Cardiovascular system

Lectures five and six

Thromboembolism and Vasculitis

Objectives:

At the end of these two lectures, the students should be able to:

(1) Understand the basic pathology of thrombogenesis
(2) Risk factors for development of deep vein thrombosis.
(3) Know the types of embolus than can occur and the pathology of pulmonary embolism.
(4) Know the common causes of vasculitis with special emphasis on the clinic-pathological features and mechanism of:
    (A) Giant cell arteritis.
    (B) Polyarteritis nodosa.
    (C) Wegener's granulomatosis.
    (D) Cutaneous hypersensitivity vasculitis and Henoch Schonlein purpura

Key principles to be discussed:

(1) Pathological aspects of thrombogenesis: vessel wall abnormality, vascular stasis or turbulent flow and increased blood coagulability.
(2) Causes of embolism formation.
(3) Predisposing factors for deep vein thrombosis.
(4) Pathology of pulmonary thromboembolism.
(5) Brief description of other forms of emboli like: fat embolism, air embolism, atherosclerotic plaque embolism, amniotic fluid embolism, nitrogen embolism and infective endocarditis.
(6) Pathology of vasculitis: giant cell arteritis, polyarteritis nodosa, Wegener's granulomatosis, Henoch-Schonlein purpura and cutaneous hypersensitivity vasculitis.

Summary:

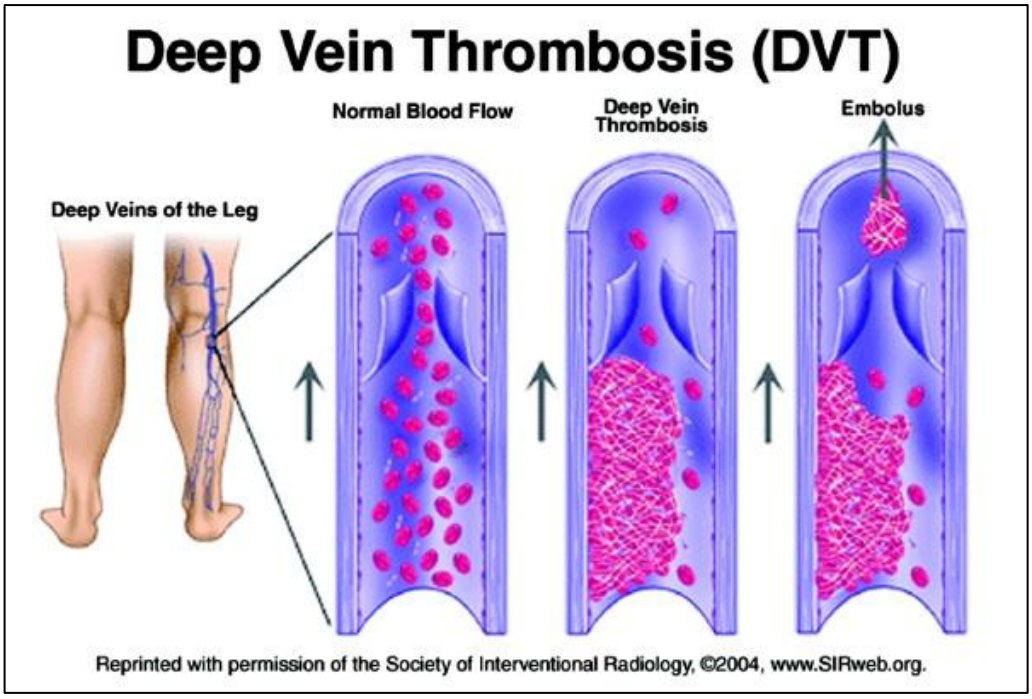
Vasculitis:

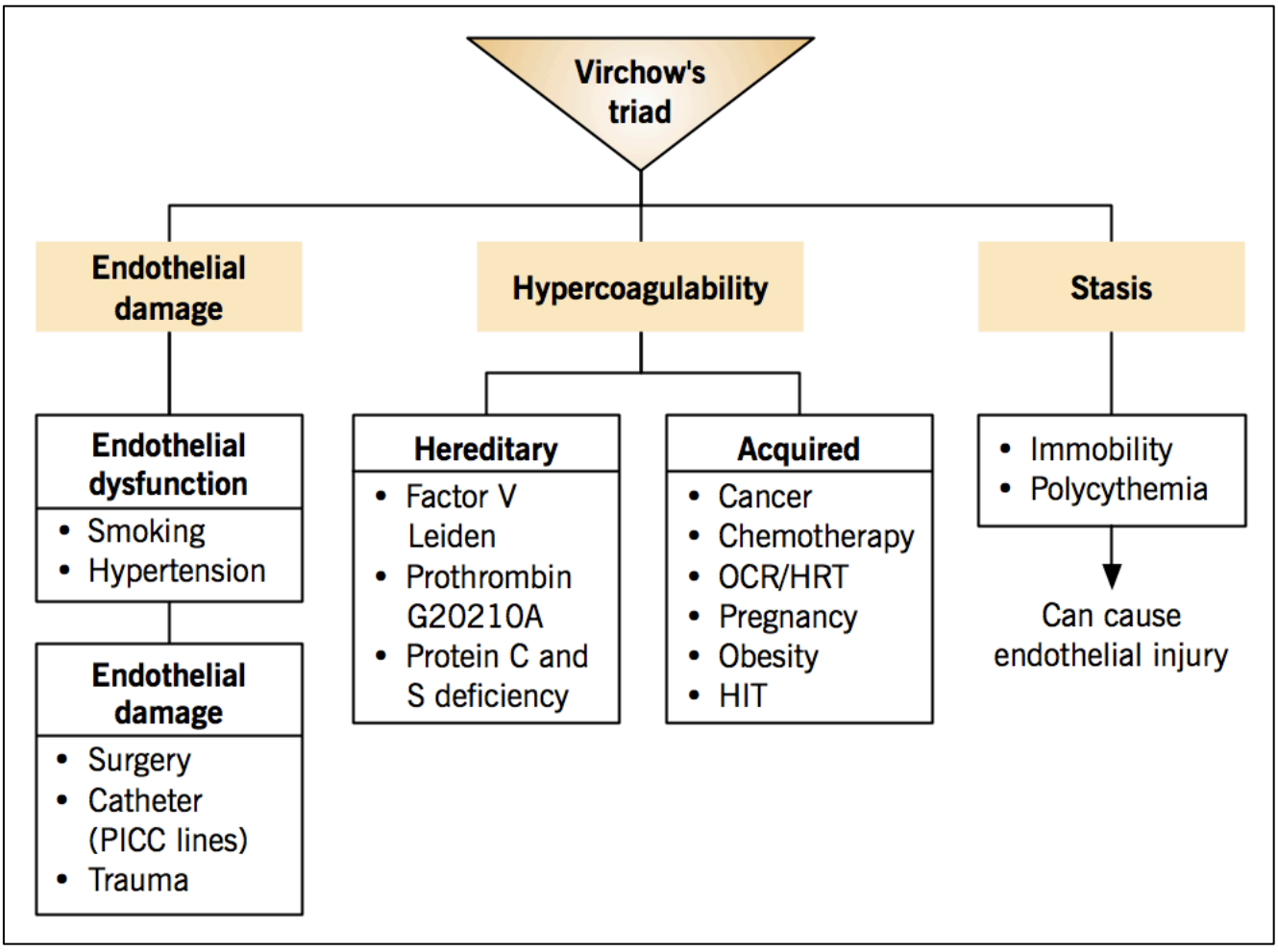
- Vasculitis is defined as inflammation of vessel walls; it frequently is associated with systemic manifestations (including fever, malaise and arthralgias) and organ dysfunction that depends on the pattern of vascular involvement.
- Vasculitis can result from infections but more commonly has an immunologic basis such as immune complex deposition, anti-neutrophil antibodies (ANCAs), or anti– endothelial cell antibodies.
- Different forms of vasculitis tend to specifically affect vessels of a particular caliber and location

Vessel	Disease	Comment
Large	Giant-cell arteritis	>50. Arteries of head.
	Takayasu arteritis	F <40. "Pulseless disease"
Medium	Polyarteritis nodosa	Young adults. Widespread. Or cutaneous
	Kawasaki disease	<4. Coronary disease. Lymph nodes.
	Thromboangiitis obliterans (Buerger disease)	Cigarette smoking, young
Small	**Wegner Granulomatosis**	Lung, kidney. C-ANCA.
	Churg-Strauss syndrome	Lung. Eosinophils. Asthma. p-ANCA.
	Microscopic polyangiitis	Lung, kidney. p-ANCA.
	Cutaneous leukocytoclastic vasculitis	Idiopathic, infectious, drugs, chemicals, cancer and sytemic disease like HNP

Giant-cell arteritis	○ Granulomatous inflammation ○ Temporal artery → pain in its course ○ Fever, facial pain or headache ○ Visual problems and acute vision loss
Polyarteritis nodosa	○ Cutaneous only or systemic ○ Medium to small size, in any organ (esp kidney and skin) ○ Hepatitis B or hepatitis C ○ Ischemia of affected tissues and organs
Leukocytoclastic vasculitis	○ Small blood vessels ○ Skin biopsy is often diagnostic ..neutrophiles, karyorrhexis ○ Idiopathic , antigenic reaction, systemic disease ○ Henoch-schonlein purpura
Thromboangiitis obliterans	○ Medium-sized and small arteries ○ Young …smokers ○ Leg and hands ○ Thrombosis….. Gangrene
Wegener's granulomatosis	○ necrotizing granulomas respiratory tract ○ necrotizing or granulomatous vasculitis (small to medium vessels) ○ renal disease …crescentic, glomerulonephritis. ○ C-ANCA

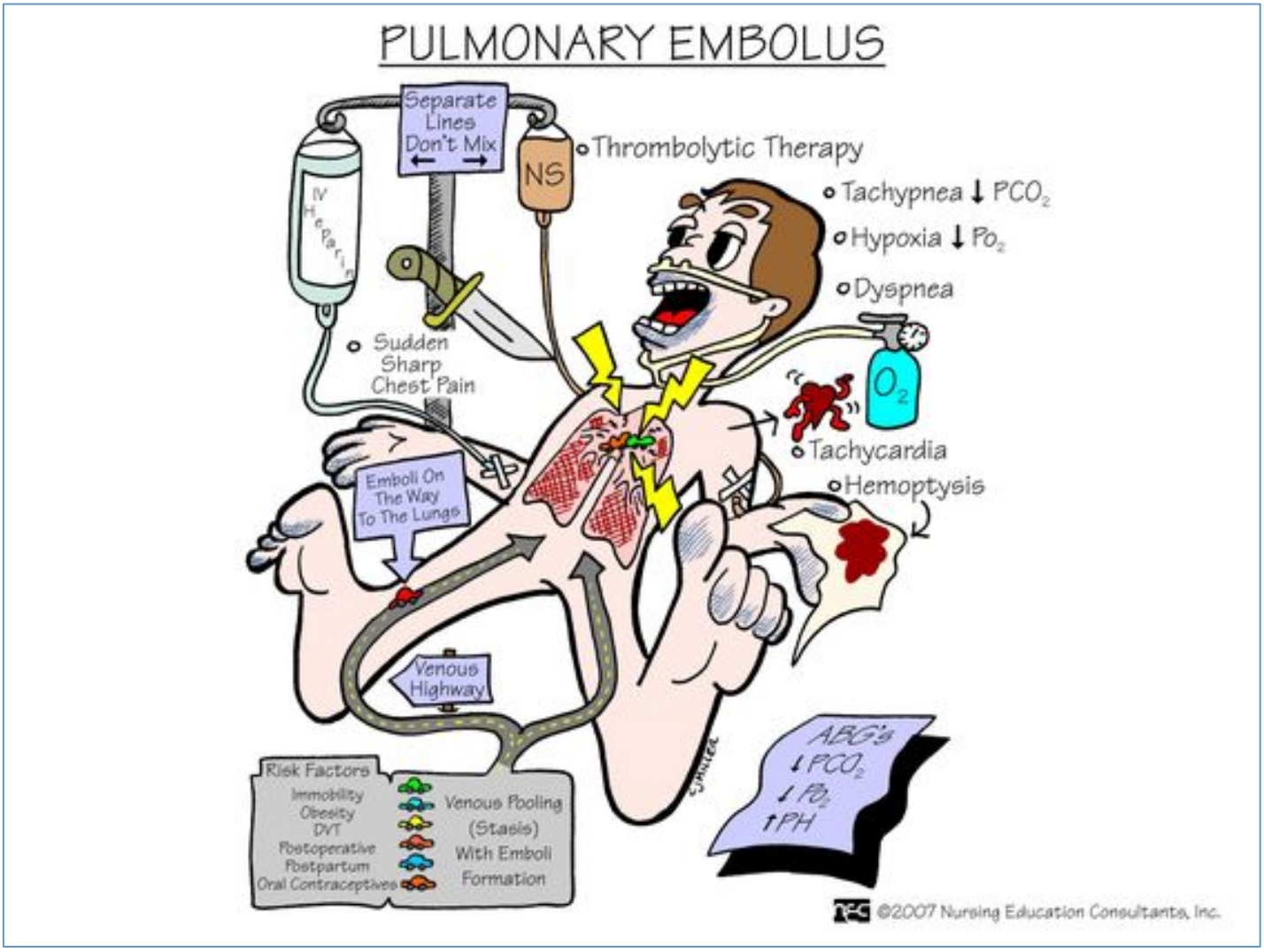
DVT:


Deep Vein Thrombosis (DVT)
Normal Blood Flow
Deep Vein Thrombosis
Embolus
Deep Veins of the Leg
Reprinted with permission of the Society of Interventional Radiology, ©2004, www.SIRweb.org.


Virchow's triad
Endothelial damage
Hypercoagulability
Stasis
Endothelial dysfunction
• Smoking
• Hypertension
Endothelial damage
• Surgery
• Catheter (PICC lines)
• Trauma
Hereditary
• Factor V Leiden
• Prothrombin G20210A
• Protein C and S deficiency
Acquired
• Cancer
• Chemotherapy
• OCR/HRT
• Pregnancy
• Obesity
• HIT
• Immobility
• Polycythemia
Can cause endothelial injury

Pulmonary Embolism

- Almost all large pulmonary artery thrombi are embolic in origin, usually arising from the deep veins of the lower leg.
- Risk factors include prolonged bedrest, leg surgery, severe trauma, CHF, use of oral contraceptives (especially those with high estrogen content), disseminated cancer, and genetic causes of hypercoagulability.
- The vast majority (60% to 80%) of emboli are clinically silent, a minority (5%) cause acute cor pulmonale, shock, or death (typically from large "saddle emboli"), and the remaining cause pulmonary infarction.
- Risk of recurrence is high.



Important notes:

Thrombus:

What does it mean?

A solid mass of blood constituents which develops in artery or vein.

Pathogenesis:

How did the blood clot inside the vessels?

Three things that lead to blood clotting: (very imp)

1- Endothelial injury (mostly) like Atherosclerosis begins with endothelial injury.
2- Stasis or turbulence of blood flow.
3- Blood coagulability:

   There are substances in the blood contributing to this that maintain the fluidity of the blood (prevent blood clotting)

In the blood we have two important things:

1- **Thrombotic (stimulates it)**

   Coagulation cascade has multiple steps leading up to the formation of thrombin which will change -- fibrinogen to fibrin

2- **Anti-thrombotic (stops it) – Fibrinolysis**

   - Antithrombin 3
   - Protien C
   - Protein S

   Deficiency of these factors will lead to thrombosis.

What is the sequence of events?

Let's say you got injured, coagulation cascade will take place by forming thrombin, which will change fibrinogen into fibrin, which will form the clot.

After that, in order for your body to stop forming thrombus it needs Anti-thrombotic fibrinolysis, which will split the fibrin by plasmin

There has to be balance between the coagulation cascade and fibrinolysis.

Hypercoaguable state: (what will increase coagulation leading to thrombosis?)

1- Primary:

- Deficiency of the factors mentioned before Antithrombin 3
- Protein C
- Protein S

2- Secondary:

Acquired state. Could be of low or high risk.

High risk (imp):

1- Prolonged bed rest or immobilization:

Venous thrombosis like after surgery or paralysis legs must move to prevent stasis of blood in the legs. Any stasis (slow blood movement) or turbulence will lead to venous thrombosis (stasis) (most imp).

2- Myocardial infarction → mural thrombus, source of embolus.

3- Tissue damage → endothelial injury

4- Cancer: release of procoagulant tumor products

Tumors could press on the vein to cause turbulence of blood flow.

5- Prosthetic cardiac valve → endothelial injury

Morphology:

- Thrombosis can occur anywhere in the body.
- Arterial or cardiac thrombosis usually begins at the sight of endothelial injury or turbulence (vessel bifurcation) (Splits)
- Venous thrombosis starts or occurs at the sight of stasis mostly in the lower limb

Propagating → spreading and increases in size
Embolus → moves from one place to the other.

- Starts as propagation then as it spreads the tail is prone to fragmentation which will create embolus that could travel anywhere in the body.
- Thrombus under the microscope we will see lines of Zahn (very imp). Contains of platelets of fibrin and RBCs (alternating lines)

What's the difference between arterial and venous thrombosis?

Arterial	Venous
○ Begins in endothelial injury or turbulence ○ Most common sight: coronary, cerebral and femoral arteries ○ Superimposed, stuck to the wall (firmly adherent)	○ Begins in stasis. ○ Because these thrombi form in a relatively static environment, they contain more enmeshed erythrocytes and are therefore known as **red**, or **stasis thrombi**. ○ Stasis of blood = more RBCs = more red = more red thrombi ○ Less sticking than arterial, loosely adherent. ○ Affecting lower extremity.

What's the difference between postmortem clots and venous thrombi?
We use this in autopsy to know if the thrombosis happened before or after death

Venous thrombus	Postpartum clots
○ Firm ○ Rich admixture of RBCs and appear red ○ Attached to the vessel wall (loosely attached)	○ Rubbery and gelatinous ○ Dark red in one side and yellow in the other. ○ Depended on the gravity, RBCs will be down and the yellow part up ○ Not attached to the vessel wall ○ So which of these attached mostly to the vessel wall? ○ Arterial – venous – postmortem

Thrombi on the heart valves:

- Endocarditis → vegetations → because of large thrombotic masses on the heart valves because of infection (bacteria mostly or fungi)
- Mural thrombus → MI (As usual like arterial thrombosis but u might see vegetations because of infection)
- Some times vegetations are non bacterial in auto-immune disease
- **(Libman-Sacks) endocarditis** in patients with systemic lupus erythematosus (not important)

What's the fate of thrombus?
We have thrombus in femoral vein what's the fate? It depends, Five things could take place:

- **Resolution**

  It's done, fibrolysis and that's it
- **Propagation**

  Spreads and increases in size

  From femoral artery to the aorta for example

  If it was in a vein it moves with the blood in the same direction to the heart

  And artery opposite to the heart
- **Embolism**
  - → Venous → mostly lung because right atrium to right ventricle to the lung
  - → Arterial → lower limb → causes gangrins (remember one of the complications of MI) or cerebral infarction
- **Organization and recanalization**

  Fibrosis → recanalization → less dangerous blood moves through it → turbulence of blood → doesn't close completely
- **Organization and incorporation into the wall.**

Deep vein thrombosis:

How can we diagnose a patient with it?

→ One of the legs is more swollen than the other, warm and dark.

→ Deep veins of the leg will have thrombosis.

What's the cause of it?

Stasis.

What's the problem?

It may embolize to the lung (pulmonary embolism).

- They are mostly asymptomatic.

What are the causes?

1. Bed rest and immobilization
2. Congestive heart failure (a cause of impaired venous return):

   Vein coming to the heart has less flow
3. Trauma, surgery, and burns
4. Pregnancy:
   - The potential for amniotic fluid infusion into the circulation at the time of delivery can cause thrombogenesis
   - Late pregnancy and the postpartum period are also associated with systemic hypercoagulability
   - Might obstruct vein in the pelvis
5. Tumors
6. Advanced age

Embolus:

Detached, could be liquid or gaseous.

Depending on the size of the embolus it may either close a big artery or a small one → leading to necrosis

Types:

- Pulmonary thromboembolism → Veins
- Systemic thromboembolism → artery
- Fat embolism
- Air embolism
- Amniotic fluid embolism

Pulmonary thromboembolism:

→ Comes from deep vein thrombosis.

→ Could be asymptomatic (clinically silent) until there is 60% obstruction of the lungs, **why?**

Because they are small closing small arteries in the lungs

→ Sudden death, right heart failure *(cor pulmonale),* occurs when 60% or more of the pulmonary circulation is obstructed with emboli.

Systemic thromboembolism:

- → Comes from artery or heart
- → Mostly arises from intracardiac mural thrombi

Fat embolism:

After fracture of long bones → bones have fat → fat goes to the artery or vein → closes it

Air embolism:

Comes from outside so How does it enter the artery or vein?

- **Obstetric procedure:**

  Gynecological examination or procedure may rupture one of the arteries in the uterus or cervix so air will enter in the circulation.
- **Chest wall injury:**

  There will be exposure between the blood and air
- **Decompression sickness:**

  Sudden change in atmospheric pressure, when it takes place air embolism happens (in scuba divers)

Amniotic fluid embolism:

- During labor and immediate postpartum period.
- During labor → rupture in amniotic sac → maternal infusion of amniotic fluid or fetal tissue (hair – skin into maternal circulation) – very rare.
- Microscopically:

  In lungs mostly – we can see fetal products

Vasculitis: Cause of vasculitis is mostly unknown.

Pathogenesis:

- Immune mediated mostly
- Caused by infection

Vasculitis can be classified according to the size of the vessel:

1- **Large:**
   Giant-cell arteritis
2- **Medium sized:**
   Poly arteritis
3- **Small**
   - LCA
   - Wegner granulomatosis
   - Henoch-Schonlein purpura

Giant- cell arteritis:

- Most-common type, usually macroscopic.
- Affects temporal arteries, so the patient will be present with headache. But if the ophthalmic artery is affected it will result in vision disturbance such as diplopia, blindness or myopic vision.
- Antineutrophil cytoplasmic antibodies (ANCAs) mean antibodies against the cytoplasm of neutrophils.
- Segmental means that not the whole artery is involved only segments and this involvement can be acute and chronic which means the patient may have areas of acute inflammation and areas of chronic inflammation
- **How can we confirm the diagnosis?**
  By biopsy and histologic confirmation where we can see the granuloma and giant cells in the artery
- Temporal artery will give ophthalmic artery → patient might be present will visual distubence → if not treated might progress to blindness

1- Giant-cell
2- Temporal
3- Headache and facial pain
4- Visual problem

Morphology:

Disruption of elastic lamina. (Fragmentation), after a while when we take a biopsy we can know the patient had vasculitis because of the fragmentation in the elastic lamina (not very important).

- Treated with corticosteroids

Poly-arteritis nodosa:

- Medium sized, can affect small vessels.
- Cutaneous (skin only) or systemic affecting any organ (specially kidney)
  Affected organ will undergo ischemic changes (except the lung)
- Associated with hepatitis B and C.
- Skin biopsy (deep) especially in the lower limb they take a deep skin biopsy. **Why deep?**
  Because first we have the epidermis, which has small vessels, and under it we have sub-cutaneous fat has medium sized vessels (it's the one affected).
- Symptoms are dependent on the organ affected, difficult to diagnose.
- Segmental → a part of the artery is affected then another isn't and so on, so you can end up with a normal part in the biopsy, because the artery isn't all abnormal.
- It can affect any organ except the lungs e.g.: in spleen in the liver and skin –the most common involved organ is kidney.
- If the skin is affected will have ulceration of skin if the gastrointestinal blood vessel is effected patient will come with bloody diarrhea and bad abdominal pain and melena (dark sticky feces containing partly digested blood)
- If the blood vessels supplying the skeletal muscle are affected it will result in acute muscle spasm -if the kidney is affected they will come with rising creatinine and blood in the urea.
- Cyclophosphamide: is an immune suppressant

Wegener granulomatosis:

- Has granuloma
- Triad:
  - Affecting respiratory tract. And Kidney problem
  - If patient presented with these Most likely he has this disease.
    1- Necrotizing granuloma of respiratory tract, mostly in the nasal and paranasl sinuses (bleeding)
    2- Renal disease. Crescentic glomerulonephritis
    3- Small-medium sized vessels
- For diagnosis:
  Blood test: C-ANCAs (very important) → Positive in serum of more than 95% of patients.
  - The main clue is C-ANCA, their blood will be +ve for C type of antineutrophilic antibodies
  - A lot of people will come with bleeding from the nose because they have ulcer in the nasal mucosa if we take biopsy we'll find granuloma.
- It has bad prognosis if not treated.

Morphology:

- **Collection of epithelioid histiocytes = granuloma**
- Fragmented smooth muscle
- Destroyed blood vessel by inflammation
- **How can we know it's a blood vessel? SMC**

- Wegener granulomatosis is the original name of disease, But the name has been changed to granulomatous polyangitis
- Wegener is germen scientist he did a lot of experiments in the Jewish population, so he induced this disease in these people to study it and he's the one who has written the best description about it.

Thromboangiitis obliterans:

→ *Thrombo: thrombosis.*
→ *Angitis= vasculitis*
→ *Obliterans=obstruct.*

- Mainly affects foot and hand.
- People affected are heavy smokers because the cigarettes contain toxin that's directly damage the blood vessels and cause inflammation in the early stages of the disease if they stop smoking the disease will stop.
- Highly associated with smoking.
- Stopping smoking will prevent the next attack.
- Present with pain → then gangria because of thrombus formation in vessels supplying hands and feet.
- Symptoms:

  They will say that when I walk I have pain and this pain is called (instep claudication) because when we walk there is more demand which blood vessel can't handle resulting in more pain. And the worst thing when the artery is affected it affects the vein next to it and the nerve next to it. All of them get inflamed which will result in severe pain.

Microscopically:

- In the middle; thrombus formation
- The wall of blood vessel inflammation
- And inside there is obliterans.

Leukocytoclastic or hypersensitivity vasculitis:

- Fibrinoid necrosis can be seen here and in in malignant hypertension.
- Hypersensitivity vasculitis → fibrin material.
- It is a disease of small vessels.
- Leukocytoclastic= leukocytes, clastic = fragmentation (karyorrhexis)
- Mostly only skin.
- It can affect other organs if it is associated with systemic disease:
  a) **Collagen vascular diseases** (lupus erythematosus, rheumatoid arthritis)
  b) **Henoch-Schonlein purpura**

Henoch-Schonlein purpura (HSP):

- IgA mediated disease.
- Affects children (pediatrics)

  Signs of it are?
  - Skin rash. Because of vasculitis.
  - Arthralgia
  - Abdominal pain

  If that's so we take a biopsy to exclude it.

Microscopically?
We can see leukocytoclastic vasculitis

Microscopic polyangiitis/polyarteritis:

NOTE: P-ANCA IS THE CLUE FOR MICROSCOPIC POLY ANGITIS

- Cutaneous leukocytoclastic
  - Cutaneous= skin
  - Leukoco =WBC
  - cytoclastic means that something is destroyed or debris
- It's the 2nd most common vasculitis after granulomatous angiitis seen in the skin
  - Leukocytoclasis refer to nuclear debris infiltrating neutrophils
- **How do we diagnose it?**

  Skin biopsy if we see the capillaries are surrounded by neutrophils and neutrophilic debris

- Unlike the poly arthritis nodosa and giant cells arteritis where we have different stages of disease in the same vessel acute in part of the artery and chronic in other part of the artery, all the lesion are the same everything is acute or everything is chronic it's not like some is acute and the other is chronic which mean consistency in the age of the lesions

What from blue box will lead to what in the red box?

1) Intracardiac mural thrombi cerebrum or gangria
2) Caisson disease
3) Saddle embolus
4) Fractures of long bones
5) Obstetric procedures
6) Decompression sickness
7) Grecian Bend
8) Deep vein thrombosis
9) Complication of labor and the immediate postpartum period
10) Deep sea divers
11) Presence of squamous cells, lanugo hair, fat, and mucin in pulmonary circulation

A) Pulmonary thromboembolism
B) Systemic thromboembolism
C) Fat embolism
D) Air embolism
E) Amniotic fluid embolism

Answers:
1- B
2- D
3- A
4- C
5- D
6- D
7- D
8- A
9- E
10- D
11- E

What from purple box will lead to what in the blue box?

1. C-ANCA
2. Smokers
3. Thrombosis→ gangrene
4. Skin biopsy is often diagnostic
5. Henoch-Schonlein purpura
6. Facial pain or headache
7. Renal disease → crescentic, glomerulonephritis.
8. Necrotizing granulomas respiratory tract
9. Visual problems and acute vision loss
10. May be Ig-A mediated
11. Hepatitis B or hepatitis C
12. Medium to small size artery
13. Large artery

a) Giant cell arteritis.
b) Polyarteritis nodosa.
c) Wegener's granulomatosis
d) Leukocytoclastic vasculitis.
e) *Thromboangiitis obliterans*

Answers:
1) c
2) e
3) e
4) d
5) d
6) a
7) c
8) c
9) a
10) d
11) b
12) b
13) a

Check your understanding with MCQs:

1. **Which of the following leads to thrombosis?**
   A. Deactivated platelets.
   B. Protein C
   C. Protein S
   D. Coagulation cascade
2. **Which of the following belongs to Virchow triad?**
   A. Endothelial injury
   B. Protein C
   C. Protein S
   D. All of the above.
3. **What can we see in a thrombus?**
   A. Lines of Zahn
   B. RBCs
   C. Platelets
   D. All the above
4. **Immunosuppressive therapy is appropriate when vasculitis is:**
   A. Infectious
   B. Immune-mediated
   C. Both
   D. None of the above
5. **Which of the following is not a characteristic of arterial thrombi?**
   A. Common site is femoral artery
   B. Friable
   C. Adherent to the injured wall
   D. Affects lower extremity
6. **Post-mortem clots are all of the following except:**
   A. Firm
   B. Rubbery
   C. Red in color
   D. Attached to the vessel wall
7. **Patients with vasculitis often have:**
   A. PR3-ANCA
   B. MPO-ANCA
   C. Both depending on the type of vasculitis
   D. None of the above

1- D	2- A	3- D	4- B	5-D	6-B	7-C

8. Which of the following is a fate of thrombus?

A. Resolution
B. Propagation
C. Embolism
D. All of the above

9. Which type of ANCA is present in Wegener granulomatosis?

A. PR3-ANCA
B. MPO-ANCA
C. PPP-ANCA
D. All of the above

10. Vegetations can be:

A. Bacterial
B. Fungal
C. Sterile
D. All of the above

11. A detached intravascular solid, liquid, or gaseous mass that is carried by the blood to a site distant from its point of origin. Is:

A. Embolus
B. Vessels
C. Blood
D. None of the above

12. Which of the following is not a type of embolus?

A. Air
B. Fat
C. Food
D. Pulmonary

13. Fat embolism syndrome is characterized by:

A. Pulmonary insufficiency
B. Hypertension
C. Gas embolus
D. Non of the above

14. Which of the following could lead to blindness?

A. Polyarteritis nodosa
B. Wegener granulomatosis
C. Giant-cell arteritis
D. Small-cell arteritis

8- D	9- A	10- D	11- A	12-C	13-A	14-C

Questions in red are important*

15. Decompression syndrome occurs when?

A. Sudden changes in atmospheric pressure
B. Elevated change in atmospheric pressure
C. Pressurized aircrafts
D. All of the above

16. Which of these people could get decompression sickness?

A. A women in labor
B. A man in a pressurized aircraft
C. Deep sea diver
D. A child in the playground

17. During an X-ray of a 27 years old woman, fragments of hair where found in the lungs, this is most likely:

A. Air embolus
B. Amniotic fluid embolus
C. Fat embolus
D. That cannot happen

18. Which of these diseases is associated with hepatitis B?

A. Polyarteritis nodosa
B. Wegener granulomatosis
C. Giant-cell arteritis
D. Small-cell arteritis

19. A patient was presented to the hospital with abdominal pain and bloody stool, the diagnosis most likely is?

A. Polyarteritis nodosa
B. Wegener granulomatosis
C. Giant-cell arteritis
D. Small-cell arteritis

20. A patient was presented to the hospital with headache and facial pain, the diagnosis most likely is?

A. Polyarteritis nodosa
B. Wegener granulomatosis
C. Giant-cell arteritis *
D. Small-cell arteritis

21. A patient was presented to the hospital with ulceration in nasopharynx and evidence of renal disease, the diagnosis most likely is?

A. Polyarteritis nodosa
B. Wegener granulomatosis *
C. Giant-cell arteritis
D. Small-cell arteritis

15- A	16- C	17-B	18- A	19-A	20-C	21-B

22. A patient was presented to the hospital with a history of heavy smoking, he feels pain in his hands even while resting, there is evidence of ulceration. The diagnosis most likely is?

A. Polyarteritis nodosa
B. Buerger disease *
C. Giant-cell arteritis
D. Small-cell arteritis

23. Palpable purpura is a characteristic of which disease?

A. Polyarteritis nodosa
B. Buerger disease
C. Giant-cell arteritis
D. Hypersensitivity vasculitis *

24. Immunoglobulin A can be found in which disease?

A. HSP*
B. DVT
C. Both
D. None

25. We can we treat Wegner granulomatosis with all of the following except?

A. Steroids
B. TNF – inhibitors
C. Rituximab
D. Smoking cessation *

22- B	23- D	24- A	25-D

Please Contact us: Pathology435@gmail.com

Team members:

خالد أبو راس	نوف التويجري
عمار صالح آل منصور	ا لجوهرة المزروع
حمزة عبدالله الفعر	رغد النفيسة
أنس بليغ محمد علي	ريم العقيل
نايف الهادي	سمر العتيبي
ريان منيف	فرح مندوزا
فارس إبراهيم الورهي	منيرة العمري
قصي عبدالباقي عجلان	نوف العبدالكريم
أحمد طه الخياري	
زياد عبدالعزيز السالم	
مشعل الحازمي	

قال صلى الله عليه وسلم: من سلك طريقًا يلتمس فيه علمًا سهّل الله له به طريقًا إلى الجنة

دعواتنَا لكم بالتوفيق.