embolism are given **anti-coagulation therapy**.

Patients with massive pulmonary embolism who are hemodynamically unstable (shock, acute right heart failure) are candidates for **thrombolytic therapy**.

Non-thrombotic pulmonary embolism

- Non-thrombotic pulmonary emboli come in several uncommon but potentially lethal forms, such as air, fat, and amniotic fluid embolism.
- Bone marrow embolism (due to the presence of hematopoietic and fat elements within a pulmonary artery) can occur after massive trauma, and in patients withbone infarction secondary to sickle cell anemia.
- Intravenous drug abuse is often associated with foreign body embolism in the pulmonary microvasculature.

Pulmonary Hypertension

- The pulmonary circulation is normally one of low resistance, and pulmonary blood pressure is only about one eighth (1/8) of systemic pressure.
- **Pulmonary hypertension (defined as pressures of 25 mm Hg or more at rest)** may be caused by a decrease in the cross-sectional area of the pulmonary vascular beds resulting increased vascular resistance or, less commonly, by increased pulmonary vascular blood flow or left heart resistance to blood flow (Example : Mitral valve stenosis).

Classification

Based on shared features, the World Health Organization has classified pulmonary hypertension into the following five groups:

3. **Pulmonary arterial hypertension (group 1)**: a diverse group of disorders that affecting small pulmonary muscular arterioles; these include:

- **Auto immune disorders such as systemic sclerosis** (thickening of the walls of arteries, it involves the pulmonary vasculature +/- interstitum) resulting an increase in vascular resistance and pulmonary hypertension.
- **connective tissue diseases, human immunodeficiency virus, and congenital heart disease with left to right shunts**.
- When all known causes are excluded, it is referred to as **idiopathic arterial pulmonary hypertension.** However, the term idiopathic is misnomer as these cases have a genetic basis.

4. **Pulmonary hypertension due to left-sided heart disease (group 2)**, including congenital or acquired systolic and diastolic dysfunction and valvular heart disease. An example is **Mitral valve stenosis** which leads to increased left-atrial pressure and therefore a sequential increase in both pulmonary venous pressure and pulmonary arterial pressure thereby inducing hypertension.

5. **Pulmonary hypertension due to lung diseases and/or hypoxia (group 3)**, including **COPD and interstitial lung disease and obstructive sleep apnea** (a common disorder associated with obesity and hypoxemia). These diseases obliterate alveolar capillaries leading to increased pulmonary resistance and therefore increase pulmonary blood pressure.

6. **Chronic thromboembolic pulmonary hypertension (group 4),** Recurrent pulmonary emboli cause pulmonary hypertension by reducing the functional cross-sectional area of the pulmonary vascular bed leading increase in pulmonary vascular resistance.

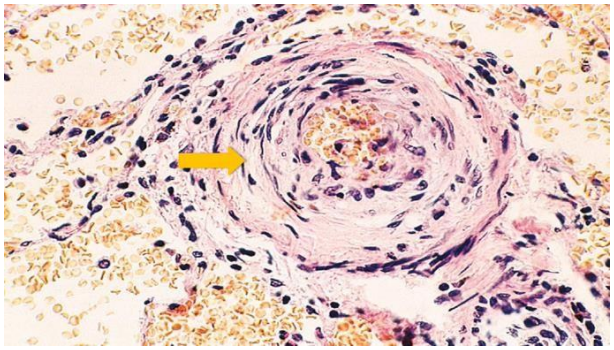
7. **Pulmonary hypertension with unclear or multifactorial mechanisms (group 5)**

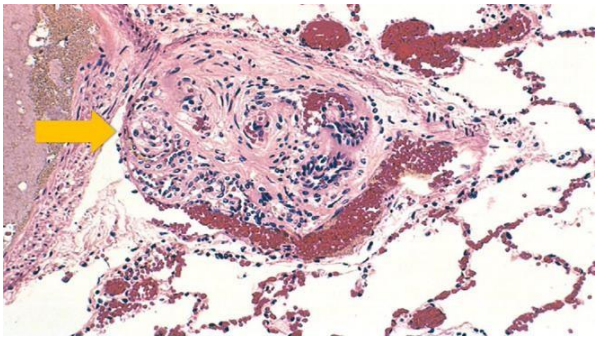
Morphology

All forms of pulmonary hypertension are associated with these morphologic features:

- Medial hypertrophy of the pulmonary muscular and elastic arteries (large vessels).
- Medial hypertrophy and intimal fibrosis of the arterioles and small arteries.
- Pulmonary arterial atherosclerosis
- Right ventricular hypertrophy
- **Plexiform lesion**, so called because a tuft of capillary formations is present, producing a network, or web, that spans the lumens of dilated thin-walled, small arteries and may extend outside the vessel. More common in group 1 and 2.

The vessel changes can involve the entire arterial tree, from the main pulmonary arteries down to the arterioles, the arterioles and small arteries are most prominently affected by medial hypertrophy and intimal fibrosis. In severe cases, atheromatous deposits form in the pulmonary artery and its major branches.





- The left figure shows the histologic appearance of medial hypertrophy affecting anarteriole.
- The right figure shows the histology of the plexiform lesion seen in small arteries. A tuft of capillary formations is present, producing a network that spans the lumens of dilated thin-walled small arteries.

Note: The presence of **organizing or thrombi** favors **recurrent pulmonary** emboli as the cause, and the **coexistence of diffuse pulmonary fibrosis, or severe emphysema and chronic bronchitis**, points to **chronic hypoxia** as the initiating event.

Clinical Features

Pulmonary hypertension produces symptoms when the disease is **advanced**. Idiopathic pulmonary hypertension **is most common in women 20 to 40 years of age** and occurs occasionally in young children. The presenting features are usually **dyspnea and fatigue**, but some patients have **anginal chest pain**.

Within 2 to 5 years, around 80% of patients develop **respiratory distress, cyanosis, and right ventricular hypertrophy**. Death from decompensated cor pulmonale may follow.

Diffuse alveolar hemorrhage syndromes

They happen as a complication of some interstitial lung disorders. There are **3 types:**

(1) Goodpasture syndrome

(2) Idiopathic pulmonary hemosiderosis

(3) Granulomatosis with polyangiitis

Goodpasture syndrome:

- Called Anti–Glomerular Basement Membrane Antibody Disease With Pulmonary Involvement.
- Goodpasture syndrome is an uncommon autoimmune disease in which lung and kidney injury are caused by circulating autoantibodies against certain domains (non-collagenous domains**) of type IV collagen** that are intrinsic to the basement membranes of **renal glomeruli and pulmonary alveoli.**

The antibodies trigger destruction and inflammation of the basement membranes in pulmonary alveoli and renal glomeruli, giving rise to **necrotizing hemorrhagic interstitial pneumonitis and rapidly progressive glomerulonephritis.**

Morphology

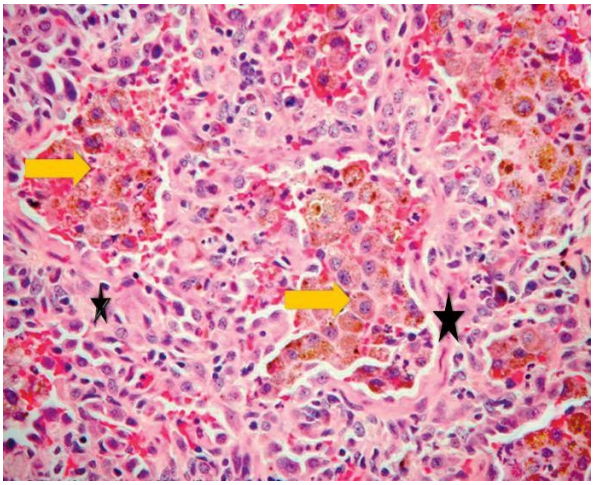
- **Grossly**, the lung shows areas of red-brown consolidation due to the **diffuse alveolar hemorrhage.**
- **Microscopic** examination shows

• **Early on**: Focal necrosis of alveolar walls associated with intraalveolar hemorrhage and abundant hemosiderin macrophages (visualized by Prussian blue stain).

• **Later on**: Fibrous thickening of septa. Hypertrophic type II pneumocytes. There is abundant hemosiderin due to earlier episodes of hemorrhage**.**

• **Direct immunofluorescence: Linear pattern of immunoglobulin deposition** (IgG, sometimes IgA or IgM) seen along the alveolar septa and renal specimens. - which is the hallmark diagnostic finding in renal biopsy specimens.

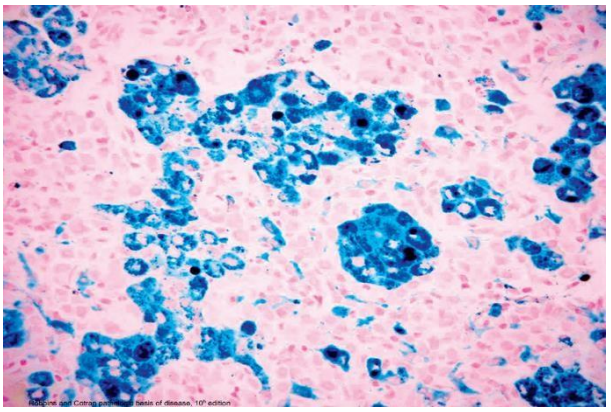
- This figure shows the histologic features of a lung biopsy, taken from a patient diagnosed with Diffuse alveolar hemorrhage syndrome.



Yellow arrows point to the large number of intra-alveolar hemosiderin-laden macrophages.

Black stars point to the background of thickened fibrous septum and the presence of actively proliferating hobnailed Type 2 pneumocytes.

- This is the same tissue (upper picture) but has been stained with Prussian blue, an iron stain that highlights the abundant intracellular hemosiderin.



Clinical Features

- Most cases of Goodpasture syndrome occur in patients in their **teens or twenties.** And is **more common in males than females**.
- Most patients are **active smokers.**
- Many cases begin with hemoptysis. Soon, manifestations of glomerulonephritis appear, leading to rapidly progressive renal failure.
- **Plasmapheresis** removes offending antibodies, and **immunosuppressive drugs** inhibit antibody production.
- With severe renal disease**, renal transplantation** is eventually required.

Granulomatosis with polyangiitis:

- Granulomatosis and Polyangiitis (formerly called Wegener granulomatosis) in this condition **more than 80% of patients develop upper-respiratory or pulmonarymanifestations** at some point along their course.
- The lung lesions are characterized by a **triad** of:
  - necrotizing angiitis
  - aseptic necrosis of upper respiratory tract and lungs •
  - focal glomerulonephritis (necrotizing, often crescentic, glomerulonephritis)
- **Lung histology** reveals:
  - necrotizing vasculitis(angiitis) of arteries and veins (With fibrinoid pattern of necrosis).
  - parenchymal necrotizing poorly formed granulomatous inflammation.
- The signs and symptoms stem from involvement of the upper-respiratory tract (chronic sinusitis, epistaxis, nasal perforation) and the lungs (cough, hemoptysis,chest pain).
- **Anti-neutrophil cytoplasmic antibodies (PR3- ANCAs, also known as C-ANCA) are present inapproximately 95% of cases.**
- Remember: C-ANCA is associated with Wegener granulomatosis, while B-ANCA is associated with primary sclerosing cholangitis, microscopic polyangiitis, churg-trauss syndrome.

Cases (clues)

1- A 45-year-old gentleman has chronic cough for the last 11 months. Physical examination, shows nasopharyngeal ulcers. on auscultation, the lungs have diffuse crackles bilaterally. Laboratory studies include a serum urea nitrogen level of 75 mg/dLand a creatinine concentration of 6.7 mg/dL. Urinalysis shows 50 RBCs per high-power field and RBC casts. His serologic titer for C-ANCA (proteinase 3) is elevated. A chest radiograph shows multiple, small, bilateral pulmonary nodules. A transbronchial lung biopsy specimen shows a necrotizing inflammatory process involving the small peripheral pulmonary arteries and arterioles. Which of the following is the most likely diagnosis?

Note: nasopharyngeal ulcers indicate upper respiratory involvement.

A. Granulomatosis with polyangiitis

B. Pulmonary hypertension

C. Goodpasture syndrome

D. Idiopathic pulmonary hemosiderosis

E. Polyarteritis nodos

2- A 33-year-old gentleman, medically free, presented with acute onset of hemoptysis. he is afebrile, with normal heart rate, increased respiratory rate and blood pressure. A transbronchial lung biopsy, shows focal necrosis of alveolar walls associated with prominent intraalveolar hemorrhage. Two days later, he has decreased urine output with abnormal serum creatinine and urea nitrogen. Which of the following antibodies ismost likely involved in the pathogenesis of his condition?

A- Anti−DNA topoisomerase I antibody

B- Anti−glomerular basement membrane antibody

C- Antimitochondrial antibody

D- Anti−neutrophil cytoplasmic antibody

E- Antinuclear antibody

The diagnosis is Goodpasture syndrome, which usually leads to renal and pulmonary lesions produced by the anti-bodies that are directed against antigens common to the basement membranes in the glomerulus and the alveolus

The End