
By: Dr Maryam Sahebari

Vasculitis:

- Definition
- Classification
- Pathophysiology
- Specific Syndromes

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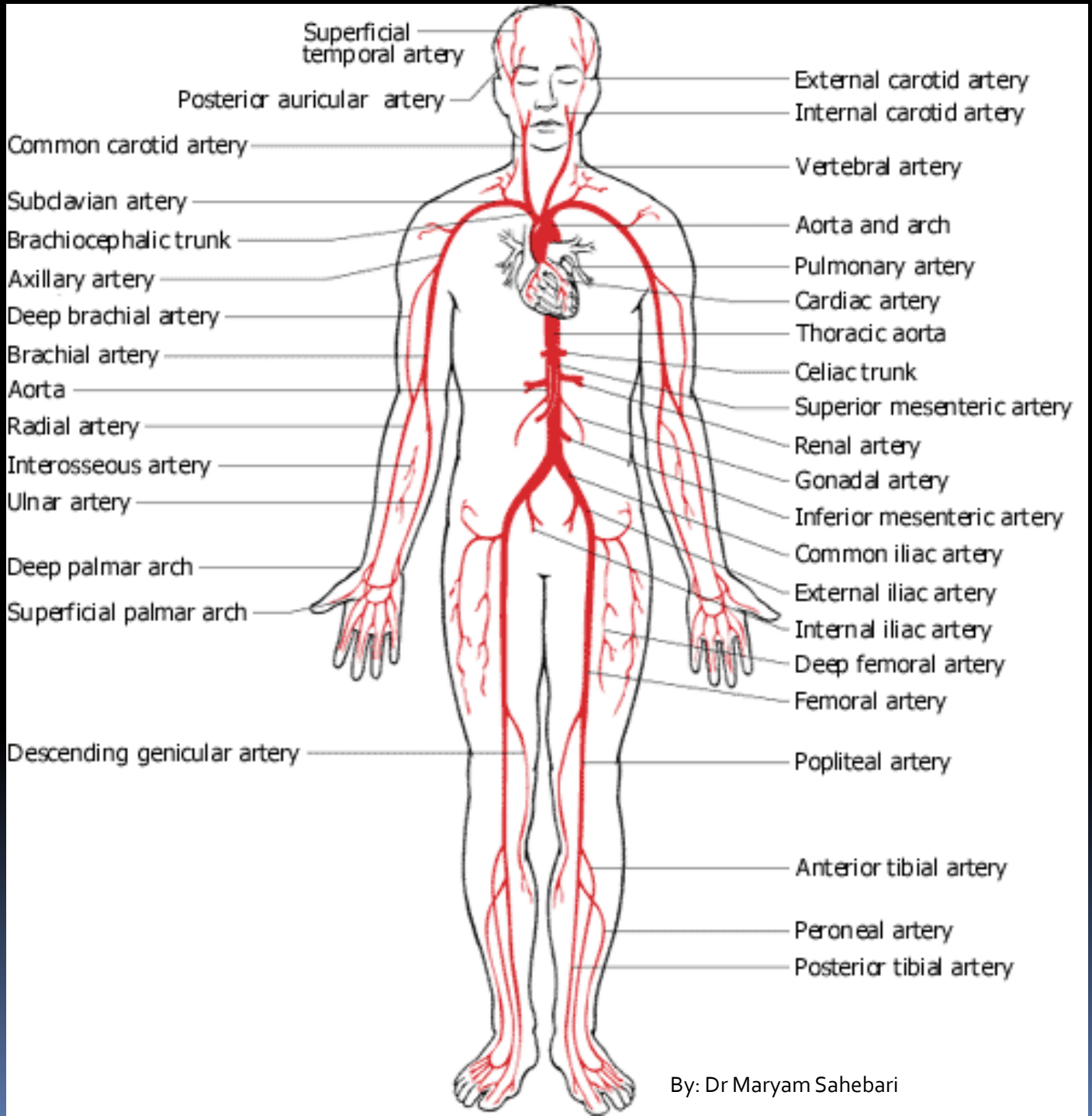
Vasculitis(Definition)

- A clinico-pathologic process characterized by inflammation of blood vessels leading to variable degrees of occlusion and tissue ischemia
  - resulting a broad and heterogeneous range of clinical syndromes, since any type, size, and location of blood vessel may be involved

Vasculitis(Definition)

- Vasculitis and its consequences may be the primary or sole manifestation of a disease, alternatively, vasculitis may be a secondary component of another primary disease.



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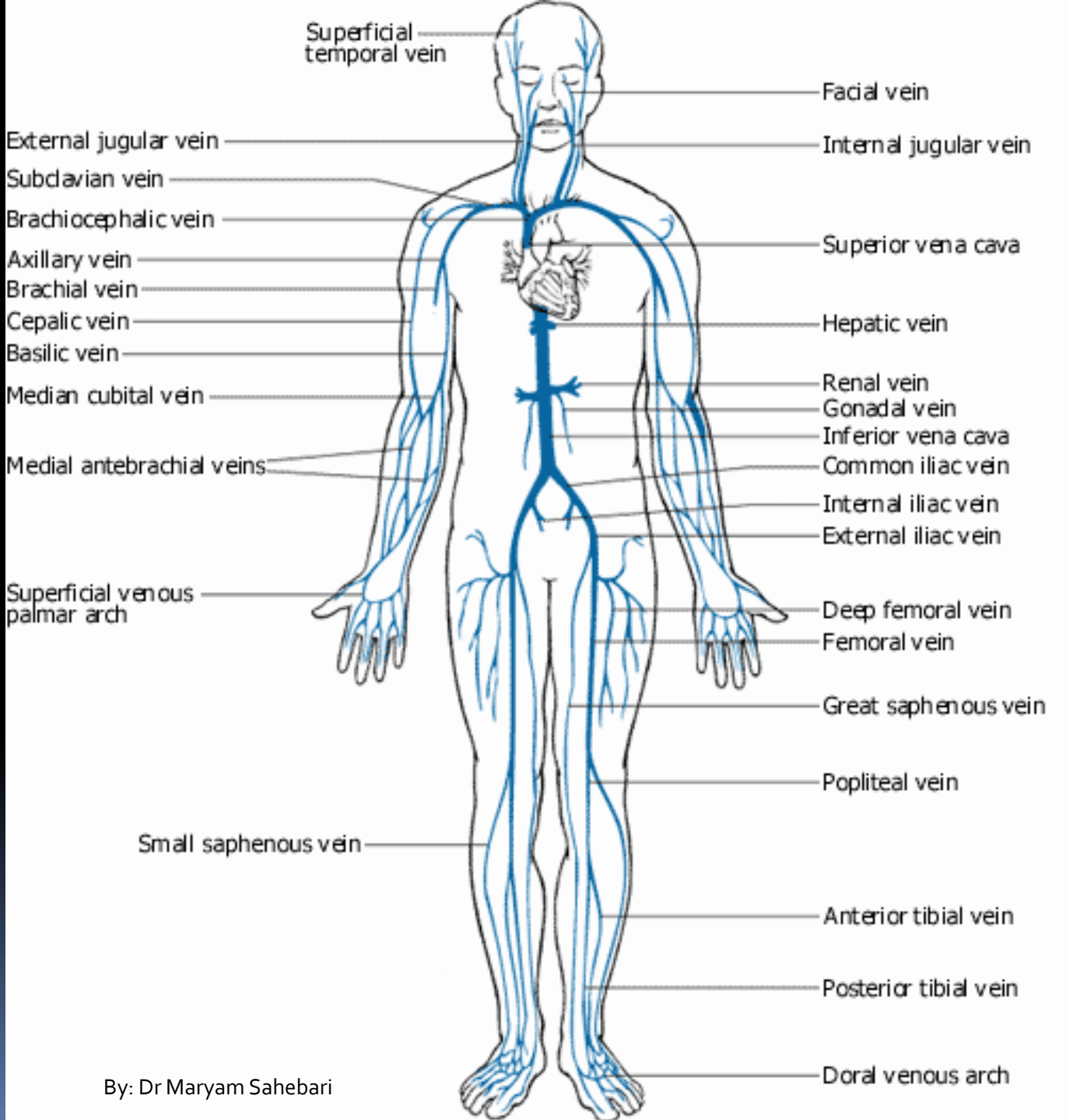

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Pathophysiology of Vasculitis:

- Unknown
- Mulifactorial

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- Antigenic Factors

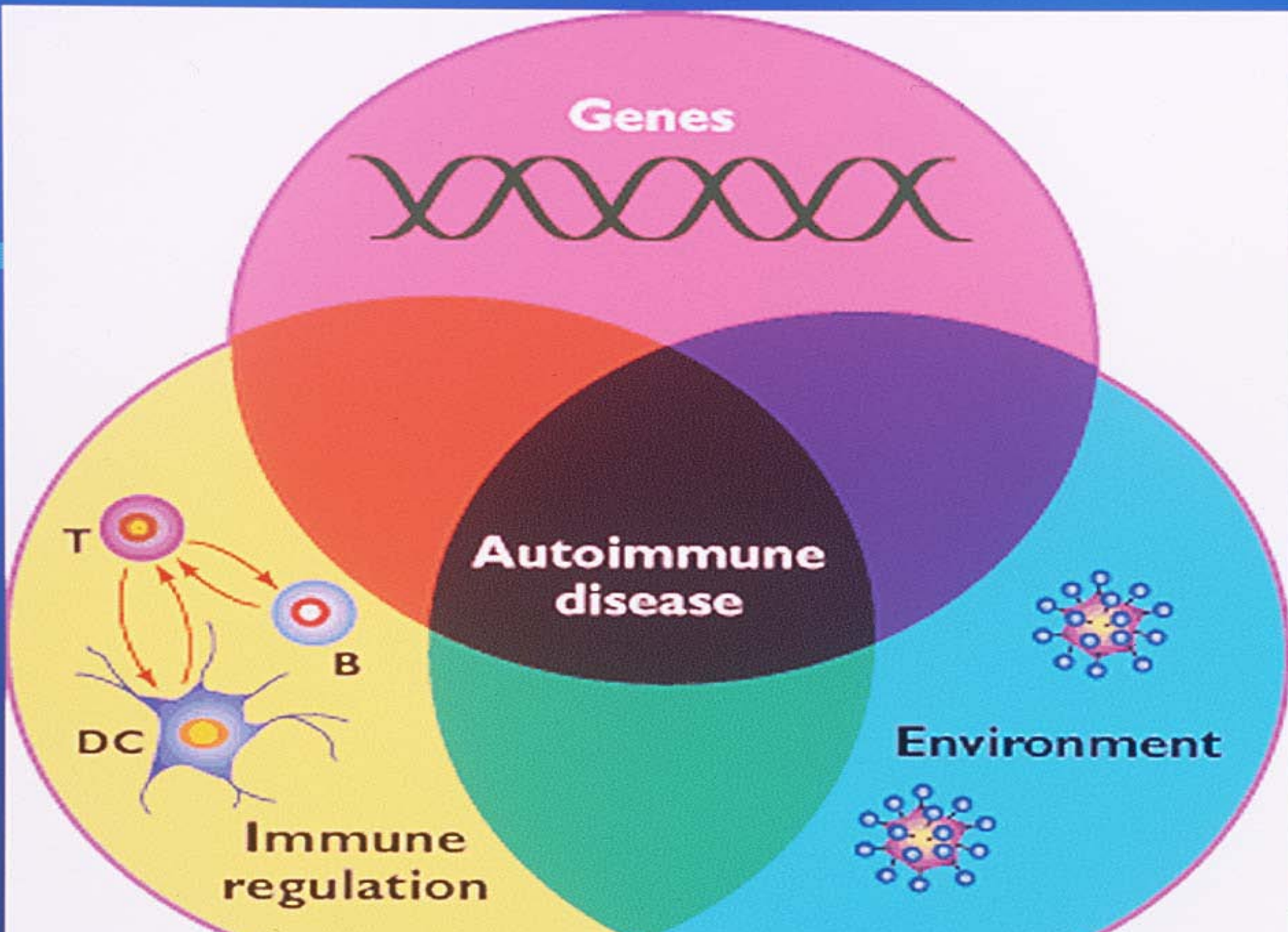
- **Exogenous:**
  - Infections (Viral , Bacteria ...)
  - Drugs
  - Toxins
  - Proteins
  - Foods
- **Endogenous:**
  - DNA
  - Cellular Proteins
  - Collagens
  - Proteoglycans

Genetic

- HLA-DR4 in Polymyalgia and Giant cell arteritis
- HLA-DR1 and HLA-DQW7 in Wegener
- HLA-BW52 in Takayasu's, HLA-DR2

Regulatory mechanisms, associated with Immune response to certain antigens:

- Why some people may develop vasculitis in response to certain antigenic stimuli where as others do not.


Genes
Autoimmune disease
T
B
DC
Immune regulation
Environment

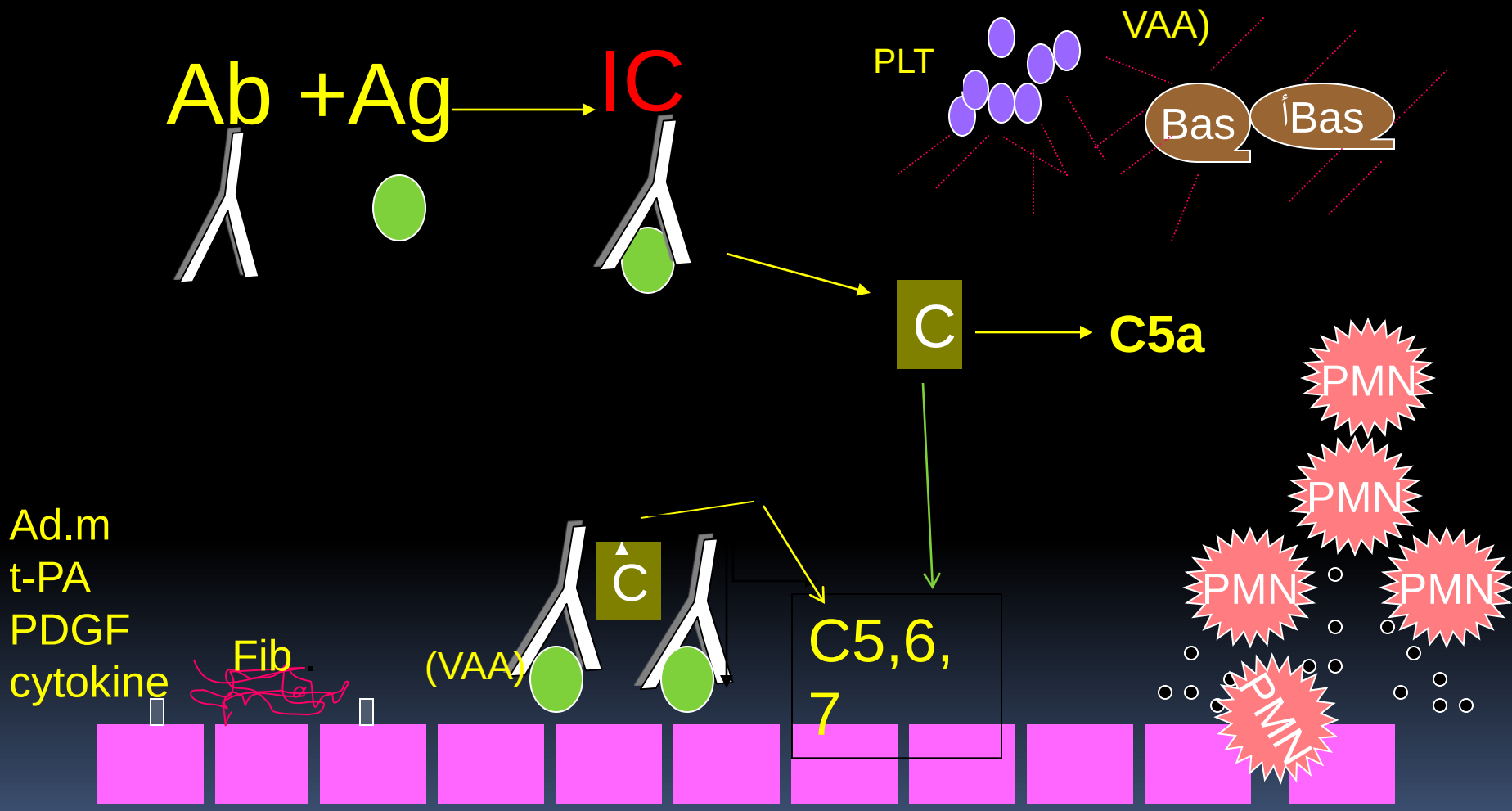
The most important theories:

- *Pathogenic Immune Complex Formation*
- *Antibody Formation: ANCA, AECA*
- *Cell mediated immunity and Granuloma formation*

1***Pathogenic Immune Complex Formation :

- Vasculitis is generally considered within the broad category of *immune –complex* disease that include serum sickness and certain of the connective tissue diseases: Lupus.
- The casual role of immune complexes has not been clearly established in most of the vasculitic syndromes.
- Deposition ?! Actual antigen ?!

Immune Comlexes & vasculitis



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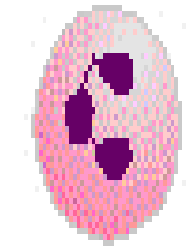
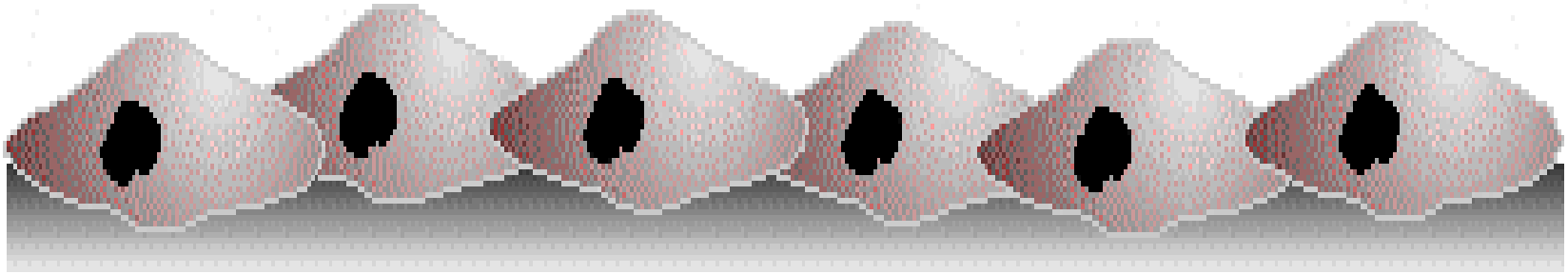
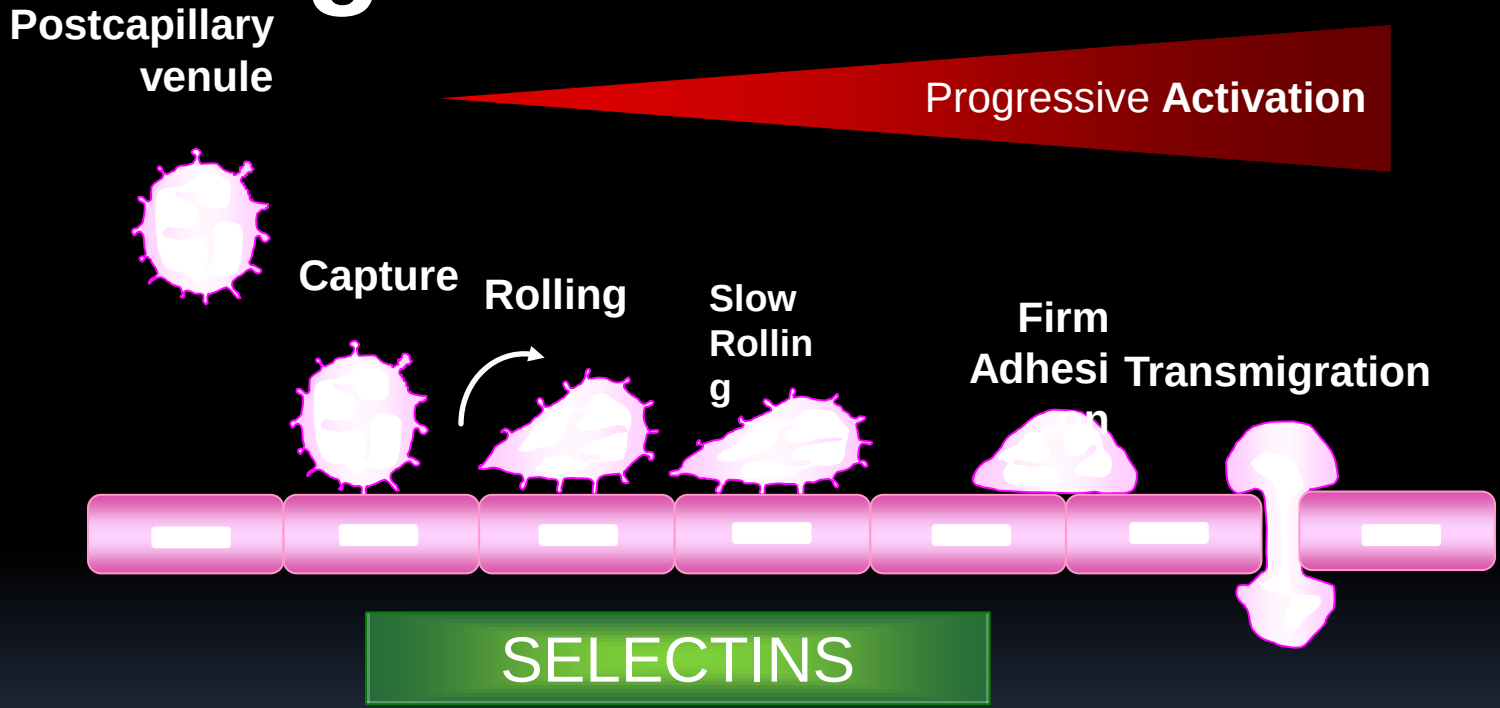




Leukocyte migration



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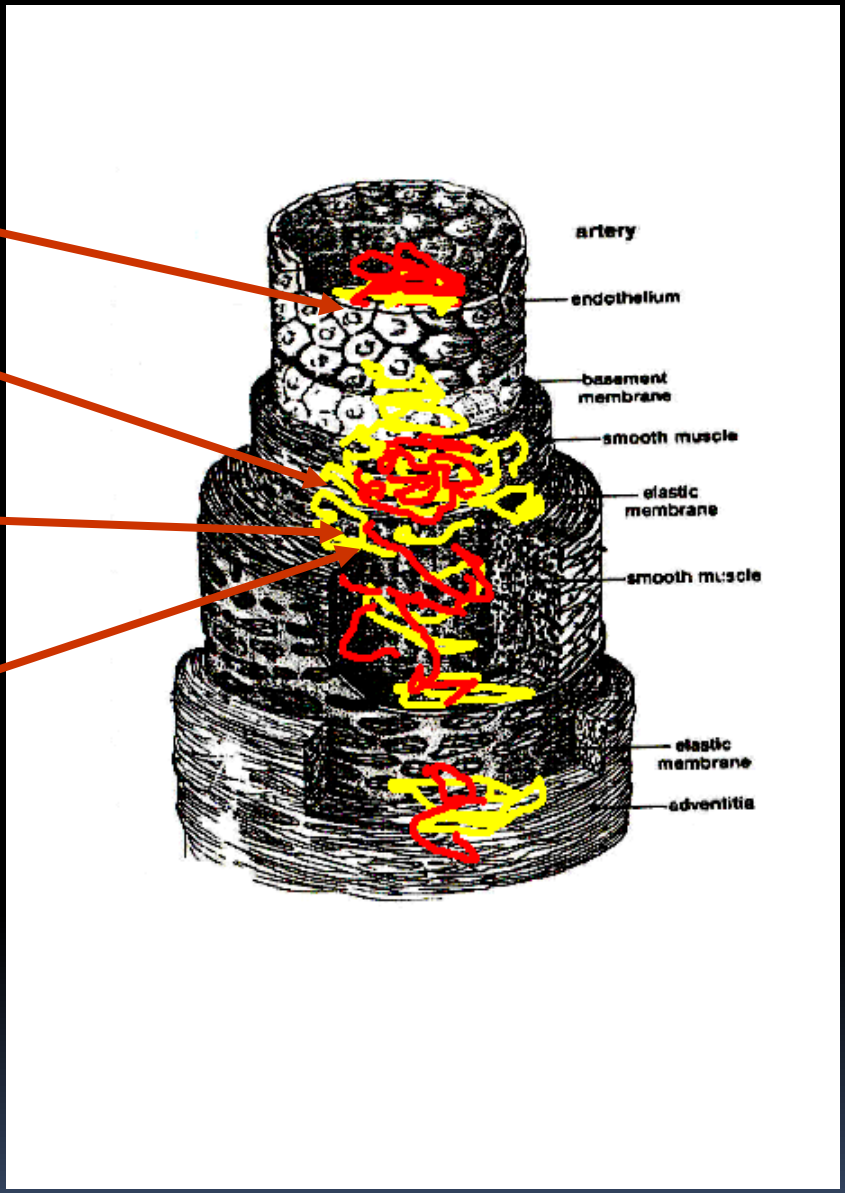
- Neutrophils which infiltrate the vessel wall, phagocytose the immune complexes, and release their intracellular enzymes, which damage the vessel wall.
- As the process become subacute or chronic, mononuclear cells infiltrate the vessel wall.

IgE immune responses

Immune complex ➔ vessel walls

Complement activation

Inflammation



R.R.C.

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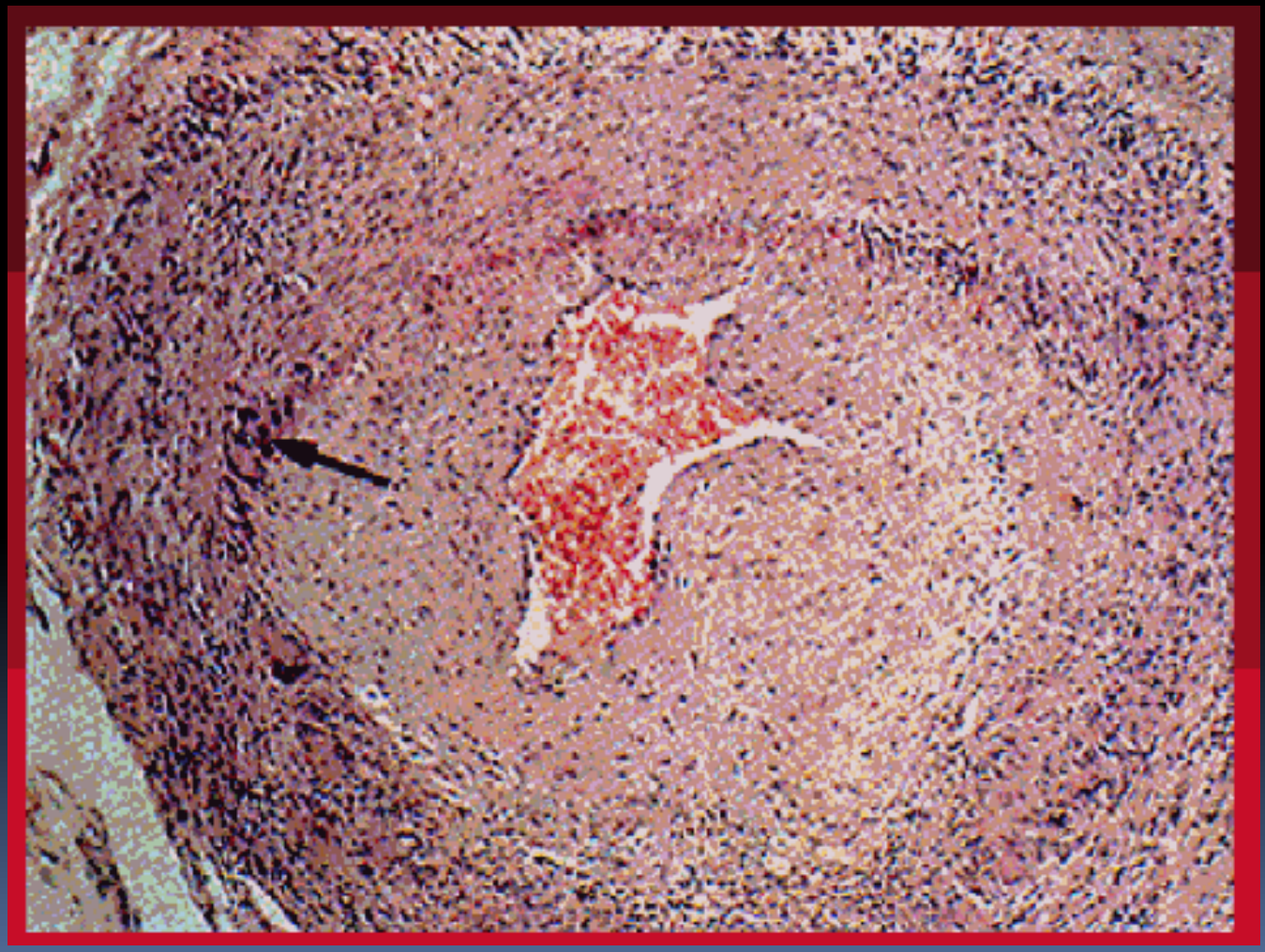
Compromising the vessel lumen with ischemic changes in the tissues which supplies by the involved vessel.



2***Antibody Formation :

- **Anti-Neutrophil Cytoplasmic Antibodies:**
  - C - ANCA
  - p - ANCA
- **Anti-Endothelial Cell Antibodies**

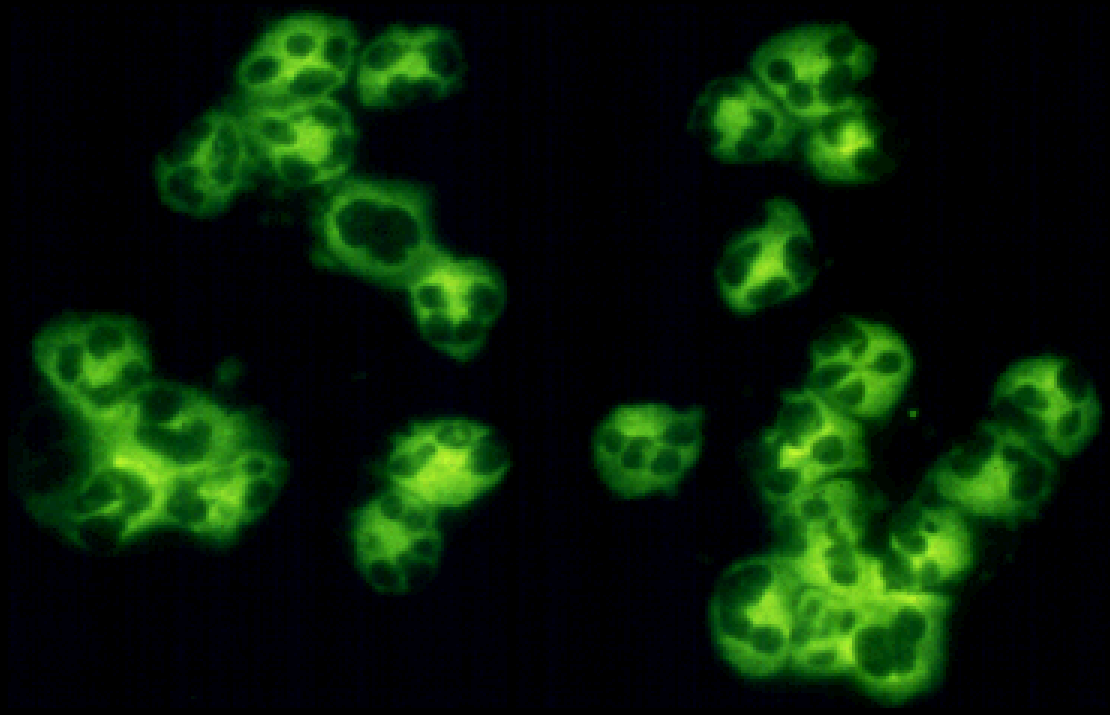
This may be the possible mechanism thereby these Abs can contribute to the pathogenesis if the vasculitis syndromes:

- Proteinase 3 and myeloperoxidase reside in azorophylic granules and lysosomes of resting cells ,they are apparently inaccessible to serum antibodies.
- When Neut and Mono are primed by TNF and IL 1, they translocate on the cell membrane and they can act by ANCAs
- The Neut s then degranulate and produce reactive O, that can cause tissue damage

continue

- ANCA-activated Neuts can adhere and kill Endothelial cells.
- Activation of Neuts and Monos can produce inflammatory cytokines like IL1 and IL8

c-ANCA



- Cytoplasmic Antinoutrophyl Cytoplasmic Antibodies
- Antibodies are directed against **Proteinase-3**
- Most patients have Wegener's granulomatosis

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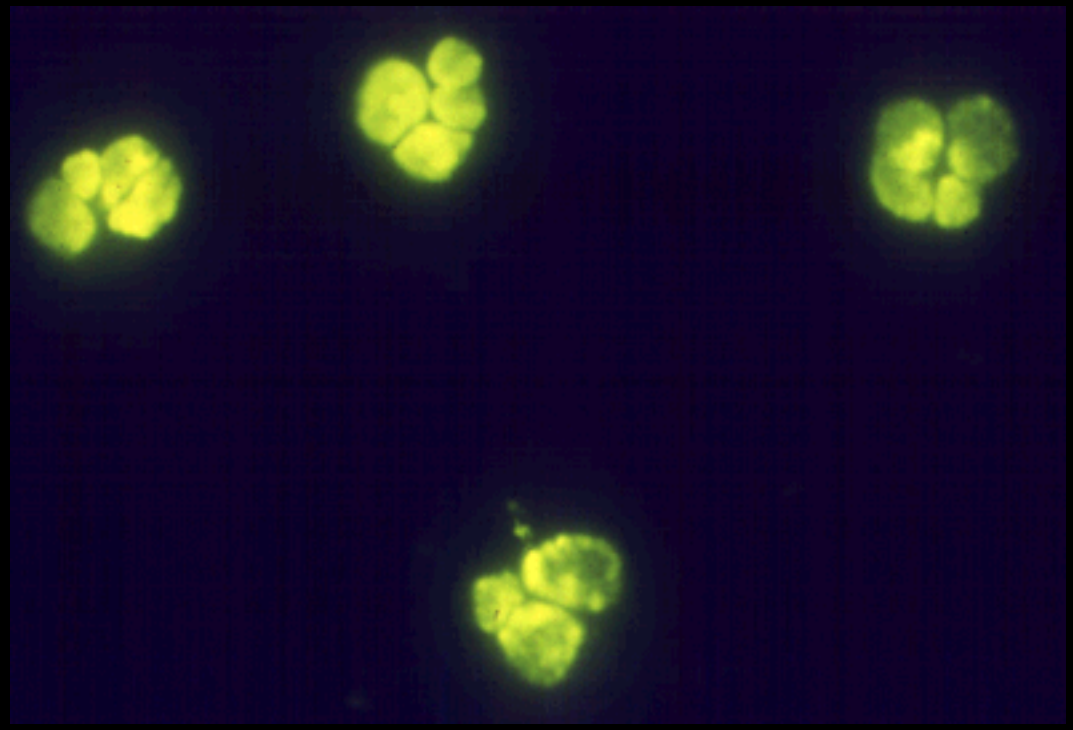
p-ANCA



- Perinuclear Antinoutrophyl Cytoplasmic Antibodies
- Staining in limited to the perinuclear region, cytoplasm is nonreactive
- Antibodies are directed against:
  Myeloperoxidase (MPO) , Lactoferrin and Elastase
- Can be seen in variety of disorders

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Anti-Neutrophil Cytoplasmic Antibodies (ANCA)

Diseases

- Wegener's Granulomatosis
- Microscopic polyangiitis
- Churg-Strauss syndrome

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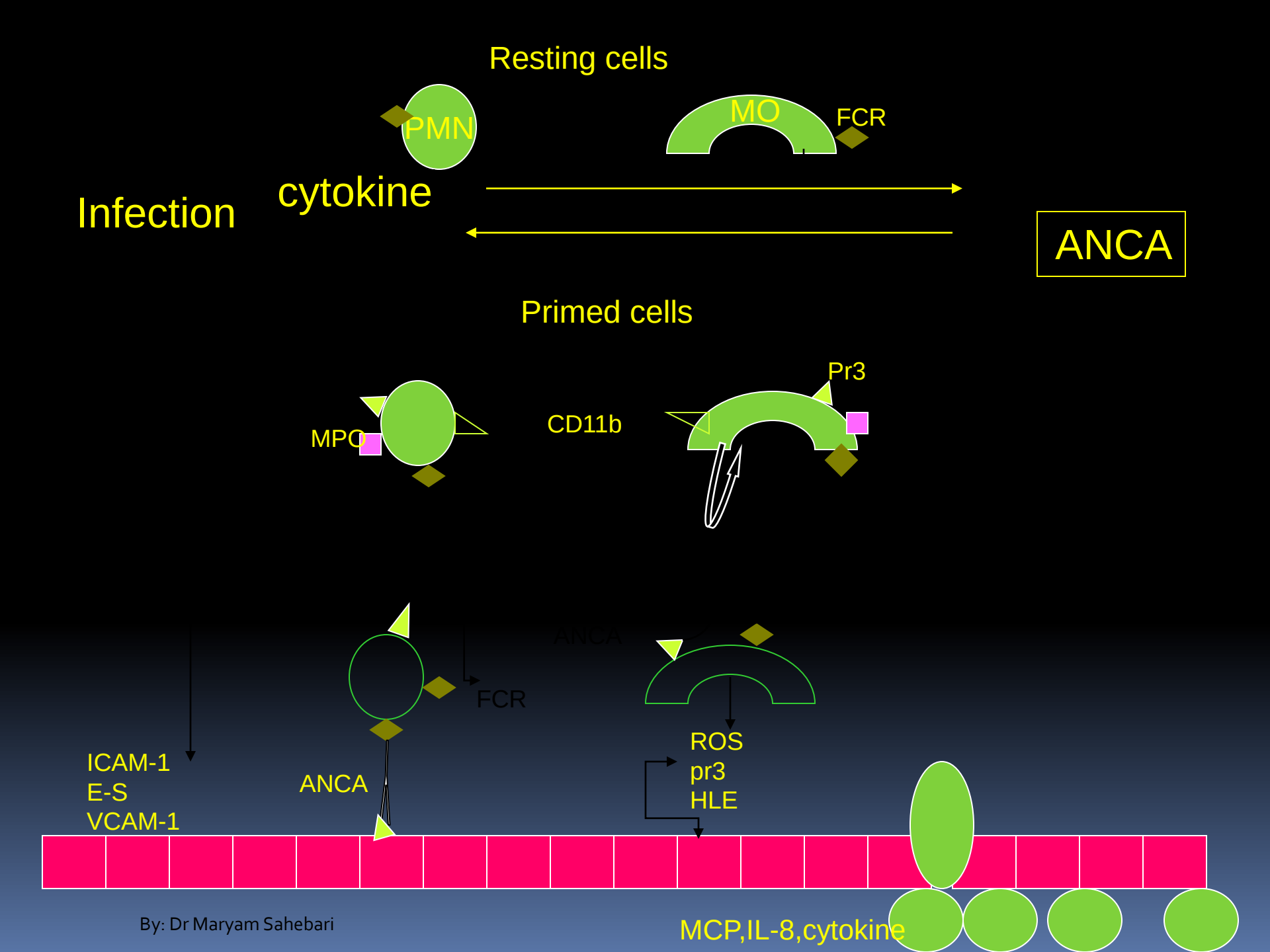

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3***Pathogenic T lymphocyte response and granuloma formation

- In granolomatous vasculitis delayed hypersensitivity and cell mediated immune injury are prominent.
- INF gamma ⟶ vascular endothelial cell ⟶ HLAII ⟶ CD_4Tcells ⟶ Inflammation and granuloma formation

Cell-mediated immune responses and Granuloma formation

Diseases

- Giant Cell arteritis
- Takayasu's arteritis
- Wegener's Granulomatosis
- Churg-Strauss syndrome
- Kawasaki syndrome

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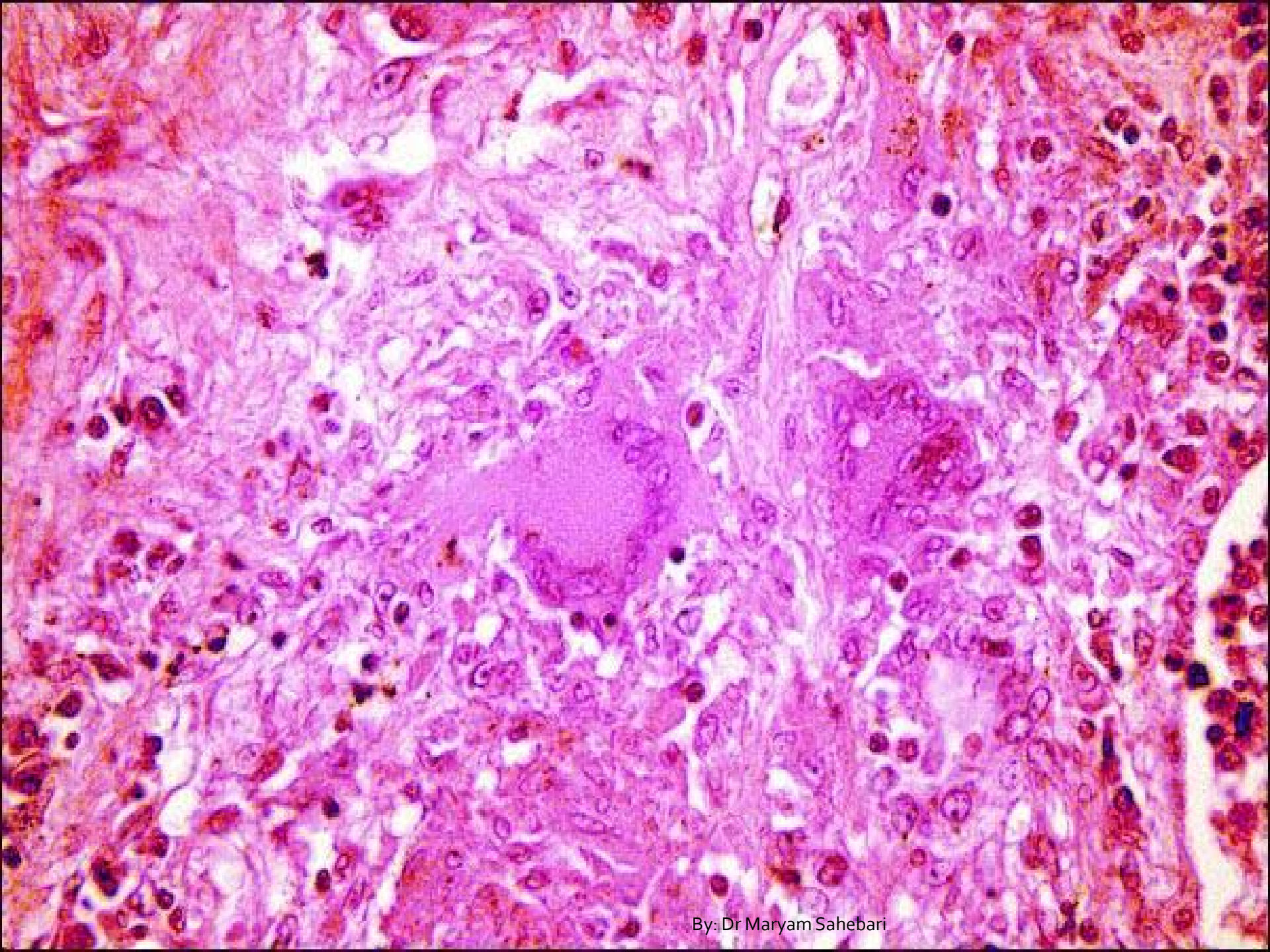
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Vasculitis
(Types)

- **Primary**
- **Secondary**
  - **Other rheumatic diseases**
  - **Infections (Viral)**
  - **Malignant diseases**

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Classification (Chapel Hill - 1992)

- **Large-vessel vasculitis**
  - Giant cell (temporal) arteritis
  - Takayasu's arteritis
- Medium-vessel vasculitis
  - Polyarteritis nodosa
  - Kawasaki's disease
- Small-vessel vasculitis
  - Wegener's granulomatosis
  - Churg-Strauss syndrome
  - Microscopic polyangiitis
  - Henoch-Schonlein purpura
  - Essential cryoglobulinemic vasculitis
  - Cutaneous leukocytoclastic angiitis

Large-vessel vasculitis

- Giant cell vasculitis:

Symptoms directly related to arteritis

- **Ischemia (cranial and extracranial)**
- **Pain**

Musculoskeletal symptoms

- **Symptoms of polymyalgia rheumatica**
- **Symptoms of peripheral synovitis**

CLASSIFICATION CRITERIA (GCA)

Age at onset more than 50 years

A new headache

Temporal artery abnormality

ESR more than 50 mm/h

Abnormal artery biopsy showing vasculitis with mononuclear cell or granulomatous inflammation usually with giant cells

At least three of the criteria

Symptoms directly related to arteritis: Cranial symptoms

- Headache
- Scalp tenderness
- Jaw claudication
- Visual loss and other ophtalmic manifestations
- Cerebrovascular accidents
- Vestibuloauditory manifestations
- Neuropsychiatric manifestations

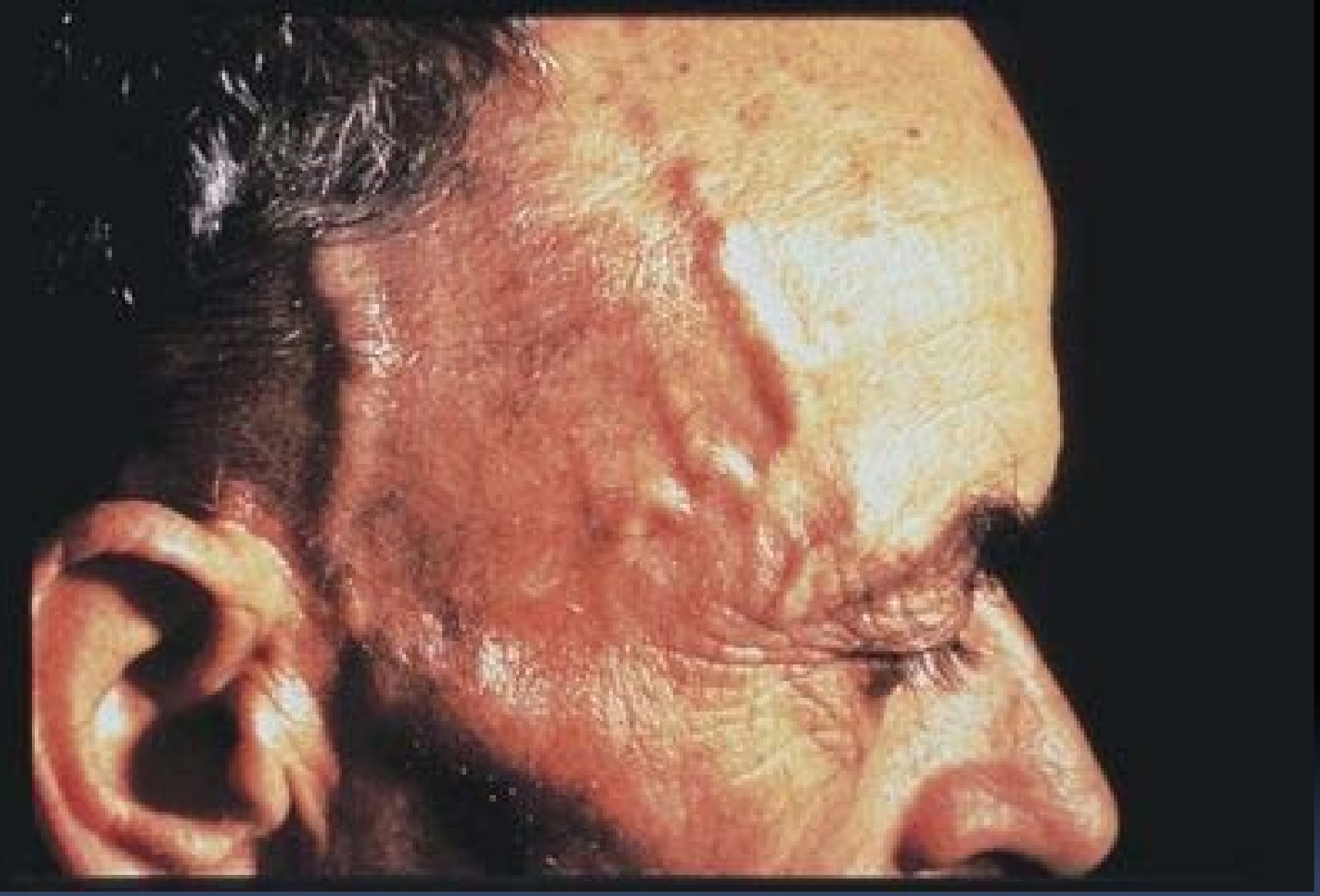
PREMONITORY VISUAL SYMPTOMS

- Blurry vision
- Amaurosis fugax
- hemifield loss
- Diplopia
- Visual hallucinations

CLINICAL FEATURES

Systemic symptoms

- **Fever**
- **malaise**
- **Anorexia**
- **Weight loss**



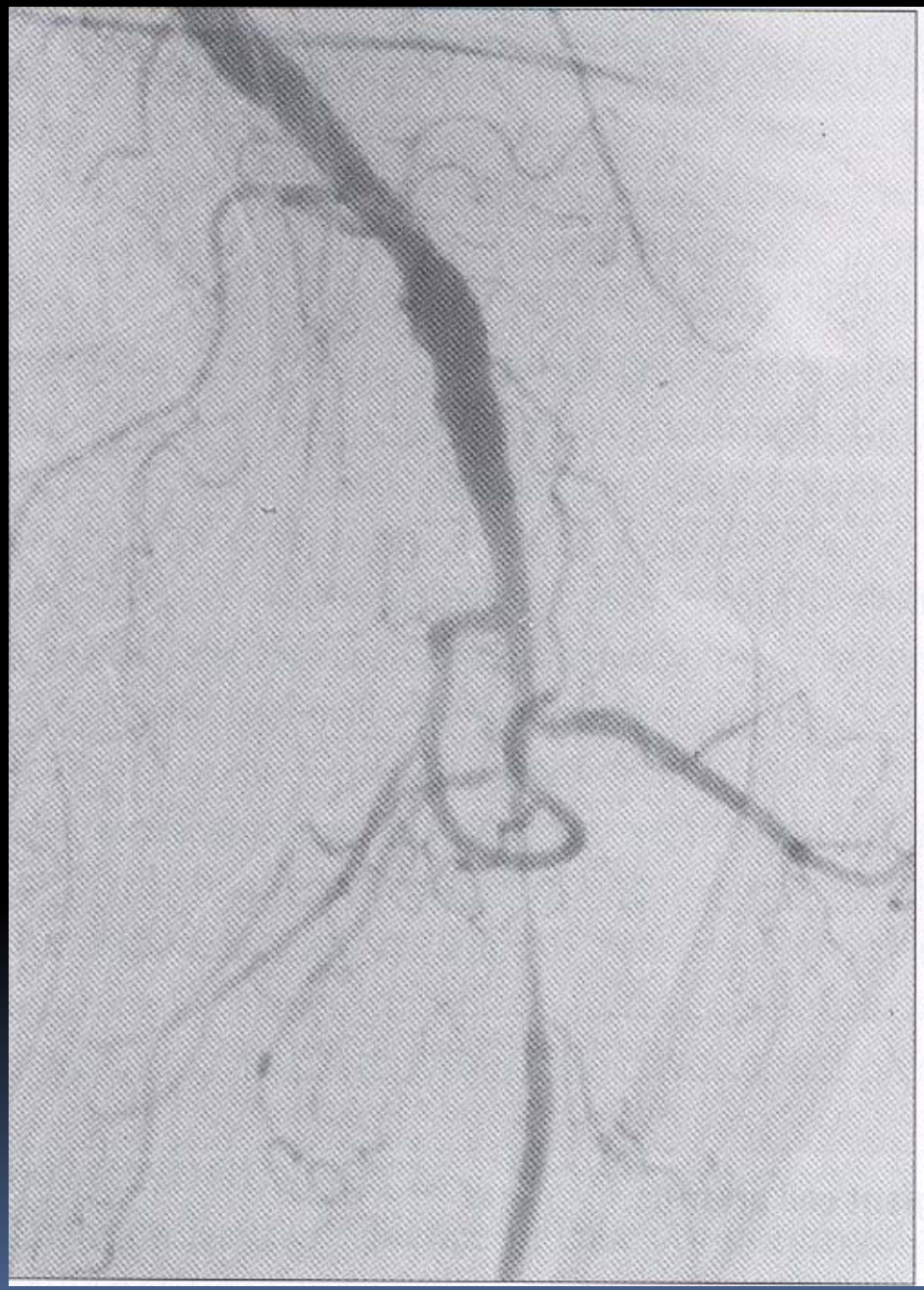
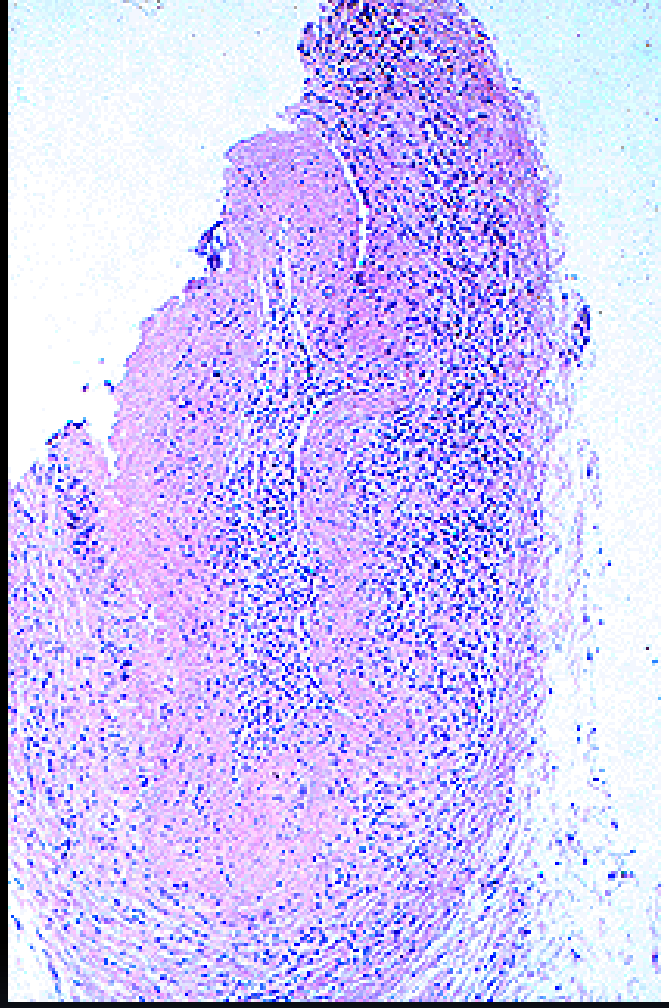
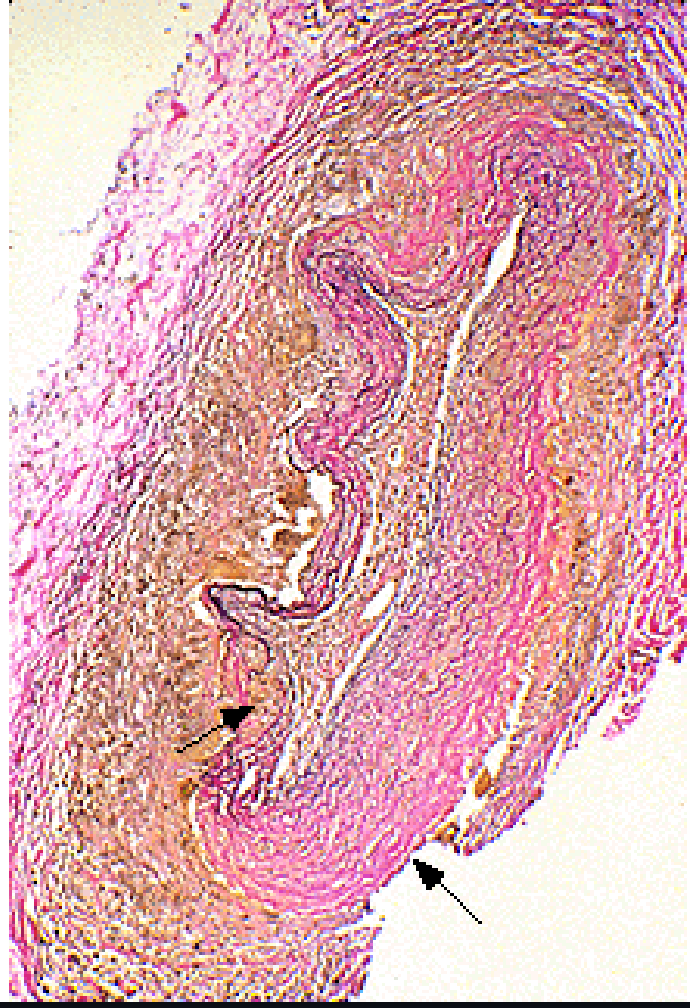


Fig. 21.5 Arteriogram showing narrowing of axillary artery in giant cell arteritis.





Left: Granulomatous and Lymphocytic inflammation in adventitia and medial wall.

Right: Disruption of the elastic (arrow) due to immunologically mediated destruction of the elastica.

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CLINICAL MANIFESTATIONS OF POLYMYALGIA RHEUMATICA

A clinical syndrome characterized by

- Aching and morning stiffness in the neck, shoulder and hip girdles
- A patient older than 50 years
- More than one month
- Systemic reaction
- Response to glucocorticoid

CLINICAL MANIFESTATIONS

Frequency of PMR in GCA patients **17-66%**

Frequency of GCA in PMR patients **6-31%**

Takayasu's Arteritis

- T.A. is a chronic vasculaitis of unknown etiology
- T.A. is a granolomatous inflammation of the aorta and its major branches
- T.A. is a panarteritis affecting aorta and its major branches
- Less frequently the pulmonary arteritis
- Age at disease onset < 40 years

Takayasu's Arteritis

Epidemiology

- Women are affected in 80 to 90 percent of cases
- Age of onset usually between 10 to 40 years
- Greatest prevalence in Asia

Takayasu's Arteritis

Pathogenesis

- The pathogenesis is poorly understood
- Cell mediate mechanisms are important
- Infiltrating cells in aorta tissue
- Mainly consist of killer cell

  (especially delta T- lymphocyts)
- Antigen in aortic tissue maybe specific or H.S.P.65
- No patient had autoantibodies associated with other forms of vascular injury

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Takayasu's Arteritis

Clinical Manifestation

- **Early phase systemic symptoms including :**

  Fatigue , Malaise , Weight loss ,Low-grade fever

  Arthralgias , Myalgias , Joint aches

- **Sometimes Erythema Nodosum**

Takayasu's Arteritis

Clinical Manifestation

As the disease progresses

- Evidence of vascular invalvement and insufficiency
- Dilation , Narrowing or occlusion
- Proximal or Distal branches of the aorta
- Extremitis cool and pain develops with use
- Arm or leg cloudication

Takayasu's Arteritis

Clinical Features

Vascular 100%

- **Subclavian Bruit (one or both subclavian arteries)**
- **Claudication (especially the upper extremities)**
- **Decrease / absent pulse (one or both Brachial arteries**
- **Asymetric BP (Differents of > 10 mmHg in systolic BP between arms)**
- **Hypertension (with narrowing of the renal artery)**

Takayasu's Arteritis

Clinical Features

Musculo skeletal 53%

- **Arthralgi**
- **Myalgia**
- **Peripheral synovitis is less common**

Takayasu's Arteritis

Laboratory Investigation

- ESR elevated in active disease
- ANCA and Anti-DNA , Anti phospholipid , Antibodies are not associated with Takayasu's Arteritis
- WBC count is usually normal

Takayasu's Arteritis

Imaging studies and Ultra sound

- Trans thoracic ultra sound may help for aorta and its branches
- Trans esophageal ultra sound provides a better view of the decending aorta
- MRA is able to image the aorta and its major branches
- MRA is able to demonstrate aortic wall thickening , stenosis and Aneurysms
- CT or MRI scans can also be used to follow the response to treatment

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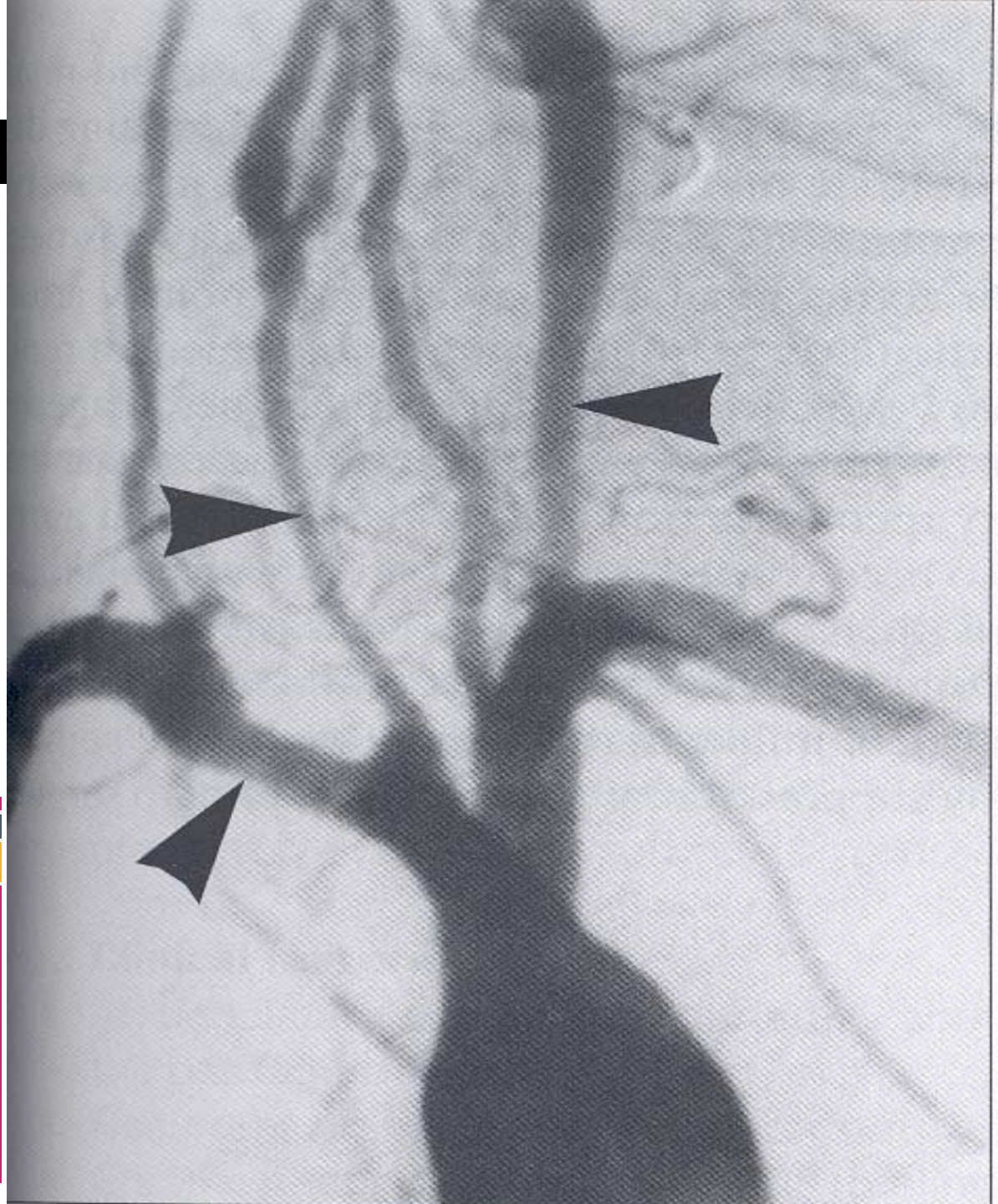

Fig. 25.4 Aortic arch arteriogram in a patient with Takayasu's arteritis. Smooth tapered stenosis of bilateral common carotid arteries (upper arrows) and of the right subclavian artery (lower arrow) can be seen. There is poststenotic dilatation beyond the left common carotid narrowed segment. Total involvement is seen along the length of the right common carotid artery.

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Medium Vessels: Polyarteritis nodosa

- **Case Presentation**

•Six moths ago, a previously healthy **67-year-old man**, developed a tingling sensation over the dorsum of the left foot.

• Over the next 3 weeks he noted left foot drop, right foot numbness, fever, malaise, polymyalgia and polyarthralgia.

• Tow months later he noted painful paresthesia and weakness,first in the left hand and then in the right.

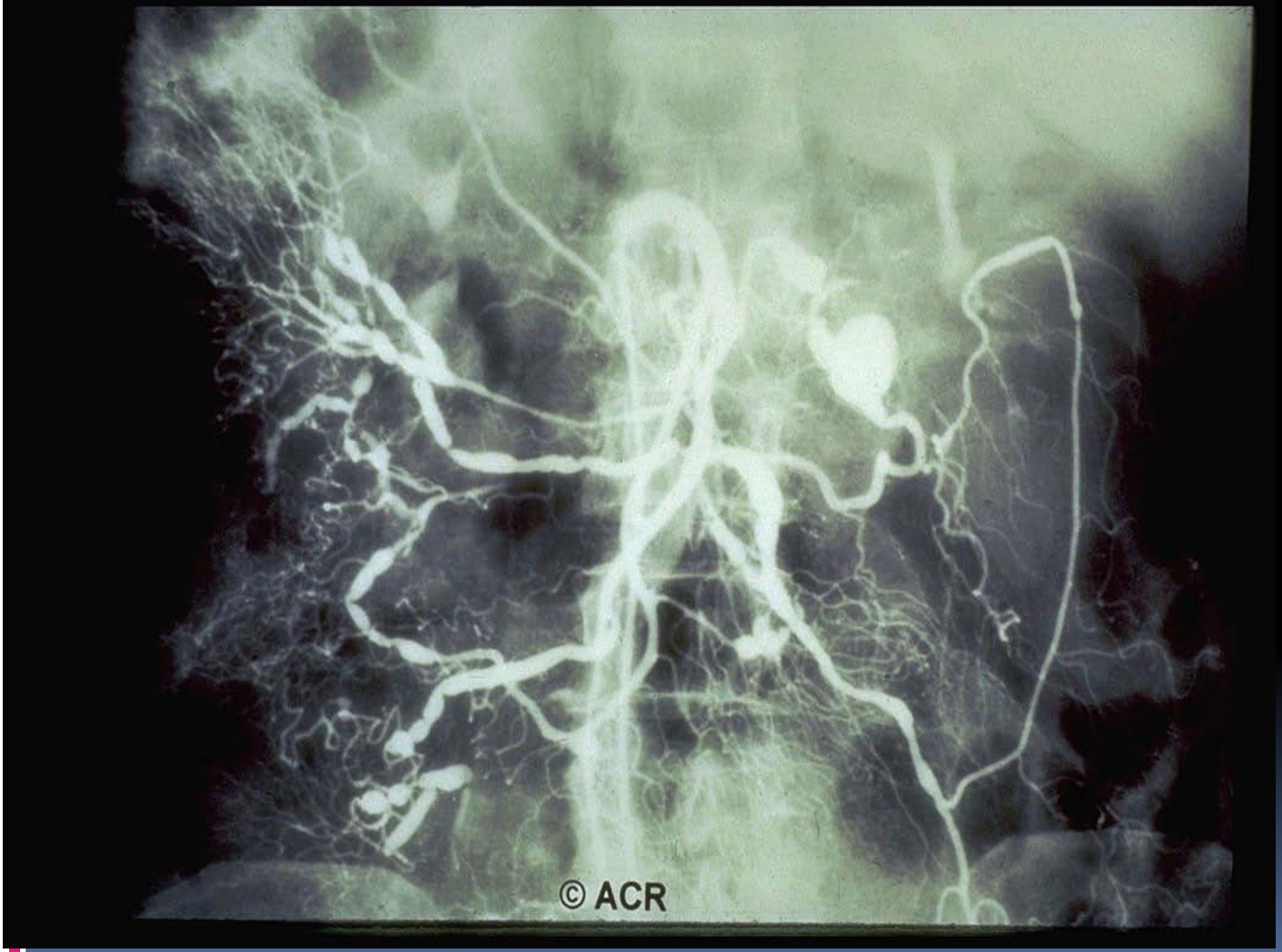
- Subsequently, he lost 10kg, stumbled frequently because of the foot drop, dropped tools because his grip had weakened and slept fitfully because of fever and painful paresthesia.

Physical Exam

- He appeared chronically ill, with a BP: 172/104 mmHg and T: 39
- He had livedo reticularis over the thighs and wasting of the interosseous muscles of the left hand and the thenar muscles of the right hand.
- He was unable to dorsiflex the left foot. He had decreased pinprick sensation over the dorsum of the left foot, the plantar aspect of the right foot, the palmar aspect of the 4^{th} and 5^{th} fingers of the left hand and the palmar aspect of the first three fingers of the right hand.

Para Clinical

- Hb: 9, Hct 27%, ESR: 121mm/h, Cr: 2.1mg/dl.
- The urinalysis showed 2+ protein and 5-10 red blood cells (RBCs) per high –power field (*400) with RBC casts.
- Electroneurologic testing revealed an axonal neuropathy involving the left peroneal, right tibial, left ulnar and right median nerves.
- A renal arteriogram showing micro aneurysms in the renal and hepatic circulation confirmed PAN.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Other Lab tests

WBC: and platelets: normal, FBS: 98,

HBs Ag(+) and HCV: Negative, HIV: negative

ANCA: negative, VDRL: negative,

AST, ALT, CPK and LDH: negative,

anti-DNA and APL: negative, TFT: normal

- What is your Diagnosis?
- What are your diff. diagnosis?

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- **Multi-system**
- **Nervous system: Mononeuritis Multiplex**
- **Constitutional**
- **Skin**
- **Kidney**
- **Lab data:** Hb:9, ESR:121mm/h, Cr:2.1mg/dl, active U/A
- **Renal arteriogram:** Micro aneurysm in renal and hepatic circulation
- **NCV:** Axonal neuropathy: left peroneal, right tibial, left ulnar, right median

What is your Diagnosis?

Most probably: Poly Arteritis Nodosa

(PAN)

PAN

Poly-arteritis Nodosa

Pan-arteritis Nodosa

Peri-arterits Nodosa

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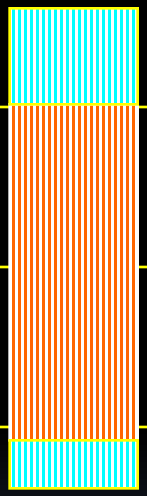
Communication between Vessel wall and PAN

Vessels	PAN
Small Vessel (Cappilary , Venule , Artery)	
Small Artery (Intra Organ)	
Medium Artery (Coronay , Hepatic , Mesenteric)	
Large Artery (Aorta , Vertebral , Temporal)	

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PAN

- Rare
- Prevalence: 6.3 in 100,000 Incidence: 0.7 in 100,000
- Age: 40 – 60
- Sex
- Hepatitis B

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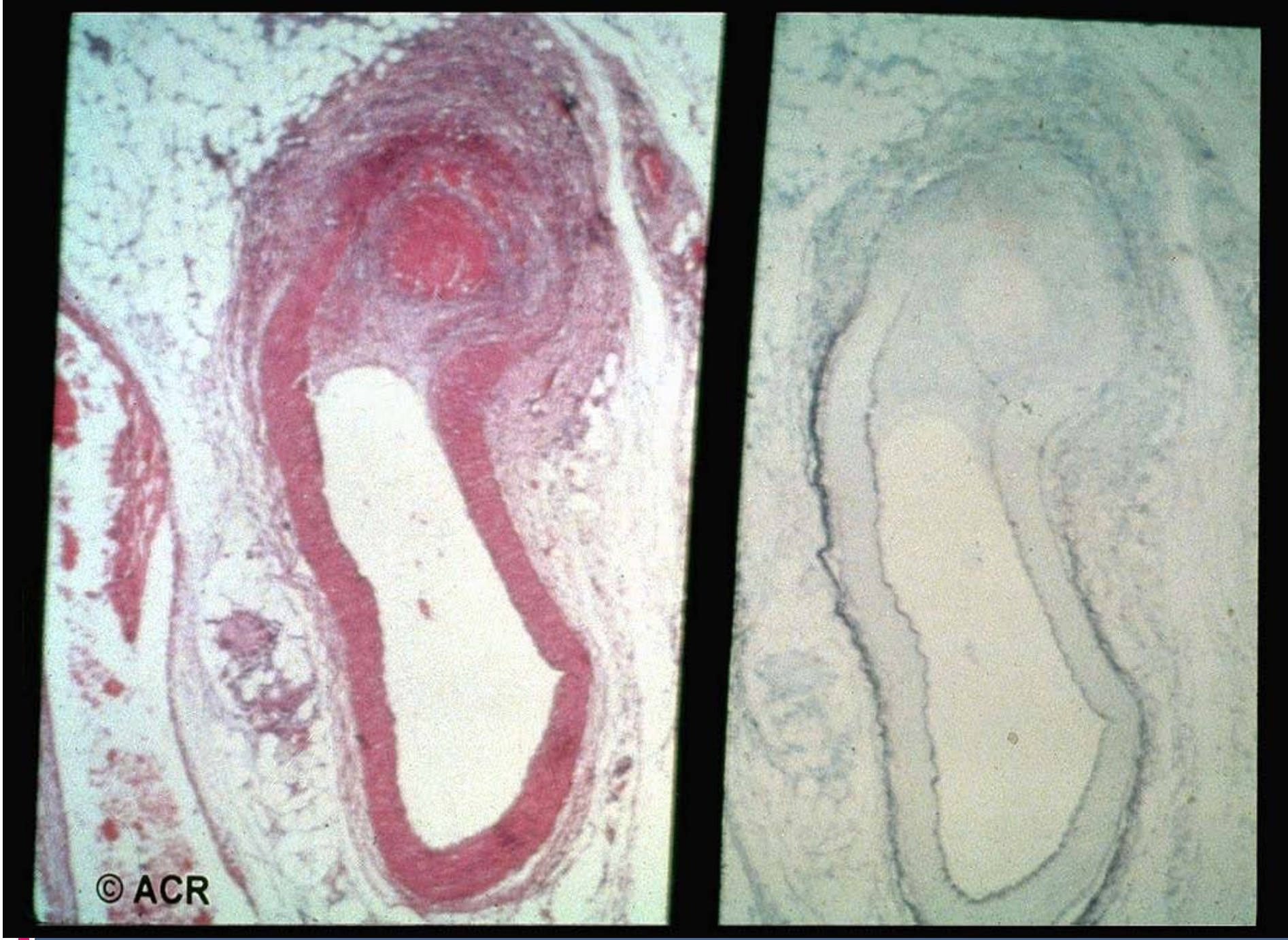
Pathology

- Necrotizing Vasculitis
- Focal and Segmental
- Arterial Biforcations
- Acute inflammations:
- Subacute and chronic inflammations:
- Hairy cell leukemia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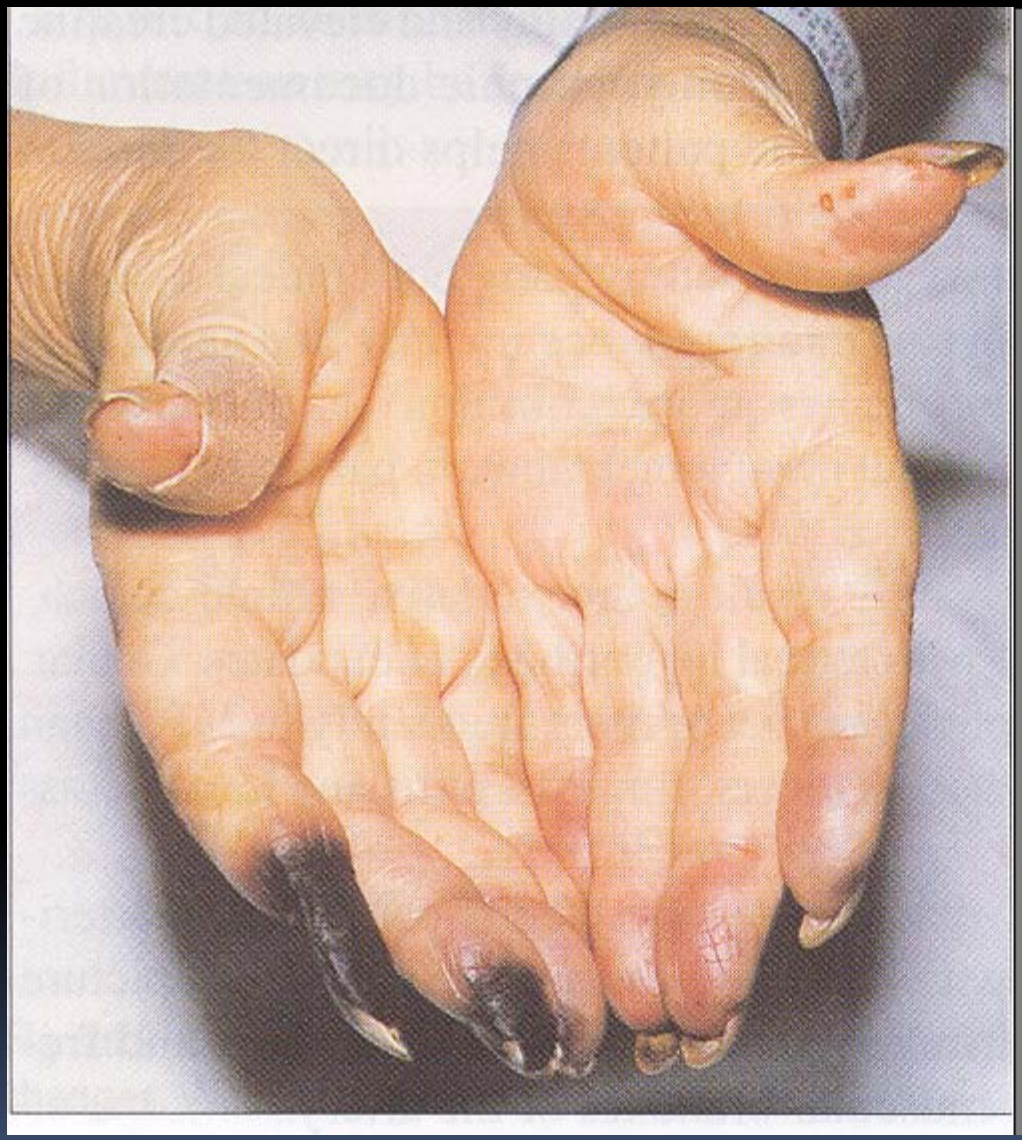
CLINICAL MANIFESTATIONS OF PAN

- Systemic
- Symptoms :

  Fatigue, weakness, fever, arthralgia, myalgia
- Signs :

  Skin, Hypertension, Renal involvement, Neurologic dysfunction, Abdominal pain



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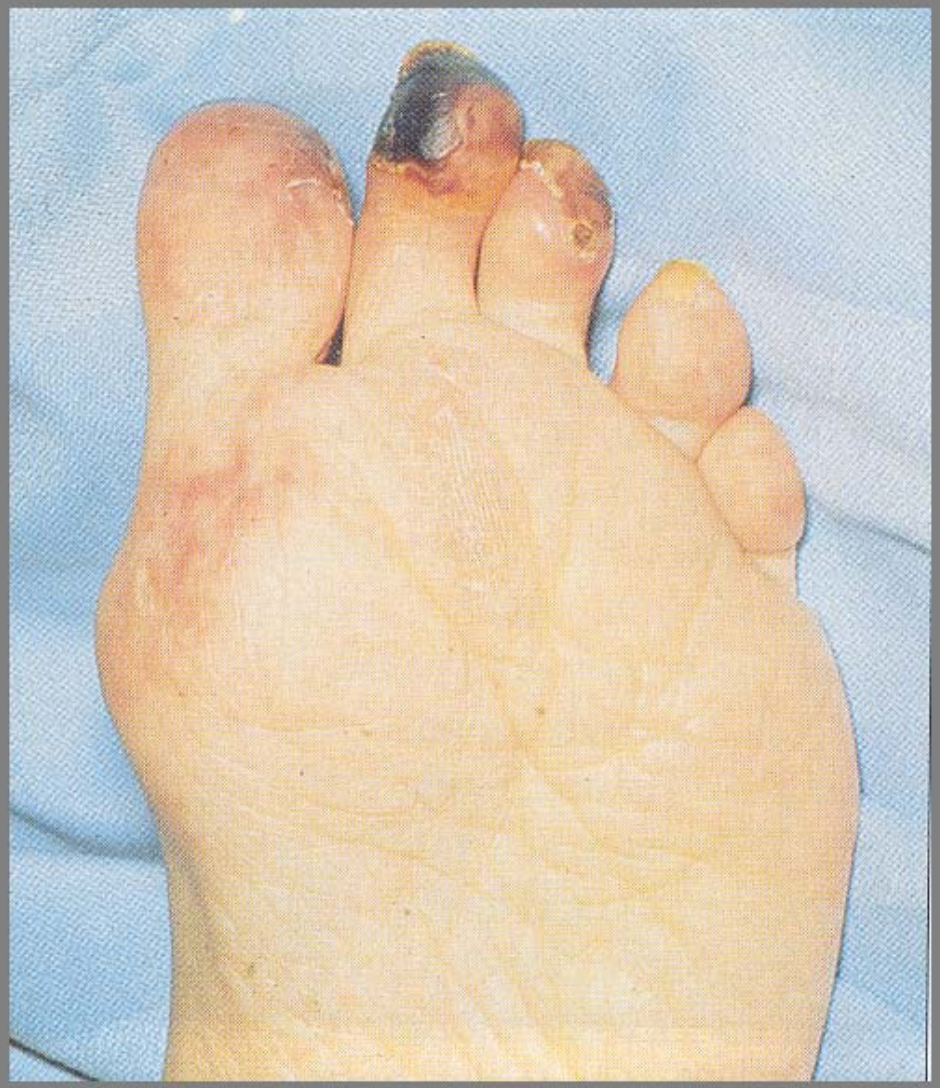

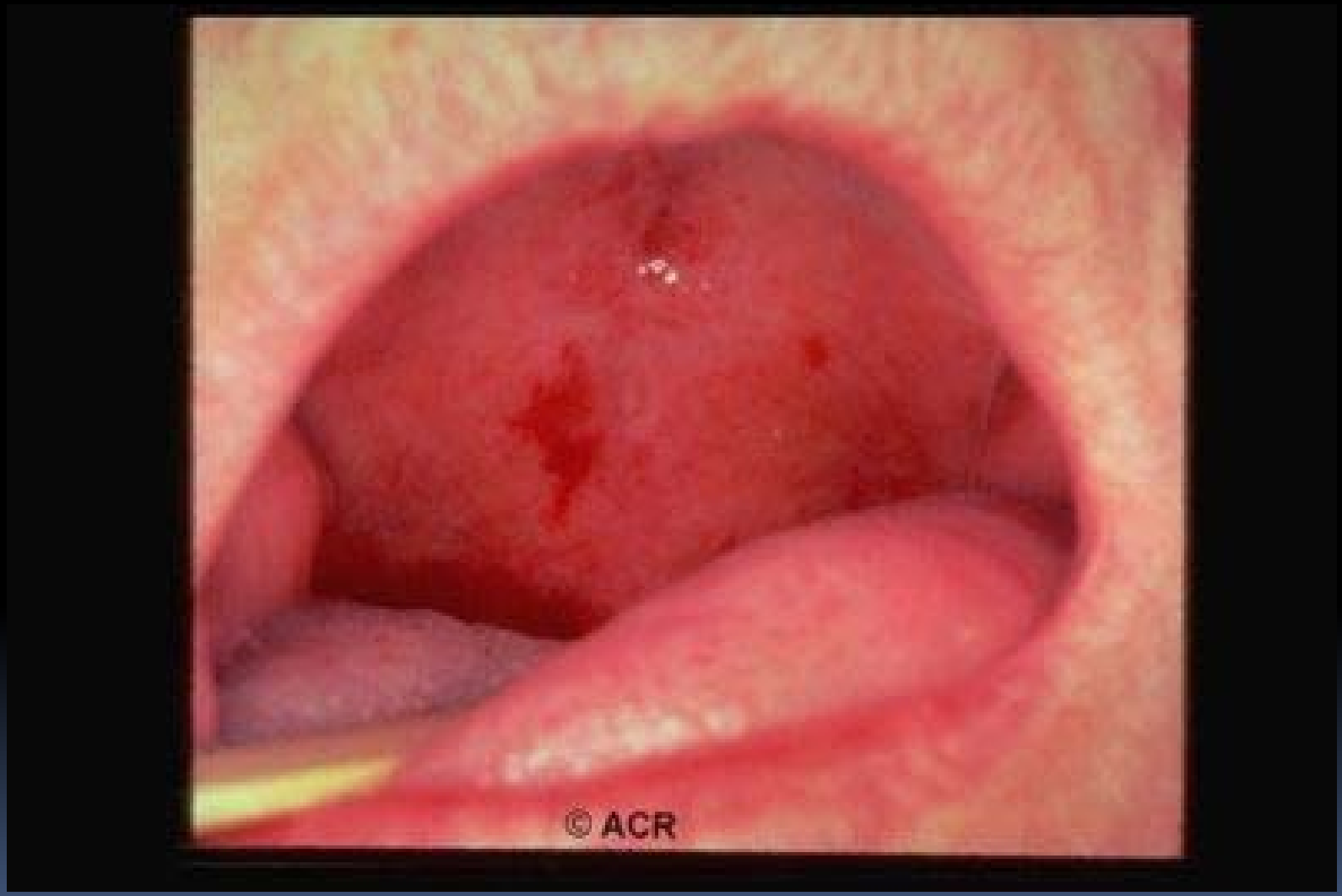
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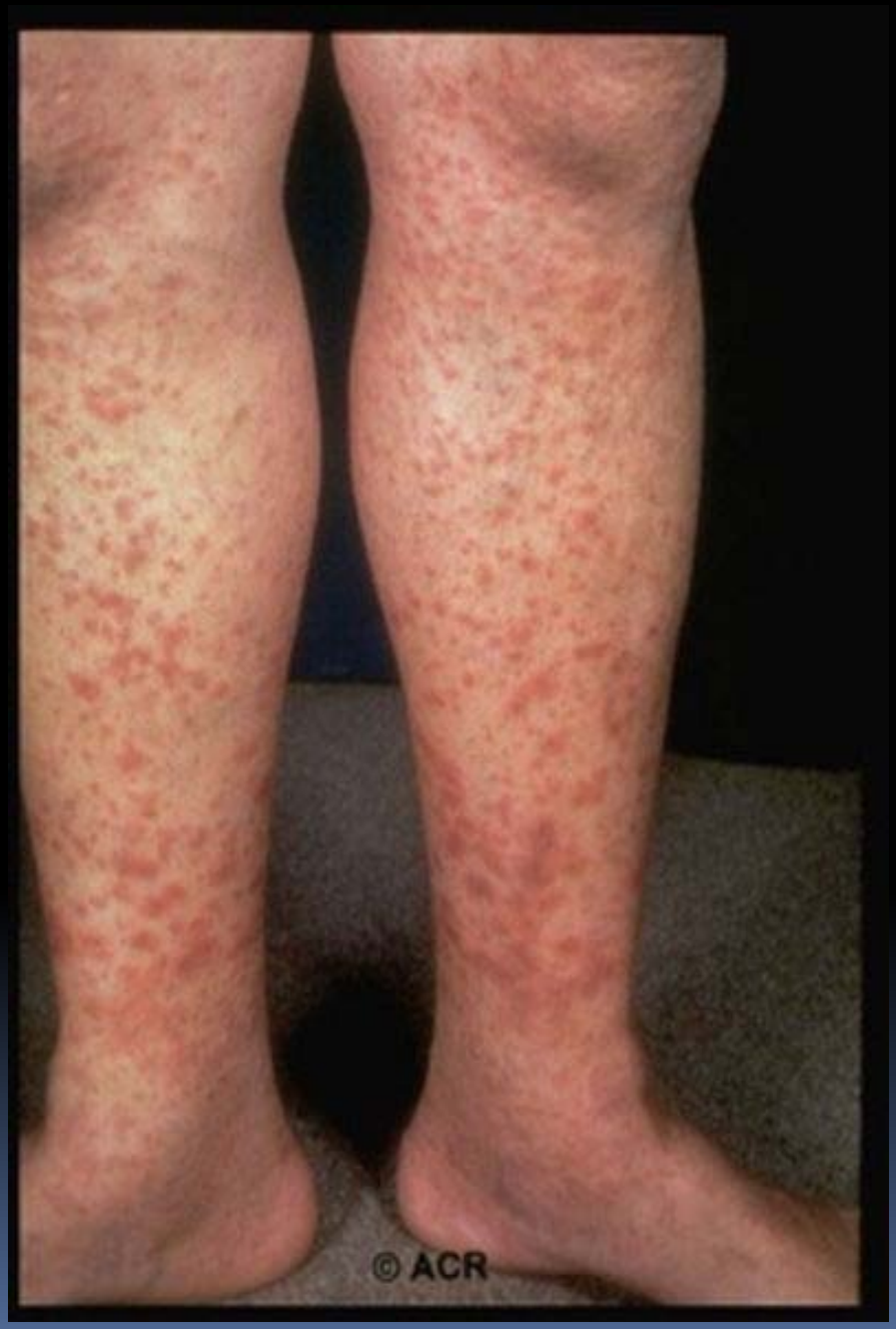

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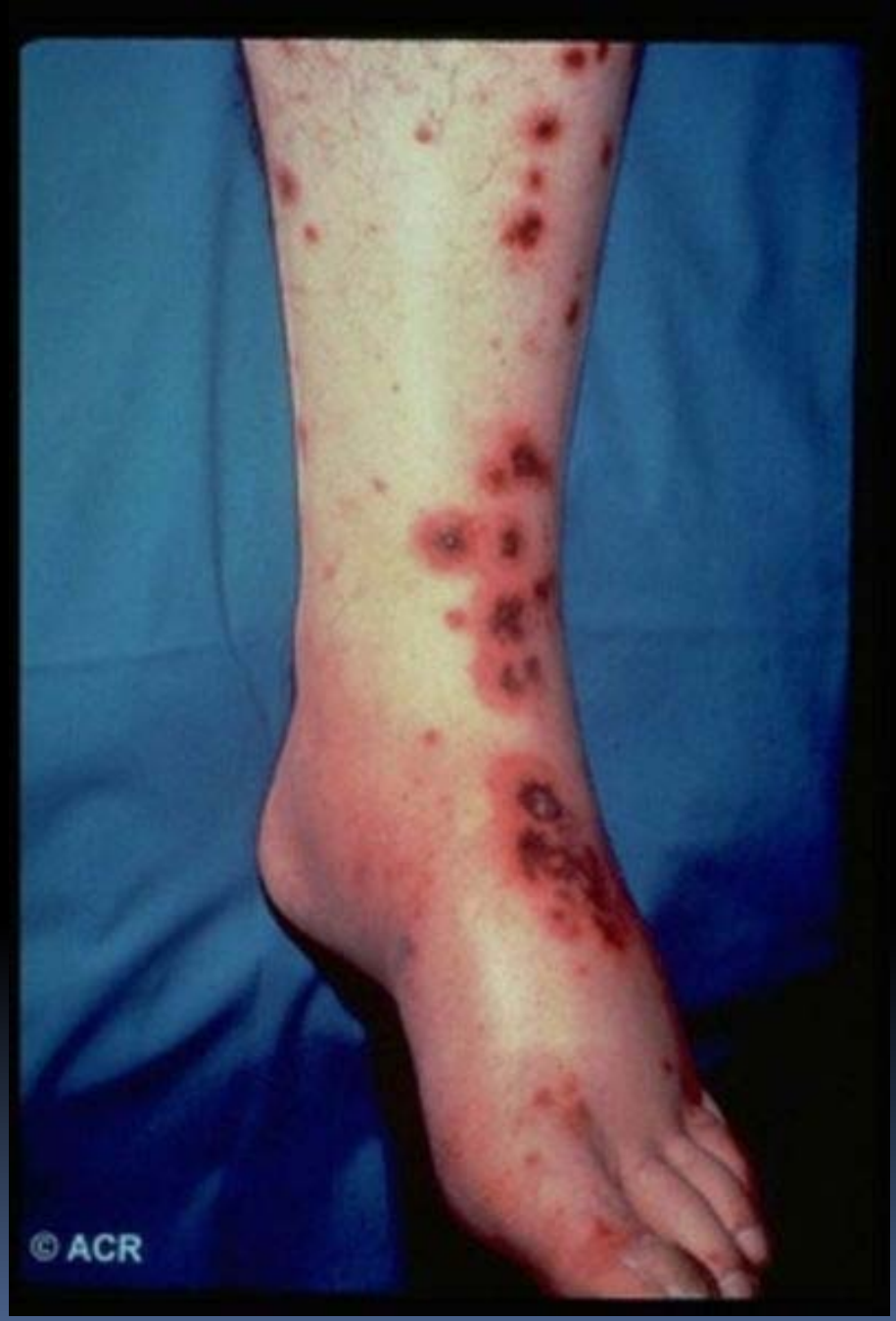

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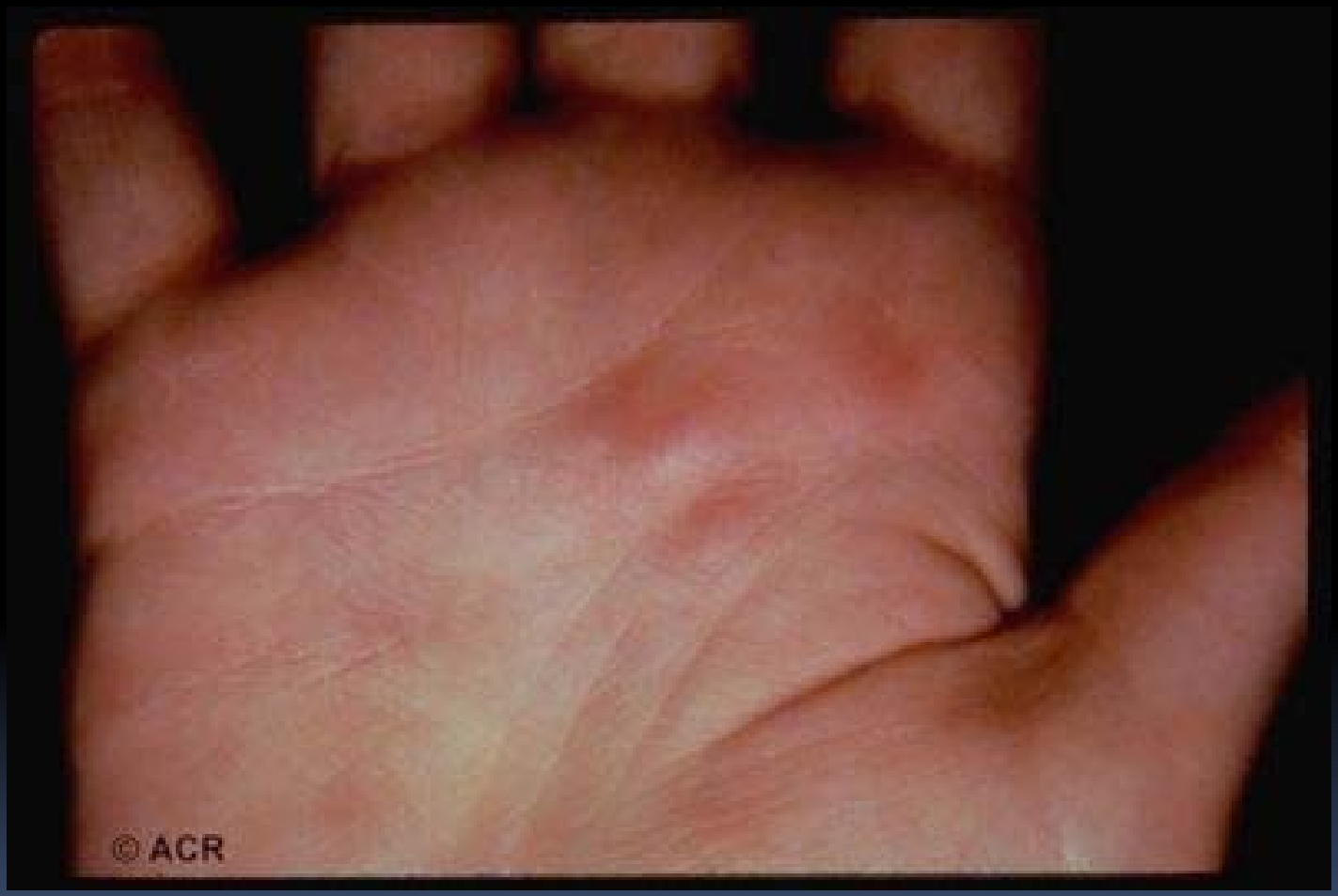

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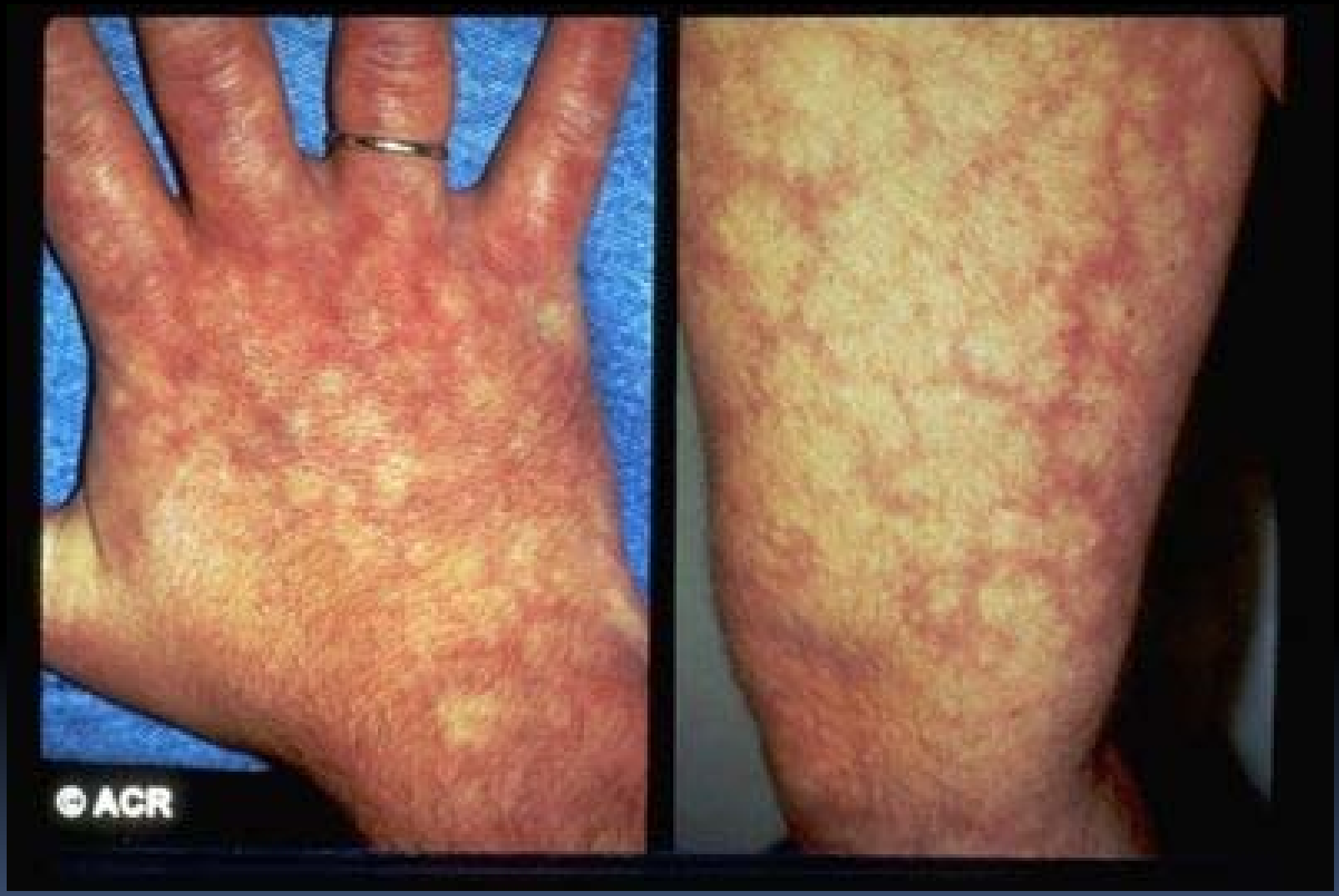

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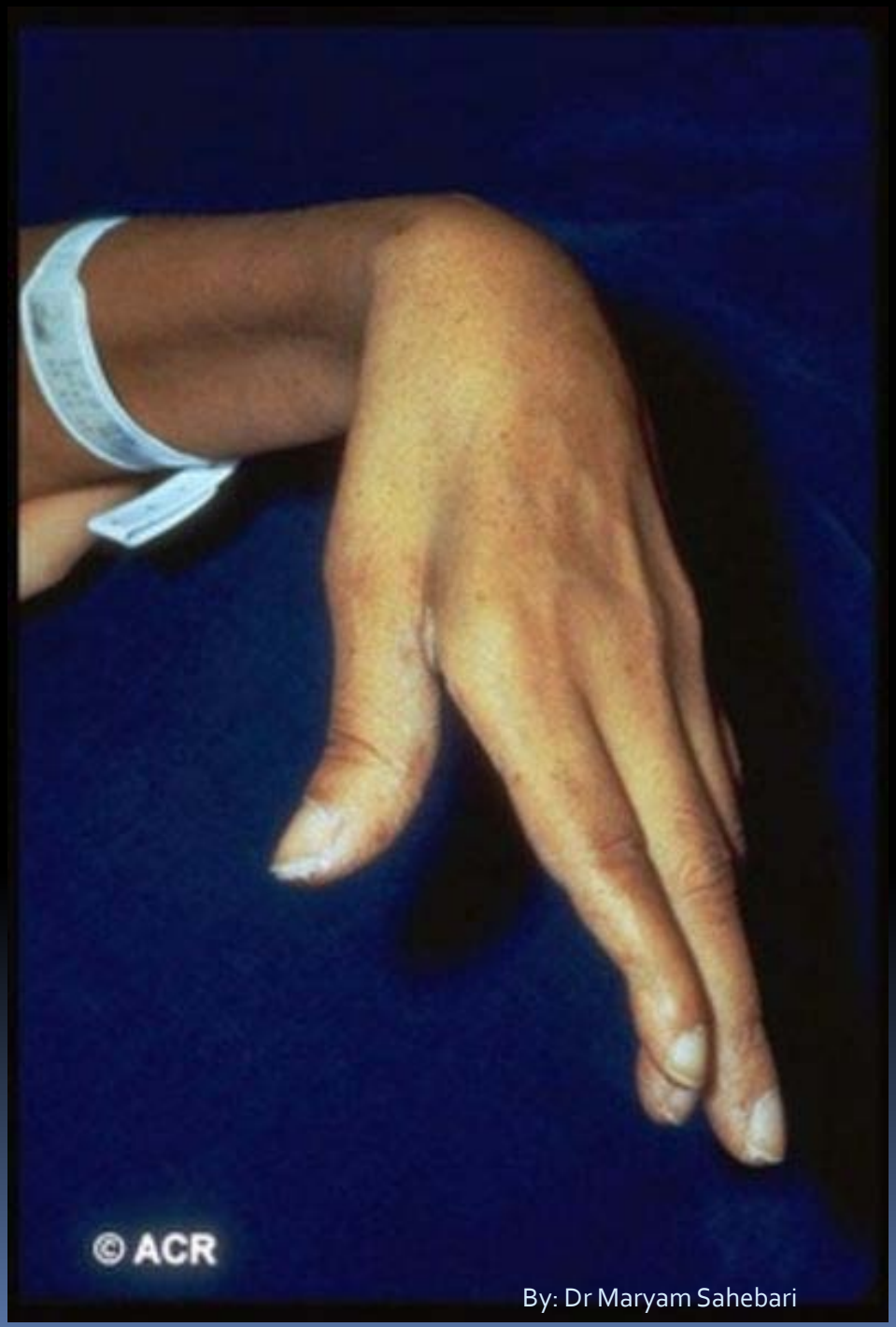

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ACR CLASSIFICATION CRITERIA

3 of 10 Criteria by ACR = PAN

1. Otherwise unexplained weight loss greater than 4 kg
2. Livedo reticularis
3. Testicular pain or tenderness
4. Myalgias (excluding that of the shoulder and hip girdle), weakness, or polyneuropathy
5. Mononeuropathy or polyneuropathy
6. New onset diastolic blood pressure greater than 90 mmHg
7. Elevated levels of serum blood urea nitrogen (>40 mg/dL or 14.3 mmol/L) or creatinine (>1.5 mg/dL or 132 μmol/L)
8. Evidence of hepatitis B virus infection via serum antibody or antigen serology
9. Characteristic arteriographic abnormalities not resulting from noninflammatory disease processes
10. A biopsy of small or medium-sized artery containing polymorphonuclear cells

Sensitivity: 82% , Specificity: 87%

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Diagnosis

- History and Physical examination
- Pathology
- Arteriography

Prognosis of PAN

- Prognosis : 50% one year , 13% for 5 years without treatments
- Major causes of death:

  Renal failure, mesenteric, cardiac, or cerebral infarction
- Progressive narrowing of the vascular lumens and arteriosclerosis.
- Preservation of tissue function is most likely if treatment is instituted early in the course of the disease.


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