PATHOLOGY TEAM
439

Revised & Approved by: Shayma Abdullah Alghanoum
Faisal Alotaibi

جامعة الملك سعود
King Saud University
1957

Vasculitis

Objectives:

·Know the common causes of vasculitis with special emphasis on the clinic-pathological features and mechanism of: Giant cell arteritis. Polyarteritis nodosa. Wegener's granulomatosis. Cutaneous hypersensitivity vasculitis. Thromboangiitis obliterans (Buerger's disease).

Index:
Important
NOTES
Extra Information

Introduction:Vasculitis

Vasculitis

It is a general term for inflammation of vessel walls of arteries (more common) and veins, has **many** possible symptoms (depending on the vessel it's affecting).

Causes of Vasculitis

Immune-mediated
Most common

Main immunological mechanisms:

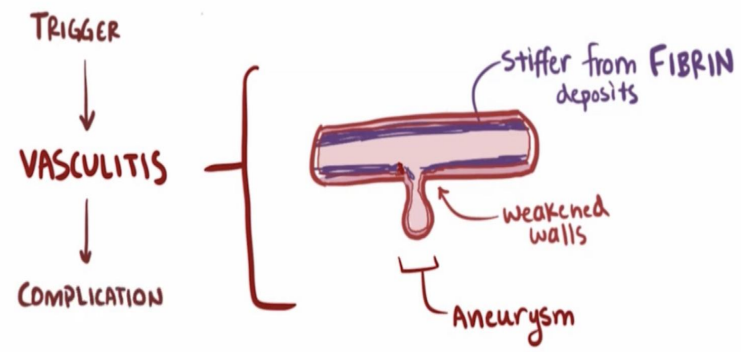
- Immune complex deposition
- Antineutrophil cytoplasmic antibodies (antibodies against cytoplasmic neutrophils)
- Anti-EC antibodies
- Autoreactive T cells

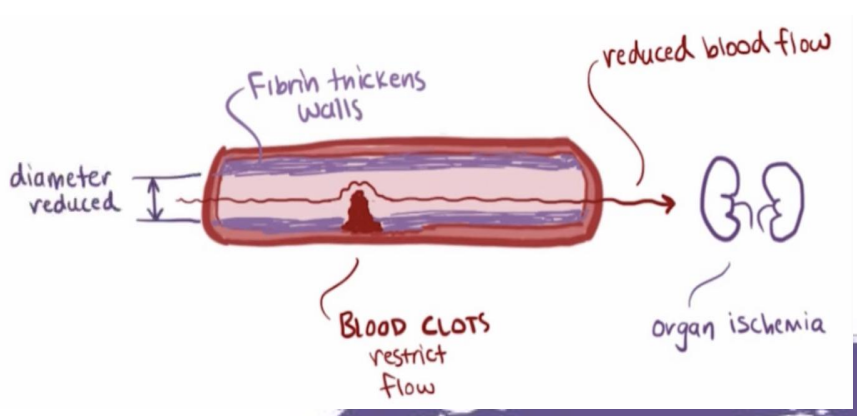
Infection, physical or chemical injury

General information about vasculitis

When endothelial cells are damaged, underlying collagen and tissue factor are exposed which will increase the chance of blood coagulation. The vessel wall will become weaker making aneurysm more likely. Vessel wall will also become stiffer due to fibrin deposition from healing process. Due to reduced blood flow, there will organ ischemia depending on what the vessel is supplying.

Watch before (osmosis)





Overview: Types of Vasculitis

Types of vasculitis are grouped according to the size of blood vessels affected.

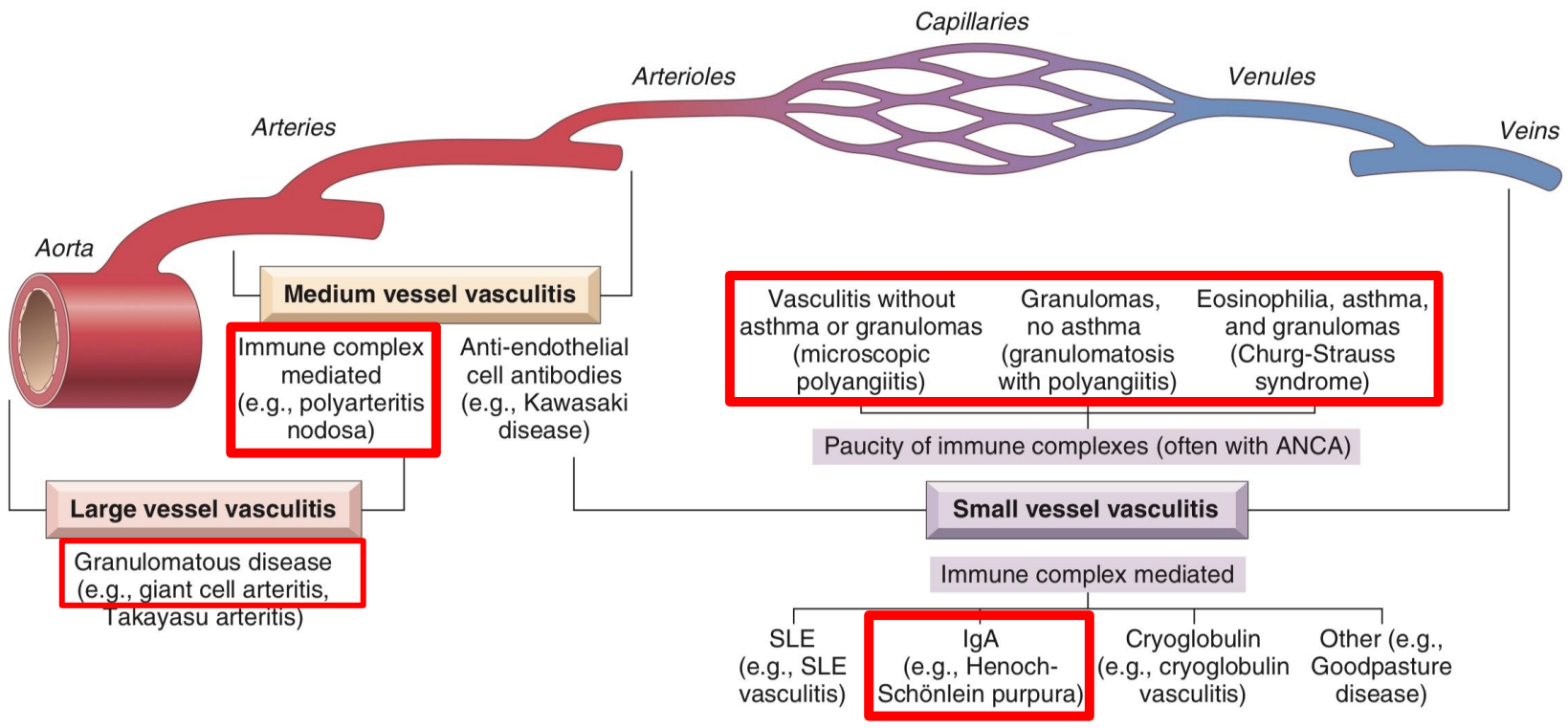


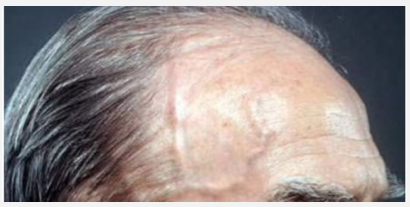
Table 10.4 Primary Forms of Vasculitis

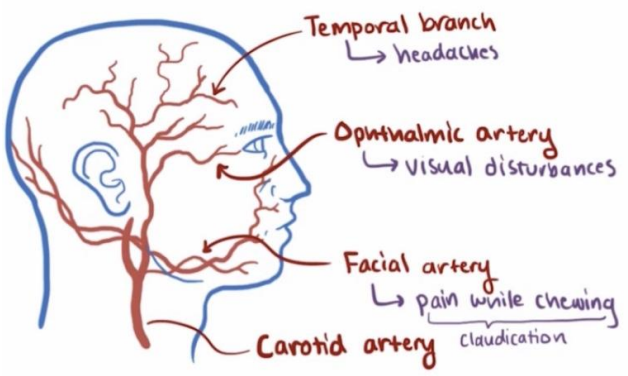
	Giant Cell Arteritis	Granulomatosis With Polyangiitis	Churg-Strauss Syndrome	Polyarteritis Nodosa	Leukocytoclastic Vasculitis	Buerger Disease	Behçet Disease
Sites of Involvement							
Aorta	+	–	–	–	–	–	–
Medium-sized arteries	+	+	+	+	–	+	+
Small-sized arteries	–	+	+	+	+	+	+
Capillaries	–	–	–	–	+	–	+
Veins	–	–	–	–	+	+	+
Inflammatory Cells Present							
Lymphocytes	+	+	+	±	±	±	±
Macrophages	+	+	+	±	±	±	±
Neutrophils	Rare	+	+	±	±	±	Required
Eosinophils	Very rare	±	Required	±	±	±	±
Other Features							
Granulomas	±*	Required*	±	–	–	–	–
Giant cells	Often; not required	±	–	–	–	–	–
Thrombosis	±	±	±	±	±	Required	±
Serum ANCA positivity	–	+	+	±	–	–	–
Clinical history	>40 years of age, ± polymyalgia rheumatica	Any	Asthma, atopy	Any	Any	Young male smoker	Orogenital ulcers

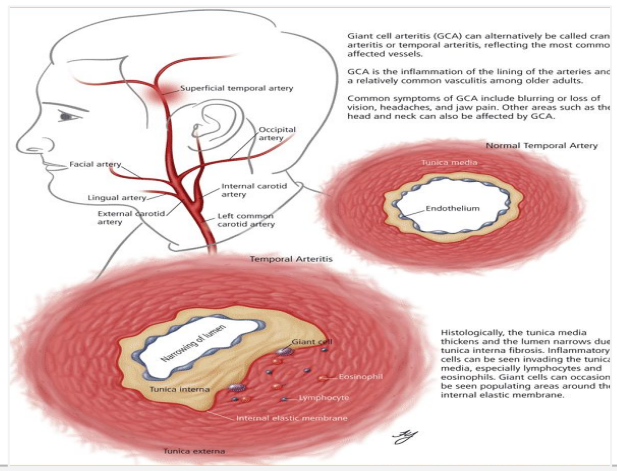
*The granulomas of giant cell arteritis are found within the vessel wall as part of the inflammation comprising the vasculitis, but need not be present to render the diagnosis. The granulomas of granulomatosis with polyangiitis are larger, spanning between vessels, and associated with areas of tissue necrosis.
ANCA, Anti-neutrophil cytoplasmic antibodies.
From Seidman MA, Mitchell RN: Surgical pathology of small-and medium-sized vessels. In Winters, GL, ed., *Current concepts in cardiovascular pathology*, Philadelphia, 2012, Saunders.

Although the diseases are similar in some ways, they often differ with respect to which organs are affected, which medications are used to treat them, and other characteristics.

Giant-Cell (Temporal) Arteritis

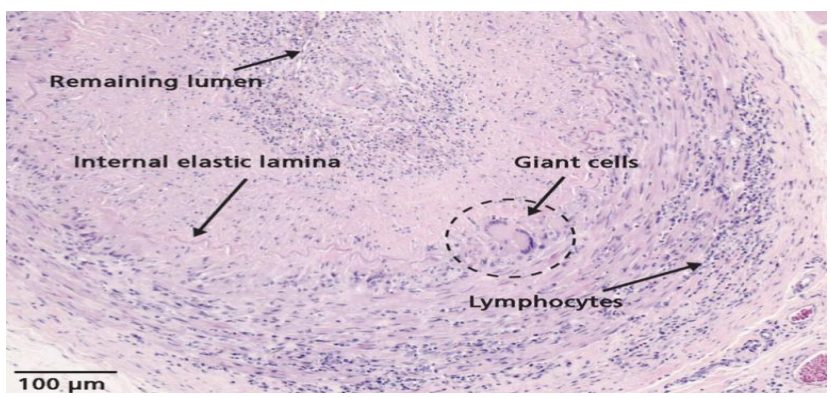
Definition 	Chronic, granulomatous inflammation of **large to medium** sized arteries, especially the **branches of the carotid artery** in the head (**temporal artery** and branches of the ophthalmic artery). The involvement is segmental, not the whole artery is affected. The inflammation could be acute or chronic in those different segments.
Epidemiology	• Most common type of vasculitis • Above **50** years old • More common in females (F:M, 2:1)
Diagnosis & Treatment	• Clinical index of suspicion that leads to obtaining a biopsy from affected area. As its segmental sometimes biopsies are negative since not the whole vessel is diseased. • The diagnosis depends on biopsy (from the temporal artery) and histologic confirmation. • Treatment - corticosteroids (weakens immune response)
Symptoms (Clinical features)	• Fever • Facial pain or headache, often most intense along the course of the superficial **temporal artery** • Visual problems and acute vision loss (due to ophthalmic artery involvement) • Thickened and painful temporal artery • Jaw pain





Morphology

- **Granulomatous inflammation of the blood vessel wall**
- **Giant cells**
- Disruption and fragmentation of internal elastic lamina
- Proliferation of the intima with associated occlusion of the lumen
- The healed stage reveals collagenous thickening of the vessel wall and the artery is transformed into a fibrous cord

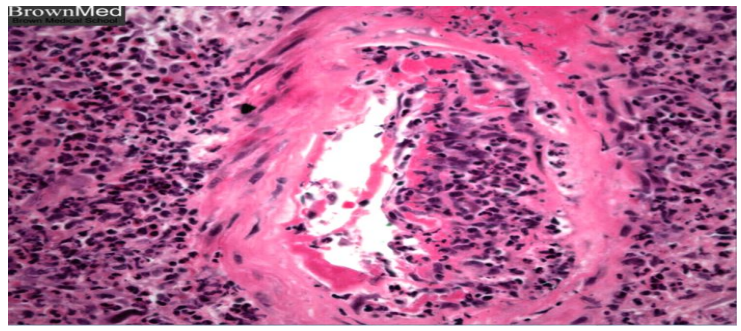


Polyarteritis Nodosa

Definition	Segmental (nodosa= nodes) necrotizing inflammation of arteries of **medium to small size**, could involve any organ except the lungs. 
Epidemiology	It's a disease of young adults.
Characteristics	• Most frequently **kidneys** (most common, so renal manifestations are seen), heart, liver, and gastrointestinal tract. • Renal arterial (most common) involvement is often prominent and is a major cause of death. • Polyarteritis nodosa has been associated with **hepatitis B or hepatitis C** virus infection. The immune cells attack the endothelium rather than hepatitis B and causing transmural inflammation (all 3 layers of vessel are affected). • Weakening of the arterial wall due to the inflammatory process may cause aneurysmal dilation or localized rupture. • Particularly characteristic of polyarteritis nodosa is that all the different stages of activity (i.e. active and chronic stages) may coexist in same artery or in different artery at the same time.
Prognosis & Treatment	**Fatal if untreated, but steroids and cyclophosphamide are curative.**
Symptoms (Clinical features)	Manifestations are due to ischemia and infarction of the affected tissue • Fever • Weight loss • Abdominal pain • Melena (bloody stool) • Muscular pain • Neuritis

Morphology

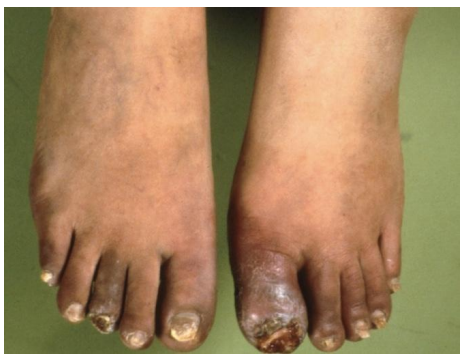
Polyarteritis nodosa with **segmental** inflammation and **fibrinoid necrosis** and occlusion of the lumen of this artery. Note that part of the vessel wall at the left side is uninvolved.



Thromboangiitis Obliterans (Buerger disease)

Thromboangiitis obliterans
Thombo- thrombus
Angiitis- vessel involvement
Obliterans- obstruction of vessel by inflammation

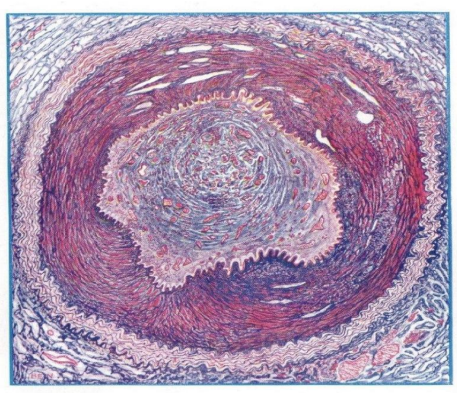
Definition	A segmental, thrombosing, acute and chronic inflammation of **medium-sized and small** arteries of the leg and hands (tibial and radial arteries), with secondary extension into adjacent veins and nerves (when inflammation is severe).
Epidemiology	• Affects people **before** the age of 35 years. ★ **Heavy smokers of** cigarettes that start at young age. Due to "Tobacco either leads to **direct toxicity of endothelium**, or **induces an immune response."**
Symptoms (Clinical features)	★ **Instep claudication: Pain** in the affected hand or foot induced by exercise. ○ Patients can have pain even at rest due to neural involvement (we mentioned before that inflammation could extend to adjacent nerves so that would induce pain at rest) why experience more pain during exercise ? because of an increase in the O2 demand by the tissue in the presence of thrombus • **Chronic ulceration** of toes or fingers may appear, followed in time by gangrene. • Abstinence from cigarette smoking in the early stages of the disease brings **relief** from further attacks. Once the disease is established it cannot be reversed, quitting smoking will not make it go away.

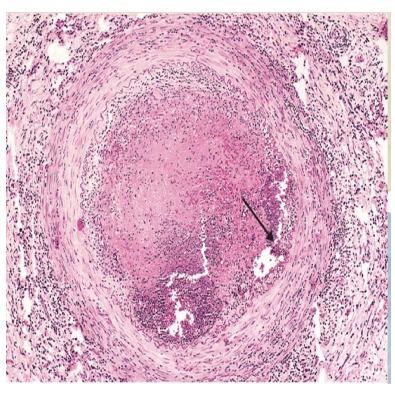


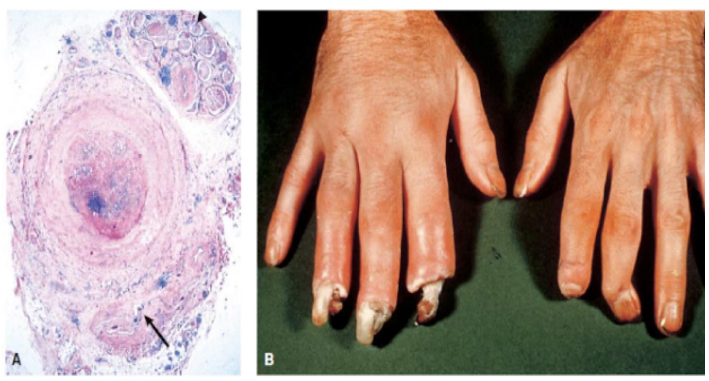
Blood vessel is affected →vessel is completely blocked (thromboangiitis obliterans) → ischemia, hypoxia → irreversible injury → coagulative necrosis

Morphology

Acute & Chronic Inflammation Accompanied with Luminal thrombosis. The inflammatory process extends into adjacent veins and nerves (rare with other forms of vasculitis), and in time all three structures become encased in fibrous tissue.







Buerger disease. A. Section of the upper extremity shows an organized arterial thrombus that has occluded the lumen. Some inflammatory cells are evident in the adventitial fat. In this instance, the vein (*arrow*) and the adjacent nerve (*arrowhead*) show foci of chronic inflammation. **B.** The hand shows necrosis of the tips of the fingers.

Granulomatosis with Polyangiitis
(Previously: Wegener granulomatosis)

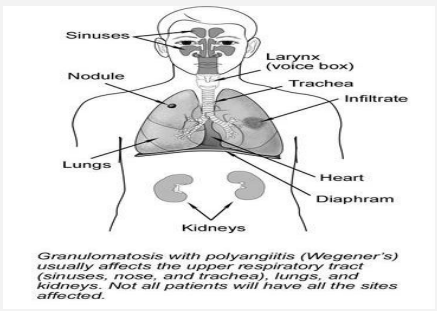
Definition

A type of necrotizing vasculitis affecting **small-medium** sized vessels characterized by **wegener's triad.** The name highlights the two central pathologic features of the disease, **granuloma formation** and **inflammation of blood vessels**. (Uncommon disease)

Epidemiology

Males are affected more often than females, at an average age of about 40 years.

Diagnostic Criteria (Wegener's triad)



Granulomatosis with polyangiitis (Wegener's) usually affects the upper respiratory tract (sinuses, nose, and trachea), lungs, and kidneys. Not all patients will have all the sites affected.

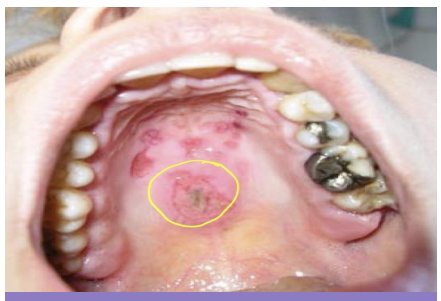
Wegener's triad is a pathomorphological diagnostic criteria that states the involvement of:

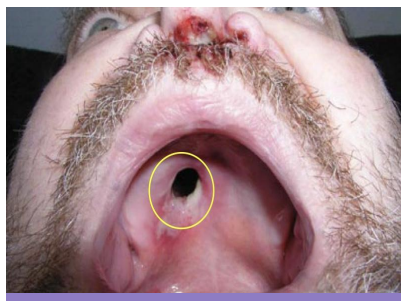
1. Necrotizing granulomas of the upper (nose,pharynx, etc) and lower respiratory tract (lung)
2. Renal disease (kidney involvement) in the form of necrotizing, **crescentic**, glomerulonephritis
3. Necrotizing **or** granulomatous vasculitis of **small to medium** sized vessels.

Symptoms (Clinical features)

Remember that manifestations depend on the organs affected by this type of vasculitis.

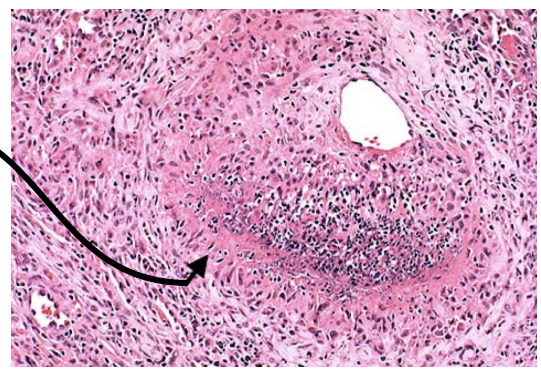
- Chronic sinusitis (URT)
- Mucosal ulcerations of the nasopharynx (URT)
- Persistent pneumonitis (LRT)
- Evidence of renal disease
- **C-ANCAs** (antineutrophilic cytoplasmic antibodies) is **positive** in serum of **more than 95%** of patients.

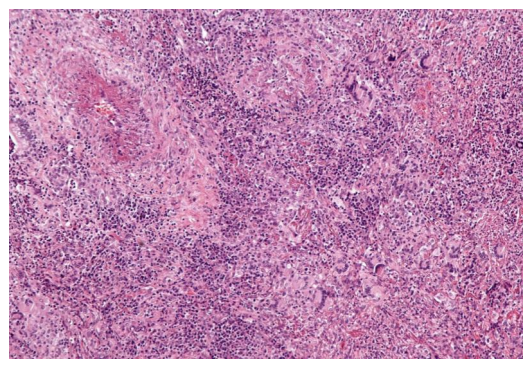

Palatal ulceration


Palatal destruction

Morphology

Epithelial cells, very destructive type.





Prognosis

May lead to **death within two years** if not treated.

Microscopic Polyangiitis/ Polyarteritis

Microscopic polyangiitis

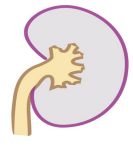
It is a **systemic**, **small** vessel vasculitis associated with **glomerulonephritis (renal disease).** In the past it has been confused with leukocytoclastic vasculitis. (Uncommon disease)

(Clinical features)

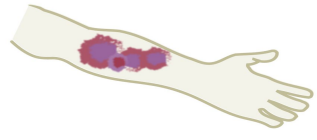
★ **P-ANCA is characteristically present**
In granulomatosis polyangiitis it was **C-ANCA**

Microscopic Polyangiitis
ANCA- Associated;
Necrotizing pauci-immune, and no granulomas

- Affects mostly small vessels, including venules and capillaries.
- Kidneys
  - Glomerulonephritis with rapid progression to renal failure.



- Skin
  - Purpuric rash



- Lungs are less commonly invovled
  - Alveolar hemrrohage, fibrosis possible.
- Tends to occur in adults 50-60 y.o.

Churg-Strauss Syndrome (additional reading)

Churg-Strauss Syndrome

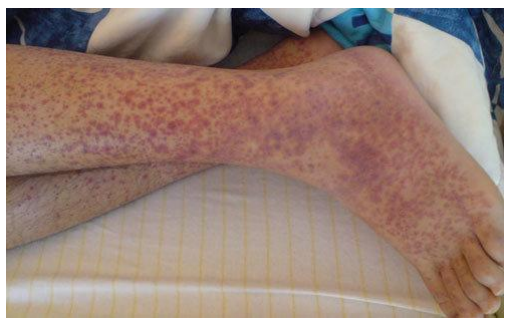
Eosinophil-rich and granulomatous inflammation involving the respiratory tract and necrotizing vasculitis affecting small vessels. (Extremely rare disease)

Symptoms (Clinical features)

Associated with **p-ANCAs**

Associated with asthma and blood eosinophilia

Cutaneous Leukocytoclastic (Hypersensitivity vasculitis/angiitis)

Definition	**Necrotizing vasculitis** of small vessels (arterioles, capillaries, venules). **Leukocytoclasis:** refers to the nuclear debris of infiltrating neutrophils in and around the vessels. (Neutrophils broken into pieces found in vessel) (Vascular damage caused by nuclear debris from infiltrating neutrophils, and they call it cutaneous since they involve the vessels of the dermis)
Characteristics	• Affects many organs e.g. **skin** (most common, why? small vessels are most superficial), mucous membranes, lungs , brain, heart, GI , kidneys and muscle. • Commonly seen in the **dermis** of skin characterized by palpable (raised) purpura (purple-colored spots of skin hemorrhage on skin).  • All lesions tend to be of the same age. • It is the most common vasculitis seen in clinical practice.
Etiology	**1. Idiopathic** **2. Immunological reaction:** To an antigen present on either: - Drugs e.g penicillin. - Infectious microorganisms e.g. strept. and other infections. - Heterologous proteins. foreign proteins (streptokinase). - Food products and toxic chemicals - Tumor antigens in various cancers. **3. Part of Systemic diseases:** - Collagen vascular diseases (lupus erythematosus, rheumatoid arthritis) - **Henoch-Schonlein purpura** **(discussed in detail in next page)**

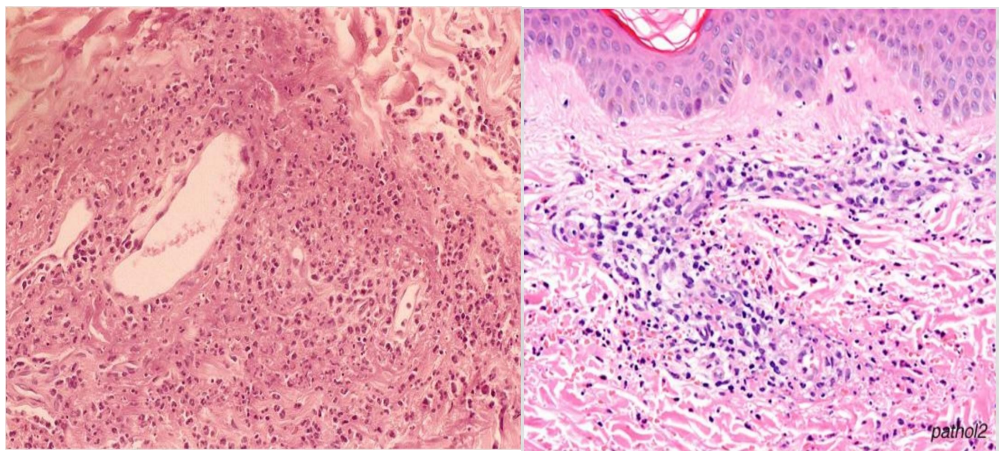
Cutaneous Leukocytoclastic: Henoch-Schonlein purpura (HSP)

Definition	It's an **IgA-mediated**, autoimmune systemic disease, of **unknown etiology** in which the **small** vessels show leukocytoclastic vasculitis of childhood (more common in children than adults). It's a disorder that causes small vessels in skin, joints, intestines, and kidneys to become inflamed and bleed. **Mucosal cells (in lungs, GI) produce IgA antibodies that will attack self-endothelial cells (molecular mimicry)**
Characteristics	• Serum levels of IgA are high • Skin biopsy will show **necrotizing leukocytoclastic vasculitis** of capillaries in the dermis. • The immunofluorescence shows IgA immunoglobulin and complement 3 (C3) deposition on the wall the affected arterioles, capillaries and venules.
Symptoms (Clinical features)	• Skin purpura • Arthritis • Abdominal pain • GIT bleeding • Orchitis (inflammation of testicles) • Nephritis

Investigation
Skin biopsy is often diagnostic

Microscopically

- Infiltration of vessel wall with neutrophils, which become fragmented called as **leukocytoclasia** or **nuclear dust**.



Leukocytoclastic vasculitis in a skin biopsy showing fragmentation of neutrophil nuclei in and around vessel walls.

Direct immunofluorescence

- Will show deposits of IgA immunoglobulin in the wall the capillaries.

Quiz

1- A 28-year-old man complains of nasal obstruction, bloody nose, cough, and bloody sputum. A chest X-ray displays cavitated lesions and multiple nodules within both lung fields. Urinalysis reveals 3+ hematuria and red blood cell casts. Laboratory studies show anemia and elevated serum levels of C-ANCA (antineutrophil cytoplasmic antibody). Peripheral eosinophils are not increased. A renal biopsy exhibits focal glomerular necrosis with crescents and vasculitis affecting arterioles and venules. What is the appropriate diagnosis?

a- Polyarteritis Nodosa	b- Wegener granulomatosis	c- Churg-Strauss syndrome	d- Hypersensitivity vasculitis

2- 30-year-old man presents with a 9-month history of fatigue and recurrent fever. He also complains of yellow skin and sclerae, abdominal tenderness, and dark urine. Physical examination reveals jaundice and mild hepatomegaly. Laboratory studies demonstrate elevated serum bilirubin (3.1 mg/ dL), decreased serum albumin (2.5 g/dL), and prolonged prothrombin time (17 seconds). Serologic tests reveal antibodies to hepatitis B core antigen (IgG anti-HBcAg). The serum is positive for HBsAg and HbeAg , The patient most likely to develop which of the following vascular inflammatory diseases?

a- polyarteritis nodosa	b- burger disease	c- giant cell vasculitis	d- none

3- A female 70 years traveled to China without developing coronavirus symptoms with a negative result , came to hospital with fever, headache, jaw pain,the biopsy show giant cells and granulomas inflammations of the vessel wall with fragmentation of internal elastic lamina , What is the most likely diagnosis?

a- temporal vasculitis	b-Wegener granulomatosis	c- Polyarteritis Nodosa	d-CV🐸?

4- A 75-year-old man has experienced headaches for the past 2 months. On physical examination, his vital signs are temperature, 37° C; pulse, 68/min; respirations, 15/min; and blood pressure, 130/85 mm Hg. His right temporal artery is prominent, palpable, and painful to the touch. His heart rate is regular, and there are no murmurs. His erythrocyte sedimentation rate is 100 mm/hr. A temporal artery biopsy is performed, and the segment of temporal artery excised is grossly thickened and shows focal microscopic granulomatous inflammation. He responds well to corticosteroid therapy. Which of the following complications of this disease is most likely to occur in untreated patients?

a- Blindness	b- Gangrene of the toes	c- Renal failure	d- Hemoptysis

5- A 50-year-old man has had a chronic cough for the past 18 months. Physical examination shows nasopharyngeal ulcers, and the lungs have diffuse crackles bilaterally on auscultation. Laboratory studies include a serum urea nitrogen level of 75 mg/dL and 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?

a- Granulomatosis with polyangiitis	b- Polyarteritis nodosa	Churg-Strauss syndrome	d-Hypersensitivity vasculitis

6- Approximately 1 week following an upper respiratory infection, a 5-year-old boy begins to develop abdominal pain, diffuse joint pain, and a urticarial rash on his bilateral lower extremities. He has no other complaints. Over the next 12-24 hours, the rash changes in character, and the boy is brought to his primary care physician. On exam, the pediatrician notes dark purple, non-blanching papules and plaques that are distributed symmetrically over the patient's buttocks and legs. A CBC and CMP show no abnormalities. What is the underlying process causing this patient's dermatological findings?

a- C-ANCAs	b- P-ANKAs	C- IgA-mediated vasculitis	d- Auto reactive T cells

1-B | 2-A | 3-A | 4-A | 5-A | 6-C

Summary

	Vessel size	Epidemiology	Organ affected	Clinical features
Giant-cell Arteritis	Large to medium	Gender: Female > males Age: Above 50	Branches of the carotid artery (temporal & ophthalmic)	- Fever, facial pain, headache. - Visual problems
Polyarteritis Nodosa	Medium to small	Young adults	Systemic: any organ except lungs. Mostly Kidney	Fever, weight loss, abdominal pain, melena & neuritis.
Thromboangiitis obliterans (Buerger disease)	Medium and small	Heavy smokers before age of 35	Leg and hands (tibial & radial arteries)	- Instep claudication - Chronic ulceration of toes leading to gangrene - Severe pain
Wegener Granulomatosis	Small to medium	Gender: males > females Age: Above 40	- Necrotizing granulomas: URT & LRT. - Renal disease	- persistent pneumonitis & mucosal ulcerations of nasopharynx C-ANCAs → +ve in serum
Cutaneous leukocytoclasis (cutaneous hypersensitivity vasculitis)	Small	All ages (more common in children)	Most common: the dermis of skin	Henoch-Schonlein purpura, Elevated IgA
Microscopic polyangiitis	Small	Idiopathic	Kidney (glomerulonephritis)	Elevated P-ANCA

Team Leaders

- Rania Almutairi
- Hadi Alhemsi

Team members

البندري العنزي
الجوهرة البنيان
ريناد الحميدي
سارة العبيد
سارة المقاطي
غادة العبدي
غادة العثمان
غيداء العسيري
فاطمة آلهلال
لمى الأحمدي
مريم الرحيمي
منى العبدلي
نوره السالم
نوره الكثيري

Team members

إبراهيم التميمي
أحمد الخياط
بسام الأسمري
بندر الحربي
حمد الربيعة
حمد الموسى
صالح القرني
عبدالرحمن الدويش
عبدالرحمن بارشيد
عبدالعزيز السحيم
عبدالعزيز الربيعة
محمد الوهيبي
ناصر السنبل
يزيد القحطاني

Editing File