Approach to a patient with Vasculitis

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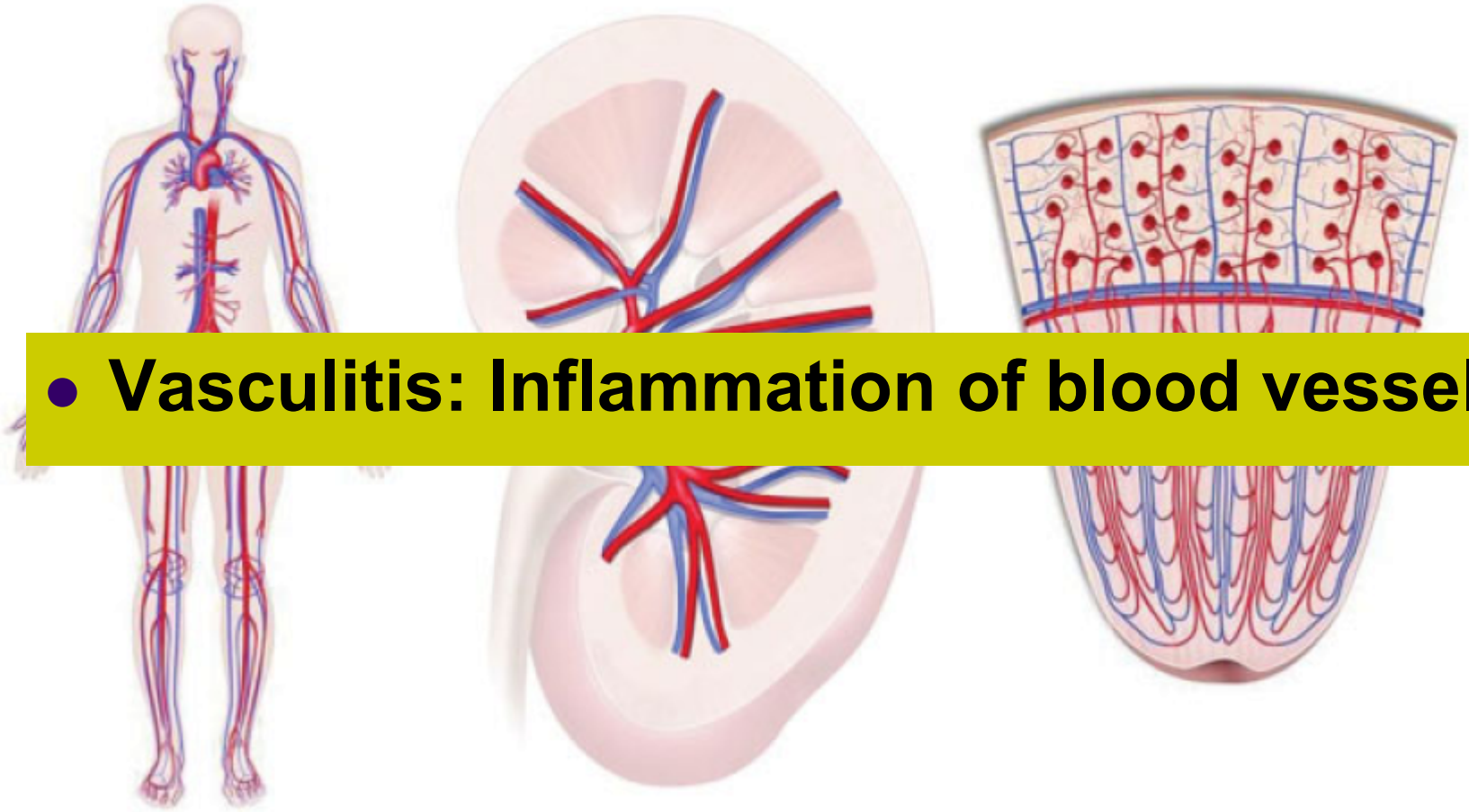
Department on Internal Medicine
Divison of Rheumatology

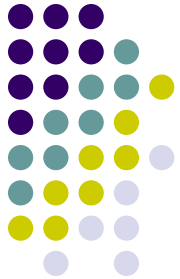
A Large Vessels B Medium Vessels C Small Vessels



- **Vasculitis: Inflammation of blood vessels**

Large vessels: Aorta and main branches with analogue veins
Medium vessels: Main visceral arteries and veins
Small Vessels: Intraparenchymal arteriol, capillaries, venules

Vasculitis
"Inflammation of vessels"



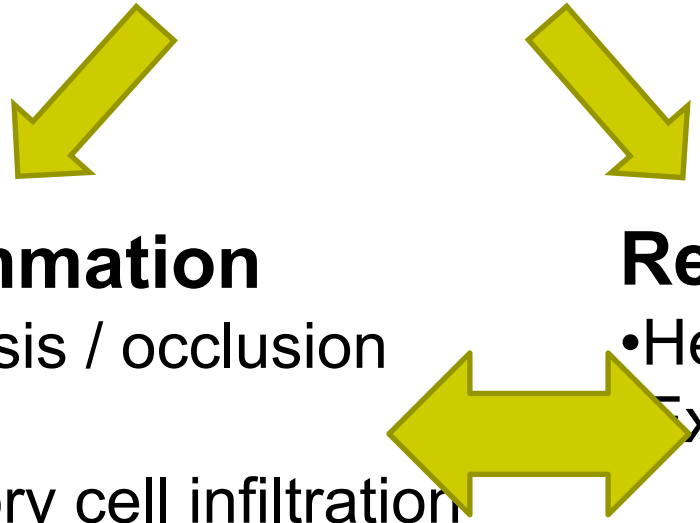
Acute inflammation

- Luminal stenosis / occlusion
  - Edema
  - Inflammatory cell infiltration
- Rupture

Repair phase

- Healing (regeneration)
- Excessive repair
  - Luminal stenosis
- Repair impairment
- Aneurysms

Vasculitis
"Inflammation of vessels"



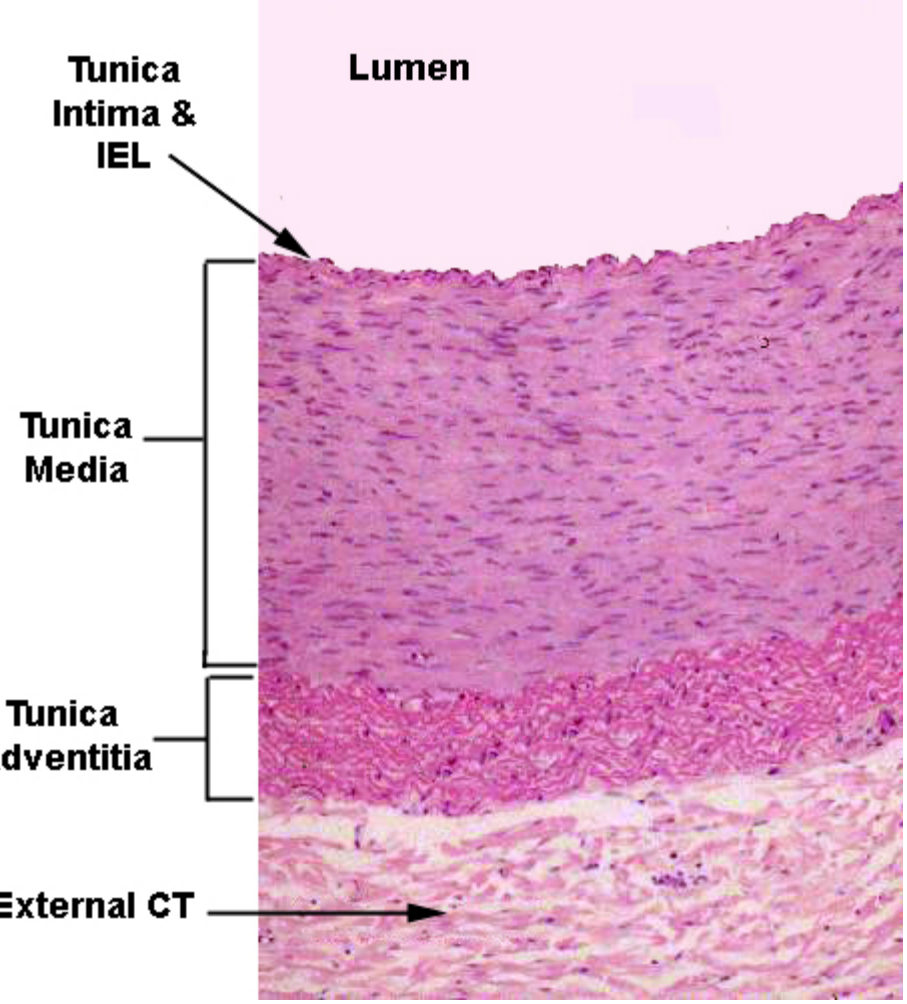
Acute inflammation

- Luminal stenosis / occlusion
  - Edema
  - Inflammatory cell infiltration
- Rupture

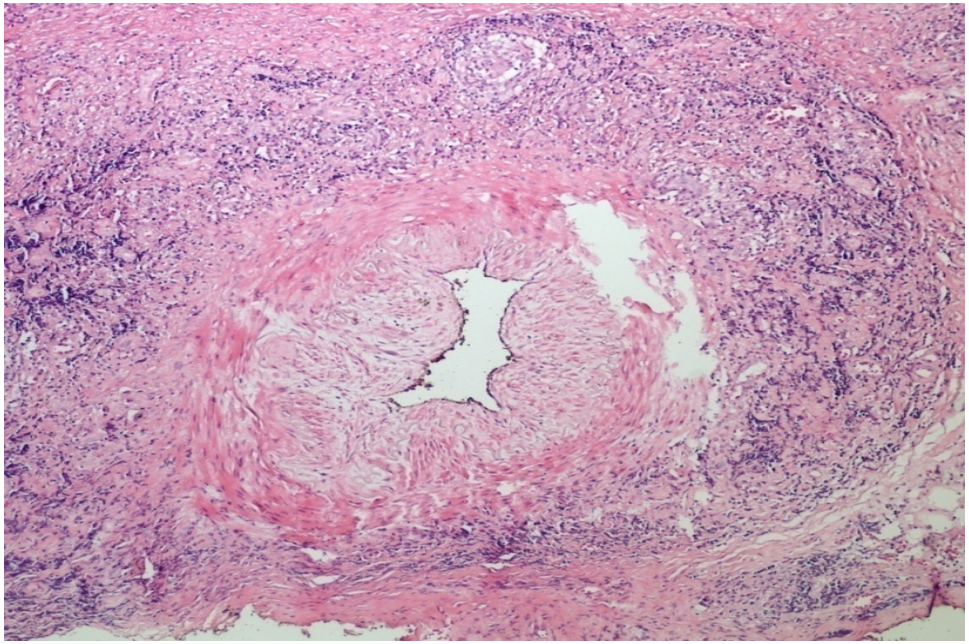
Repair phase

- Healing (regeneration)
- Excessive repair
  - Luminal stenosis
- Repair impairment
- Aneurysms

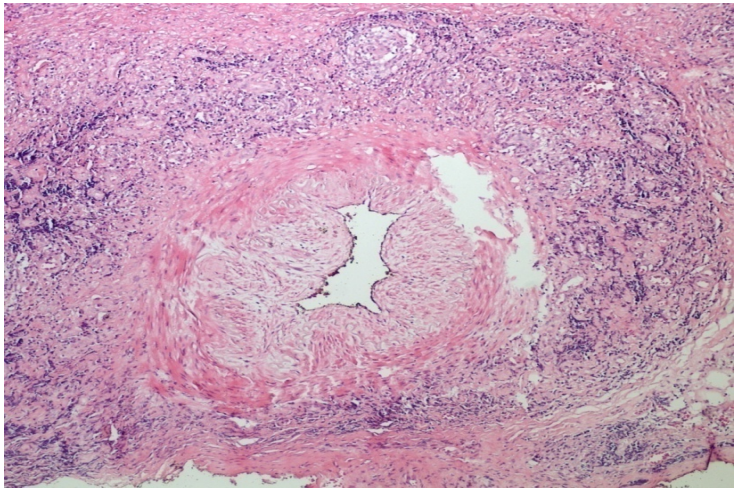
Both acute and repair mechanisms could be seen at the same time

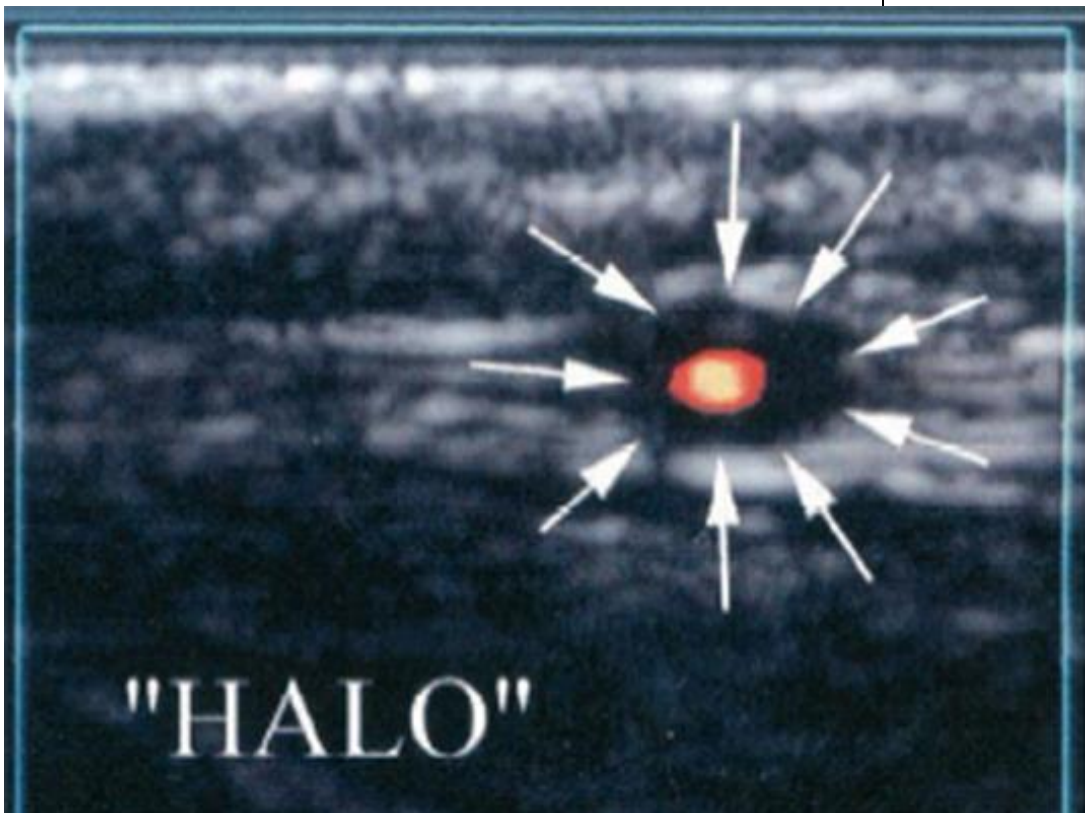


Normal vessel histology



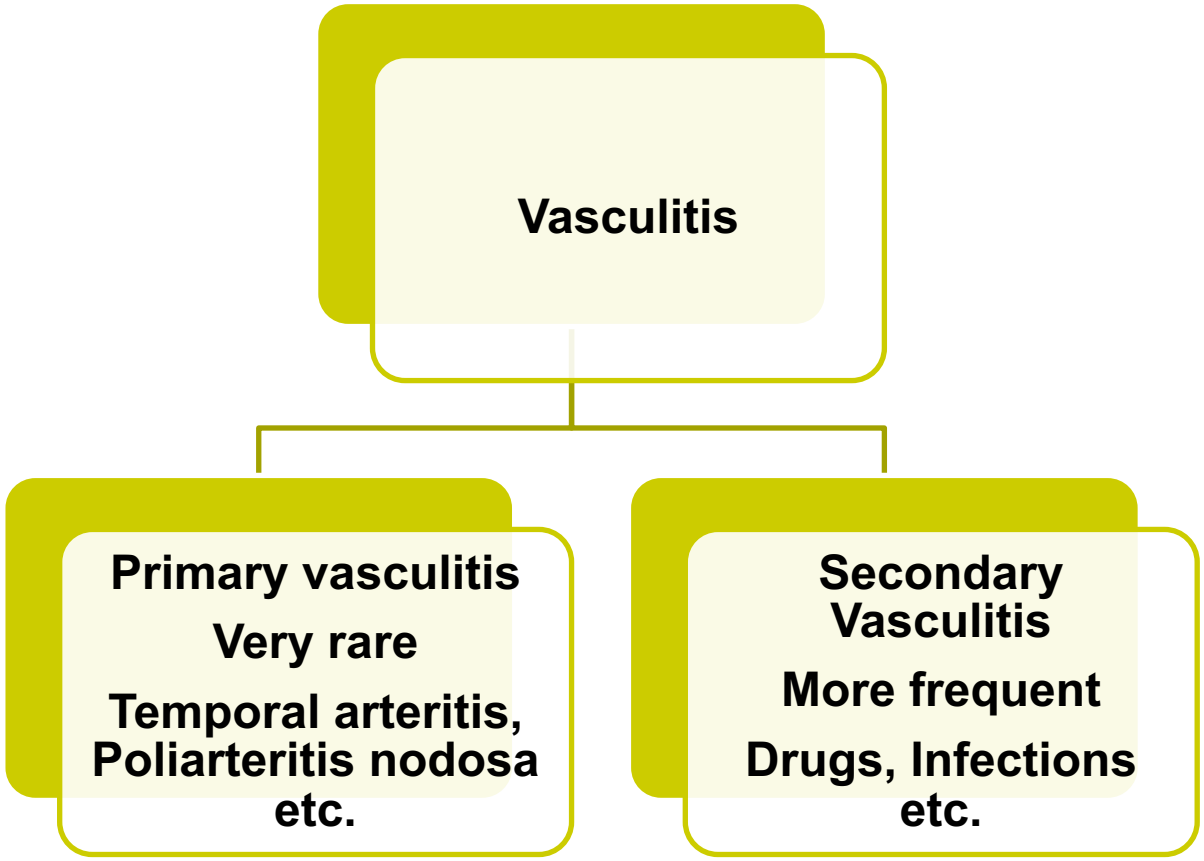
Temporal arteritis
Inflammatory cell infiltration





Doppler US

Temporal arteritis / vessel wall edema


Vasculitis
Primary vasculitis
Very rare
Temporal arteritis, Poliarteritis nodosa etc.
Secondary Vasculitis
More frequent
Drugs, Infections etc.

Secondary Vasculitides
-Antigens presumably involved-

Exogenous antigens

Microbial antigens

Bacterial

- Streptococci
- Staphylococci
- *Mycobacterium leprae*
- *Treponema pallidum*
- Others

Viral

- Hepatitis B/C virus
- HIV, CMV, EBV

Others

- Protozoal, Plasmodia

Non-microbial antigens

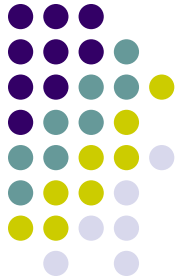
- Heterologous proteins
  - e.g:murine,
  - chimeric monoclonal antibodies
- Allergens
- Drugs
- Tumor antigens

Autologous antigens

- Nuclear antigens(antinuclear antibodies)
- Immunoglobulin G (RF, cryoglobulins)

Others

Drug induced Vasculitis

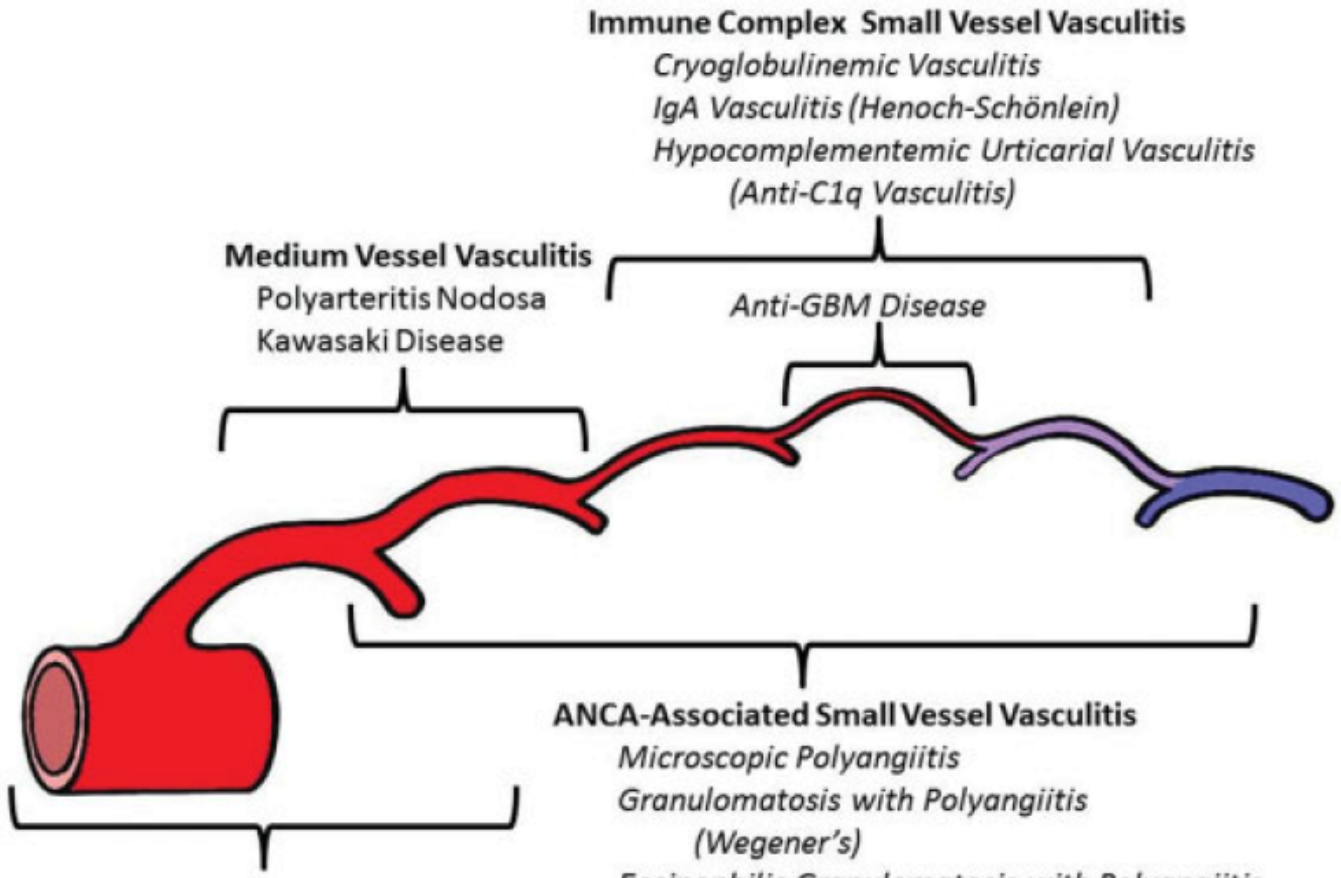


- Klozapin
- Hidralazin
- Propiltiourasil
- Sulfasalazin
- D-penisilamin
- Siprofloksasin
- Fenitoin
- Growth factors
- Allopurinol
- Interferon
- TNF blockers
- Leukotrien inhibitors

Clues of drug induced vasculitis

- Eosinophilia in biopsy
- Palpable purpuras with same age
- Drugs used in last 6 months questioned

Primary Vasculitides



Variable vessel vasculitis (VVV)
- Behçet's disease (BD)
- Cogan's syndrome (CS)

Single-organ vasculitis (SOV)
- Cutaneous leukocytoclastic angiitis
- Cutaneous arteritis
- Primary central nervous system vasculitis
- Isolated aortitis
- Others

Vasculitis associated with systemic disease
- Lupus vasculitis
- Rheumatoid vasculitis
- Sarcoid vasculitis
- Others

Vasculitis associated with probable etiology
- Hepatitis C virus–associated cryoglobulinemic vasculitis
- Hepatitis B virus–associated vasculitis
- Syphilis-associated aortitis
- Drug-associated immune complex vasculitis
- Drug-associated ANCA-associated vasculitis
- Cancer-associated vasculitis
- Others

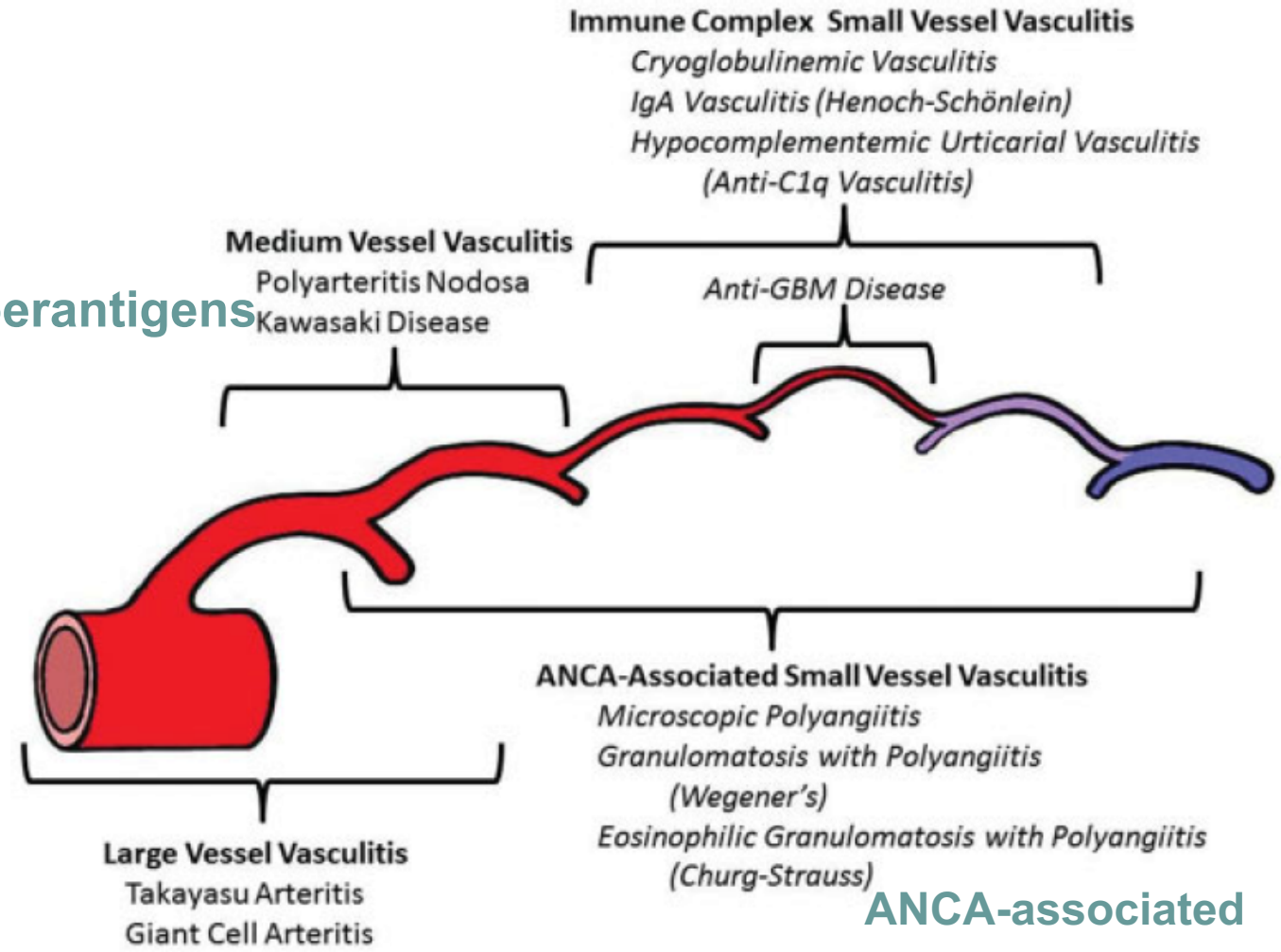
EPIDEMIOLOGY OF SELECTED VASCULITIDES

Disease	United States	Elsewhere	Age, Gender, and Ethnic Predispositions
Giant cell arteritis	Incidence: 240/million (Olmsted County, MN)	220–270/million (Scandinavian countries)	Age >50 yr, mean age 72 yr; females 3:1; northern European ancestry
Takayasu's arteritis	Incidence: 3/million	200–300/million (India)	Age <40 yr; females 9:1; Asian
Behçet's disease	Prevalence: 3/million	3000/million (Turkey)	Silk Route countries
Polyarteritis nodosa	Incidence: 7/million	7/million (Spain)	Slight male predominance
Kawasaki's disease	Incidence: 100/million[*]	900/million (Japan)	Children of Asian ancestry
Wegener's granulomatosis	Incidence: 4/million	8.5/million (United Kingdom)	Whites ≫ blacks

Gonzalez-Gay MA, Garica-Porrua C: Epidemiology of the vasculitides. Rheum Clin North Am 2001;27:729–749.

Immunopathogenesis

- Immune complex–mediated



Superantigens

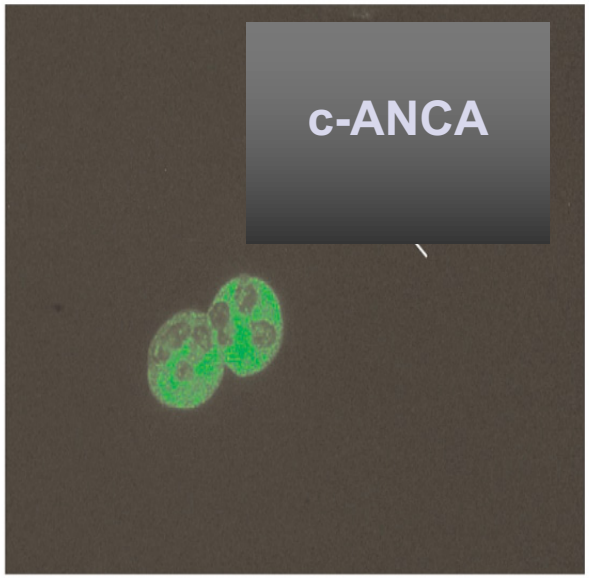
ANCA-associated

- Cell-mediated immune response & granulomatous inflammation

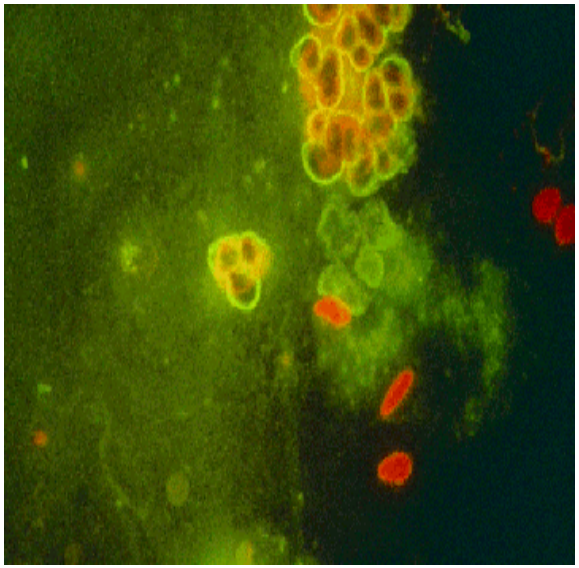
PATHOLOGIC CHARACTERISTICS OF SELECTED FORMS OF VASCULITIS

	Takayasu's Arteritis	Polyarteritis Nodosa	Wegener's Granulomatosis	Churg-Strauss Syndrome	Henoch-Schönlein Purpura
Organ involvement	Aorta, aortic arch major branches pulmonary arteries	Skin, peripheral nerve, gastrointestinal tract, and other viscera	Upper respiratory tract, lungs, kidneys, skin, eyes	Upper respiratory tract, lungs, heart, peripheral nerves	Skin, joints, gastrointestinal tract, kidneys
Type of vasculitis and inflammatory cells	**Granulomatous** with some giant cells; fibrosis in chronic stages	**Necrotizing,** with mixed cellular infiltrate	Necrotizing or granulomatous (or both); mixed cellular infiltrate plus occasional eosinophils	Necrotizing or granulomatous (or both); **prominent eosinophils** and other mixed infiltrate	Leukocytoclastic, with some lymphocytes and variable eosinophils **IgA deposits in** affected tissues

ANCA: Anti neutrophil cytoplasmic antibody



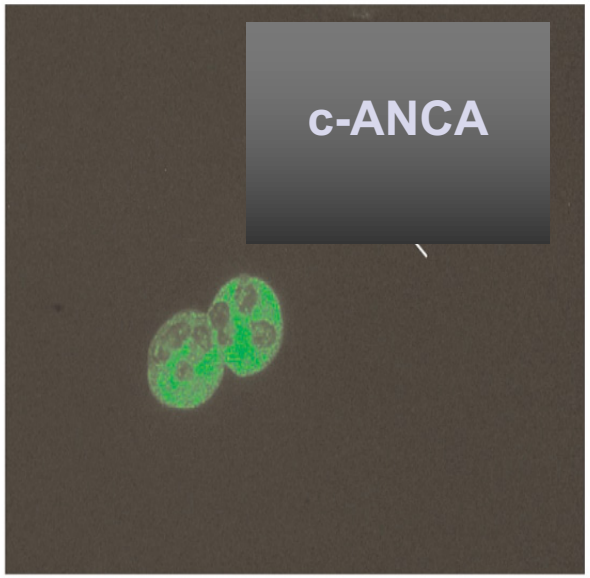
Immunoflorescein
Cytoplasmic (C-ANCA)



Immunoflorescein
Perinuclear (p-ANCA)

Wiik A. Mod Rheumatol 2009

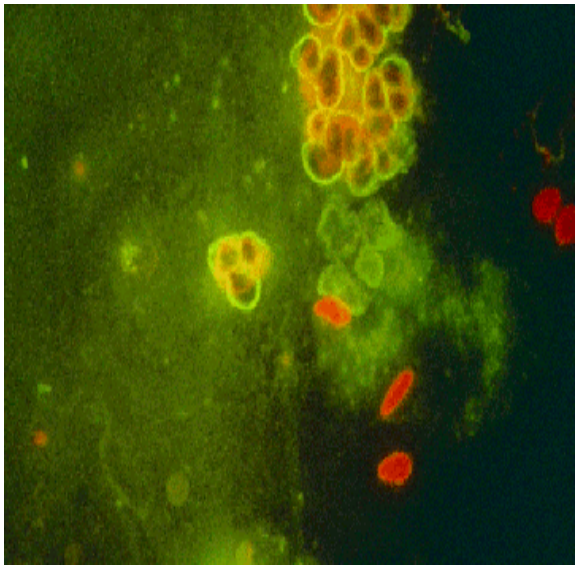
ANCA: Anti neutrophil cytoplasmic antibody



Cytoplasmic (C-ANCA)

ELISA: proteinase-3 (PR3-ANCA)

Wegener's granulomatosis



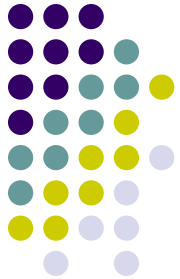
Perinuclear (p-ANCA)

ELISA: myeloperoxidase (MPO-ANCA)

Churg Strauss syndrome, microscopic poliangiitis

Wiik A. Mod Rheumatol 2009

Pathogenesis of antineutrophil cytoplasmic antibody (ANCA)-induced vasculitis

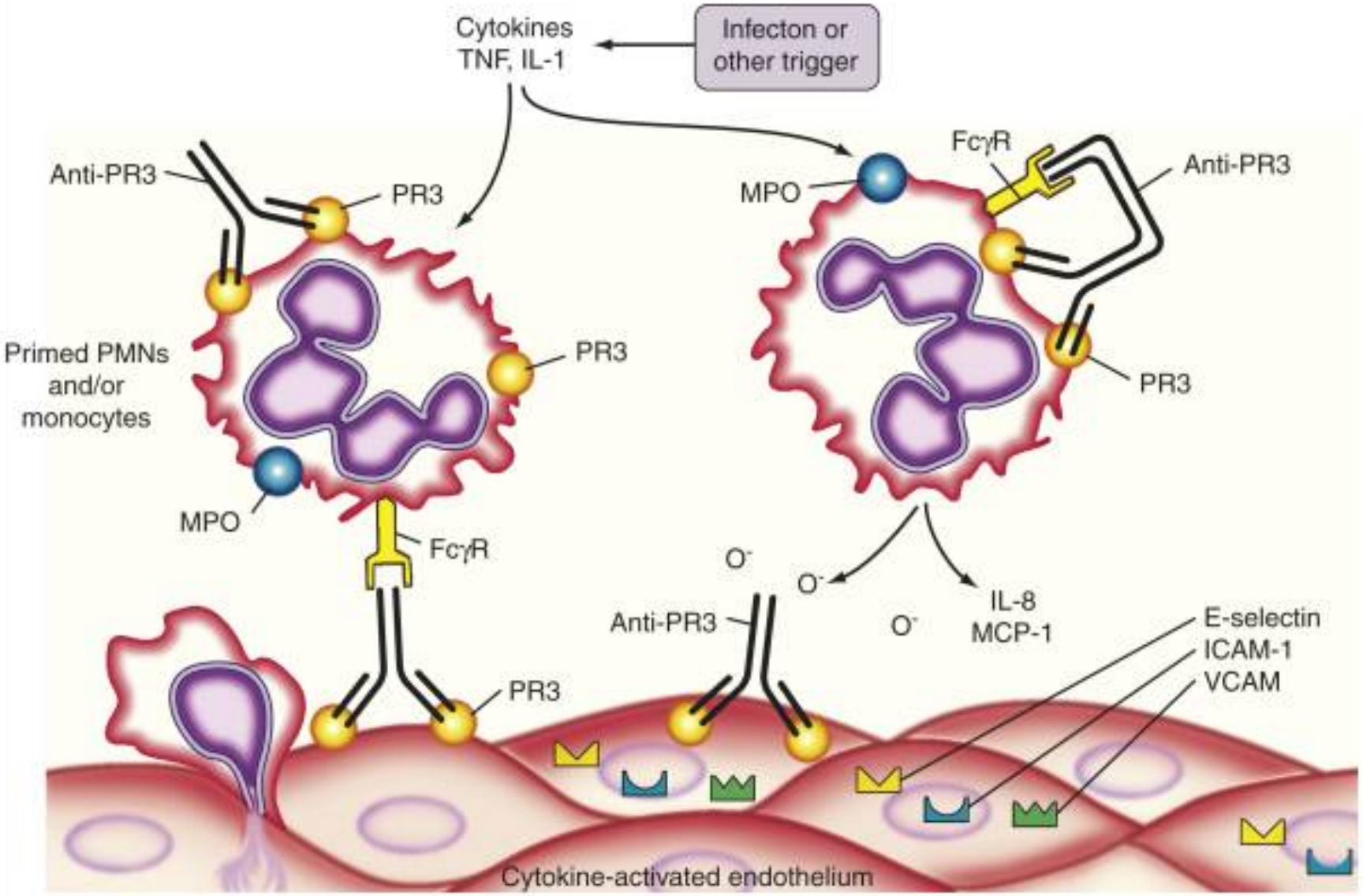


- Circulating quiescent neutrophiles contain ANCA antigens **not accessible to interaction with ANCA.**

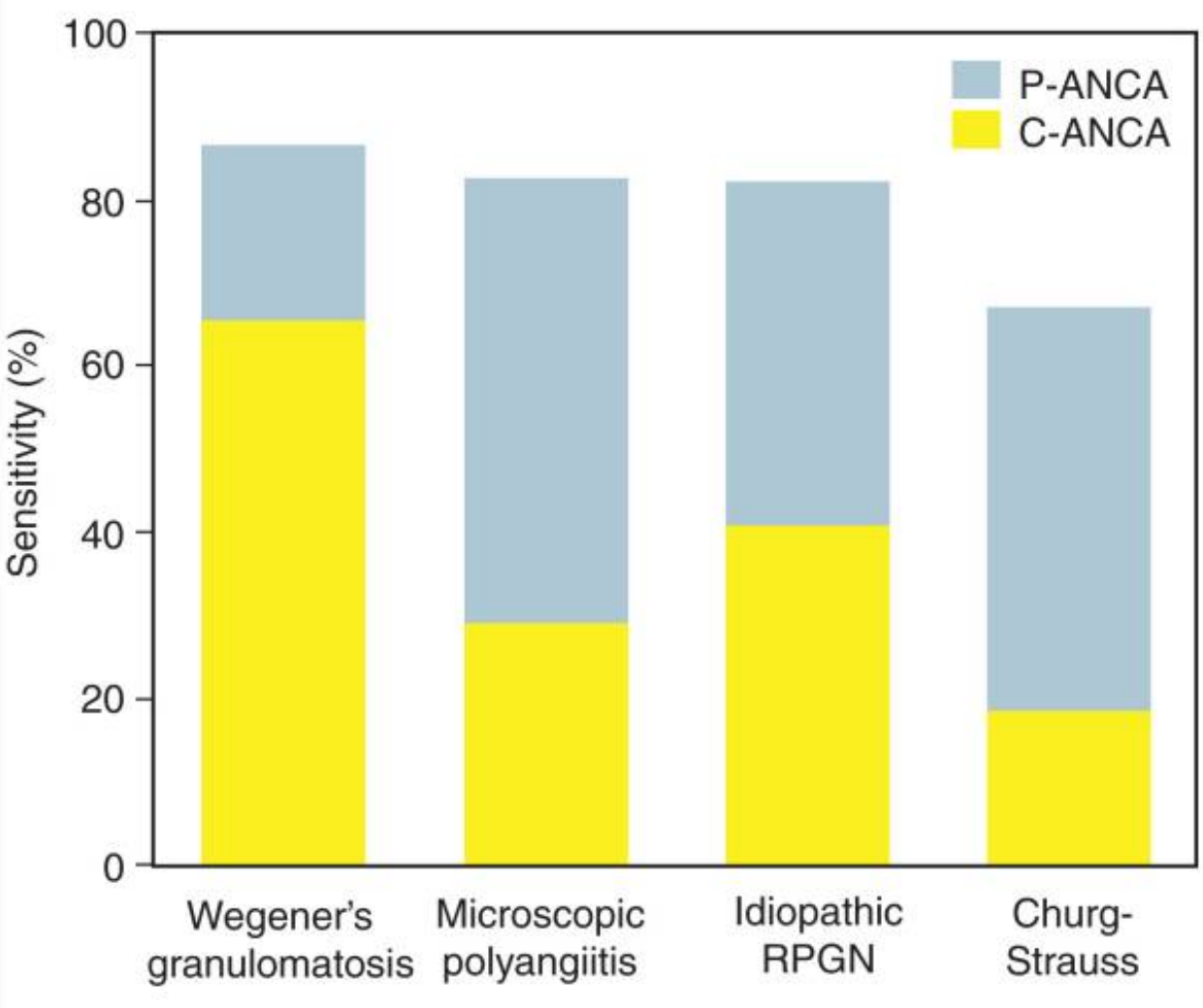
- **Priming of neutrophiles** by cytokines such as interleukin (IL)-1 and tumor necrosis factor (TNF), resulting in the expression of ANCA antigens at the cell surface.

- ANCA bind to target antigens at the cell surface.
- **Neutrophiles release toxic oxygen metabolites**.
- Neutrophiles adhere to endothelial cells via adhesion molecules and ligands.

- **Vessel wall injury leading to fibrinoid necrosis**


Cytokines
TNF, IL-1
Infecton or
other trigger
Anti-PR3
PR3
Primed PMNs
and/or
monocytes
PR3
MPO
FcγR
MPO
FcγR
Anti-PR3
PR3
O⁻
O⁻
O⁻
Anti-PR3
IL-8
MCP-1
E-selectin
ICAM-1
VCAM
PR3
Cytokine-activated endothelium

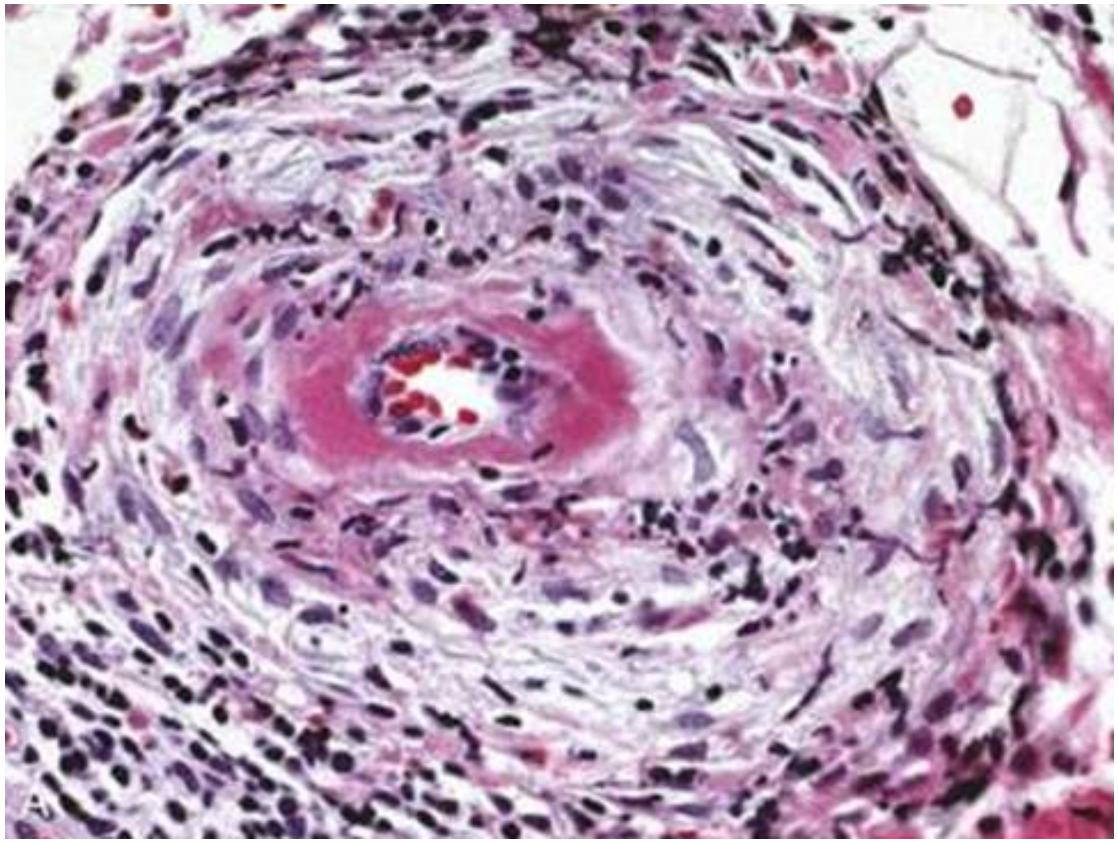
ANCA antibody and subgroups



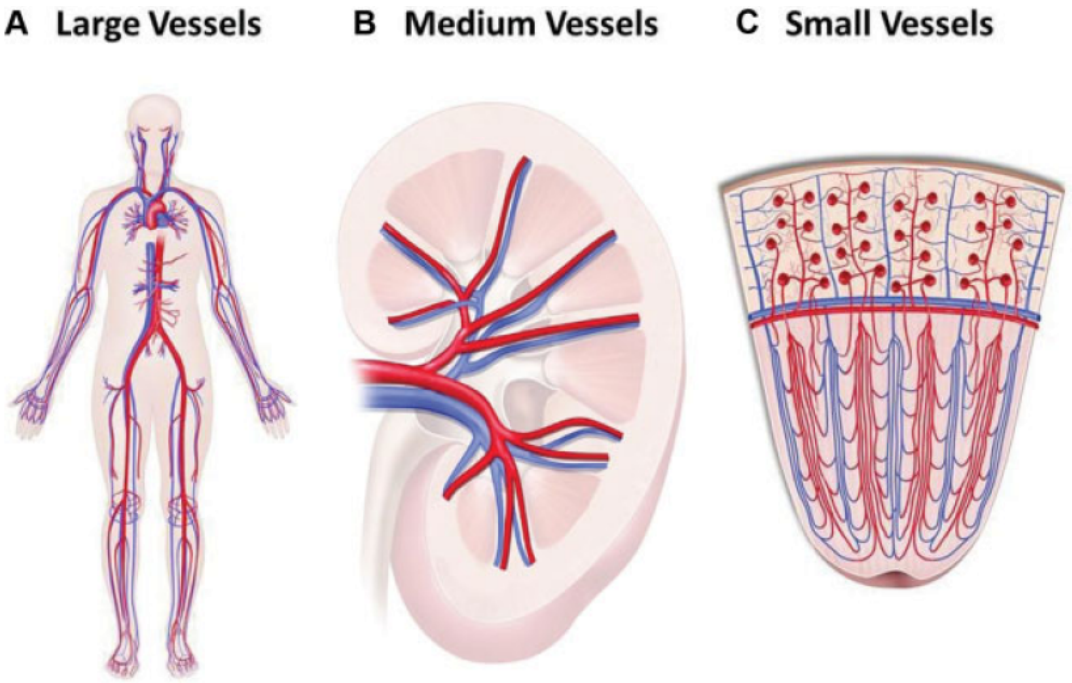
ANCA-associated vasculitides “pauci-immune”

- Granulomatous Poliangiitis (Wegener’s)
- Eosinophilic granulomatosis with poliangiitis (Churg-Strauss)
- Microscopic polyangiitis

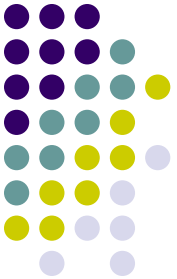
Fibrinoid necrosis in poliarteritis nodosa



Clinical manifestations of vasculitis



Ischemia /Infarct	**Organ failure**
Hemorrhage	**Tissue destruction**



Constitutional Symptoms

Fever

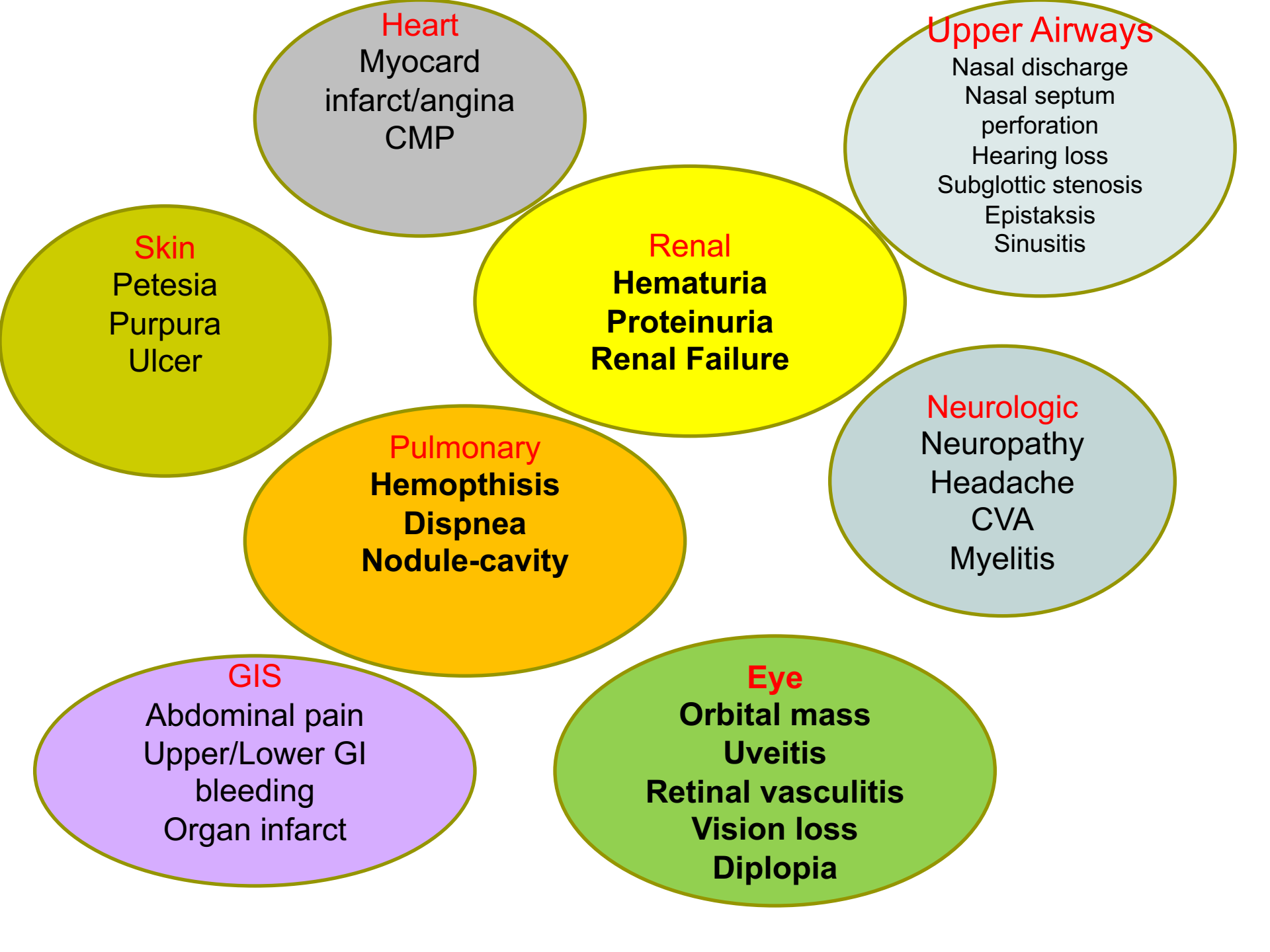
Malasia

Fatigue

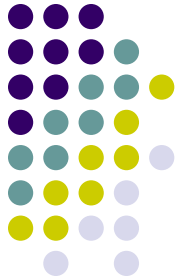
Weight loss

Myalgia

Arthralgia


Heart
Myocard infarct/angina
CMP
Upper Airways
Nasal discharge
Nasal septum perforation
Hearing loss
Subglottic stenosis
Epistaksis
Sinusitis
Skin
Petesia
Purpura
Ulcer
Renal
Hematuria
Proteinuria
Renal Failure
Neurologic
Neuropathy
Headache
CVA
Myelitis
Pulmonary
Hemopthisis
Dispnea
Nodule-cavity
GIS
Abdominal pain
Upper/Lower GI bleeding
Organ infarct
Eye
Orbital mass
Uveitis
Retinal vasculitis
Vision loss
Diplopia

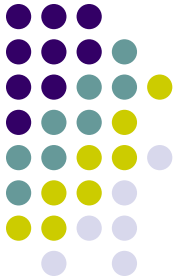
In case of probable vasculitis questions should be asked?



1. Is it a vasculitis or a vasculitis mimicker state?
2. Is there a secondary cause?
3. Which organs/systems are involved?
4. How can I confirm the diagnosis of vasculitis?
5. What's the name of vasculitis?

Vasculitis Mimickers	Secondary Vasculitis	
Atherosklerosis	Infections	TBC
Atheroembolic disease		Hepatitis B
Anti phospholipid syndrome		Hepatitis C
Multiple Myeloma		Parvovirus
İnfective endocarditis		Cystic Fibrosis
Chronic infections	Malignite	Lymphoma
Paraneoplastic syndromes		Solid Organ Malignancy
Genetic vascular diseases	Connective Tissue Diseases	Rheumatoid arthritis
(Marfan syndrome)		SLE
Autoinflammatory syndromes		Sjögren syndrome
Hypersensitivity reactions	Drugs	Penicilamine
Cocaine, Amphetamine		Prophyltiurasil
		Hydralazine
		Minoxidil
		Cocaine

Mimicers of Vasculitis



Multisystem Disease

Infection

(subacute bacterial endocarditis, rickettsiae, Neisseria)

Malignancy

(metastatic carsinoma, paraneoplastic)

Other

Sweet's syndrome

Occlusive Vasculopathy

Embolic

(Cholesterol crystals, atrial myxoma, infection, calciphylaxis)

Thrombotic

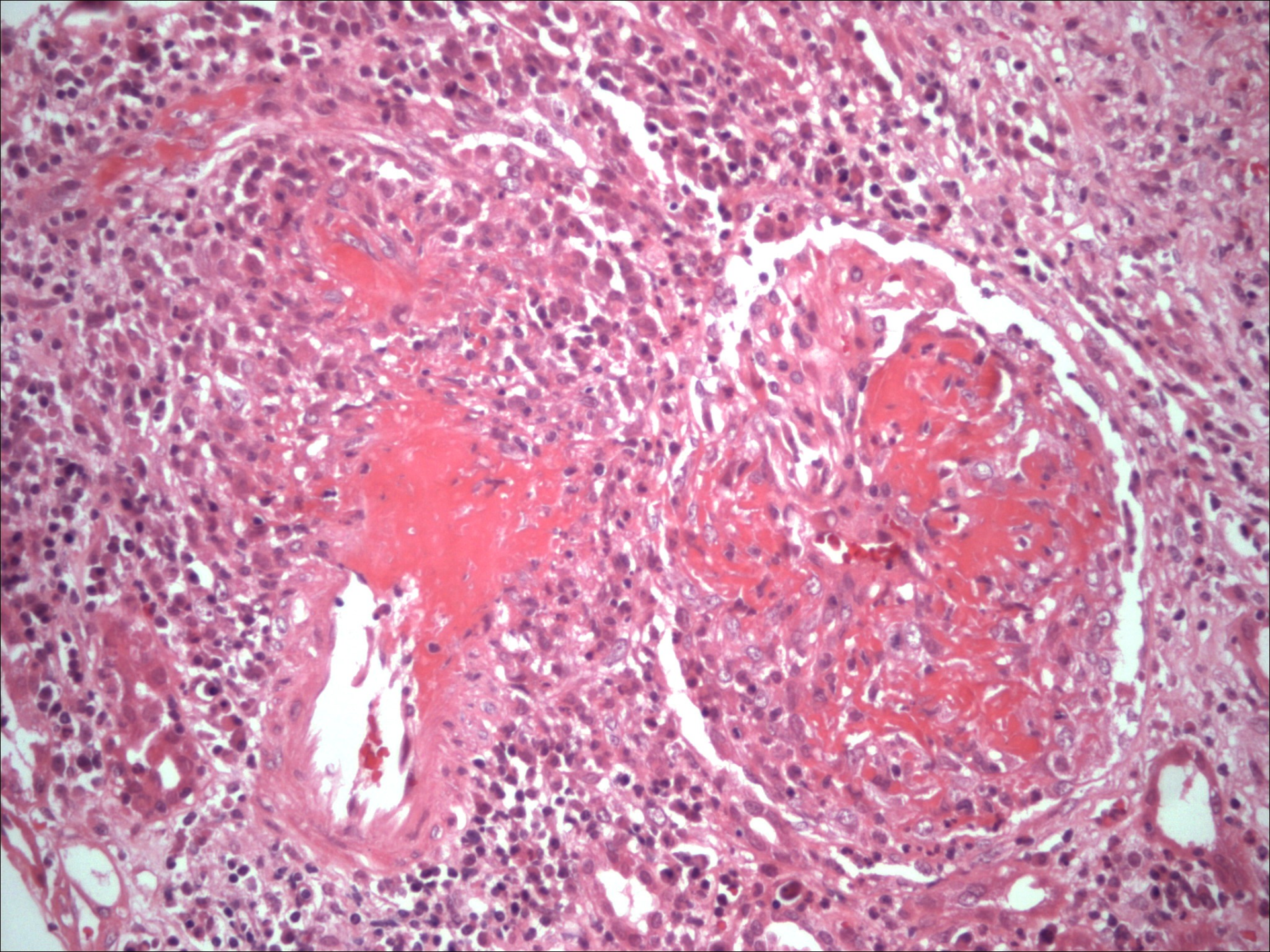
(Antiphospholipid syndrome, procoagulant states, criyofibrinogenemia)

Others

(Ergot, radiation, Degos syndrome, severe Raynaud's phenomenon)

Angiographic

(Fibromuscular dysplasia, neurofibromatosis (aneurysmal), coarctation (oc



Rapidly Progressive Glomerulonephritis

Immune complex

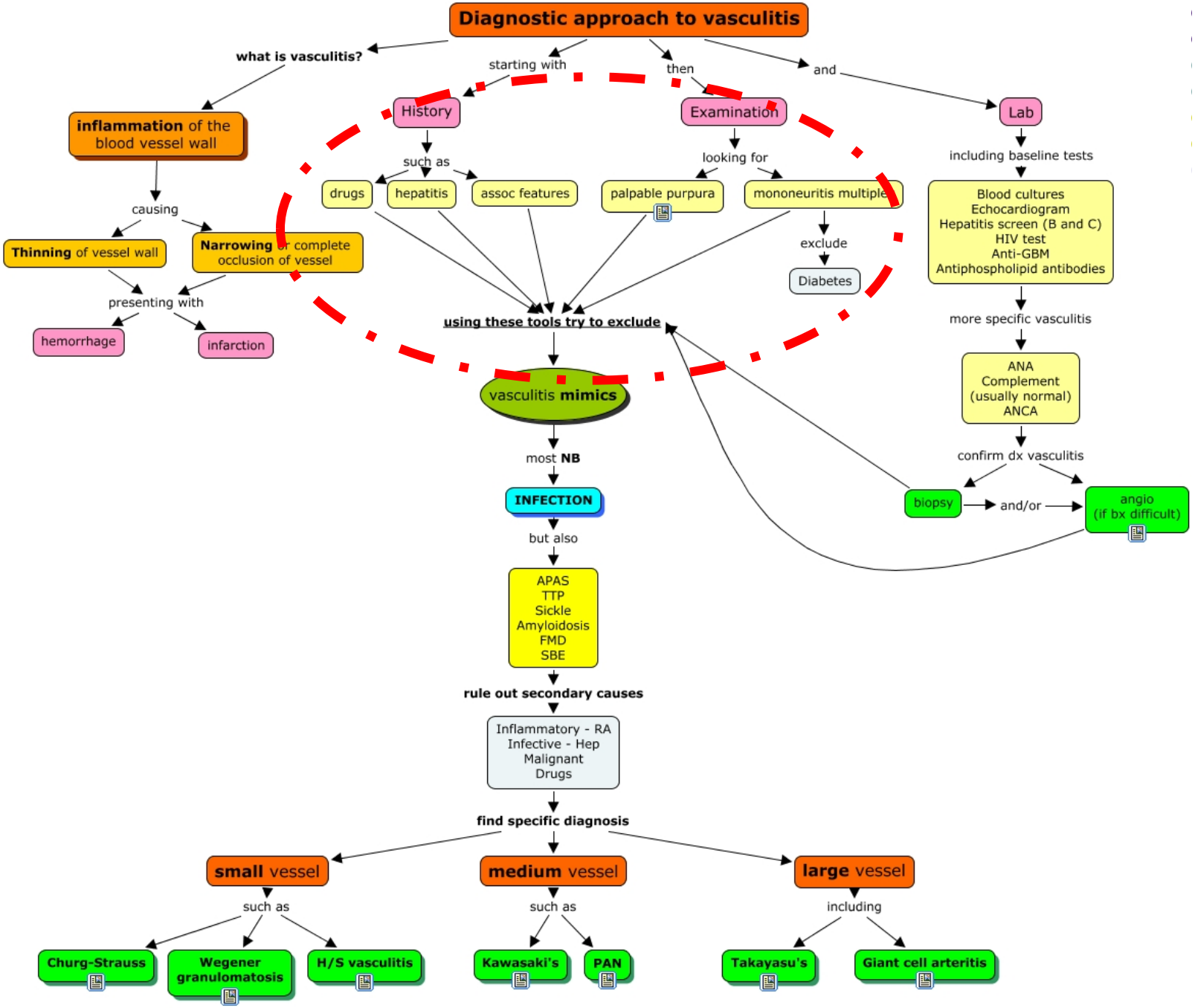
- Postinfectious (staphylococci/streptococci)
- Collagen-vascular disease
- Lupus nephritis
- Henoch-Schönlein purpura (immunoglobulin A and systemic vasculitis)
- Immunoglobulin A nephropathy (no vasculitis)
- Mixed cryoglobulinemia
- Primary renal disease
- Membranoproliferative glomerulonephritis
- Fibrillary glomerulonephritis
- Idiopathic

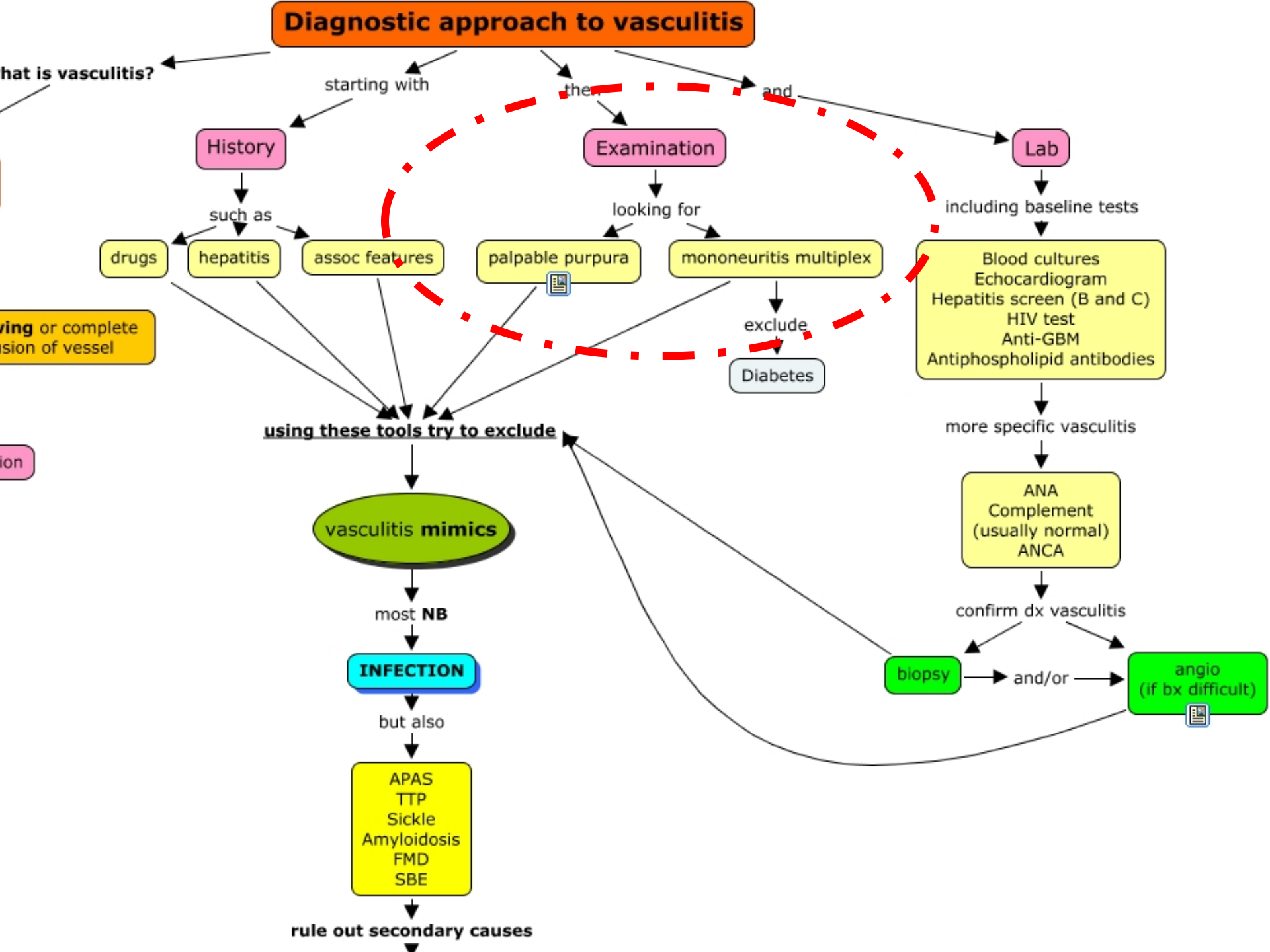
Pauci-immune

- Wegener granulomatosis (WG)
- Microscopic polyangiitis (MPA)
- Renal-limited necrotizing crescentic glomerulonephritis (NCGN)
- Churg-Strauss syndrome

Anti-GBM disease

Note: 10-40% of patients may be ANCA positive.


Diagnostic approach to vasculitis
what is vasculitis?
starting with
then
and
inflammation of the blood vessel wall
History
Examination
Lab
such as
looking for
including baseline tests
drugs
hepatitis
assoc features
palpable purpura
mononeuritis multiple
Blood cultures
Echocardiogram
Hepatitis screen (B and C)
HIV test
Anti-GBM
Antiphospholipid antibodies
causing
exclude
Diabetes
Thinning of vessel wall
Narrowing or complete occlusion of vessel
presenting with
hemorrhage
infarction
using these tools try to exclude
more specific vasculitis
ANA
Complement
(usually normal)
ANCA
vasculitis mimics
confirm dx vasculitis
most NB
biopsy
and/or
angio
(if bx difficult)
INFECTION
but also
APAS
TTP
Sickle
Amyloidosis
FMD
SBE
rule out secondary causes
Inflammatory - RA
Infective - Hep
Malignant
Drugs
find specific diagnosis
small vessel
medium vessel
large vessel
such as
such as
including
Churg-Strauss
Wegener granulomatosis
H/S vasculitis
Kawasaki's
PAN
Takayasu's
Giant cell arteritis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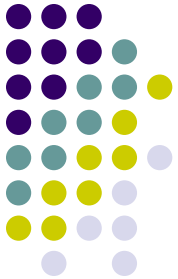
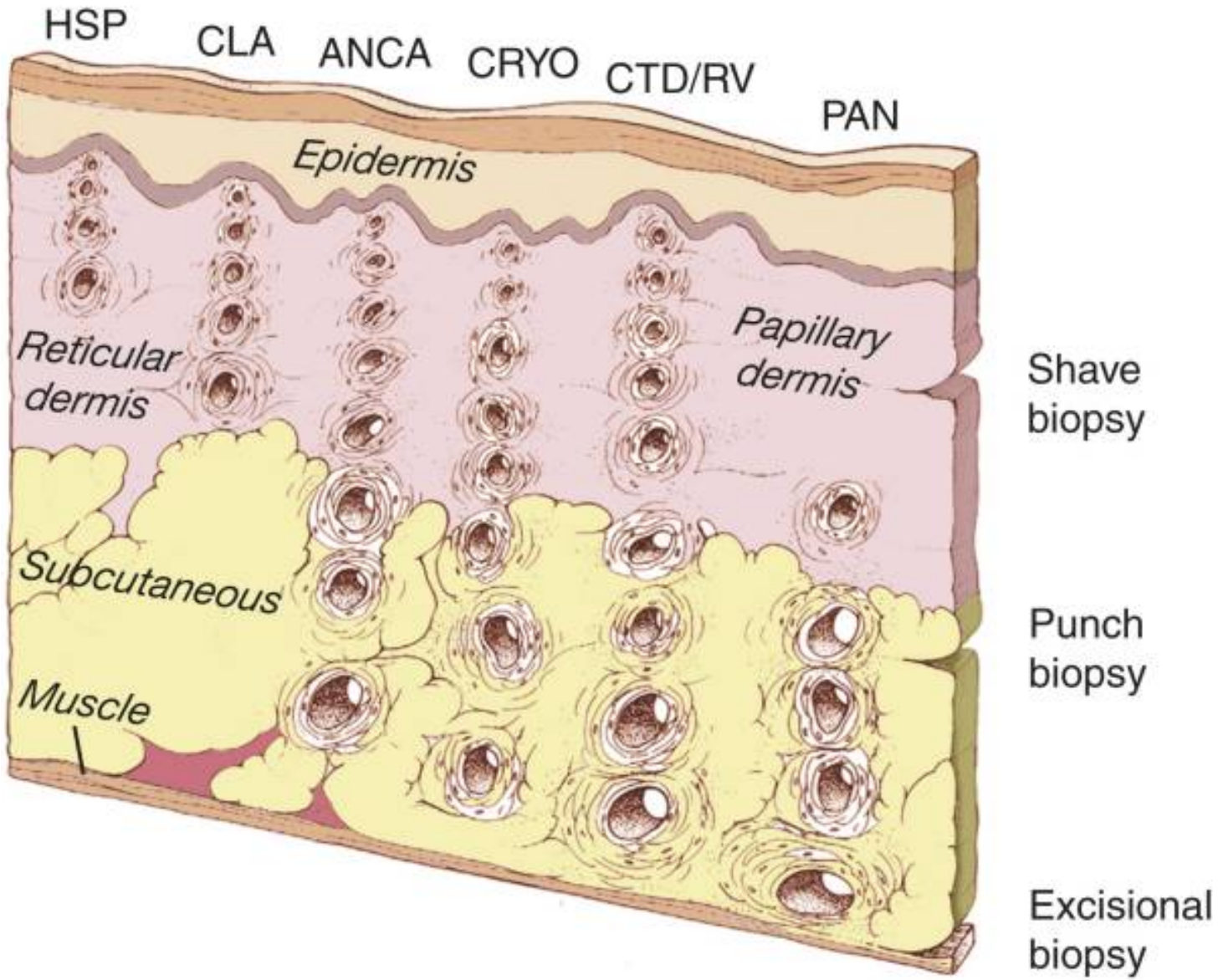
rule out secondary causes

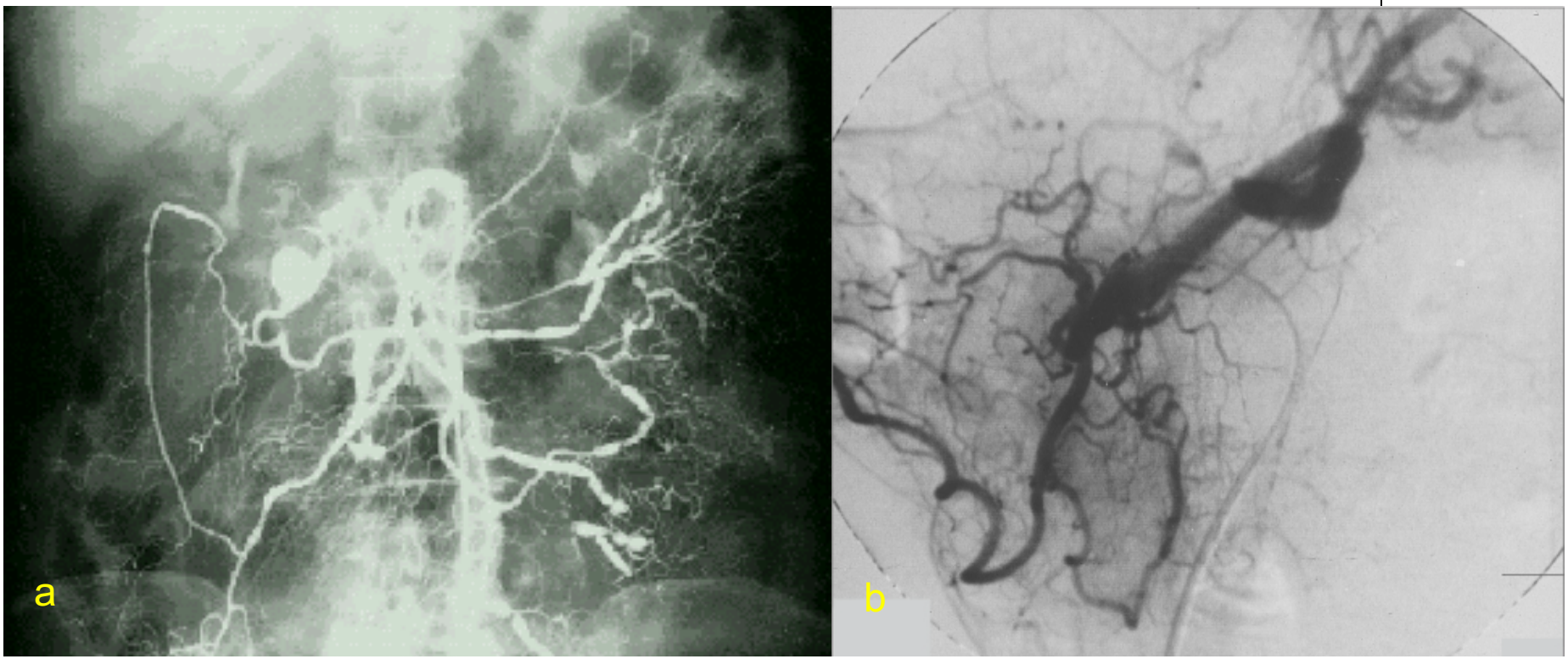
Primary Vasculitis



- Increased acute phase reactants
  - ESH, CRP
- Biopsy
- Imaging
  - Angiography

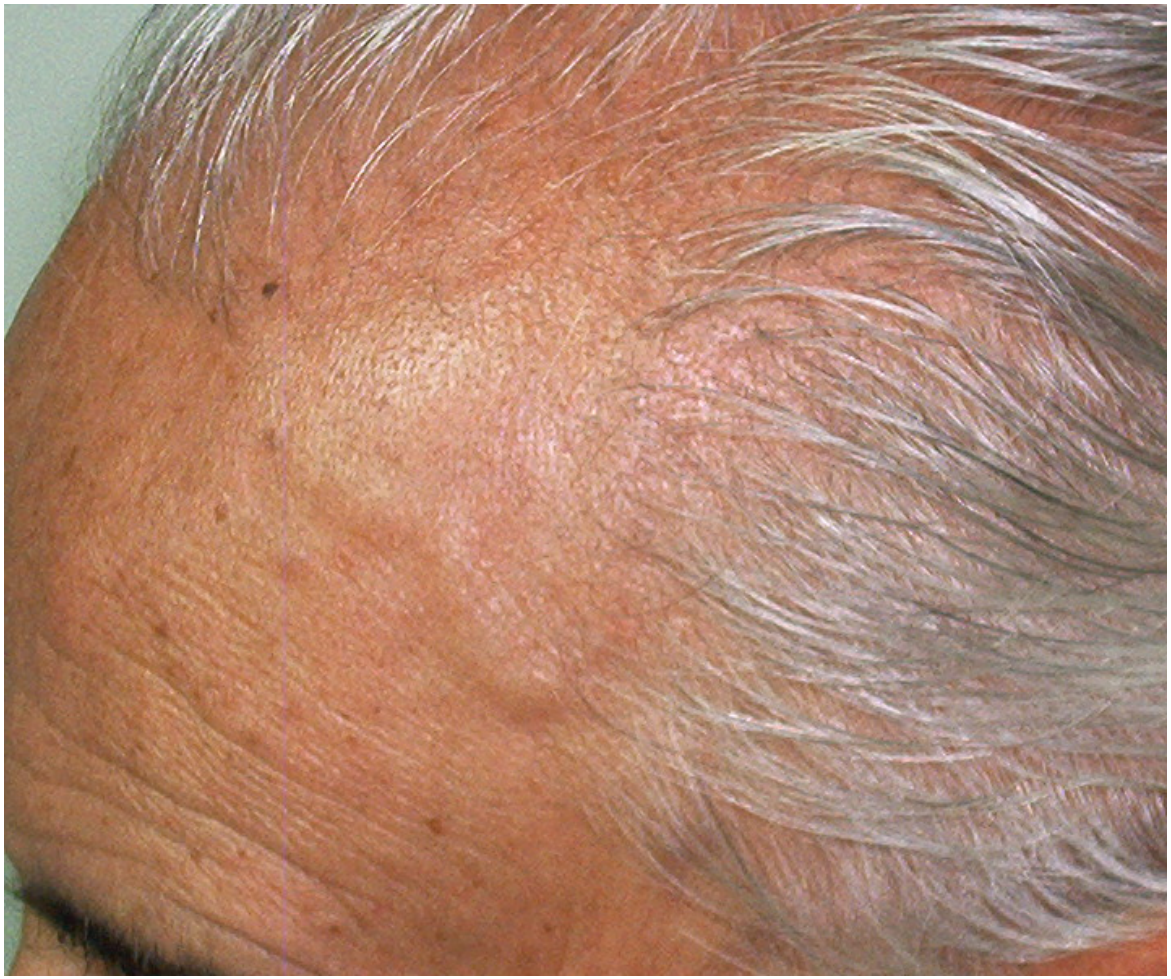

HSP
CLA
ANCA
CRYO
CTD/RV
PAN
Epidermis
Reticular dermis
Papillary dermis
Subcutaneous
Muscle
Shave biopsy
Punch biopsy
Excisional biopsy

Poliarteritis nodosa



Segmental occlusions and aneurisms of mesenteric arteries

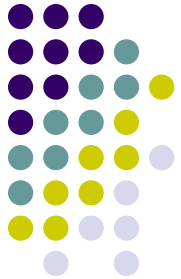
Temporal Arteritis



Temporal arterit ödem (Halo)
Sensitivite %88, spesifite %97

Christopher J. J Vasc Surg 2002
Karassa FB, Ann Int Med. 2005

Temporal Arteritis
1990 ACR CLASSIFICATION CRITERIA



- Age at disease onset ≥ 50 years
- New headache
- Temporal artery abnormality
- Erythrocyte sedimentation rate >50 mm/h
- Abnormal temporal artery biopsy

3 of 5 criteria for classification

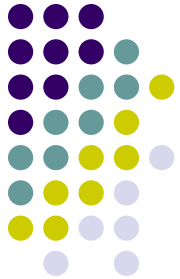
sensitivity %93.5, specificity 91.2%

Expanded ACR GCA criteria

Dejaco….. & Dasgupta Rheumatology Aug 2016

Orignial criteria	Suggested expansion
Age at disease onset >=50 years	Age at disease onset >=50 years
New onset headache of or new type of localized pain in the head	**Any of the following:** • New onset headache of or new type of localized pain in the head • **Visual symptoms, sight loss** • **Polymyalgia rheumatica** • **Constitutional symptoms** • **Jaw/tongue claudication**
Abnormality of temporal artery (tenderness to palpation or decreased pulsation unrelated to arteriosclerosis)	Abnormality of temporal **and/or extra-cranial arteries** (tenderness to palpation or decreased pulsation, **bruits of extra-cranial arteries** unrelated to arteriosclerosis)
ESR ≥50mm/hour	ESR ≥50mm/hour and/or **CRP levels ≥10mg/L**
Abnormal artery biopsy	Abnormal artery biopsy and/or **abnormal imaging result** **(ultrasound, MRI and/or ^{18}F-FDG-PET)**

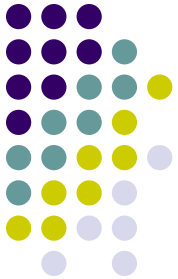
Takayasu Arteritis



EARLY PHASE		LATE PHASE
Non-specific symptoms Fever, fatique, weight loss	→	Decreased arterial pulses Vascular inflammation → Vascular occlusions

Takayasu Arteritis

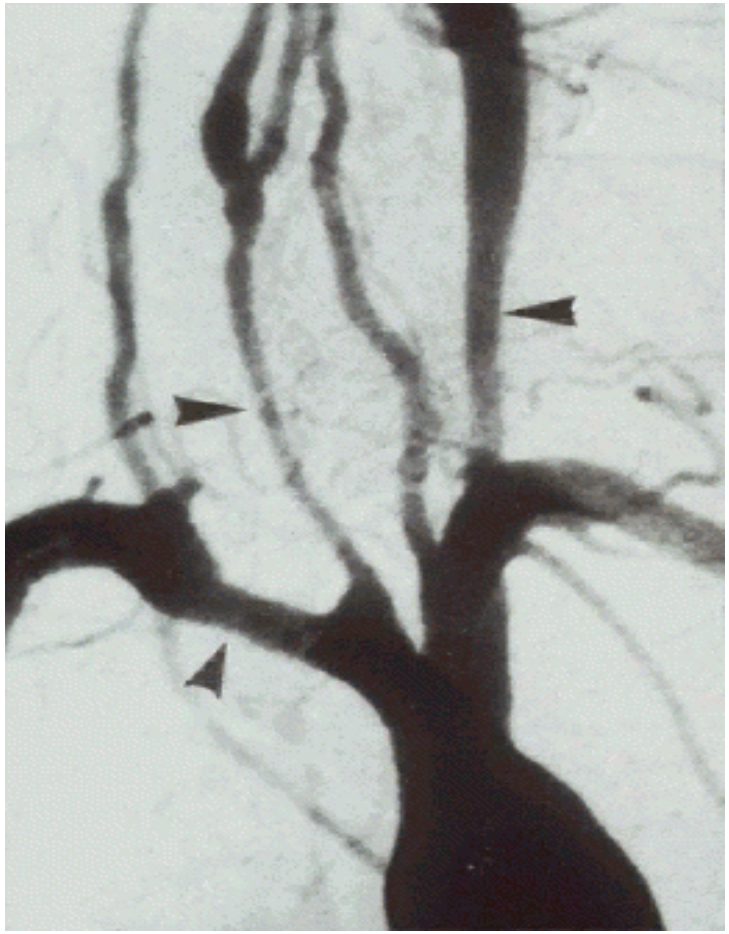
ACR CLASSIFICATION CRITERIA



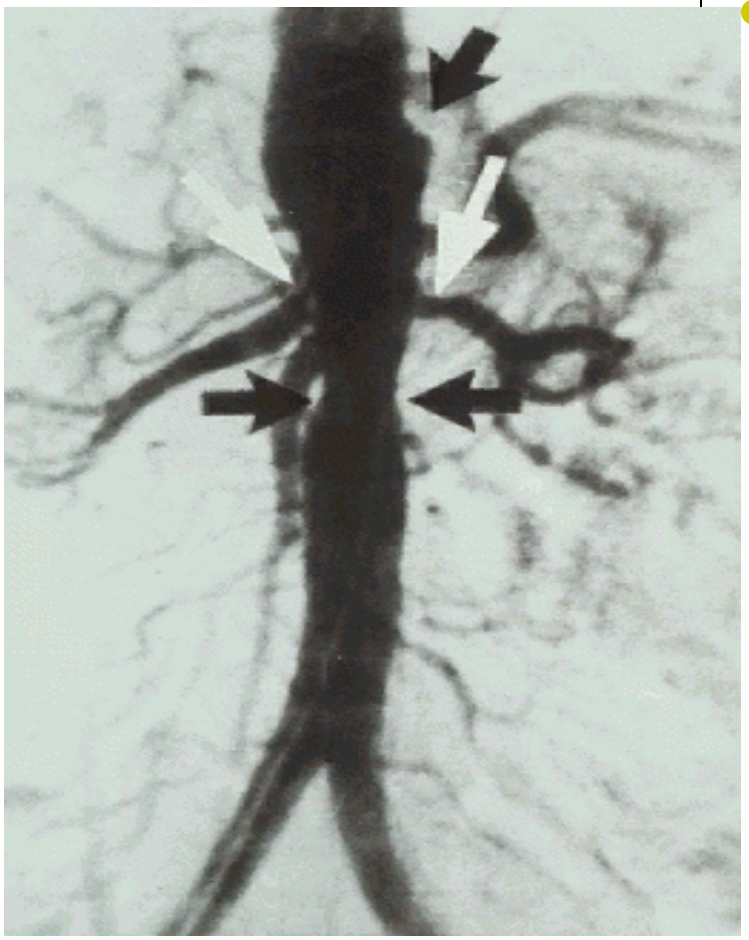
- Age at disease onset ≤ 40 years
- Claudication of extremities
- Decreased brachial artery pulse
- Blood pressure (BP) >10 mm Hg difference (between arms)
- Bruit over subclavian arteries or aorta
- Arteriogram abnormality

  - 3 of 6 criteria for classification

Takayasu Arteritis

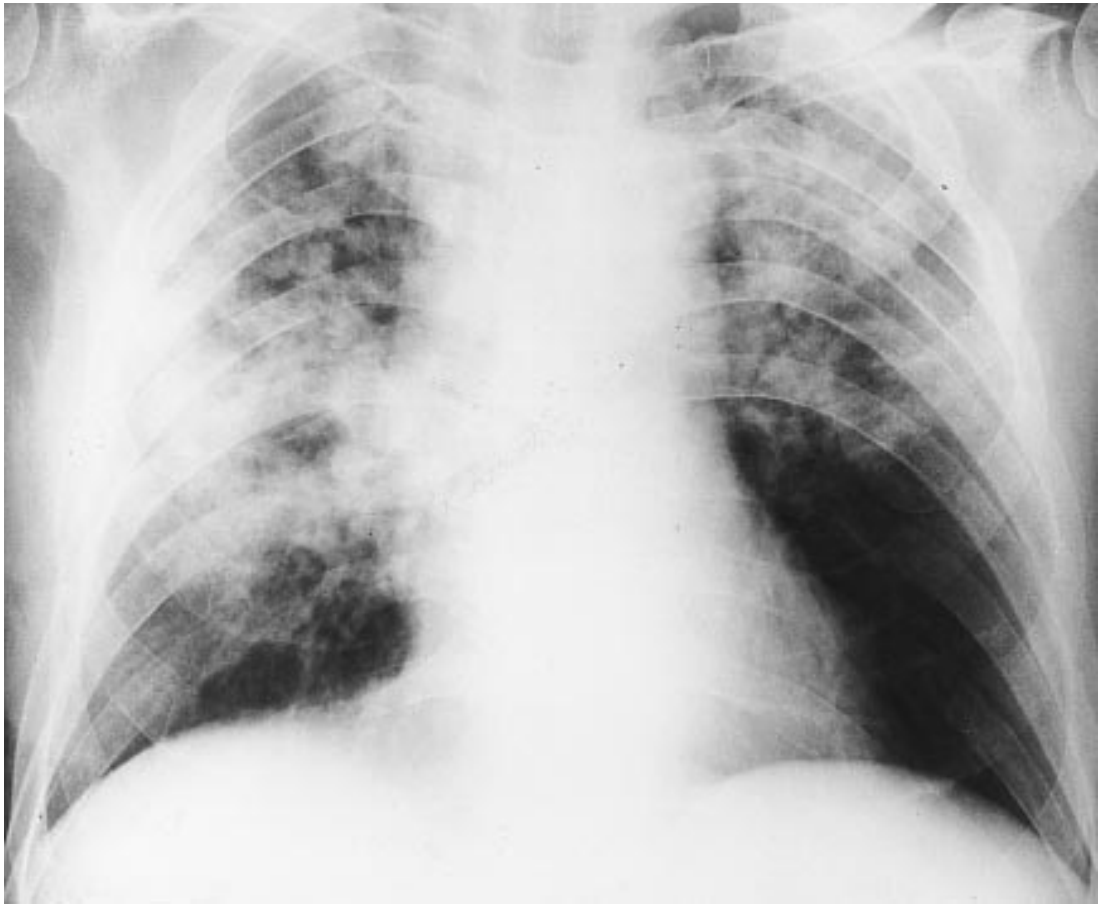


Arcus aorta



Abdominal aorta/renal arteries

WG - Alveolar Hemorrhage

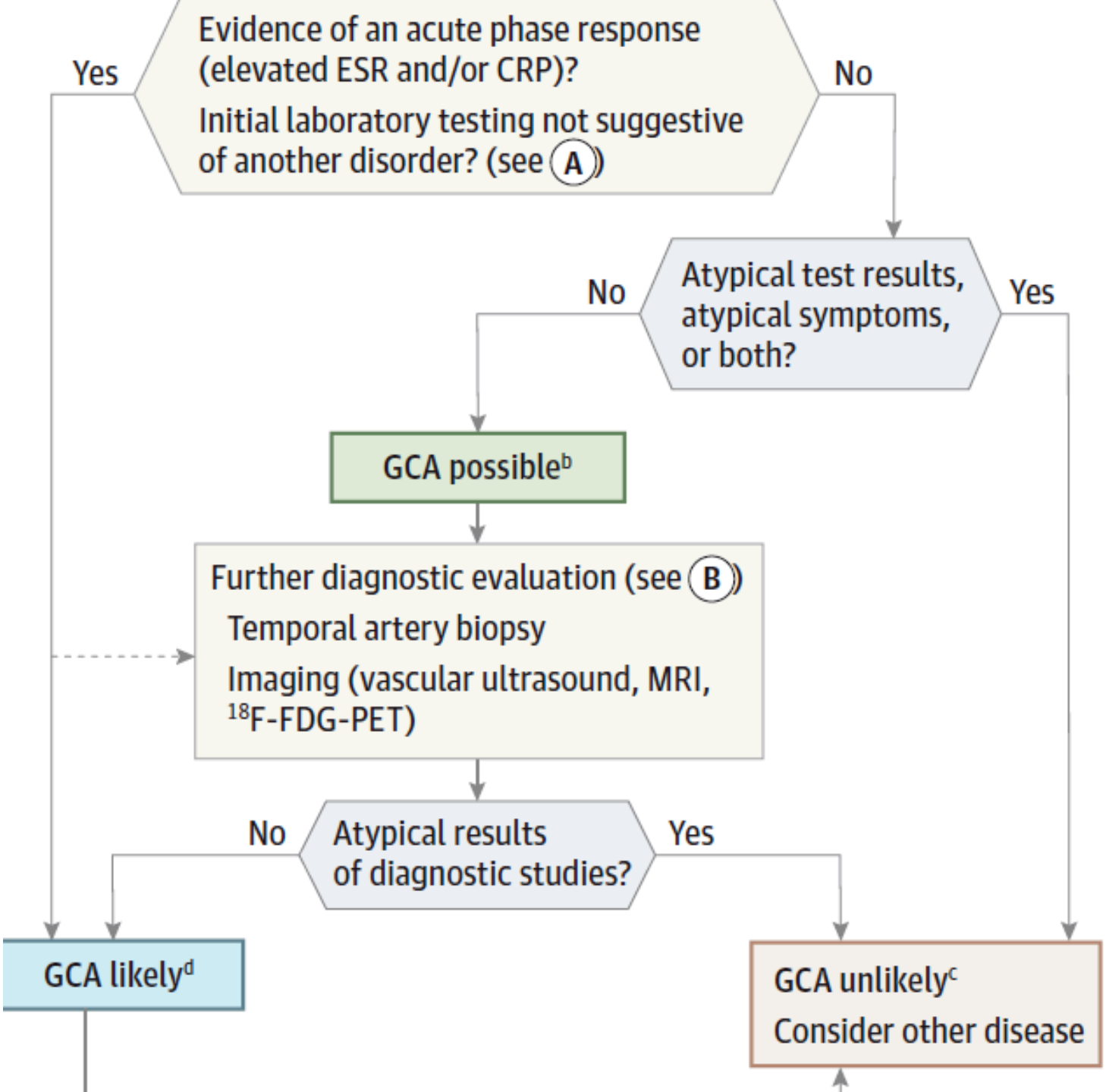


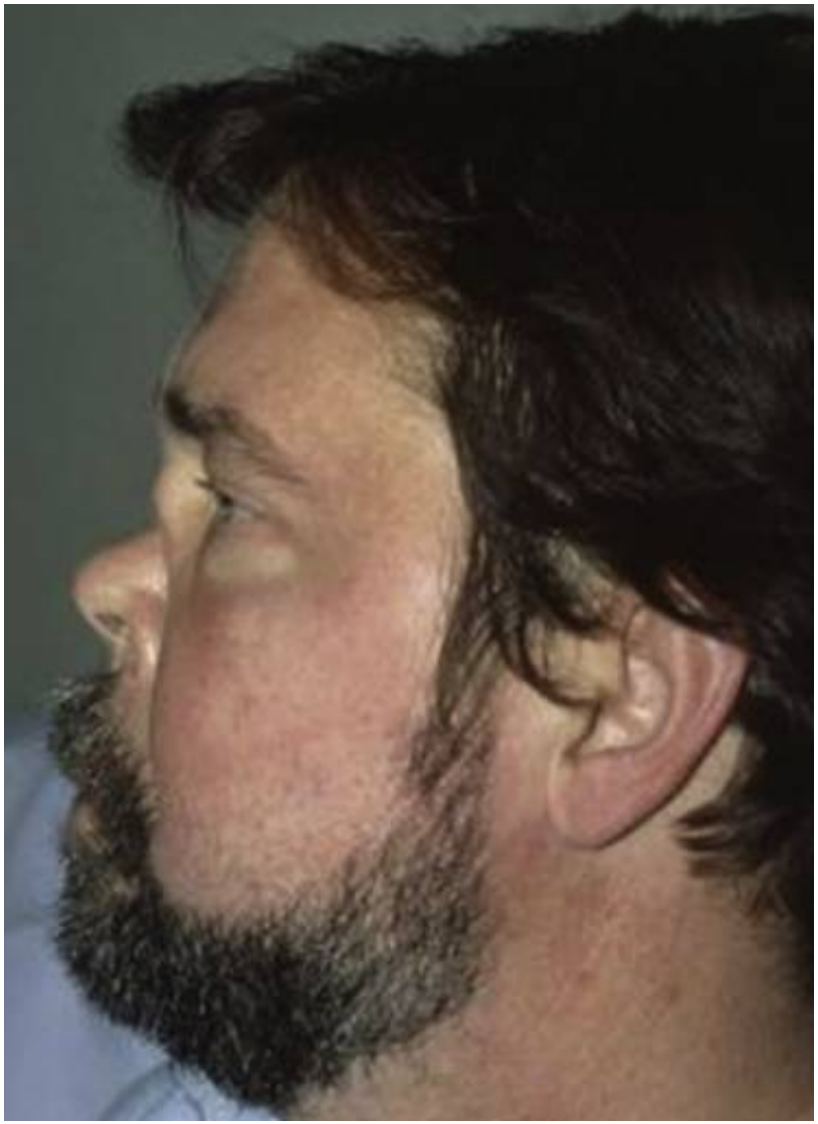
Seo JB, Im JG, Chung JW. The British Journal of Radiology, 73 (2000), 1224±1231

- Antineutrophil cytoplasmic antibodies (ANCA) testing is useful for the diagnosis of ANCA-associated vasculitis in patients with its symptoms and should be performed in patients with pulmonary-renal syndrome.
- False-positive ANCA can be seen in other autoimmune diseases, cancer, and infections.[8]
- Some patients with ANCA-associated vasculitis, especially those with eosinophilic granulomatosis with polyangiitis (≤70%), may have negative ANCA test results.
- Whenever possible, histologic confirmation of vasculitis should be pursued.

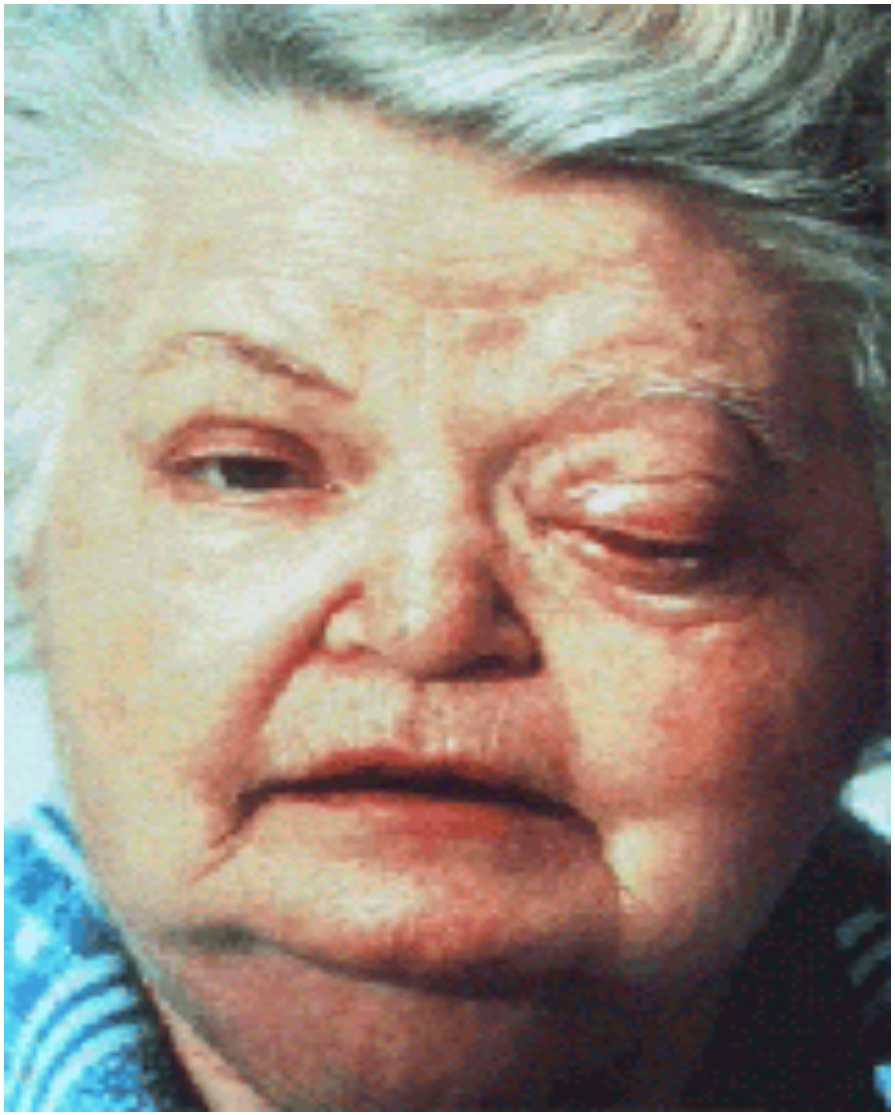
Symptoms suggestive of GCA

- Abrupt-onset headache ± scalp tenderness
- Jaw, tongue, or limb claudication
- Temporal artery abnormality
- Visual disturbances
- Symptoms of polymyalgia and/or constitutional symptoms (fever, fatigue, weight loss)


Evidence of an acute phase response (elevated ESR and/or CRP)?
Initial laboratory testing not suggestive of another disorder? (see A)
Yes
No
Atypical test results, atypical symptoms, or both?
No
Yes
GCA possible[b]
Further diagnostic evaluation (see B)
Temporal artery biopsy
Imaging (vascular ultrasound, MRI, ^{18}F-FDG-PET)
Atypical results of diagnostic studies?
No
Yes
GCA likely[d]
GCA unlikely[c]
Consider other disease



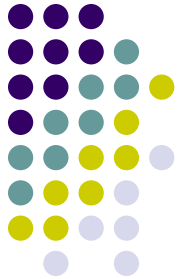
WG -saddle-nose



WG- Orbital pseudotumor

Granulomatous poliangiitis -Wegener granulomatosis-

1990 ACR CLASSIFICATION CRITERIA



- Nasal or oral inflammation
- Abnormal chest radiograph
- Urinary sediment
- Granulomatous inflammation on biopsy

2 of 4 criteria for classification

GPA

Clinical	Sino-nasal disease	+3
	Hearing loss	+1
	Cartilagenous involvement	+2
Tests	cANCA or PR3- antibody positive	+5
	Nodules, mass or cavitation on chest imaging	+2
	Granuloma, extravascular granulomatous inflammation or giant cells on biopsy	+2
	Inflammation, consolidation or effusion of the nasal/ paranasal sinuses, or mastoiditis on imaging	+1
	Pauci-immune GN on biopsy	+1
	pANCA or MPO- antibody positive	-1
	Eosinophil count ≥ 1 ($x10^9$/L)	-4

≥ 5 is needed for GPA

MPA

Sino-nasal disease	-3
pANCA or MPO antibody positive	+6
Fibrosis or ILD on chest imaging	+3
Pauci-immune GN on biopsy	+3
cANCA or PR3 antibody positive	-1
Eosinophil count ≥ 1 ($x10^9$/L)	-4

≥ 5 is needed for MPA

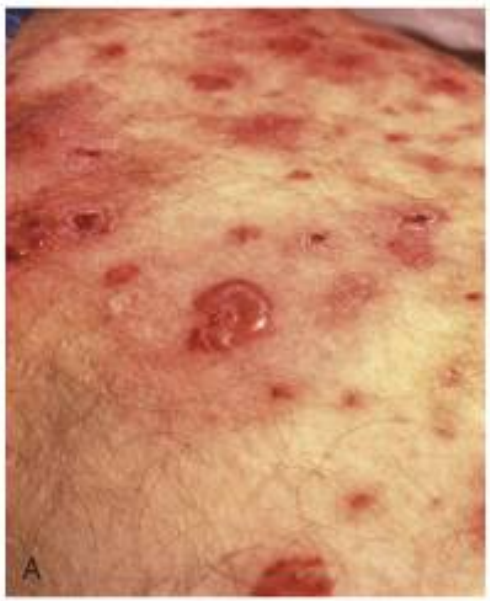
EGPA

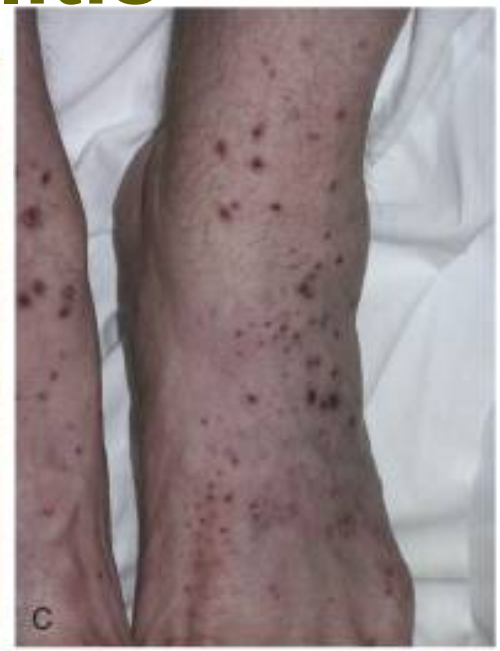
Obstructive airways disease	+3
Nasal polyps	+3
Mononeuritis multiplex or motor neuropathy	+1
Eosinophil count ≥ 1 ($x10^9$/L)	+5
Extravascular eosinophil predominant inflammation/increased eosinophils in bone marrow	+2
Microscopic hematuria	-1
cANCA or PR3- antibody positive	-3

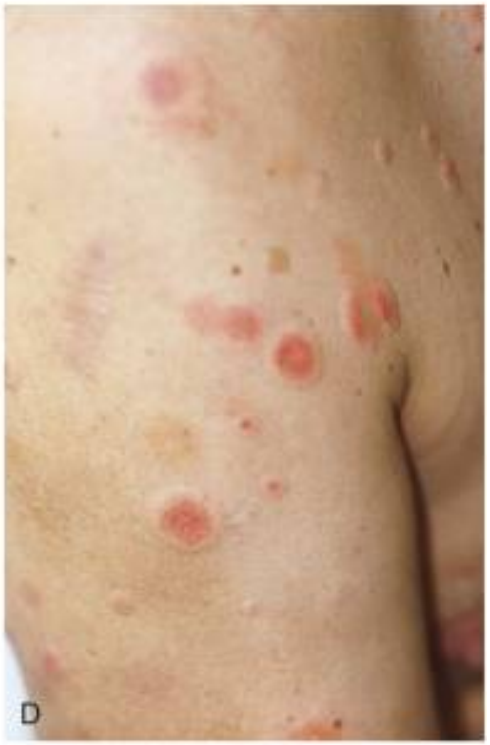
≥ 6 is needed for EGPA

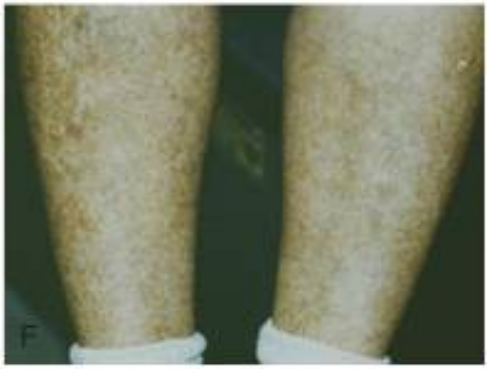
DCVAS

Purpura Leucocytoklastic vasculitis



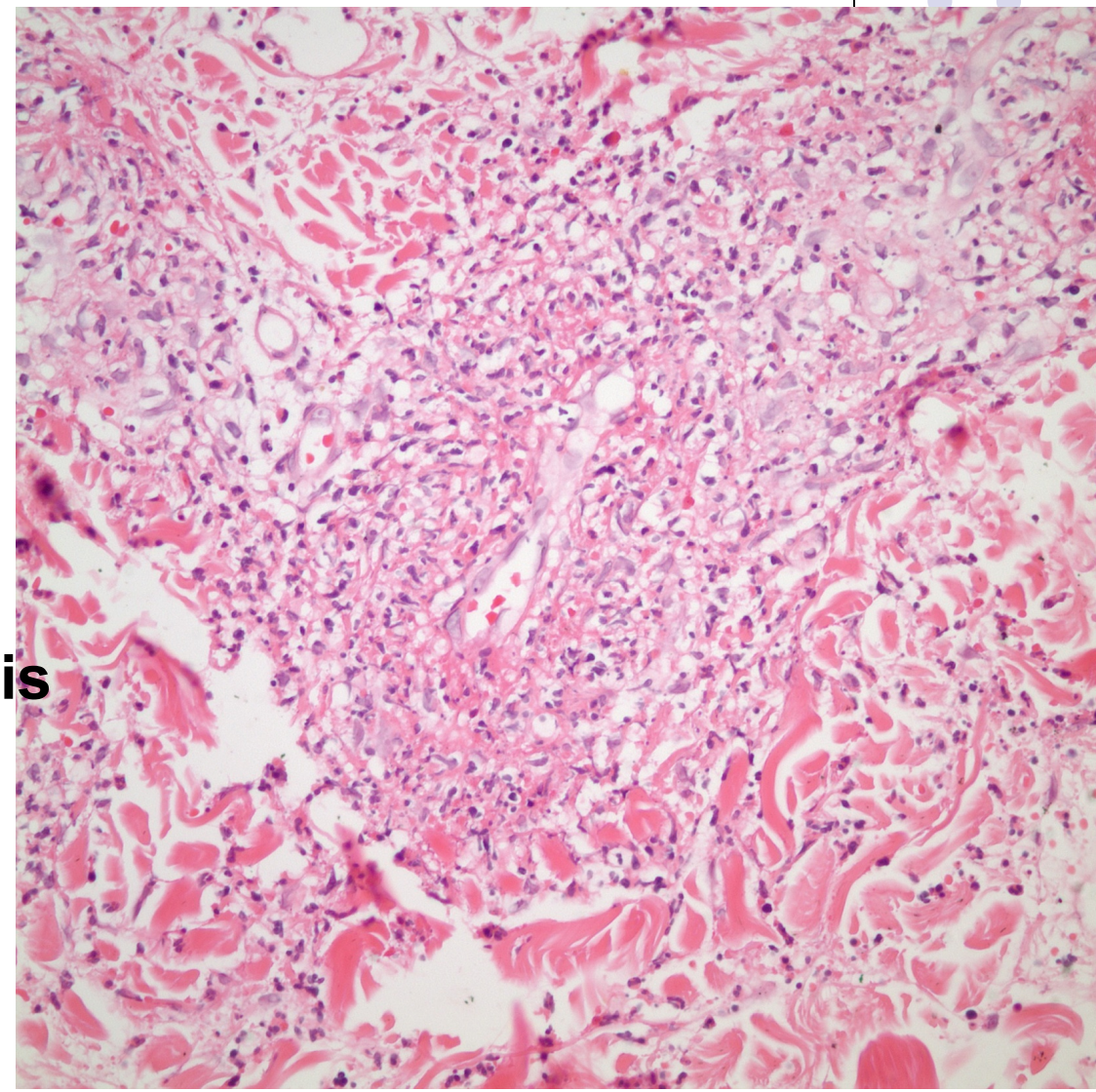




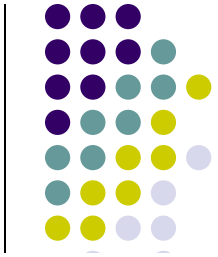


Leucocytoclastic Vasculitis

Skin biopsy
Leucocytoclastic Vasculitis



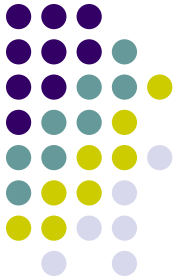
Leucocytoclastic Vasculitis



- 1/3 idiopathic
- Drugs and food
- Infections (Upper resp.s
- Connective tissue disea
- Inflammatory Bowel dis
- Paraneoplastic (Cancer

- Also in course of other vasculitis
  - GPA
  - PAN
  - EGPA
  - Cryoglobulinemic Vasculitis
  - IgA Vasculitis (HSP)
  - Cutaneous Leucocytoclastic angiitis

Henoch-Schönlein purpura



- Henoch-Schönlein purpura is the most common vasculitis syndrome of childhood.
  - Purpuric rash (lower extremities)
  - Arthritis (large joints)
  - Abdominal cramping (bloody stools)

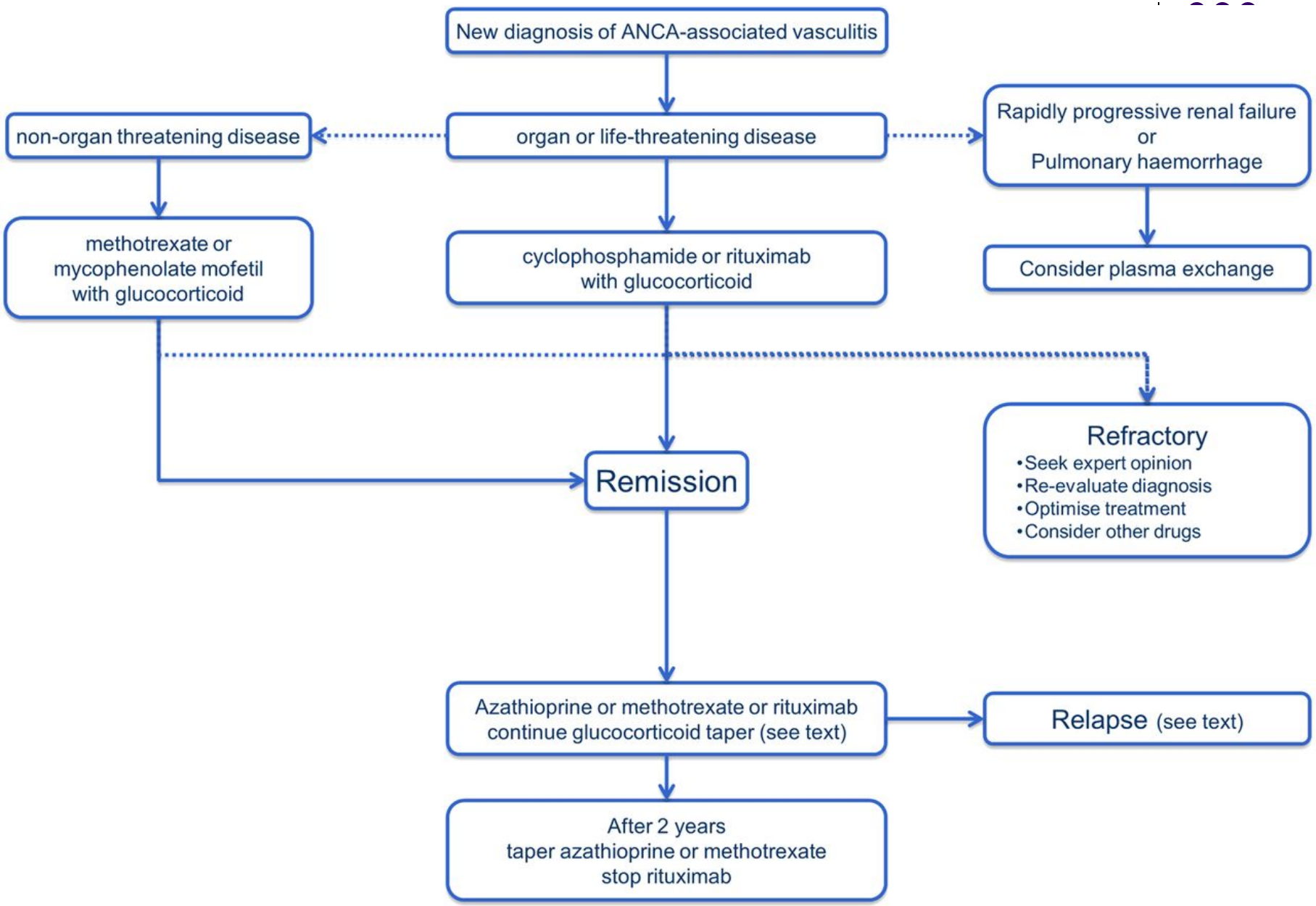
- Microscopic and/or gross hematuria

  biopsy showing predominant IgA deposition

Empirical therapy

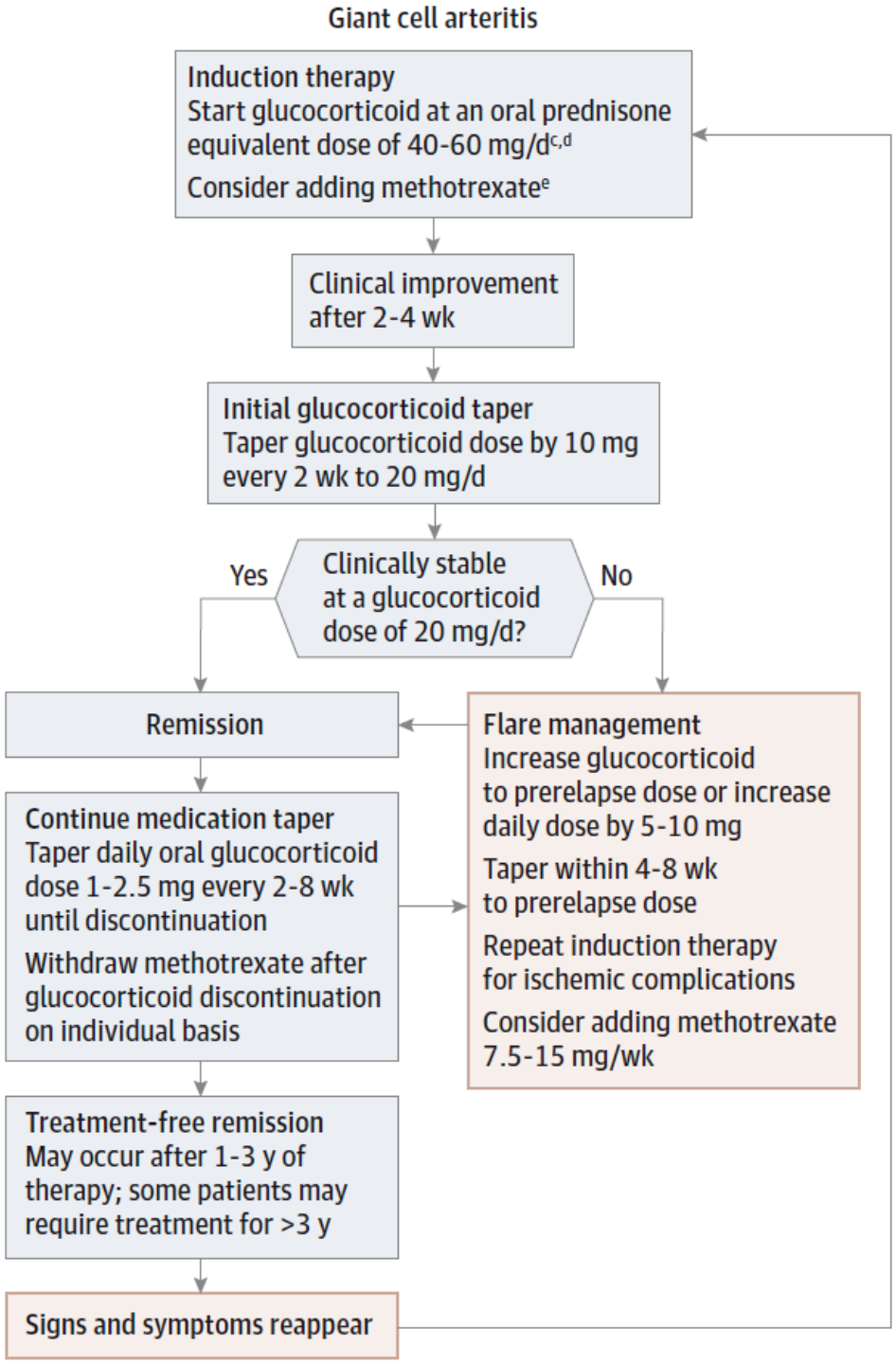
- Targets:
  - Revealing symptoms
  - Protect organ damage
  - Protect majör organ involvement

- Treatment should be specialized in to each patient
  - According to dominant symptom/finding
  - Recurrence/ severity



M Yates et al. Ann Rheum Dis 2016;75:1583-1594

ARD

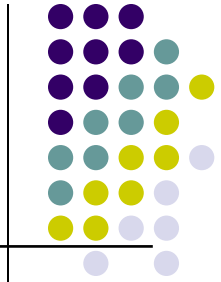

Giant cell arteritis
Induction therapy
Start glucocorticoid at an oral prednisone equivalent dose of 40-60 mg/d[c,d]
Consider adding methotrexate[e]
Clinical improvement after 2-4 wk
Initial glucocorticoid taper
Taper glucocorticoid dose by 10 mg every 2 wk to 20 mg/d
Clinically stable at a glucocorticoid dose of 20 mg/d?
Yes
No
Remission
Flare management
Increase glucocorticoid to prerelapse dose or increase daily dose by 5-10 mg
Taper within 4-8 wk to prerelapse dose
Repeat induction therapy for ischemic complications
Consider adding methotrexate 7.5-15 mg/wk
Continue medication taper
Taper daily oral glucocorticoid dose 1-2.5 mg every 2-8 wk until discontinuation
Withdraw methotrexate after glucocorticoid discontinuation on individual basis
Treatment-free remission
May occur after 1-3 y of therapy; some patients may require treatment for >3 y
Signs and symptoms reappear

Treatment

- Steroids and immunosuppressant agents
  - Remission-induction

    (Cyclophoshamide-Metotrexate-Azathioprine-Rituximab)
  - Maintanance
- HBV-HCV related vasculitis: anti viral treatment
- Kawasaki disease: IVIG+aspirin

Drugs:



Azatioprine

Cholchicine

Ciclosporin A

Cyclophosphamide

Methotrexate

Clorambucil

Mycophenolate

Metotreksat

Interferon α

Etanercept

Infliksimab

Adalimumab

Talidomide

Corticosteroids

Aspirin

Anticoagulant

Penisiline

NSAI Drugs

Questions& Answers

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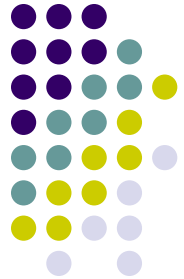
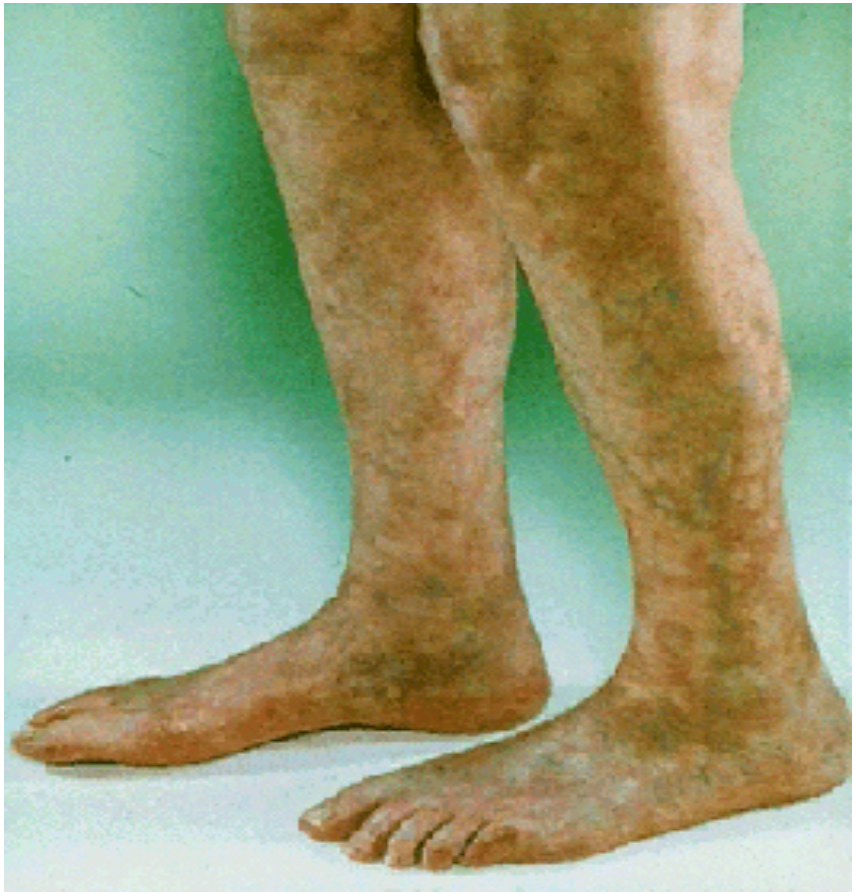
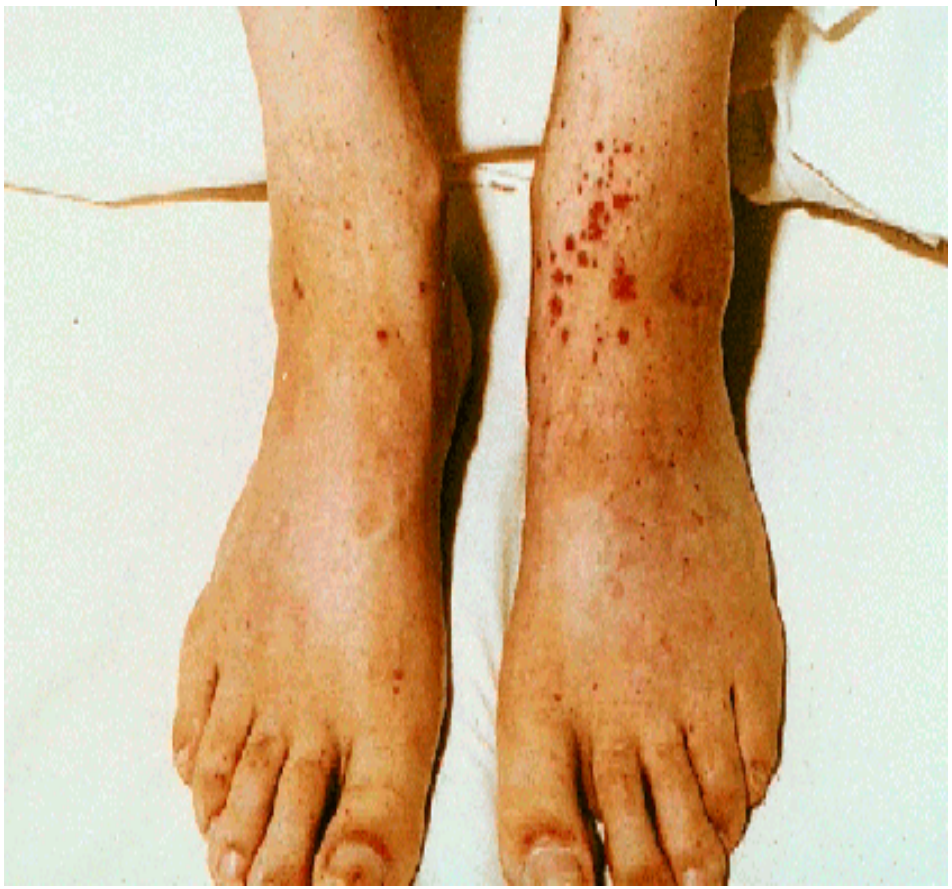
Hacettepe

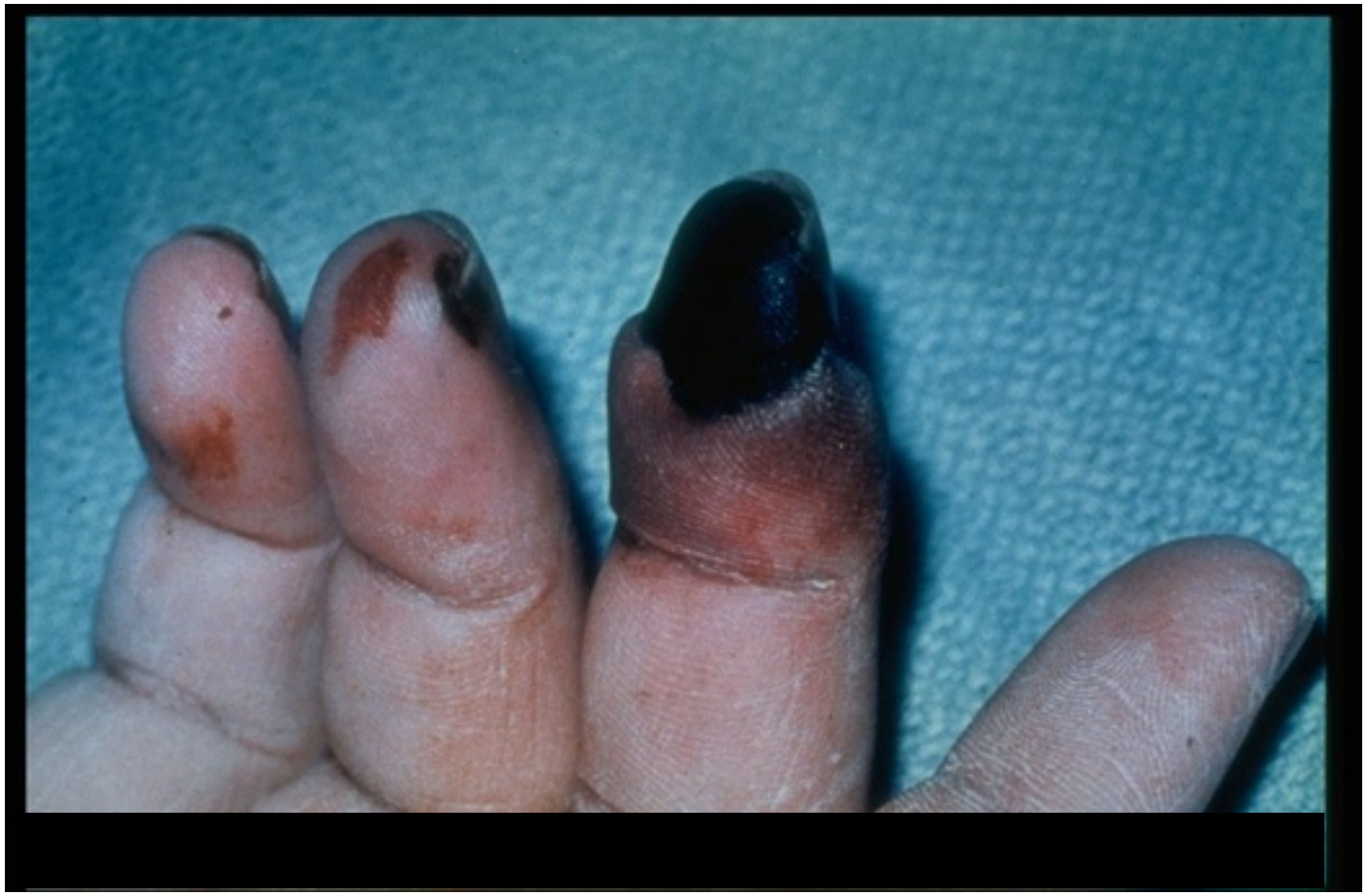




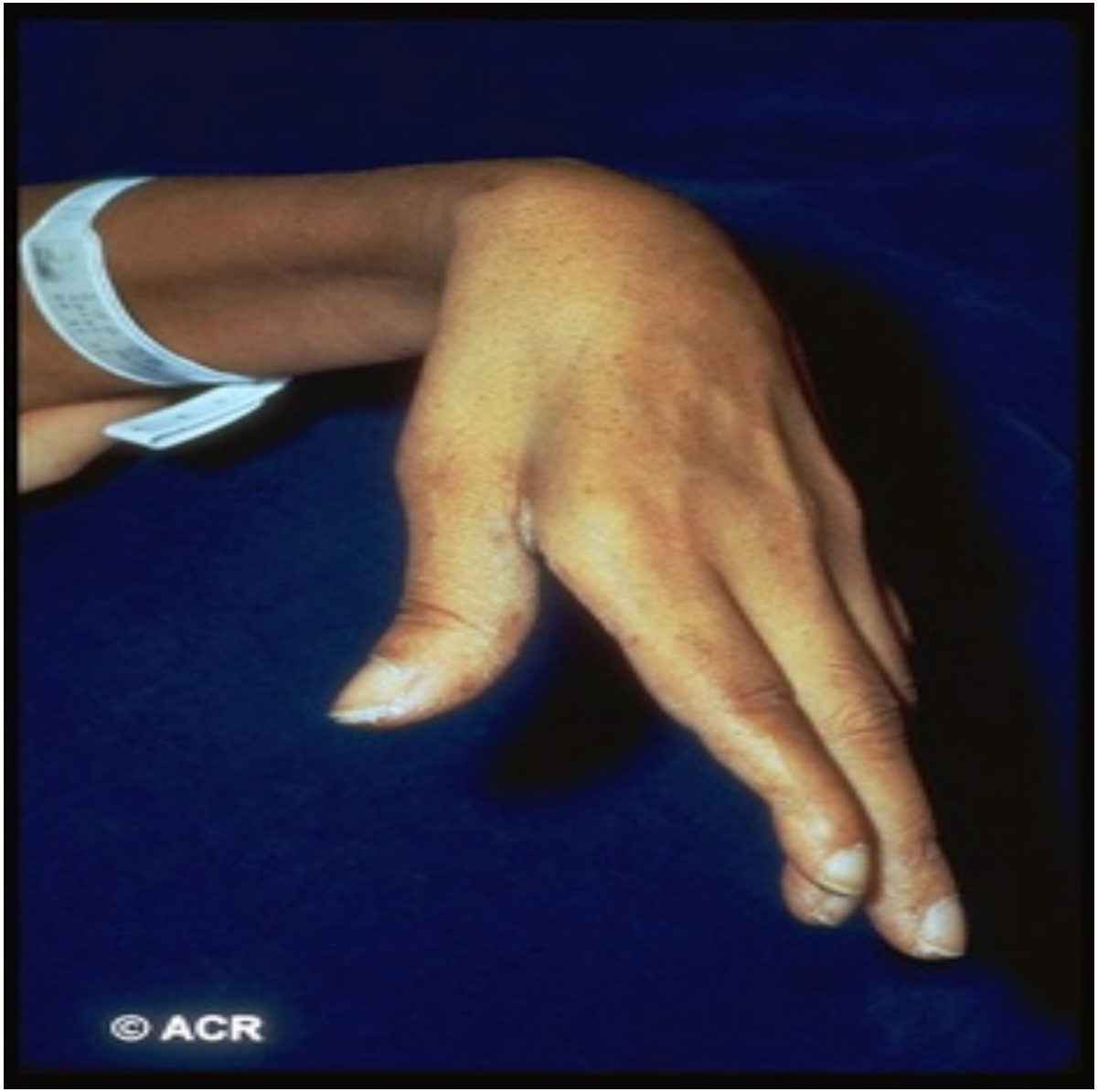
Livedo retikülaris



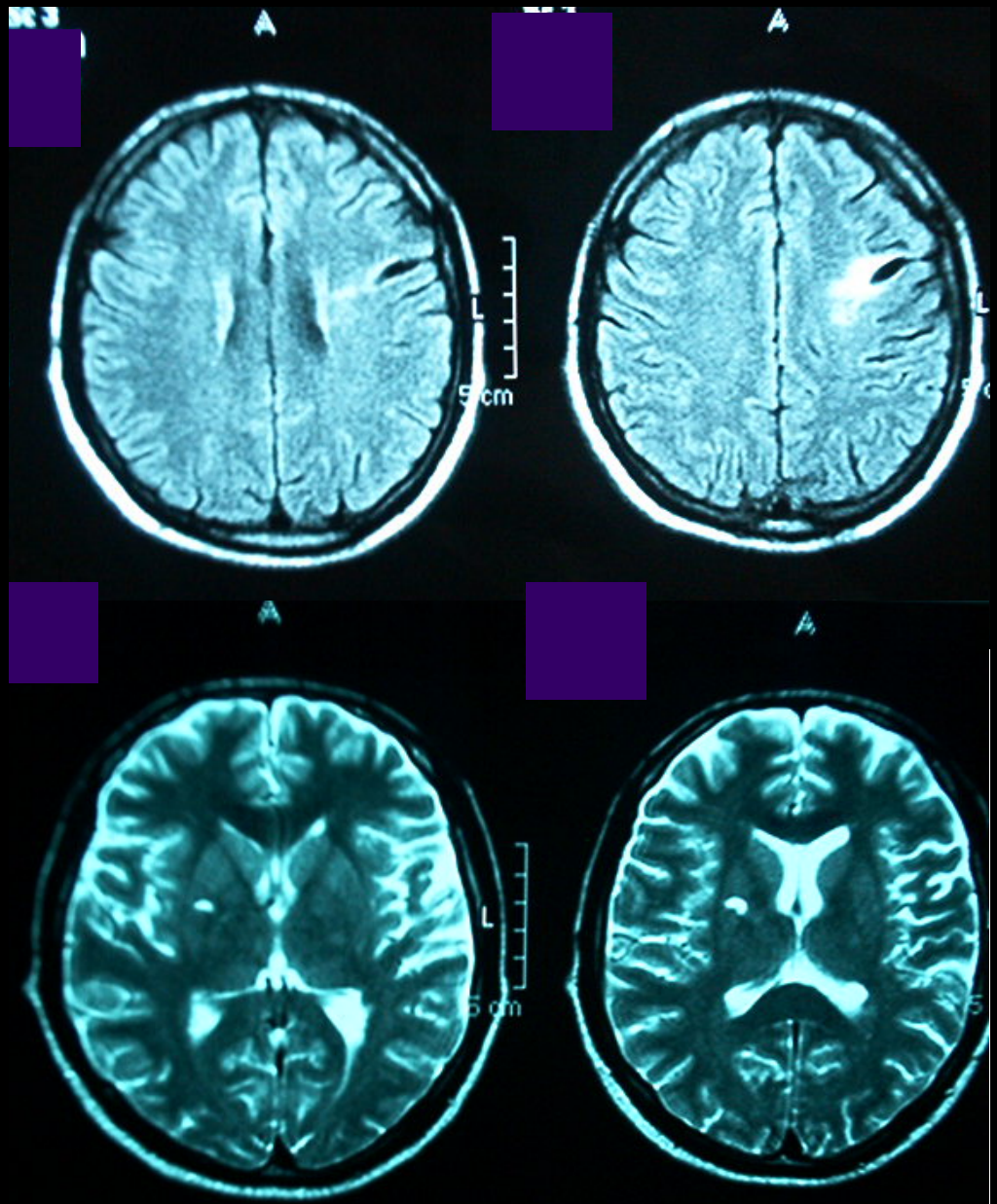
Palpable purpura



Digital gangrene



Dropped hand due to neural ischaemia



Poliarteritis nodosa (PAN)

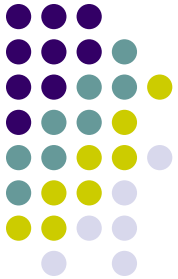
- İschaemic gliotic lesions in MRI

PAN

- was defined as ‘Necrotizing arteritis of medium or small arteries without glomerulonephritis or vasculitis in arterioles, capillaries, or venules, and not associated with ANCAs

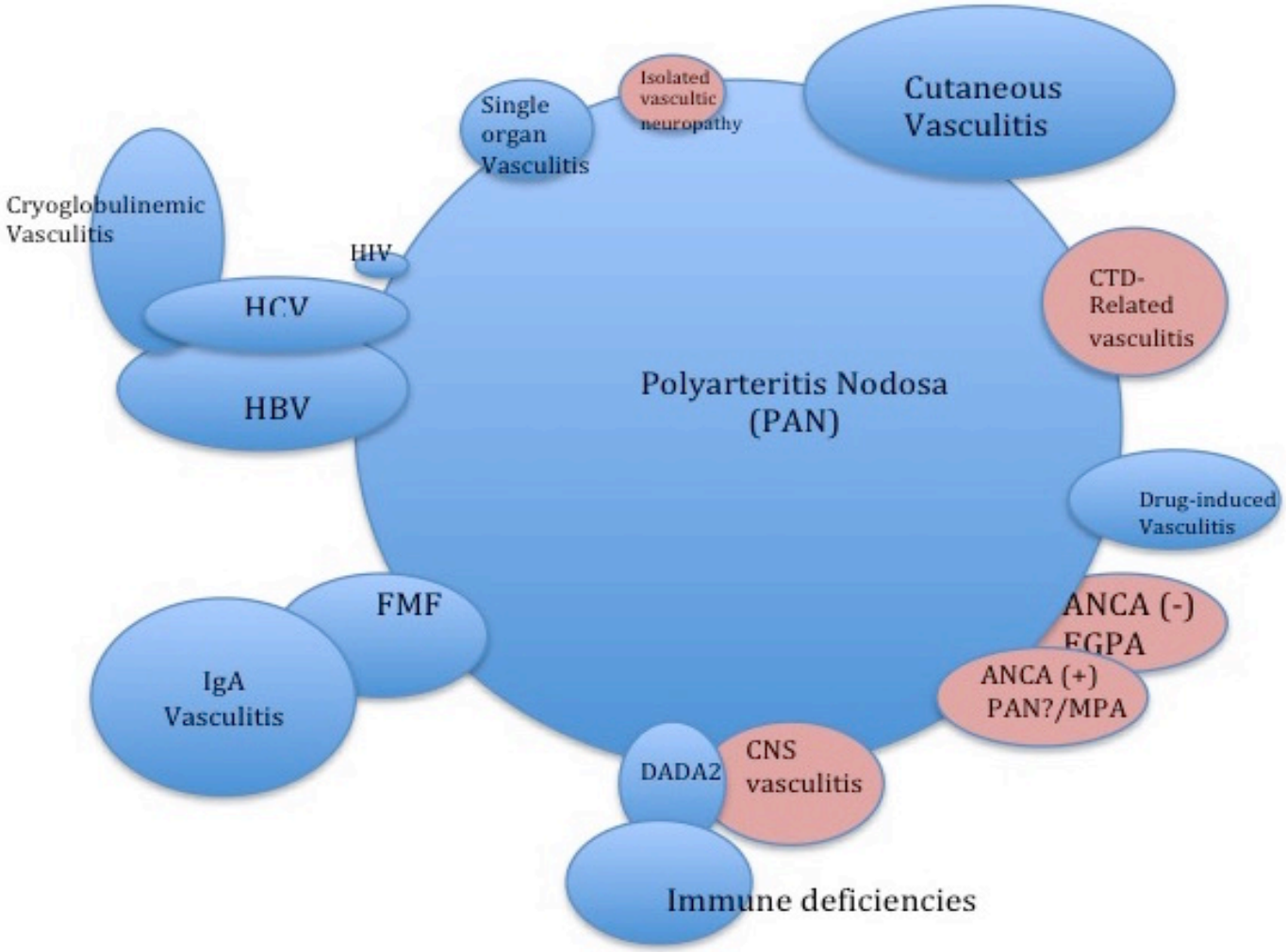
Polyarteritis Nodosa

ACR CLASSIFICATION CRITERIA

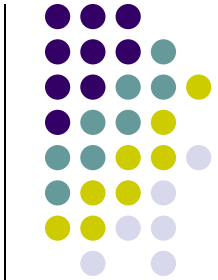


- Weight loss ≥ 4 kg
- Livedo reticularis
- Testicular pain or tenderness
- Myalgias, weakness, or leg tenderness
- Mononeuropathy or polyneuropathy
- Diastolic BP > 90 mm Hg
- Elevated blood urea nitrogen or creatinine
- Hepatitis B virus
- Arteriographic abnormality
- Biopsy of small or medium-sized artery containing polymorphonuclear neutrophils

  - 3 of 10 criteria for classification,
  - Sensitivity: 82.2%, specifity : 86.6%)


Polyarteritis Nodosa (PAN)
Cutaneous Vasculitis
Isolated vasculitic neuropathy
Single organ Vasculitis
Cryoglobulinemic Vasculitis
HIV
HCV
HBV
CTD-Related vasculitis
Drug-induced Vasculitis
ANCA (-) EGPA
ANCA (+) PAN?/MPA
FMF
IgA Vasculitis
DADA2
CNS vasculitis
Immune deficiencies

Essansiyel Cryoglobulinemic Vasculitis



- Cryoglobulinemia is characterized by the presence in the serum of one or more immunoglobulins that precipitate at temperatures below 37° C and redissolve on rewarming.
- >%90 HCV related
- Clinical Manifestations
  - Rash (leukocytoclastic vasculitis)
  - Arthritis
  - Myalgia
- Low compleman levels are characteristic
- Renal involvement, multiplex mononeuritis can be seen

- Treatment: Interferon + ribavirin
- Plasma exchange, pulse steroid-immunesuppressives