Vasculitis

Objectives:

(1) 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)

Editing file

Black: original content.
Red: Important.
Light Purple:From Robbin's.
Blue:only found in boys slides.

Green: Boy's doctor notes .
Dark orange: Girl's Doctor notes.
Grey: Explanation.
Pink: Only found in girls slides.

Reviewed by Razan AlRabah & Ibrahim AlDakhil

MED438 KING SAUD UNIVERSITY

Pathology Teamwork 438

Vasculitis

Definition

It is inflammation of vessel walls with many possible symptoms.

Etiology

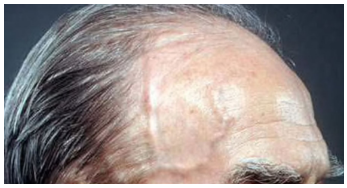
Usually immune mediated	Infection, physical or chemical injury
• Immune complex deposition[1] • Antineutrophil cytoplasmic antibodies (ANCAs) • Anti-endothelial cell antibodies • Autoreactive T cells[2]	• including that due to radiation, mechanical trauma, and toxins • Infections can indirectly precipitate immune-mediated vasculitis

Overview

Vessel	Disease	Comment
Large	Giant-cell arteritis	>50yrs and women are at high risk, it affects the head Arteries.
	Takayasu arteritis[3]	F <40yrs. "Pulseless disease"
Medium	Polyarteritis nodosa	Young adults. Widespread.
	Kawasaki disease[4]	<4yrs. Coronary disease. Lymph nodes.
Small	Wegener 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 systemic disease like HNP

(1): such as the arthus phenomenon and serum sickness
(2): cause injury in some forms of vasculitides characterized by formation of granulomas
(3): is a granulomatous vasculitis of medium- and large-sized arteries characterized principally by ocular disturbances and marked weakening of the pulses in the upper extremities. Manifests with thickening of the aorta. occur in those younger than 50 years. associated with Japanese ethnicity.
(4): an acute, febrile, usually self-limited illness of infancy and childhood associated with an arteritis of mainly large- to medium-sized vessels.

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)
- Involvement is segmental[1], acute and chronic.

Epidemiology:

- Most common type of vasculitis
- Patients older than 50yrs.
- Female: Male = **2:1**

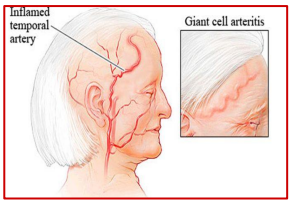
Pathogenesis:

- occurs as a result of a T-cell– mediated immune response to antigen.
- Pro-inflammatory cytokines (especially TNF) and anti-EC antibodies.
- The characteristic granulomatous inflammation, an association with certain MHC class II haplotypes, and the excellent therapeutic response to steroids, all strongly support an immune etiology.

Symptoms

fever, facial pain or headache, often most intense along the course of the superficial temporal artery

Jaw pain



Thickened and painful temporal artery[2]

Visual problems and acute vision loss[3]

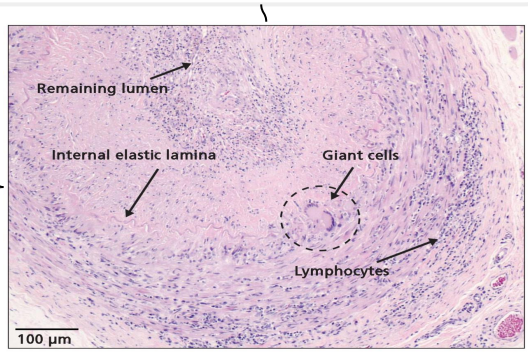
- The diagnosis depends on biopsy (from the temporal artery) and histologic confirmation.
- Treatment: **corticosteroids** [4] or anti-TNF therapies.

Morphology:

The healed stage reveals collagenous thickening of the vessel wall and the artery is transformed into a **fibrous** cord

Granulomatous inflammation of the blood vessel wall

Proliferation of the intima with associated occlusion of the lumen.

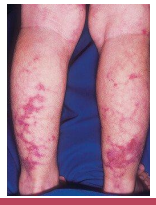


Giant cells

Disruption and fragmentation of internal elastic lamina

(1):Only a portion is involved and not the entire artery
(2): palpable
(3): can lead to blindness, can see 2 of everything, because it effect the ophthalmic artery.
(4): Must give the treatment ASAP to decrease the immune system activity
Dr note: the case will most likely be a **+50 years old female** complaining of severe headache and fever.

polyarteritis nodosa[1]



Definition

Necrotizing vasculitis involving multiple organs, **lungs are spared**.
(Cutaneous only or systemic)

Epidemiology

Disease of young adults

Characteristics:

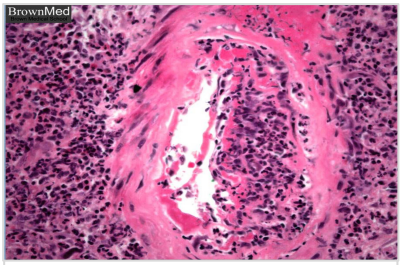
1. There is segmental necrotizing[2] inflammation of arteries of medium to small size, in any organ (especially kidney and skin) except the lungs.
2. Most frequently kidneys (most common), skin,heart, liver, and gastrointestinal tract.
3. Polyarteritis nodosa has been associated with hepatitis B or hepatitis C virus infection. (because the immune system will attack the endothelial cells confusing it with HBV)
4. Weakening of the arterial wall due to the inflammatory process may cause aneurysmal dilation[3] or localized rupture.
5. Renal arterial involvement is often prominent and is a major cause of death.
6. Particularly characteristic of PAN 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.

Fatal if untreated, but steroids and cyclophosphamide are curative.

Clinical manifestations

Some clinical manifestations are due to ischemia and infarction of affected tissues/ organs

- Fever
- Weight loss
- muscular pain
- abdominal pain
- Melena (bloody stool)
- Neuritis



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.

(1): more than one artery forming nodule
Polyarteritis nodosa can cause blood in the urine.
(2): fibrinoid necrosis and luminal thrombosis
(3): check "lecture 2" for more details

Buerger disease
(Thromboangitis obliterans)

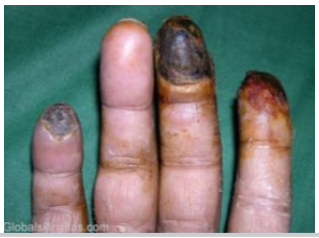
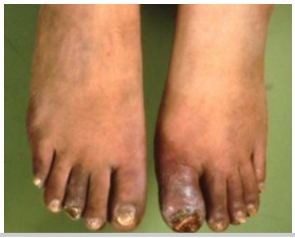
Characterized

- **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.

Risk factors

- occurs almost exclusively in **heavy smokers** of cigarettes (Abstinence from cigarette smoking in the early stages of the disease brings relief from further attacks).
- Tobacco either leads to **direct toxicity** to endothelium, or induces an immune response.
- usually begins before age 35

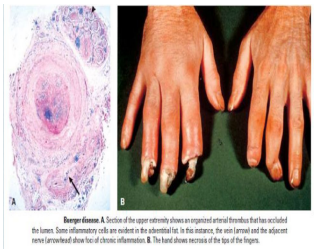
Clinical features include

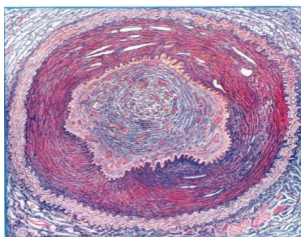
Pain in the affected hand or foot **induced by exercise** (called ***instep claudication***) Even at rest due to the neural involvement	Chronic **ulcerations** of the toes, or fingers may appear, followed in time by **gangrene**.
	

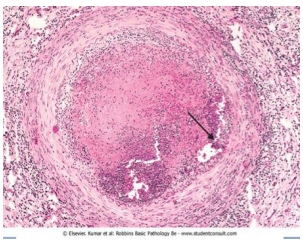
Morphology

Acute & chronic Inflammation
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.

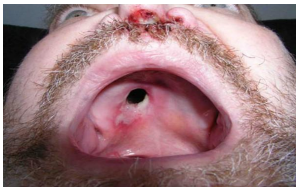
luminal thrombosis







Wegener granulomatosis (Granulomatosis with polyangiitis)



Definition

Necrotizing granulomatous vasculitis involving nasopharynx, lungs, and kidneys.
Also known as Granulomatosis with Polyangiitis.

Epidemiology

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

Classic presentation is a middle-aged male with sinusitis or nasopharyngeal ulceration, hemoptysis with bilateral nodular lung infiltrates, and hematuria due to rapidly progressive glomerulonephritis.

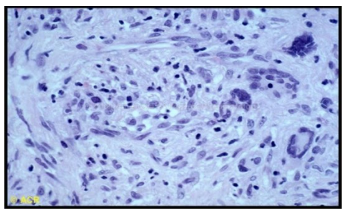
Characterized by the *triad* of

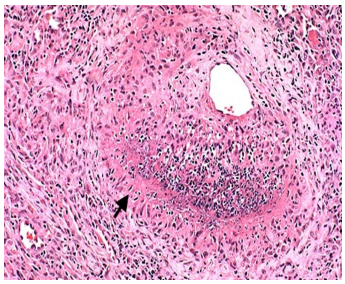
- Necrotizing granulomas of the upper and lower respiratory tract.[2]
- Necrotizing or granulomatous vasculitis of small to medium-sized vessels.
- Renal disease in the form of necrotizing, crescentic, glomerulonephritis.

Clinical features(1):

C-ANCAs [4] (antineutrophilic cytoplasmic antibodies) is positive in serum of more than 95% of patients.

Persistent pneumonitis, chronic sinusitis, mucosal ulcerations[3] of the nasopharynx, and evidence of renal disease.





Prognosis

May lead to death within 2 years if not treated.

(1) The patient usually complains of 2 things: 1- respiratory problems: like epistaxis (nose bleeding). 2-Renal problems: like hematuria (blood in the urine).
(2) : unlike polyarteritis nodosa, Wegener involves the lung
(3): causes a hole in the nasal septum (Palatal ulceration and destruction)
(4): ANCAs are a heterogeneous group of autoantibodies directed against constituents (mainly enzymes) of neutrophil primary granules, monocyte lysosomes, and ECs. classified according to their antigen specificity:

- Anti-proteinase-3 (PR3-ANCA), previously called c-ANCA. PR3 is a neutrophil azurophilic granule constituent that shares homology with numerous microbial peptides
- Anti-myeloperoxidase (MPO-ANCA), previously called p-ANCA. (next slide)

Microscopic polyangitis/polyarteritis

Definition

It is a systemic small vessel vasculitis associated with glomerulonephritis[1].

Clinical features:

- **P-ANCA**[2] is characteristically present.
- In the past it has been confused with leukocytoclastic vasculitis.

EXTRA but important

Microscopic polyangiitis is very similar to Granulomatosis with polyangiitis but there are 3 key differences between them:

1- Microscopic polyangiitis doesn't affect nasopharynx(only kidney,lungs).

2- No granulomas in microscopic polyangiitis.

3- We will find P-ANCA in microscopic polyangiitis instead of C-ANCA.

Churg-Strauss syndrome (additional reading)

Definition

Eosinophil-rich and granulomatous inflammation involving the respiratory tract and necrotizing vasculitis affecting small vessels.

Clinical features:

- Associated with **P-ANCAs** [2]
- Associated with asthma and blood eosinophilia.

(1): with no necrosis

(2): is a lysosomal granule constituent involved in oxygen free radical generation

Cutaneous leukocytoclastic (Hypersensitivity vasculitis/Angiitis)

Definition

Necrotizing vasculitis of arterioles, capillaries, venules. (Can be Cutaneous only or systemic)

What is Leukocytoclasis[1]?

The nuclear debris of infiltrating neutrophils (karyorrhexis of neutrophils) in and around the vessels.

Characteristics

- Inflammation of small blood vessels (commonly seen in the post-capillary venules in the dermis).
- Characterized by **palpable purpura**. (Extravasated RBC).
- All lesions tend to be of the same age.
- It affects many organs e.g. skin (most common), mucous membranes, lungs , brain, heart, GI , kidneys and muscle.
- The most common vasculitis seen in clinical practice.

Etiology

Immunological reaction to an antigen that may present as:

- Drugs e.g penicillin, foreign proteins (streptokinase).
- Infectious microorganisms e.g. strept. and other infections.
- Heterologous proteins.
- Food products and toxic chemicals
- Tumor antigens in various cancers

It may be part of a systemic disease eg:

- collagen vascular diseases (lupus erythematosus, rheumatoid arthritis),
- **Henoch-Schonlein purpura**[2] (skin rash, abdominal pain, hematuria)

Idiopathic

(1): Leukocytoclasis: WBC breakdown
(2): Purpura: hemorrhagic spots on the skin (red and purple discoloration)

Henoch-Schonlein purpura:

What is Henoch-Schonlein purpura?

It's an IgA-mediated, autoimmune systemic disease, in which the small vessels show leukocytoclastic vasculitis of childhood.

Etiology	Unknown
Characteristics	• Serum levels of IgA are high in HSP • 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. • It causes Skin purpura, arthritis, abdominal pain, GIT bleeding, orchitis and nephritis.

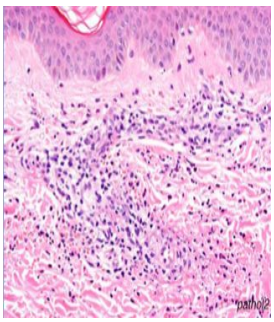
Cutaneous leukocytoclastic (Hypersensitivity vasculitis/Angiitis)

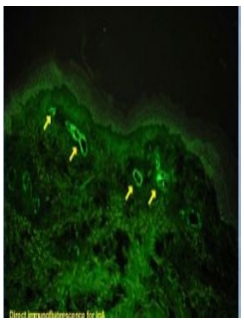
Investigations

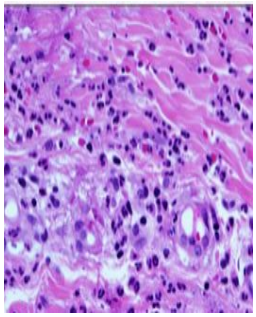
- **Skin biopsy is often diagnostic**

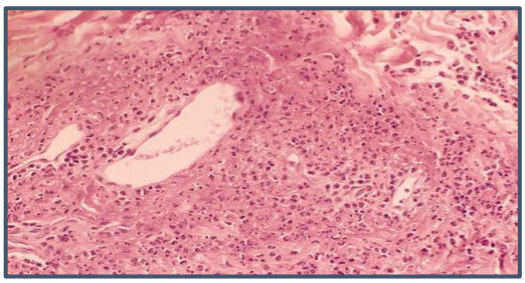
Histologically:
Infiltration of vessel wall with neutrophils, which become fragmented called as leukocytoclasia or nuclear dust

Direct immunofluorescence:
Will show **deposits of IgA** immunoglobulin in the wall the capillaries



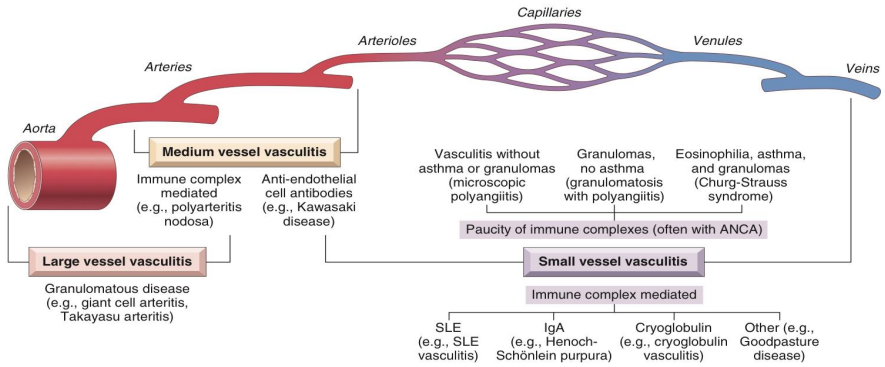






Leukocytoclastic vasculitis in a skin biopsy showing fragmentation of neutrophil nuclei in and around vessel walls.

Summary (Robbins)



	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.

Summary

Vasculitis

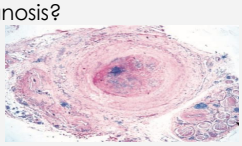
It is inflammation of vessel walls with many possible symptoms

	Vessel size	Epidemiology	Organ affected	Clinical features
Giant-cell arteritis	**Large** to medium vessels	Females> Males. Ages Above 50	Branches of the carotid artery (temporal & ophthalmic)	- Fever, facial pain, headache. - Visual problems
Polyarteritis Nodosa	**Medium** to small vessels	Young adults	Systemic: any organ **except** lungs. Mostly Kidney	Fever, weight loss, abdominal pain, melena & neuritis.
Wegener granulomatosis	**Small** to medium vessels	Males > Females Age of 40	- Necrotizing granulomas: **URT & LRT.** - Renal disease	- Persistent pneumonitis & mucosal ulcerations of nasopharynx. **C-ANCAs → +ve in serum**
Thromboangiitis obliterans (Buerger disease)	**Medium & small** vessels	Heavy smokers before 35	Leg and hands (tibial & radial arteries)	- Instep claudication - Chronic ulceration of toes → Gangrene - sever pain
Cutaneous hypersensitivity vasculitis (Cutaneous leukocytoclastic)	**Small** vessels	All ages	Most common: the dermis of skin	Henoch-Schonlein purpura **Elevated IgA**
Microscopic polyangiitis	**Small** vessels	Idiopathic	Kidney (Glomerulonephritis)	**Elevated P-ANCA**

Quiz

Answer key: Answers Explanation File

1) A 45-year-old man presents with pain in the legs upon exercise and destruction of the tips of his fingers. He has an 80-pack-year history of smoking. Laboratory values include hemoglobin of 16 g/dL, WBC of 8,500/μL, serum cholesterol of 220 mg/dL, fasting blood sugar of 90 mg/dL, and negative tests for antinuclear antibodies. Biopsy of the affected area(shown in the image) reveals intraluminal thrombi in medium-sized arteries and inflammation extending from arteries to neighboring veins and nerves. What is the appropriate diagnosis?



A) Buerger disease.
B) Churg-Strauss disease.
C) Kawasaki disease.
D) Polyarteritis nodosa.
E) Takayasu arteritis.

2) A 25-year-old woman with a recent history of acute hepatitis B infection presents with reddish-blue lesions on her lower extremities, fever, muscle pain, and mild weight loss. Physical examination reveals numerous regions of red-purple discoloration affecting the skin of both legs. Laboratory tests demonstrate positive P-ANCA and an elevated erythrocyte sedimentation rate. Urinalysis shows 2+ proteinuria. Biopsy of lesional skin is shown in the image. Which of the following is the most likely diagnosis?

A) Benign arteriosclerosis.
B) Fibromuscular dysplasia.
C) Henoch-Schönlein purpura.
D) Mönckeberg medial sclerosis.
E) Polyarteritis nodosa.

3) A 20-year-old woman complains of double vision, fainting spells, tingling of the fingers of her left hand, and numbness of the fingers of her right hand. Physical examination reveals absence of pulse in her right arm. Laboratory tests show elevated erythrocyte sedimentation rate and thrombocytosis. An aortogram demonstrates narrowing and occlusion of branching arteries, including the right subclavian artery. The patient subsequently develops heart failure and dies of massive pulmonary edema. At autopsy, the aorta has a thickened wall and shows vasculitis and fragmentation of elastic fibers. Which of the following is the most likely diagnosis?

A) Buerger disease.
B) Churg-Strauss disease.
C) Kawasaki disease.
D) Polyarteritis nodosa.
E) Takayasu arteritis.

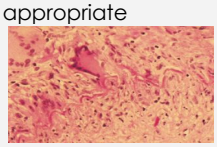
4) A 19-year-old man with a history of recent-onset asthma presents with chest pain, intermittent claudication, and respiratory distress that is unresponsive to bronchodilators and antibiotics. Physical examination reveals mild hypertension (blood pressure = 150/100 mm Hg), bilateral wheezing, and numerous purpuric skin lesions on the feet. Laboratory studies demonstrate that leukocytes are increased to 14,000/μL with increased eosinophils and platelets are increased to 450,000/μL. BUN is elevated to 30 mg/dL, and serum creatinine is elevated to 3.5 mg/dL. The serum antineutrophil cytoplasmic antibody test is positive. Urinalysis discloses 3+ proteinuria and RBCs. A renal biopsy demonstrates vasculitis of medium-sized arteries, accompanied by eosinophilia. Which of the following is the most likely diagnosis?

A) Churg-Strauss disease.
B) Henoch-Schönlein purpura.
C) Loeffler syndrome.
D) Polyarteritis nodosa.
E) Wegener granulomatosis

5) A 6-year-old girl presents with a 2-week history of a skin rash over her buttocks and legs and joint pain. The parents report seeing blood in the urine. Physical examination reveals palpable purpuric skin lesions and markedly swollen knees. The results of laboratory studies reveal abnormally high erythrocyte sedimentation rate (30 mm/h), BUN of 25 mg/dL, and serum creatinine of 3 mg/dL. Urinalysis demonstrates RBCs and RBC casts. The stool guaiac test is positive. Biopsy of lesional skin reveals deposits of IgA in the walls of small blood vessels. Which of the following is the most likely diagnosis?

A) Henoch-Schönlein purpura.
B) Hypersensitivity vasculitis.
C) Kawasaki disease.
D) Polyarteritis nodosa.
E) Poststreptococcal glomerulonephritis.

6) A 70-year-old woman complains of a throbbing unilateral headache and vision problems. She reports weight loss and mandibular pain while eating. The patient also has a history of recurrent bouts of fever accompanied by malaise and muscle aches. Physical examination reveals nodular enlargement of the temporal artery with pain on palpation. A biopsy is obtained (shown in the image). What is the appropriate diagnosis?



A) Giant cell arteritis.
B) Hypersensitivity angiitis.
C) Kawasaki disease.
D) Polyarteritis nodosa.
E) Wegener granulomatosis.

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THANK YOU