Doctor.021

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RS PATHOLOGY

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Slides will be in orange and doctor's notes in black

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

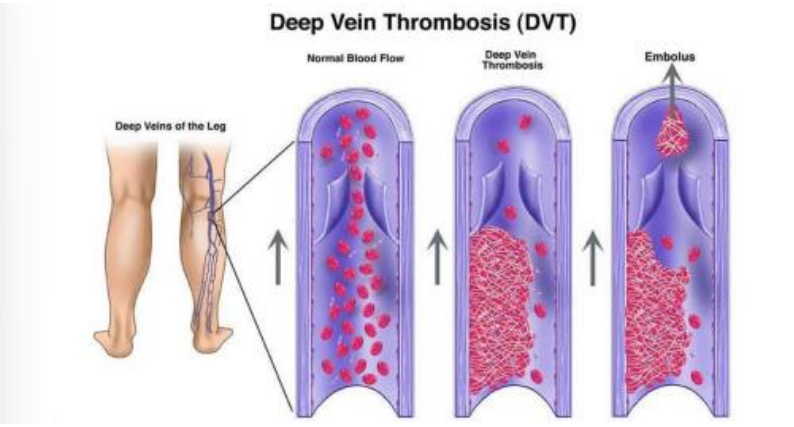
1. **Pulmonary embolism (liquid, gas, solid), haemorrhage and infarction**
2. **Pulmonary hypertension**
3. **Diffuse alveolar haemorrhage syndromes**

PULMONARY EMBOLISM

PULMONARY EMBOLSIM INCLUDES THROMBOEMBLOSIM & NONTHROMBOTIC PUMONARY EMBLOI

THROMBOEMBOLSIM

Blot clots that occlude large pulmonary arteries are almost always embolic in origin, and more than 95% of pulmonary emboli arise from thrombi within the large deep veins of the legs, most often they involve popliteal vein, and larger veins above it.



Risk factors of venous thrombosis

1. Prolonged bed rest - Especially with immobilization of the legs.
2. Surgery - Particularly orthopedic surgery on the knee or hip.
3. Severe trauma - As in burns, multiple fractures.
4. Congestive heart failure.
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:**

1. **Increase in pulmonary artery pressure due to the blockage of flow and vasospasm via the release of mediators, like thromboxane A2, and serotonin.**
   So, if a major vessel occluded, an abrupt increase in the pulmonary pressure will follow, and the heart will be pumping against higher resistance resulting in decreased cardiac output and right sided heart failure which is called acute cor pulmonale which in some cases result in sudden death.

   If smaller vessels are occluded, the result will be less catastrophic and maybe clinically silent.

2. **Ischemia and decrease blood flow to the downstream pulmonary parenchyma.**

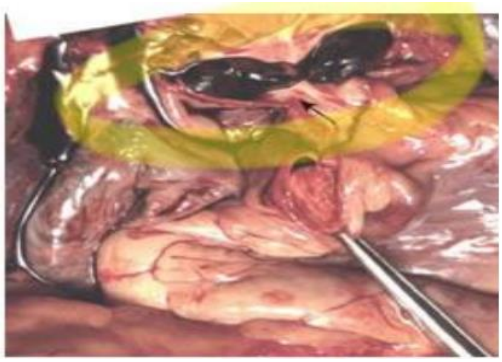
And as you know, the lungs are oxygenated not only by the pulmonary arteries, but also bronchial artery and directly from the air in the alveoli, so ischemic necrosis is not common affect only 20% of patients with thromboembolic.

➢ **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.**



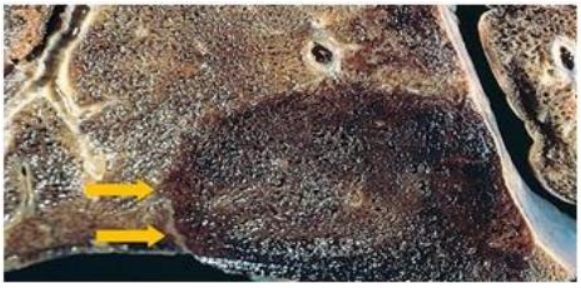
MORPHOLOGY

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

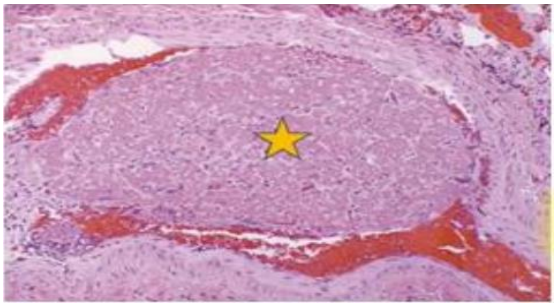
- **As in large embolus (may cause sudden death), it may embed in the main pulmonary and cause death, so there is no time for morphologic alteration.**
- **Smaller emboli may cause alveolar haemorrhage and may occur because of ischemic damage to the endothelial cells.**

- **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 haemorrhagic 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 graywhite peripheral zone which eventually converts the infarct into a scar.**

➢ **This figure shows small, roughly wedge-shaped haemorrhagic pulmonary infarct of recent occurrence.**



➢ **While this figure shows a thromboembolism 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 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.

• Pulmonary embolism is associated with obstruction of small to medium pulmonary branches (10% to 15% of cases) causes pulmonary infarction **especially 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)

1. Prophylactic therapy which may include anticoagulation, early ambulation for postoperative patients, application of elastic stockings, intermittent pneumatic calf compression, and isometric leg exercises for bedridden patients.
2. Those who develop pulmonary embolism are given anti-coagulation therapy.
3. Patients with massive pulmonary embolism who are hemodynamically unstable (shock) 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.

1. **Bone marrow embolism (due to the presence of hematopoietic and fat elements within a pulmonary artery) can occur after massive trauma, and in patients with bone infarction secondary to sickle cell anemia.**
2. **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 or, less commonly, by increased pulmonary vascular blood flow.**

CLASSIFICATION

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

1. **Pulmonary arterial hypertension (group1), which include heritable forms of pulmonary hypertension and diseases that affecting small pulmonary muscular arterioles, these include:**
   connective tissue diseases, human immunodeficiency virus, and congenital heart disease with left to right shunts.

2. Pulmonary hypertension due to left-sided heart disease (group 2), including congenital or acquired systolic and diastolic dysfunction and valvular heart disease.
3. Pulmonary hypertension due to lung diseases and/or hypoxia (group 3), including COPD and interstitial lung.
4. Chronic thromboembolic pulmonary hypertension (group 4).
5. Pulmonary hypertension with unclear or multifactorial mechanisms (group 5).

MORPHOLOGY

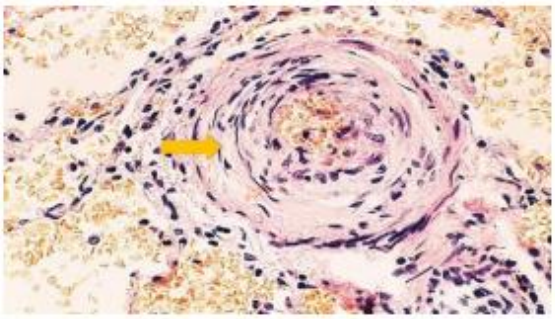
All forms of pulmonary hypertension are associated with these morphologic features:

- Medial hypertrophy of the pulmonary muscular and elastic arteries (small arteries and arterioles).
- Medial hypertrophy and intimal fibrosis of the arterioles and small arteries.
- Pulmonary arterial atherosclerosis (pulmonary artery and it's major bronchioles).
- Right ventricular hypertrophy.

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

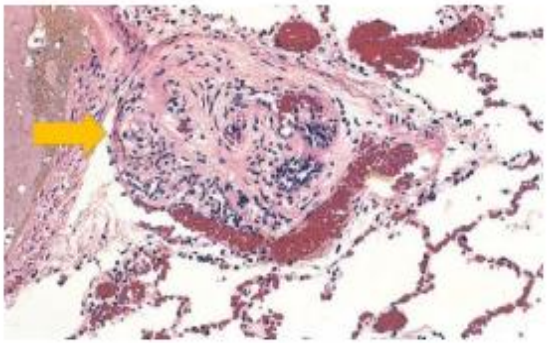
The vessel changes can involve the entire arterial tree, from the main pulmonary arteries down to the arterioles, the arterioles and small arteries are most prominently affected by medial hypertrophy and intimal fibrosis. In severe cases, atheromatous deposits form in the pulmonary artery and its major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

➢ The figure shows the histologic appearance of medial hypertrophy affecting an arteriole.



- Plexiform lesion, uncommon 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.

➢ The 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.



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

- **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 haemorrhagic interstitial pneumonitis and rapidly progressive glomerulonephritis.**

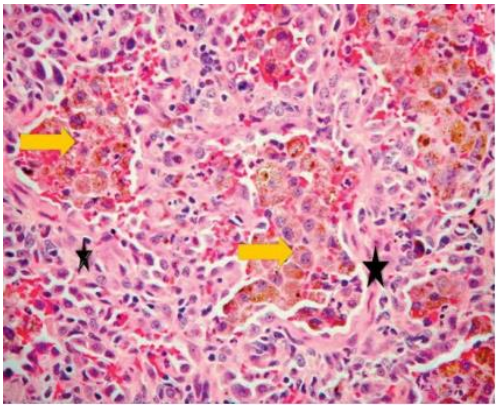
MORPHOLOGY

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

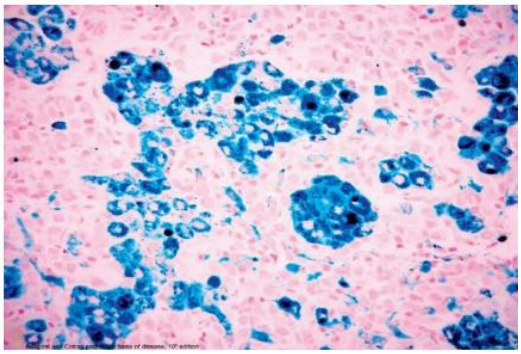
➢ **Microscopic examination shows:**

- **Focal necrosis of alveolar walls associated with intraalveolar hemorrhage and abundant hemosiderin macrophages.**
- **Fibrous thickening of septa.**
- **Hypertrophic type II pneumocytes.**
- **There is abundant hemosiderin due to earlier episodes of hemorrhage.**
- **Linear pattern of immunoglobulin deposition usually (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 haemorrhage syndrome.
Yellow arrows point to the large number of intra-alveolar hemosiderin-laden macrophages.
Black stars point to the background of thickened fibrous septum.



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



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 haemoptysis. 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 POLYANGITIS

- **Granulomatosis and Polyangiitis (formerly called Wegener granulomatosis) in this condition more than 80% of patients develop upper-respiratory or pulmonary manifestations at some point along their course.**
- **The lung lesions are characterized by a combination of necrotizing vasculitis ("angiitis") and parenchymal necrotizing granulomatous inflammation.**
- **The signs and symptoms stem from involvement of the upper-respiratory tract (chronic sinusitis, epistaxis, nasal perforation) and the lungs (cough, haemoptysis, chest pain).**
- **Focal necrotizing, often crescentic, glomerulonephritis.**
- **Anti-neutrophil cytoplasmic antibodies (PR3- ANCAs, also known as C-ANCA) are present in approximately 95% of cases.**

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