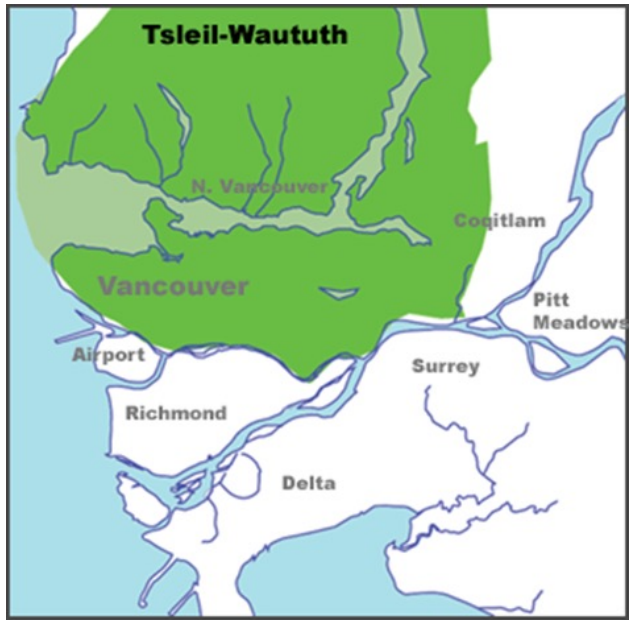
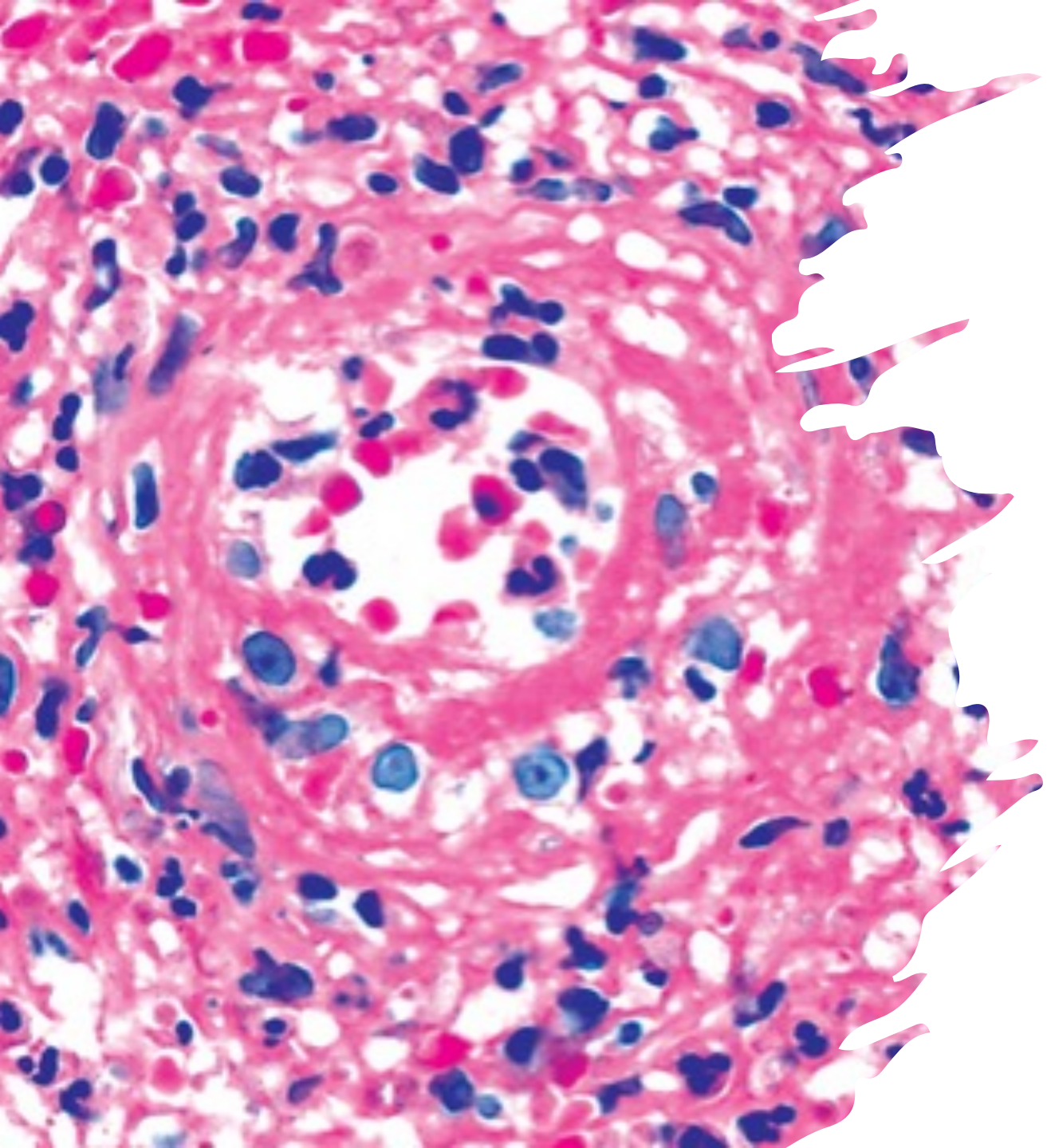
We would like to acknowledge that we are gathered today on the traditional territories of the Musqueam, Squamish and Tsleil-Waututh peoples.

Source: www.johomaps.net/na/canada/bc/vancouver/firstnations/firstnations.html





Cutaneous Manifestations of Vasculitis

Dr. Daniel Ennis &
Dr. Mohammad Bardi

June 28, 2022

Disclosures

- Journal Club Support – Abbvie
- Ad Board – Abbvie, Janssen, Lilly
- No relevant disclosures to this content

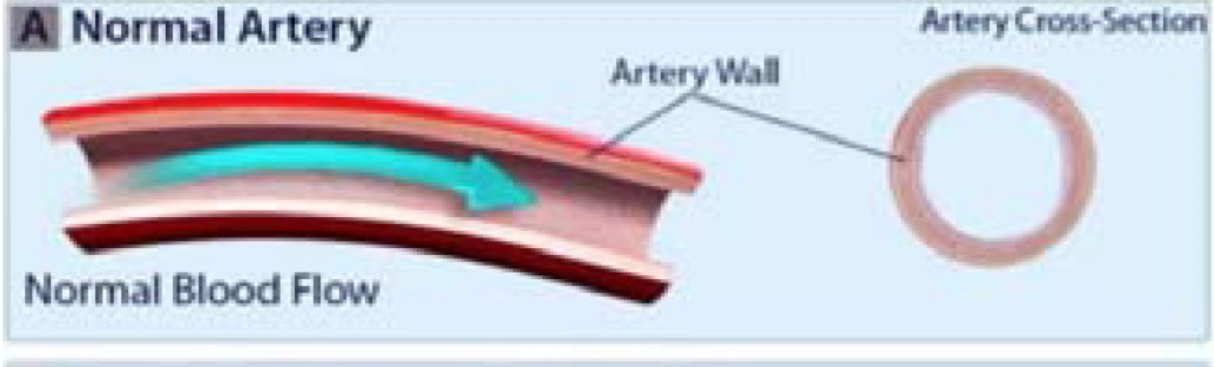
Objectives

1. What is vasculitis?
2. How is vasculitis classified?
3. When to consider vasculitis?
4. Types of vasculitis
5. How to apply an approach to cases of cutaneous vasculitis

What is vasculitis?

What is vasculitis?

- VASCUL ITIS
- Pathologic definition
  - Inflammatory destruction of blood vessels with **ischemia, occlusion and thrombosis**
- Clinical definition
  - A multi-system disease with inflammatory destruction of blood vessels leading to downstream ischemia of tissues
  - Can be life threatening!



Etiology

- Unknown but multifactorial with combination of genes, gender & environment

- **Primary or secondary?**

  - Primary = vasculitis is the principal feature of disease

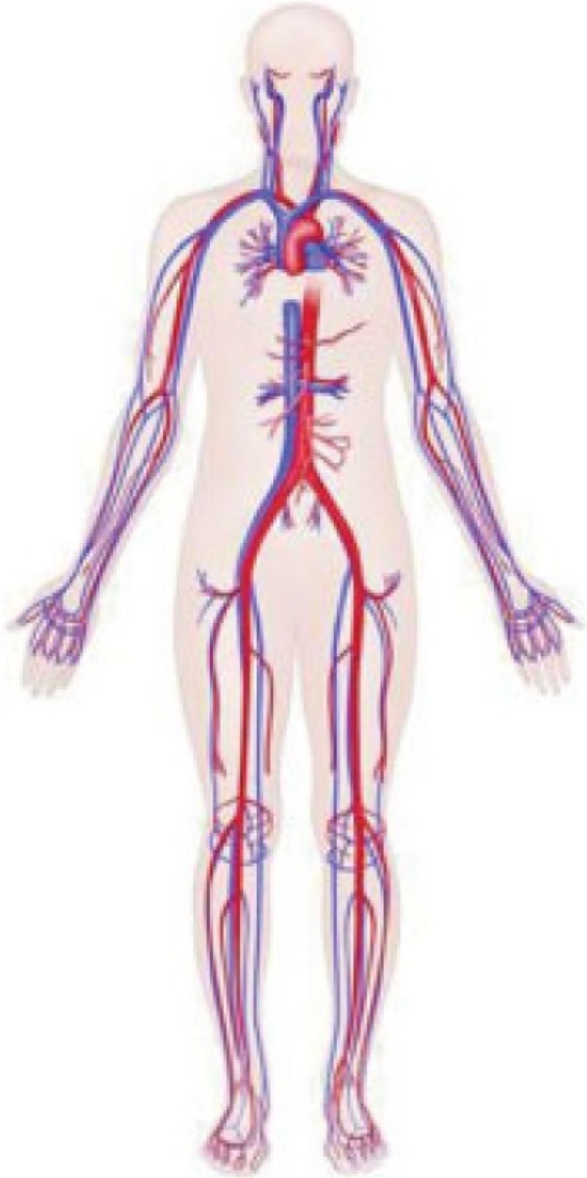
  - Secondary = complication of *another* disease
    - Rheumatoid Arthritis
    - Lupus
    - Infection (e.g. syphilis, TB)
    - Drugs/toxins (e.g. cocaine)

How is vasculitis classified?

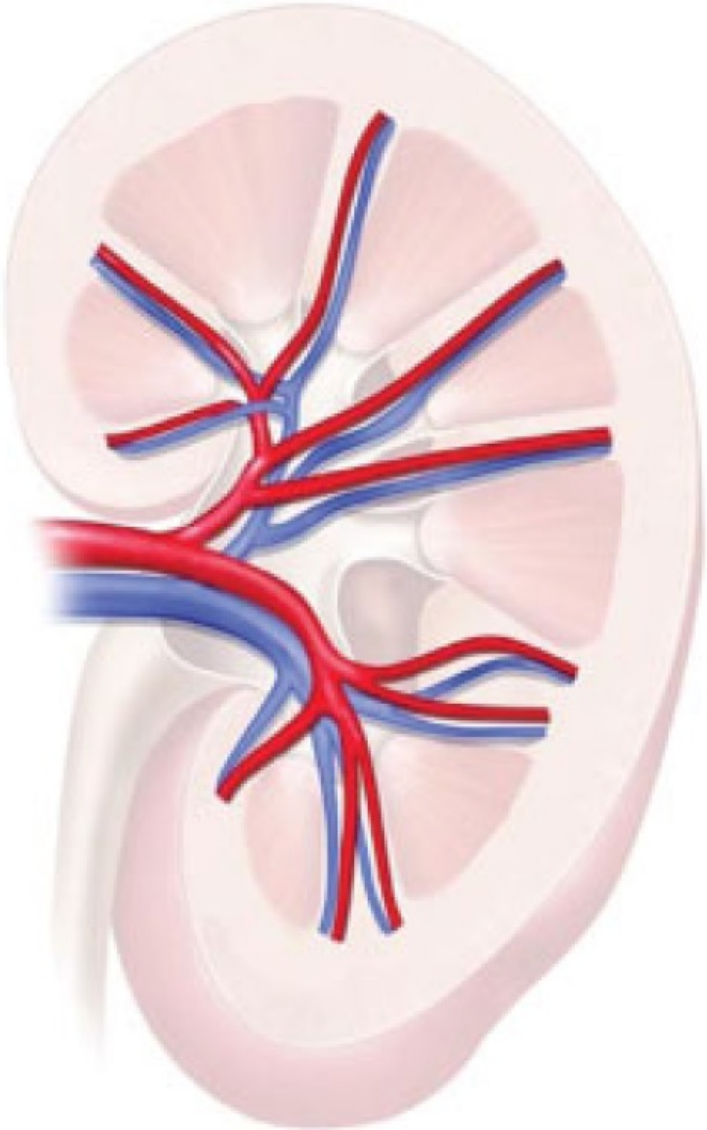
How is vasculitis classified?

- Primary vs Secondary
- Vessel Size (ie. Chapel Hill Criteria)
- ANCA-associated vs immune mediated

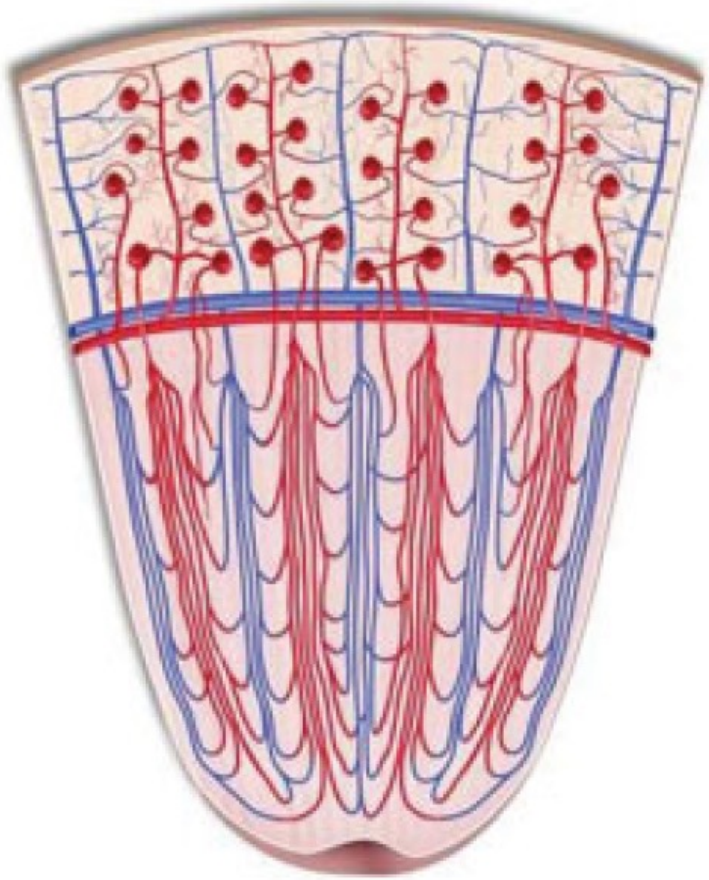
A Large Vessels

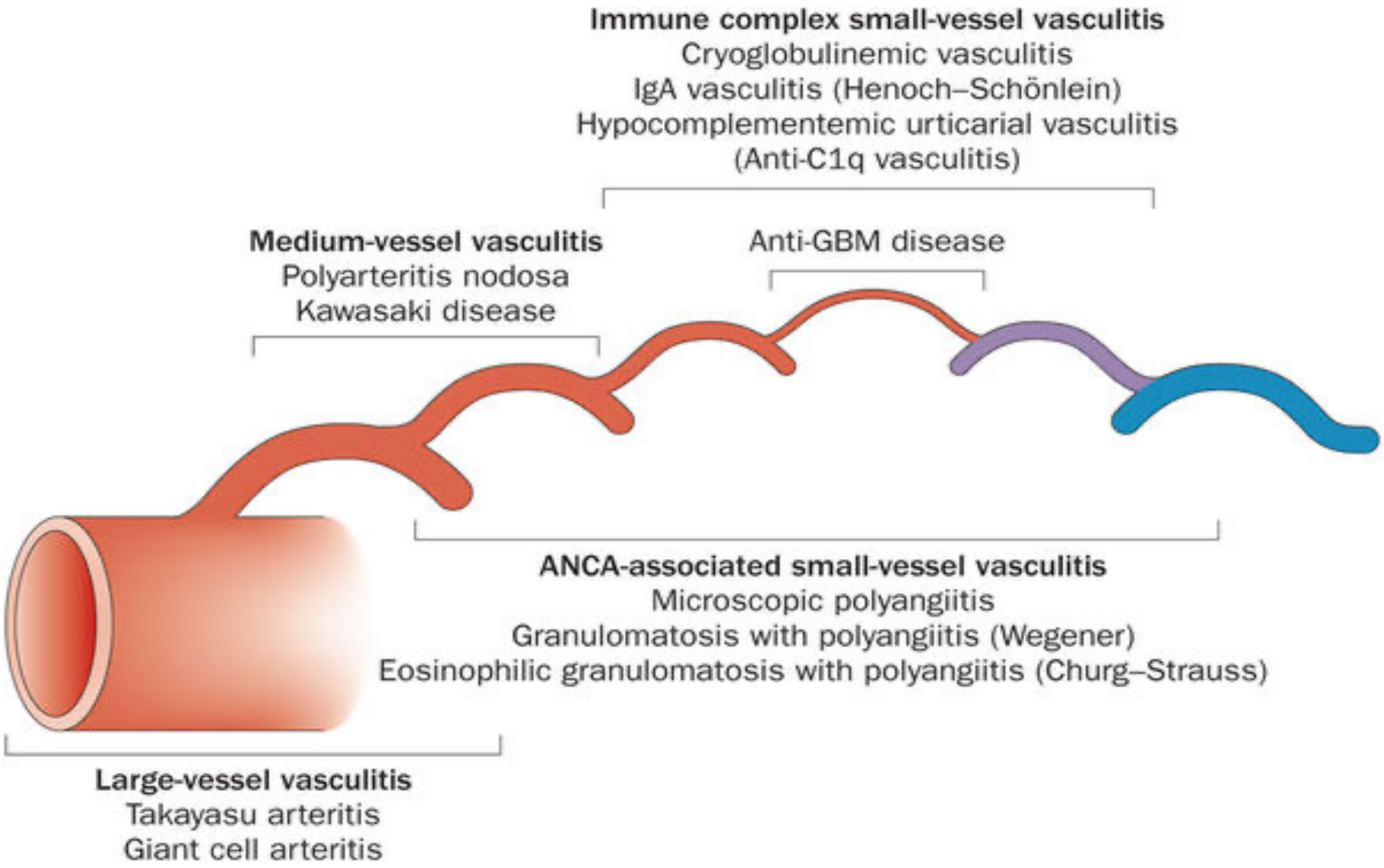


B Medium Vessels



C Small Vessels




Immune complex small-vessel vasculitis
Cryoglobulinemic vasculitis
IgA vasculitis (Henoch–Schönlein)
Hypocomplementemic urticarial vasculitis
(Anti-C1q vasculitis)
Medium-vessel vasculitis
Polyarteritis nodosa
Kawasaki disease
Anti-GBM disease
ANCA-associated small-vessel vasculitis
Microscopic polyangiitis
Granulomatosis with polyangiitis (Wegener)
Eosinophilic granulomatosis with polyangiitis (Churg–Strauss)
Large-vessel vasculitis
Takayasu arteritis
Giant cell arteritis

Examples of Vasculitis by Size

Large Vessel	Medium Vessel	Small Vessel
Giant Cell Arteritis	Polyarteritis Nodosa (PAN)	ANCA vasculitis
Takayasu	Kawasaki	IgA vasculitis (HSP)
		Cryoglobulinemia
		Urticarial Vasculitis

Examples of Vasculitis by Size

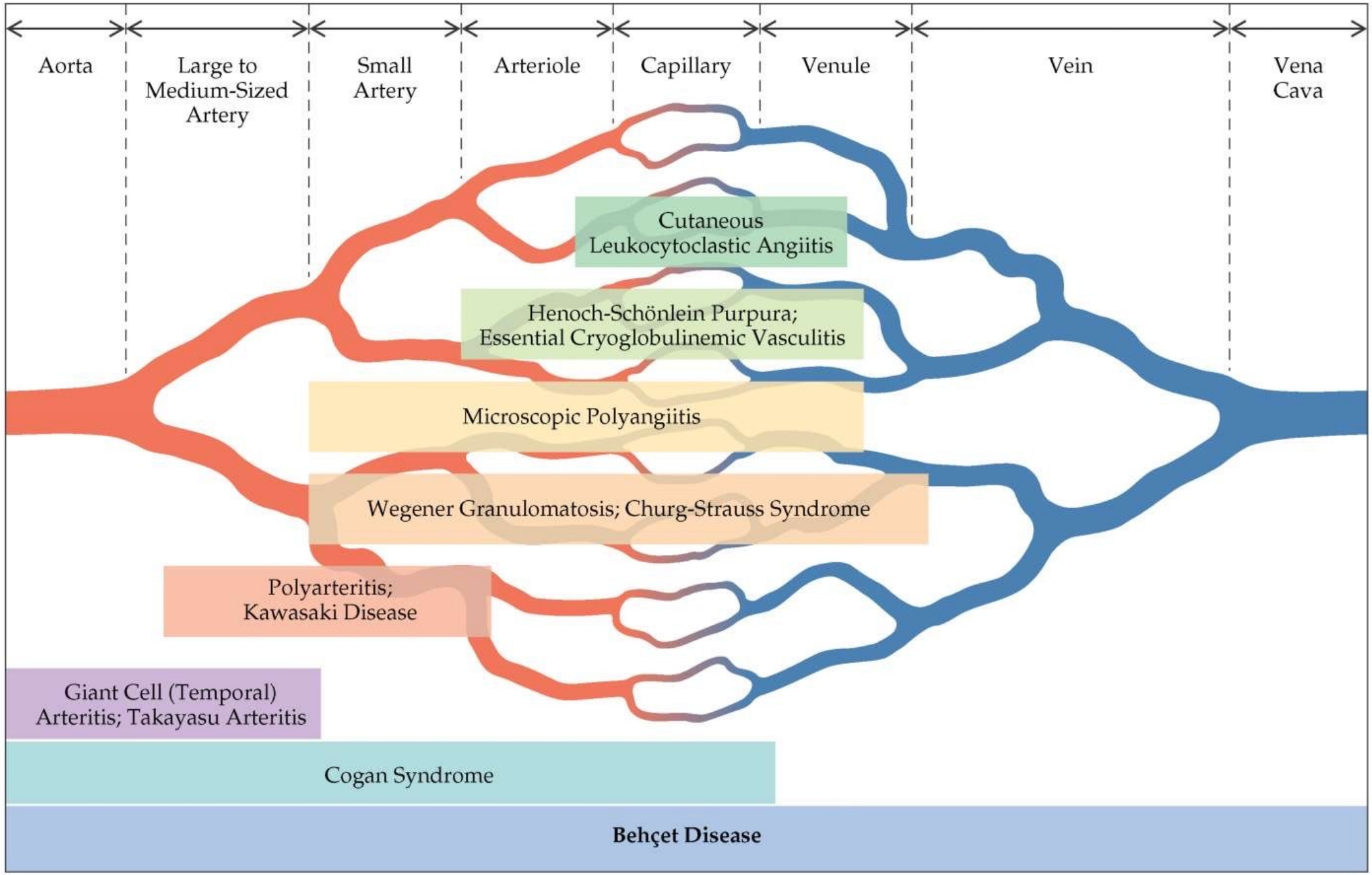
Large Vessel	Medium Vessel	Small Vessel
Giant Cell Arteritis	Polyarteritis Nod	ANCA vasculitis
Takayasu		IgA vasculitis (HSP)
		Cryoglobulinemia
		Urticarial Vasculitis

There is always overlap

How is vasculitis classified?

- Also **variable** vessel vasculitis
  - Behcet's disease
  - Cogan's syndrome

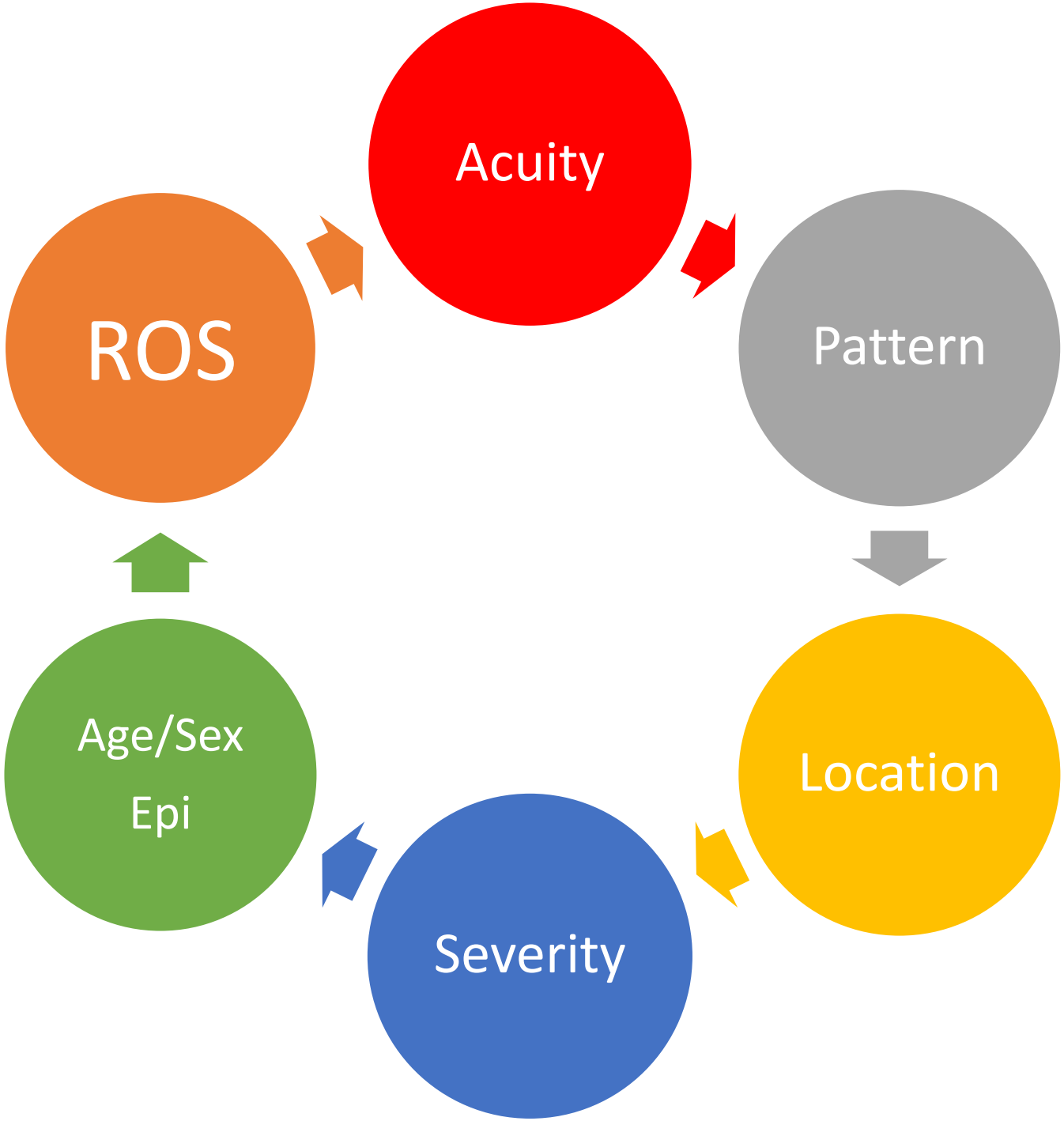
- Single Organ vasculitis
  - Leukocytoclastic vasculitis (LCV)
  - Primary central nervous system vasculitis (PACNS)
  - Isolated aortitis


Aorta
Large to Medium-Sized Artery
Small Artery
Arteriole
Capillary
Venule
Vein
Vena Cava
Cutaneous Leukocytoclastic Angiitis
Henoch-Schönlein Purpura; Essential Cryoglobulinemic Vasculitis
Microscopic Polyangiitis
Wegener Granulomatosis; Churg-Strauss Syndrome
Polyarteritis; Kawasaki Disease
Giant Cell (Temporal) Arteritis; Takayasu Arteritis
Cogan Syndrome
Behçet Disease

When to consider vasculitis?

When to suspect vasculitis

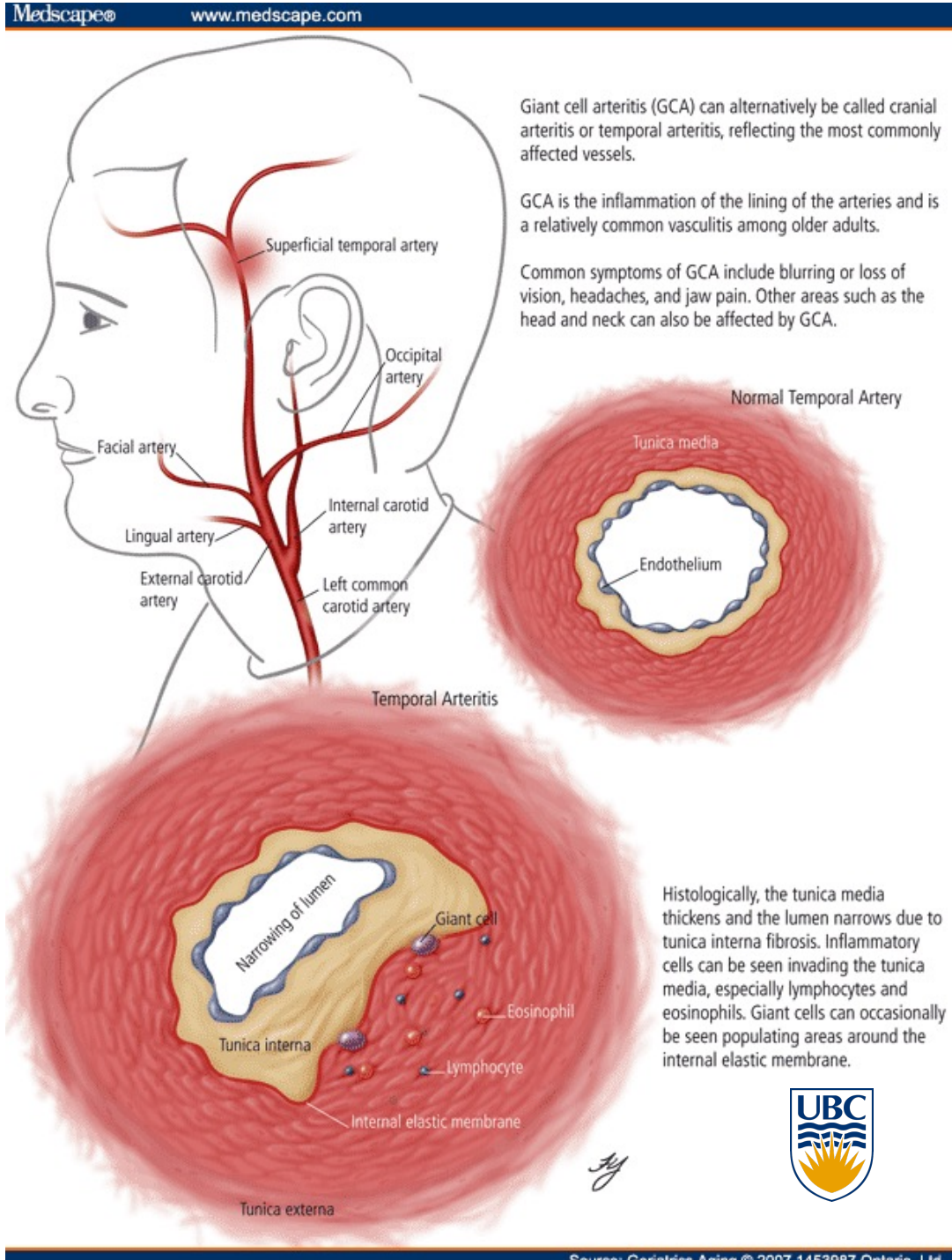
- Multisystem disease with unexplained etiology
- Constitutional symptoms
- Pulmonary symptoms (hemoptysis)
- Rapidly progressive renal failure
- Skin lesions


Acuity
Pattern
Location
Severity
Age/Sex
Epi
ROS

Large vessel vasculitis

Giant Cell Arteritis (GCA)

- Affects patients (>50 years old)
- F > M (3:1)
- Cranial and extracranial involvement
- Pathology
  - *Segmental* vessel inflammation
  - Multinucleated giant cells on pathology



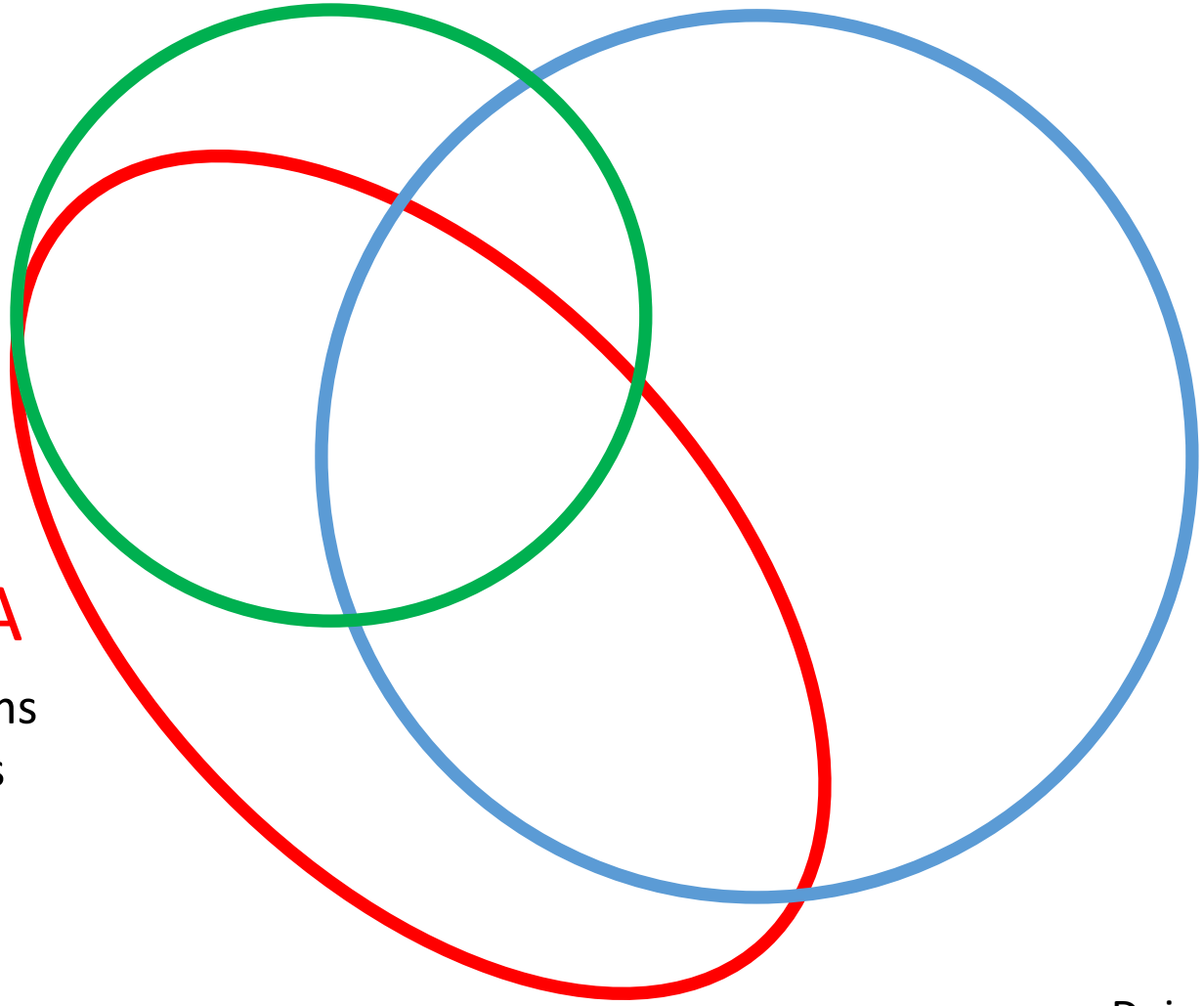
Clinical manifestations

Cranial GCA

- Headache
- TA abnormality
- Visual symptoms
- Jaw claudication
- Tongue claudication

Large Vessel GCA

- Constitutional symptoms
- Claudication Symptoms
- Raynaud's



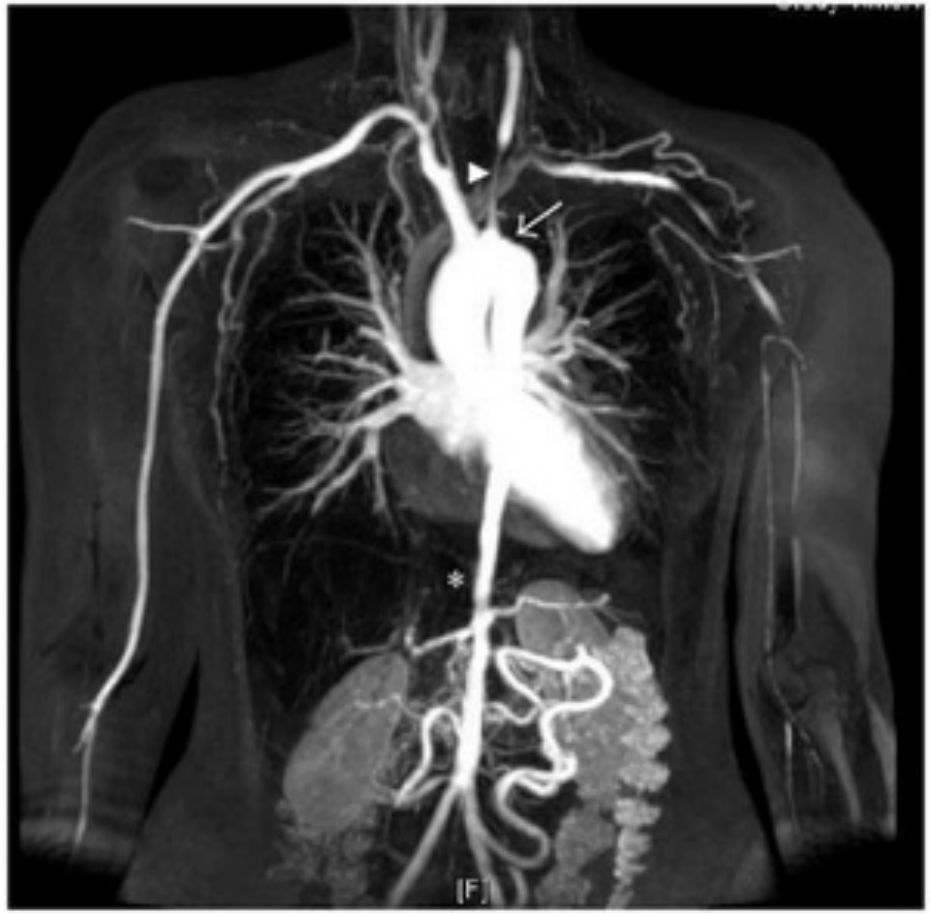
Polymyalgia Rheumatica

- Hip & shoulder girdle pain
- Morning stiffness

Dejaco C et al. Rheumatology 2016

Takayasu arteritis

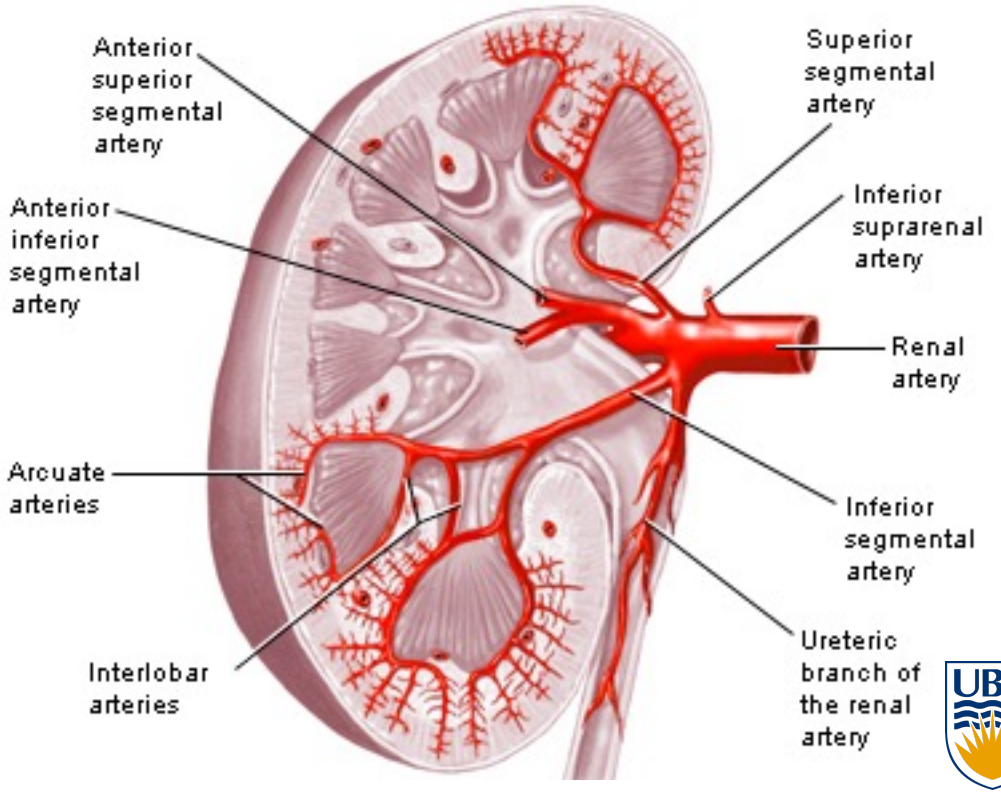
- Large vessel vasculitis affecting typically younger female patients <40
- Also known as “pulseless” disease
- Bruits particularly over subclavian arteries
- Affects aorta and large branches
- Can cause renovascular HTN



Medium vessel vasculitis

Polyarteritis nodosa (PAN)

- Medium vessel vasculitis
- Presents with abdominal pain (intestinal ischemia), testicular pain
- Involvement of renal arteries and AKI
- Hypertension
- Arthralgias/myalgias
- Mononeuritis multiplex
- Does NOT involve the lungs
- Many skin manifestations



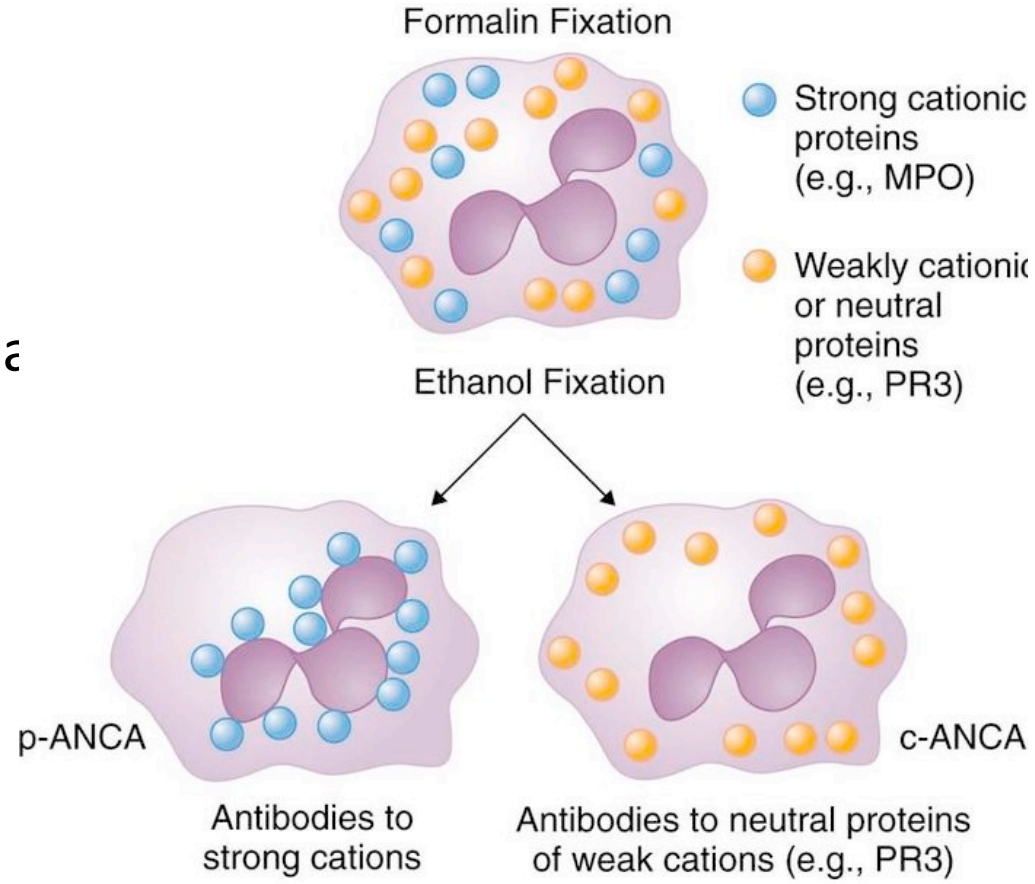
Diagnosis

- Need biopsy!!
- CT-angiogram/conventional angiograms can be helpful to show medium vessel inflammation
  - Can also show microaneuryms
- If nerve involvement → get EMG/NCS and/or nerve biopsy

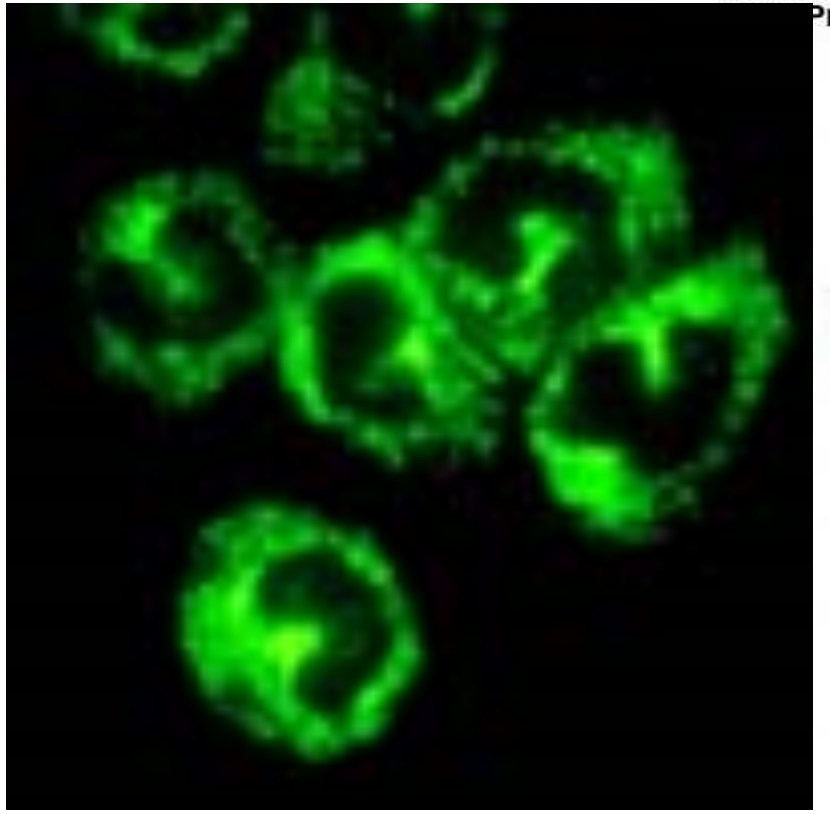
Small vessel vasculitis (ANCA associated)

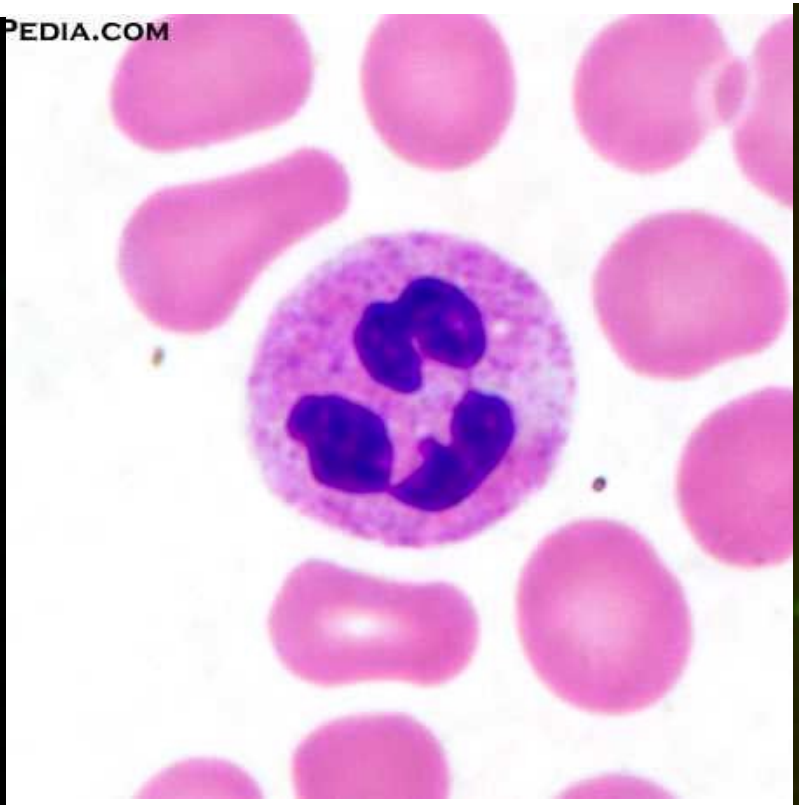
Anti-neutrophilic cytoplasmic antibodies

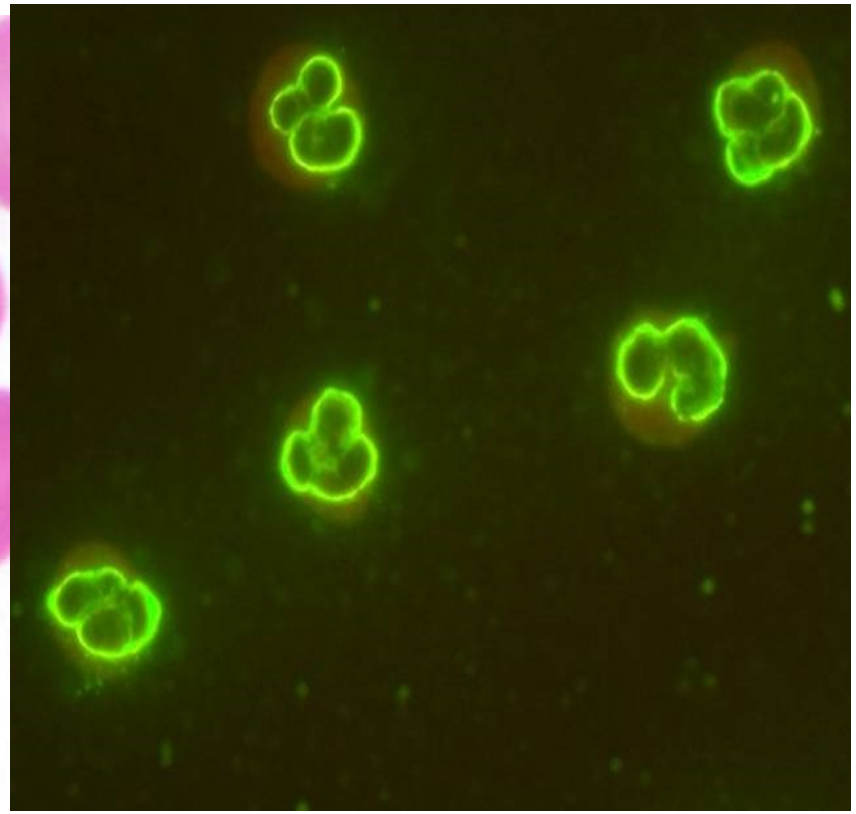
- 3 different types
  - C-ANCA = cytoplasmic
  - P-ANCA = perinuclear
  - Atypical = neither cytoplasmic or perinuclea



ANCA immunofluorescence







c-ANCA

p-ANCA

ANCA

C-ANCA

- Antibody against proteinase 3
- Called PR3-ANCA

- More commonly detected in patients with Granulomatosis Polyangitis (GPA) also known as Wegener's Granulomatosis

P-ANCA

- Antibody against myeloperoxidase
- Called MPO-ANCA

- Predominates in patients with Microscopic polyangiitis and Churg-Strauss Syndrome

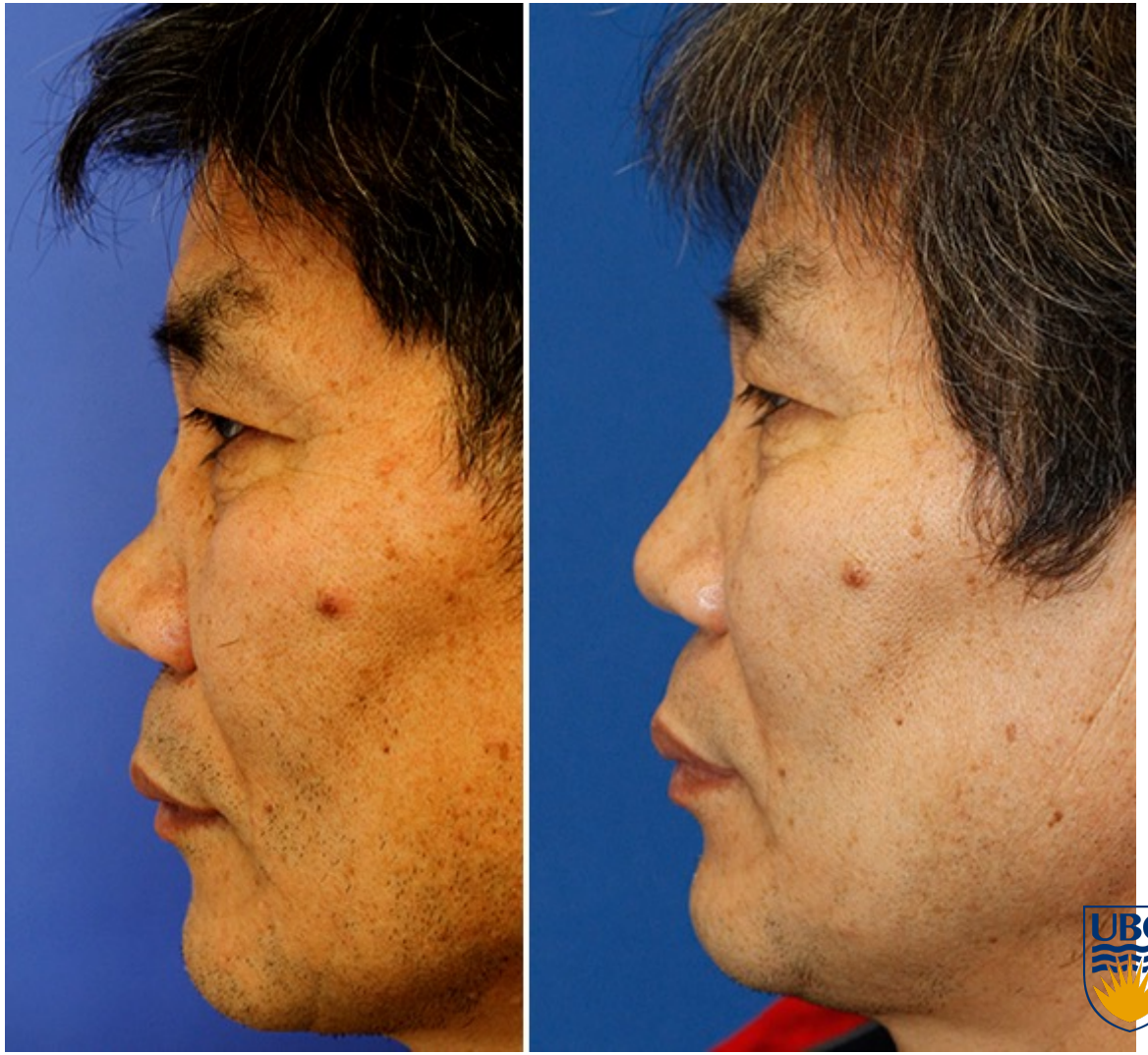
ANCA vasculitis

- Small vessel vasculitis
- “pulmonary-renal” syndrome
- Distinct in that they are associated with ANCA antibodies

	c-ANCA/PR3	p-ANCA/MPO
GPA	70 - 80%	10%
MPA	10%	50%
EGPA (CSS)	5%	40%

Granulomatosis with Polyangiitis (GPA)

- "ELKS"
  - ENT
  - Lungs
  - Kidneys
  - Skin
- Uveitis
- Mononeuritis
- Almost always associated with C-ANCA and PR3



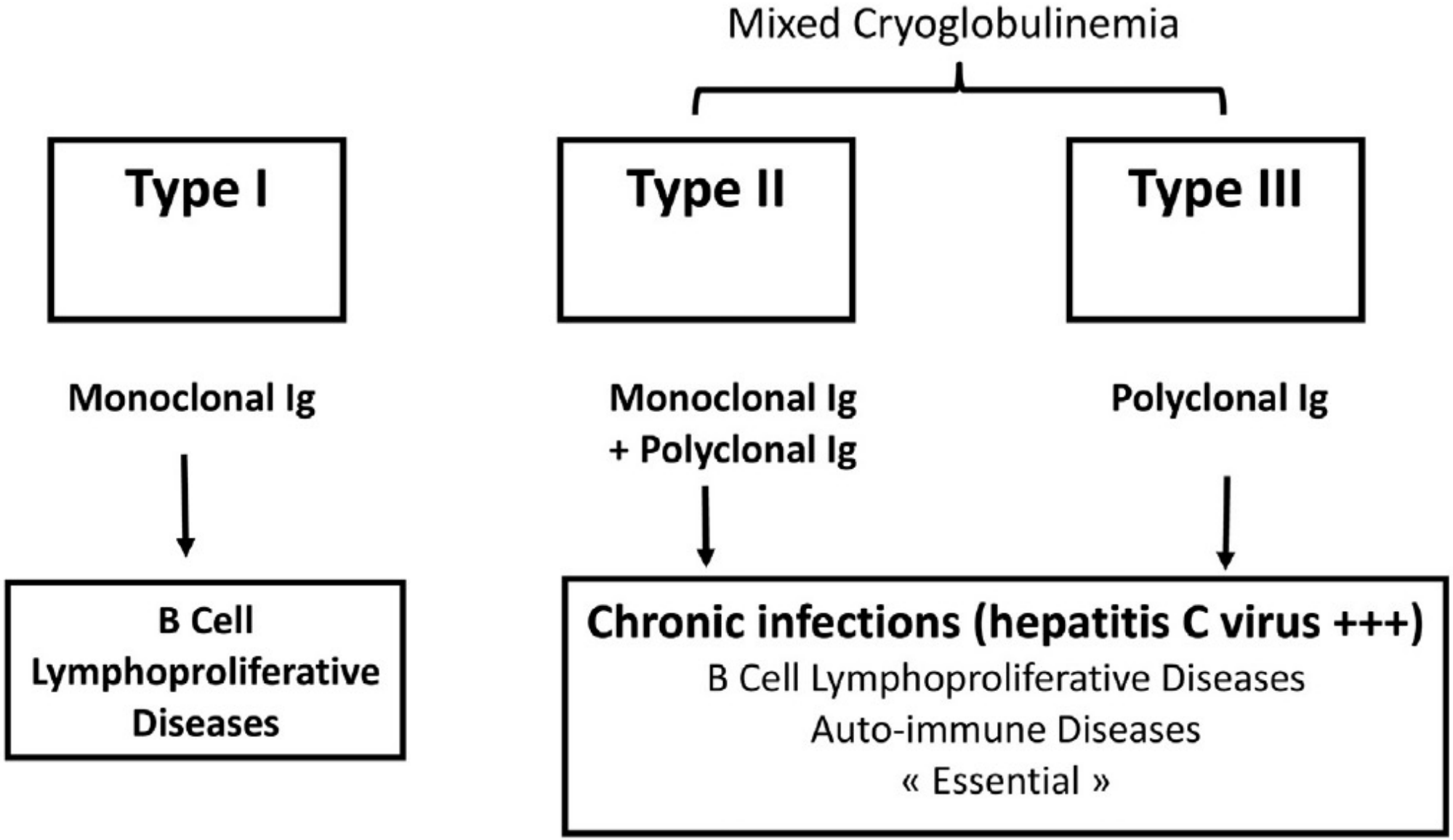
EGPA - Churg Strauss Syndrome

- Nearly ***all*** patients will have a history of asthma
- Three phases of disease
  1. Prodromal – atopic disease, allergic rhinitis, asthma
  2. Eosinophilic – peripheral blood and eosinophilic organ deposition
  3. Vasculitic – GN and pulmonary hemorrhage
- Other manifestations
  - Mononeuritis commonly see in up to 70% of patients
  - Subcuatneous nodules
  - Can have eosinophilic myocarditis and heart failure
- Associated with P-ANCA and MPO
  - Up to 50% are ANCA negative

Small vessel vasculitis (immune mediated)

Cryoglobulinemia

- Cryoglobulins = circulating immunoglobulins (Ab) that precipitate when cooled below 4 degrees and dissolve when re-heated
- Associated with chronic infections (HCV)
- Clinical manifestations
  - Palpable purpura (LCV)
  - Weakness
  - Arthralgia
  - Renal involvement (GN)
  - Neurologic manifestations


Mixed Cryoglobulinemia
Type I
Type II
Type III
Monoclonal Ig
Monoclonal Ig
+ Polyclonal Ig
Polyclonal Ig
B Cell
Lymphoproliferative
Diseases
Chronic infections (hepatitis C virus +++)
B Cell Lymphoproliferative Diseases
Auto-immune Diseases
« Essential »

IgA vasculitis (Henoch-Schonlein Purpura)

- More common to see in children/young adults but also adults
- Classic triad
  - Abdominal pain
  - Arthritis/arthralgia
  - AKI (immune complex GN)
- Lower extremity palpable purpura
- Pathology
  - IgA deposition → need to ask for immunofluoresence
- Typically self limited

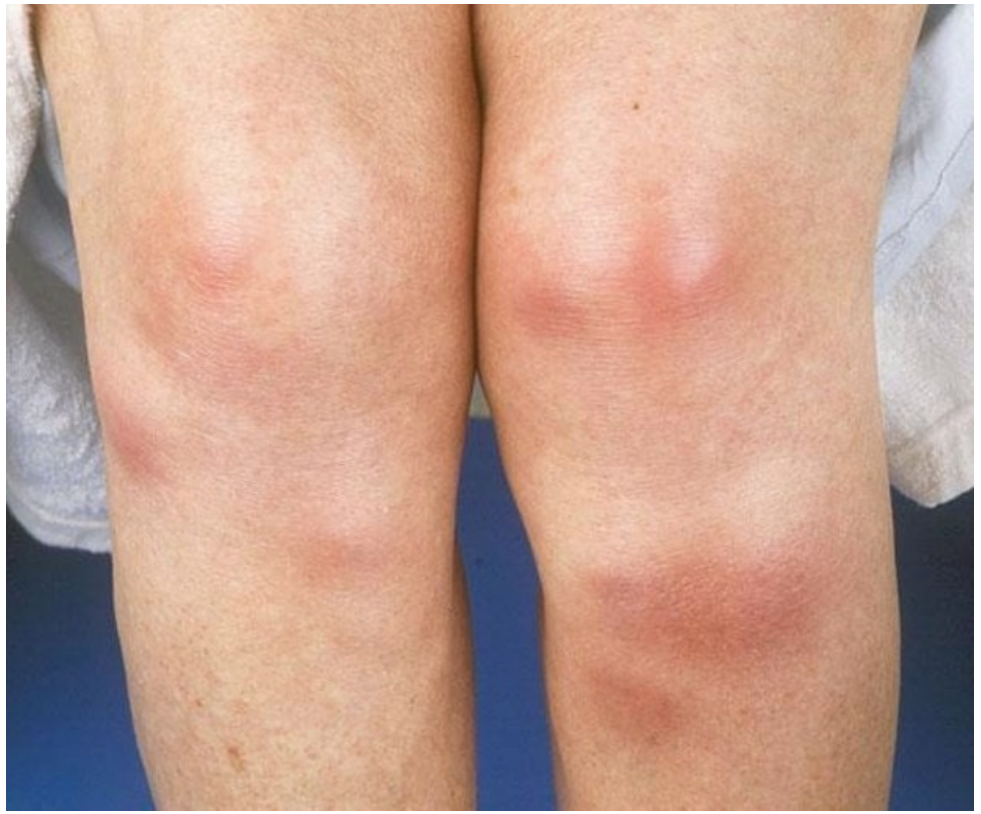
Variable Vessel Vasculitis

Behçet's Syndrome

- Common present with oral/genital ulcers as well as cutaneous, ophthalmologic, neurologic and rheumatologic manifestations
- Epidemiology
  - Geographic variability: (along the silk road)
    - More common in Turkey, Mediterranean and Japan
  - Genetic predisposition
  - Pathophysiology:
    - neutrophilic vascular reaction +/- leukocytoclastic vasculitis

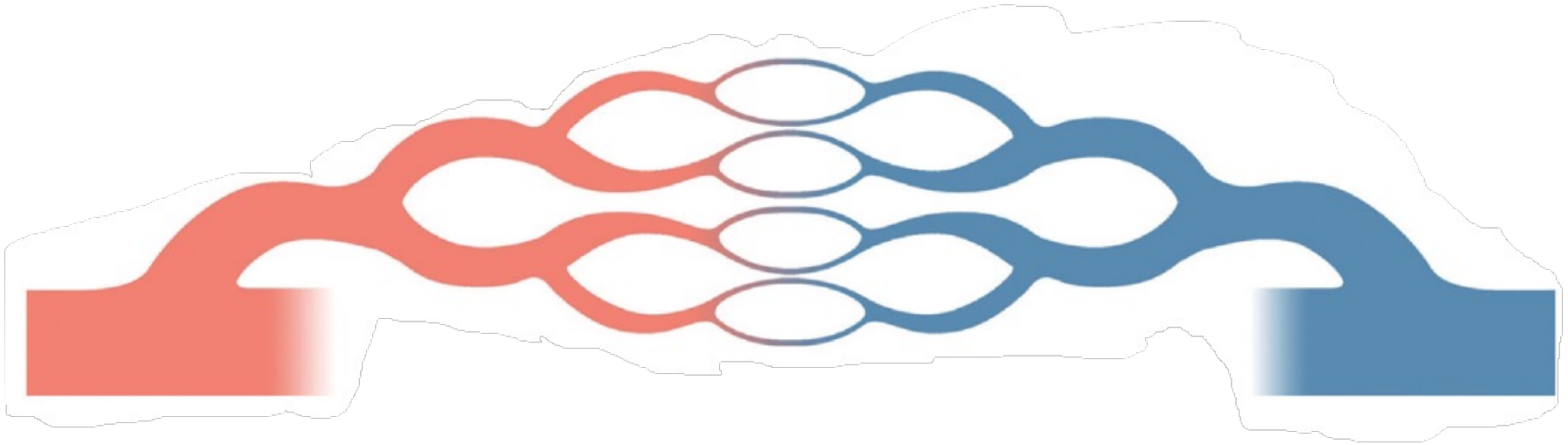
Behcet Diagnosis

- Recurrent Oral Ulceration
- Plus two of the following criteria:
  - Recurrent Genital Ulceration
  - Eye Lesions (Uveitis or retinal vasculitis)
  - Skin Lesions
    - Erythema nodosum
    - Pseudofolliculitis
    - Papulopustular
    - Acneiform nodules
    - Positive Result on Pathergy Testing



Behcet Other Clinical Manifestations

- Arthritis: nonerosive asymmetric oligoarthritis
- Neurologic: neuro-Behçet's syndrome
- Gastrointestinal ulcerations
- Vascular:
  - Aneurysms
  - Venous thrombosis



Vasculitis and the Skin

Daniel Ennis MD, FRCPC

Rheumatology and Vasculitis

Disclosures

- Journal Club Support – Abbvie and UCB
- No relevant disclosures to this content.

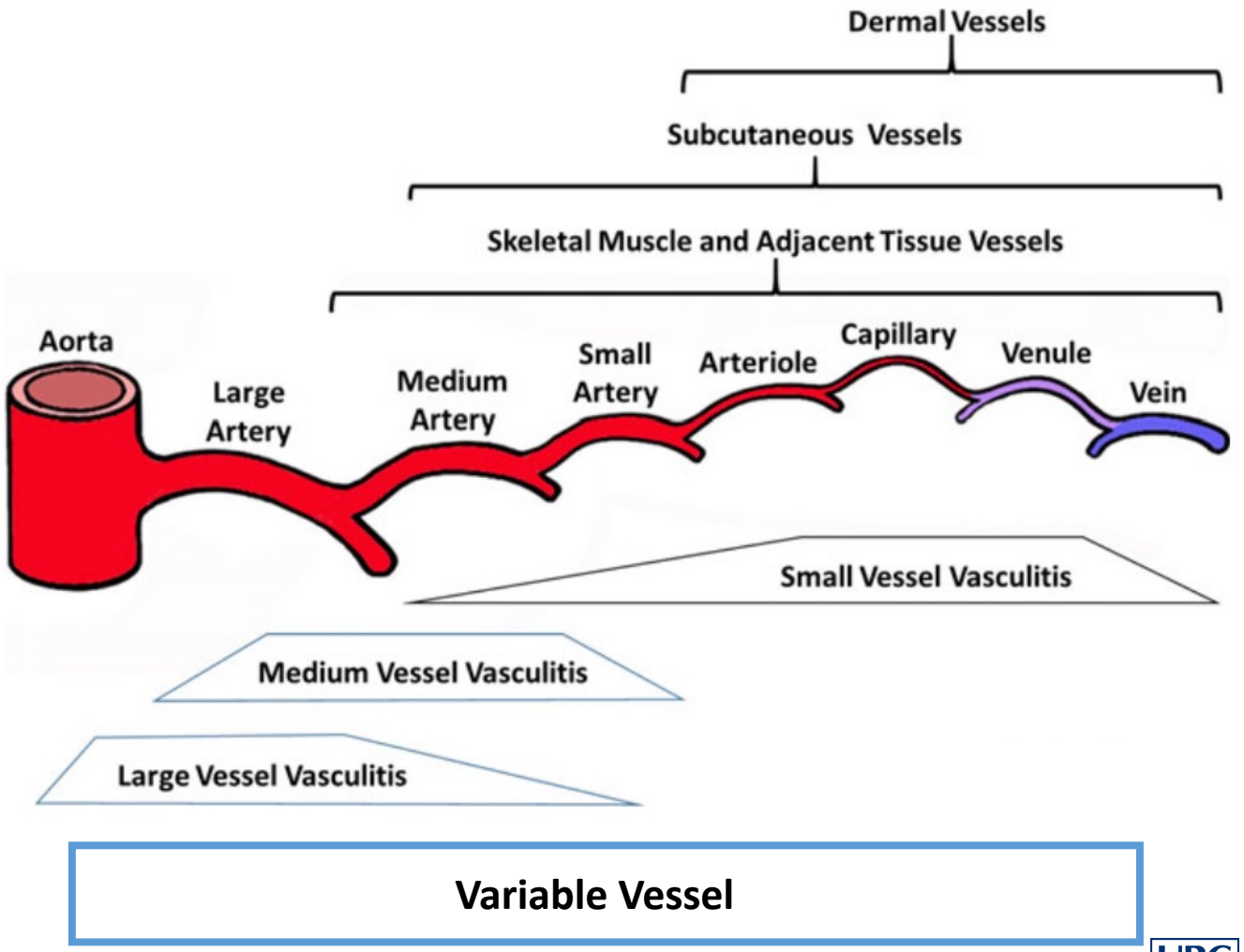
Addendum to the Chapel Hill Criteria

"Large Vessel Vasculitis" has minimal overlap with the "Subcutaneous" and "Dermal Vessels"

- Not many rashes!

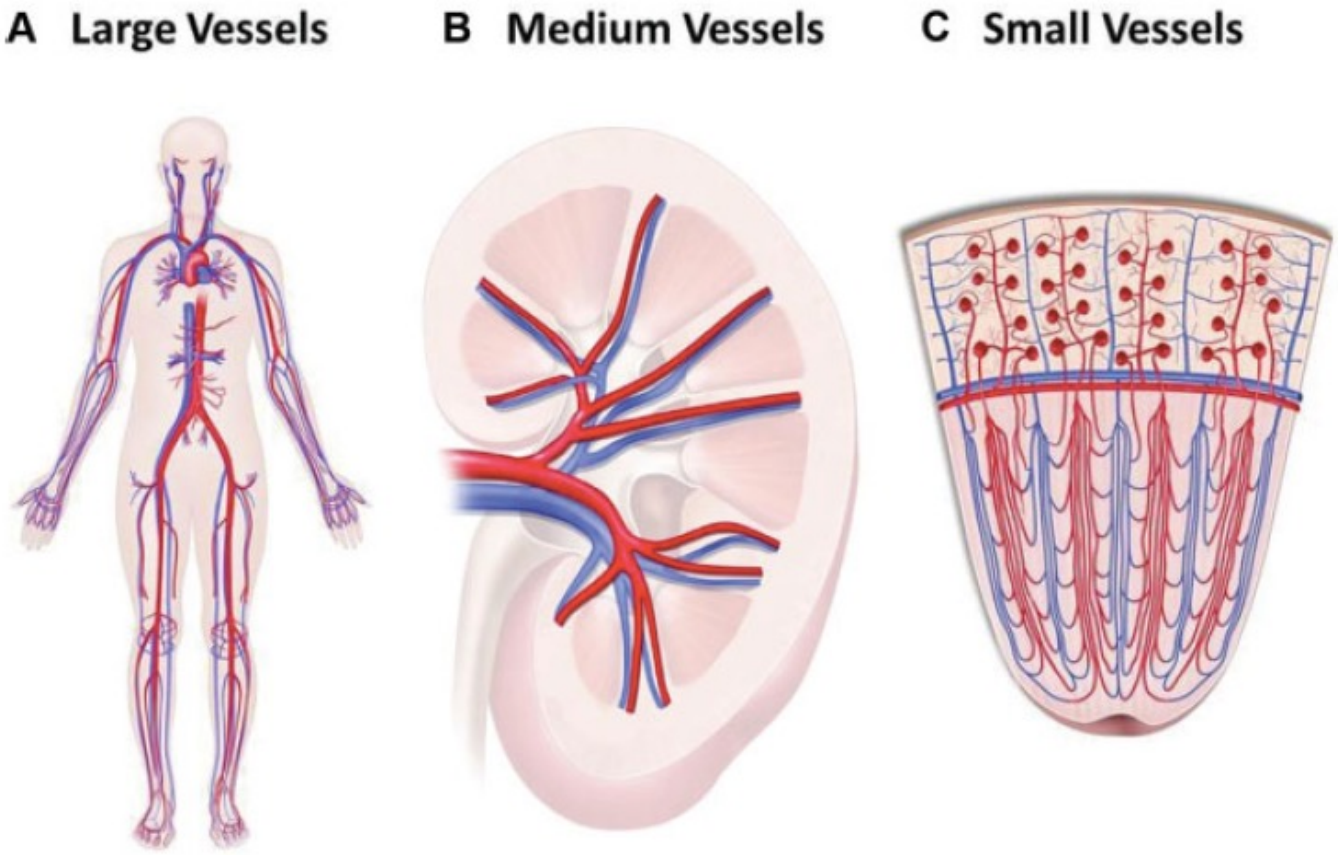
Don't forget about variable vessel vasculitis category!!

- Behcet's Disease
- Cogan's Disease



Sunderkotter, A&R. 2018

How can we determine vessel size?



The skin manifestation depends on the **size of vessels**

Approach to diagnosis

What is this rash called?

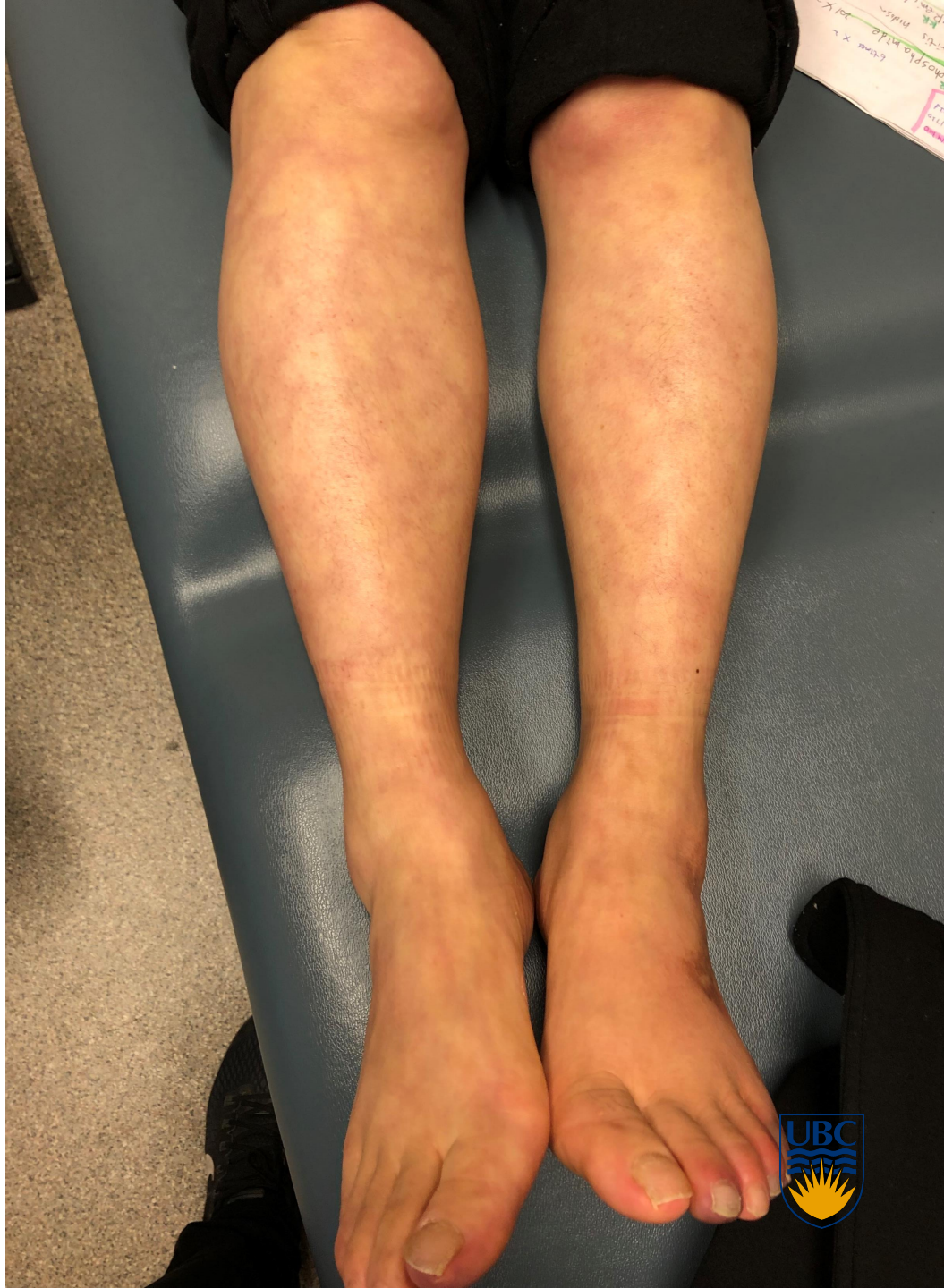
What size vessel causes this rash?

What types of vasculitis routinely affect this vessel size

Cases

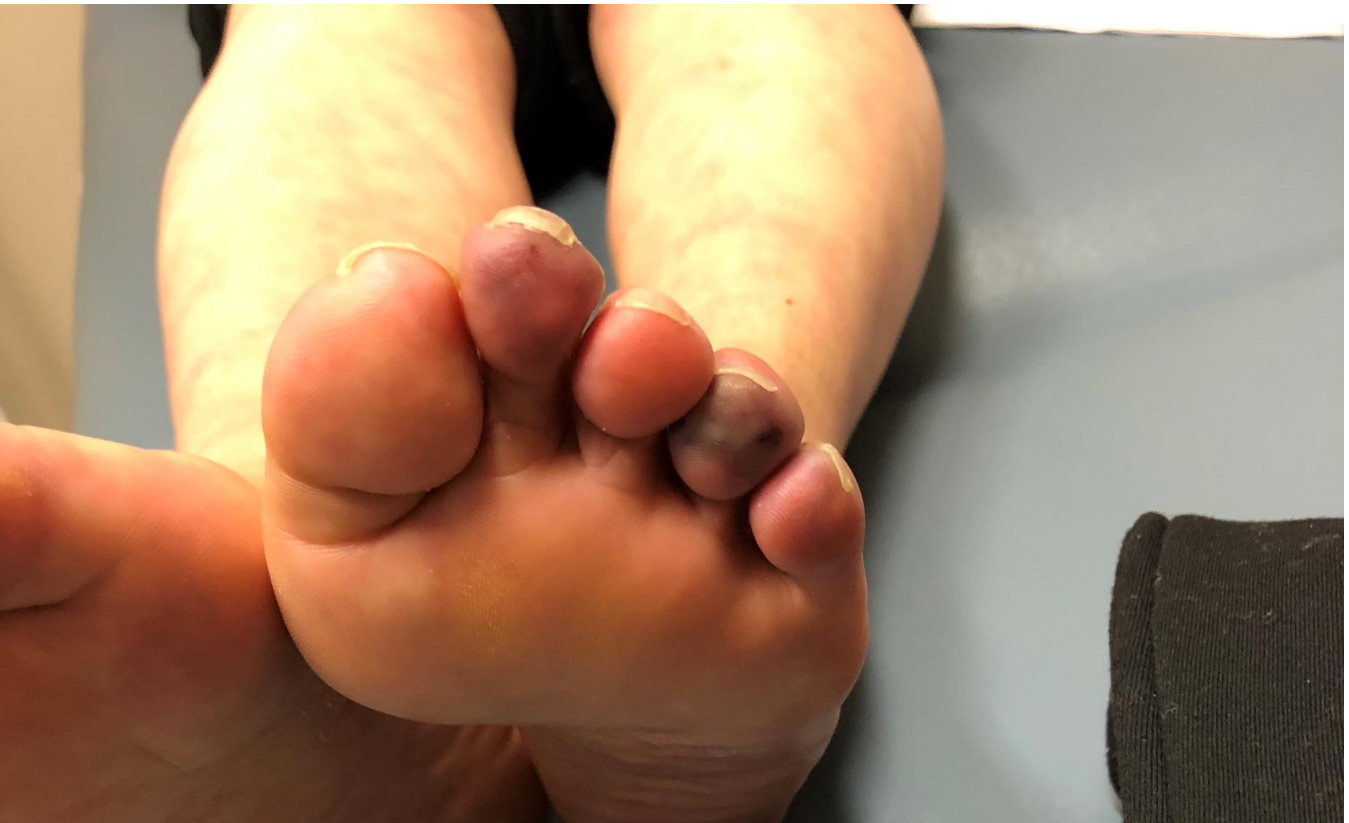
Case 1

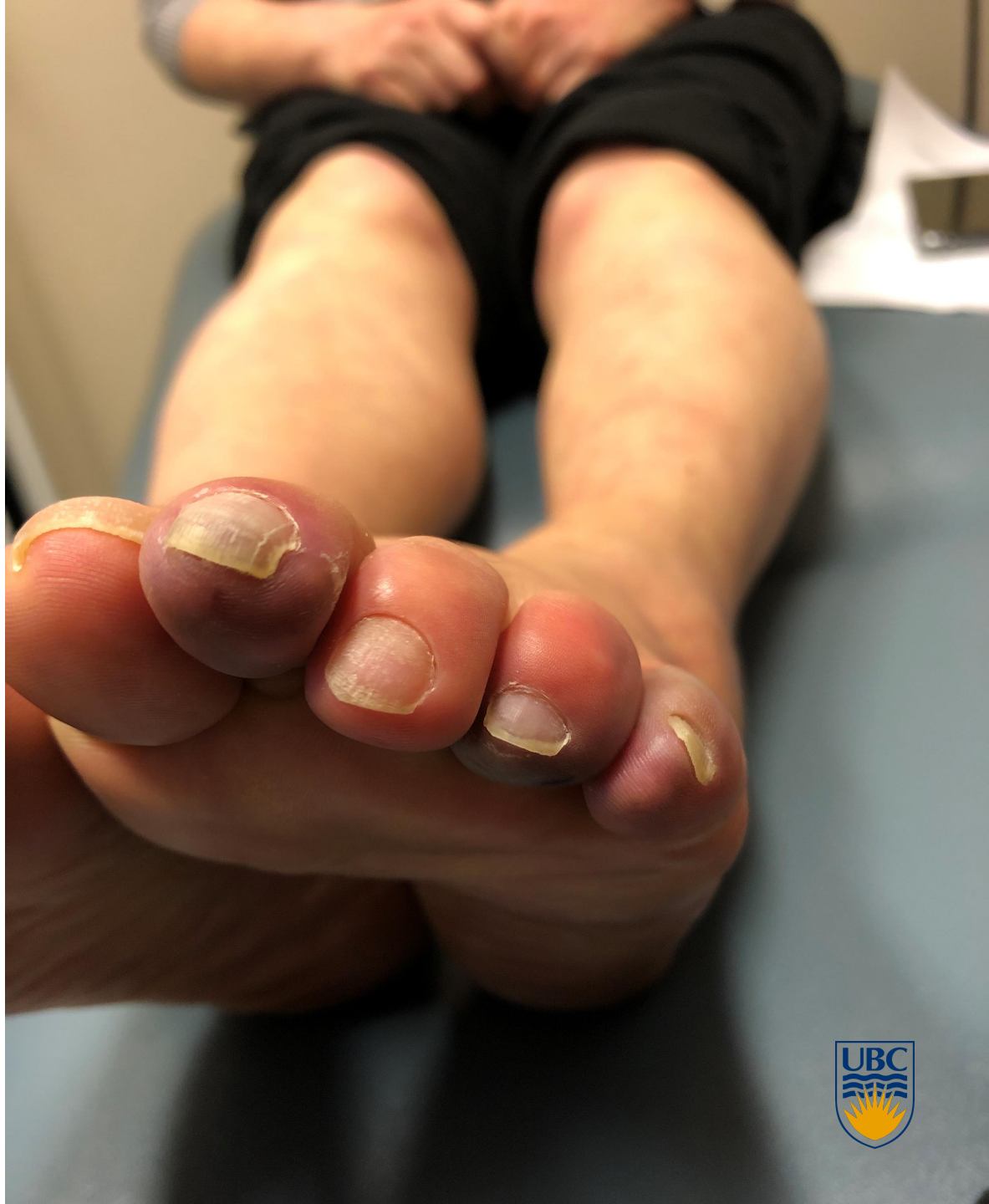
- 40 year old woman presenting to GP with 3 month history of post-prandial abdominal pain
- 8 weeks - onset Raynaud's → lacy rash
- 4 week – necrotic skin lesions and toe gangrene (begin to auto-amputate)
- 1 week – Foot can no longer dorsiflex (foot drop)



Purple Toes

- What does this suggest?
- Cyanosis?
- Raynaud's?
- Ischemia?





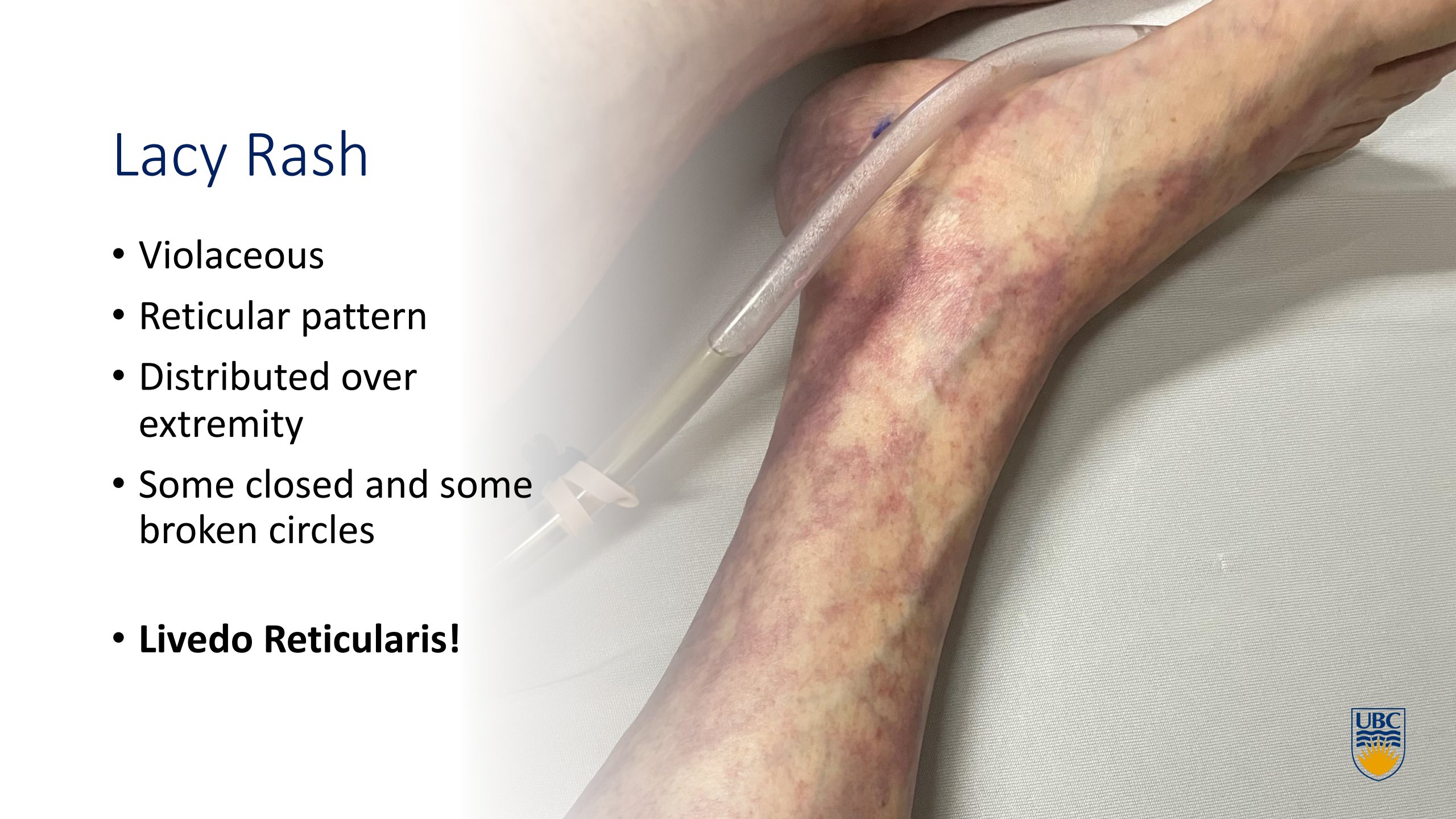
Exam

- BP – 170/120 (symmetric)
- Cardio: normal heart sounds and no bruits in the neck/chest. Renal artery bruits detected.
- Resp: Clear
- Peripheral vascular: Poor pulses in the extremities (particularly radials), poor cap refill. Allen's Test Positive
- Derm: Multiple deep necrotic ulcers, Necrotic/gangrenous fingers. Lacy rash noted

Lacy Rash

- Violaceous
- Reticular pattern
- Distributed over extremity
- Some closed and some broken circles

- **Livedo Reticularis!**

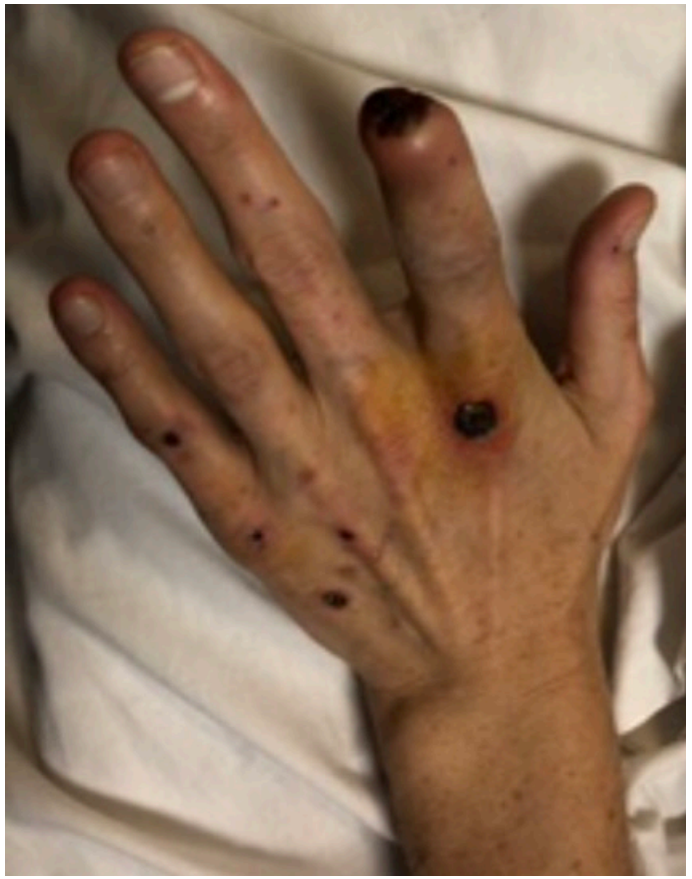


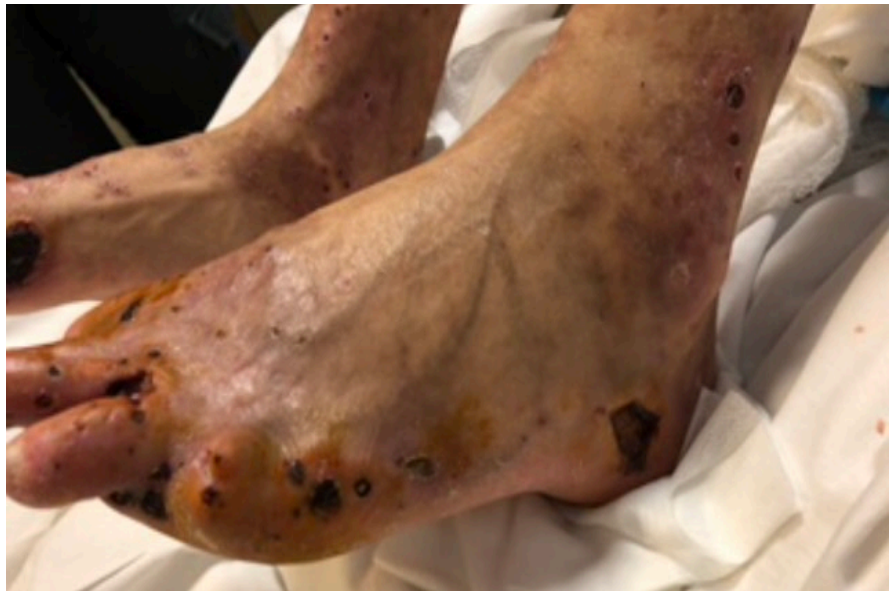
Livedo Reticularis

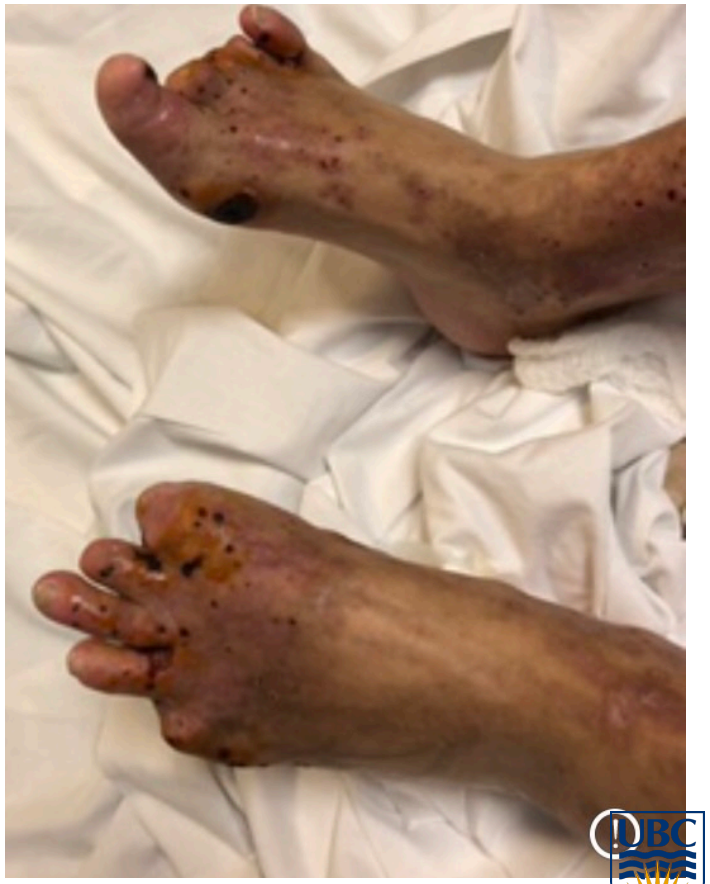
- “the persistent, not reversible with rewarming, violaceous, red or blue, reticular or mottled pattern of the skin of trunk, arms or legs, consisting of regular unbroken circles (regular livedo reticularis) or irregular-broken circles (livedo racemosa).”

Miyakis, J Thromb Haemost, 2006

Necrotic skin lesions + digital gangrene







Approach to Diagnosis

What is this rash called?

→ Livedo Reticularis
Cyanotic toes
Necrotic skin lesions
Auto Amputation

What size vessel causes this rash?

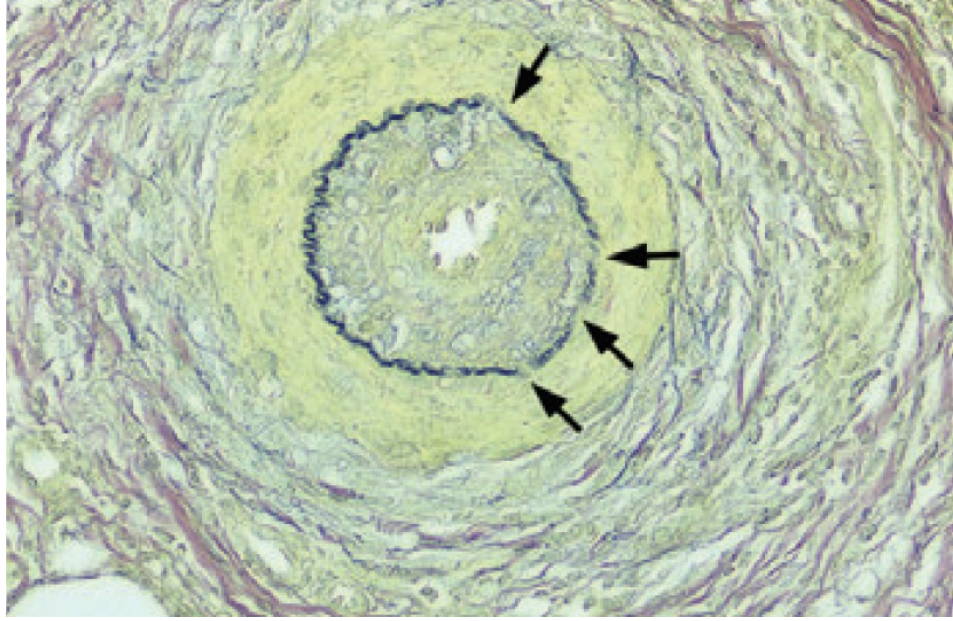
→ Commonly seen in MEDIUM vessel vasculitis

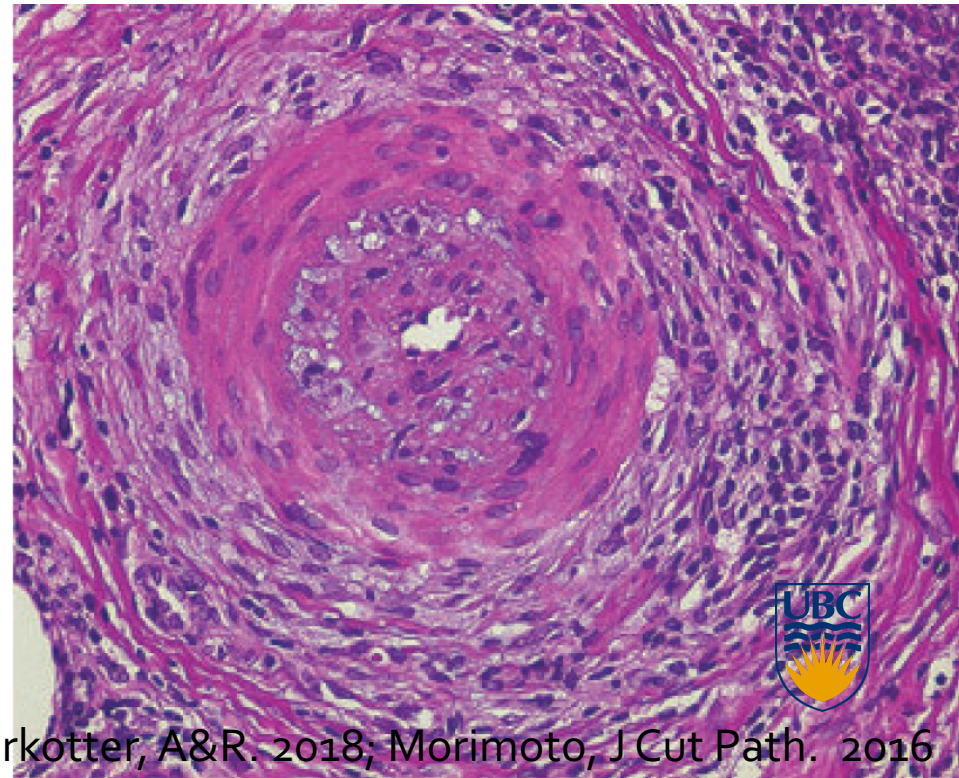
What types of vasculitis routinely affect this vessel size

→ Kawasaki Disease
Polyarteritis Nodosa

Diagnosis

- This is Polyarteritis Nodosa!
- Skin findings consistent with involvement of **medium vessels** are skin infarction, livedo reticularis, intradermal nodules, and deep ulcers
  - Both slides show i**ntimal thickening, lymphocytic infiltration**, **disruption of the internal elastic lamina, pan-arteritis.**
  - **No granulomas**





Sunderkotter, A&R. 2018; Morimoto, J Cut Path. 2016

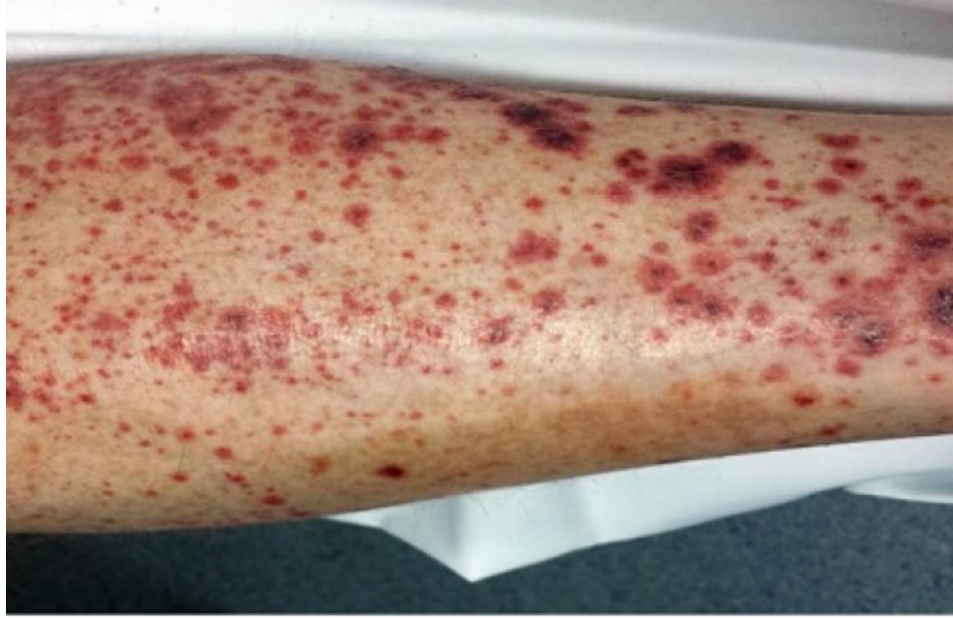
What you should do

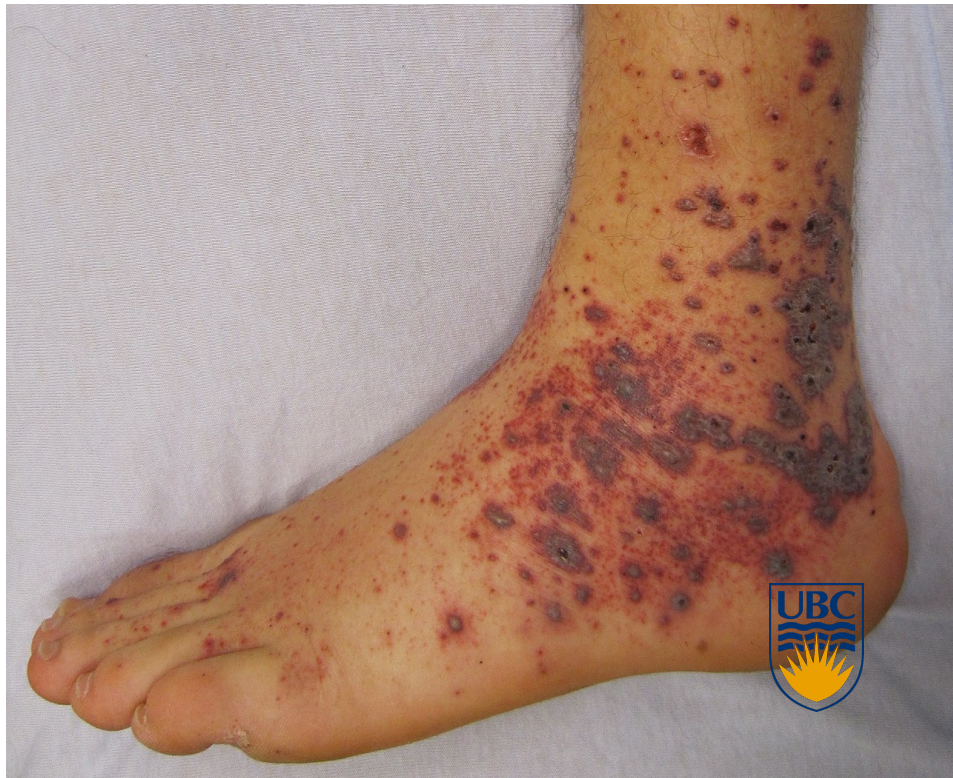
- **Deep punch biopsy of the most proximal lesion.**
- May require deep tissue biopsy/surgical biopsy by Derm or Plastics.
- Does not technically require a second biopsy for Immunofluorescence

- If they have evidence of nerve involvement then nerve +/- muscle biopsy is indicated, but this can be considered by Rheum or Neuro colleagues.

Case #2

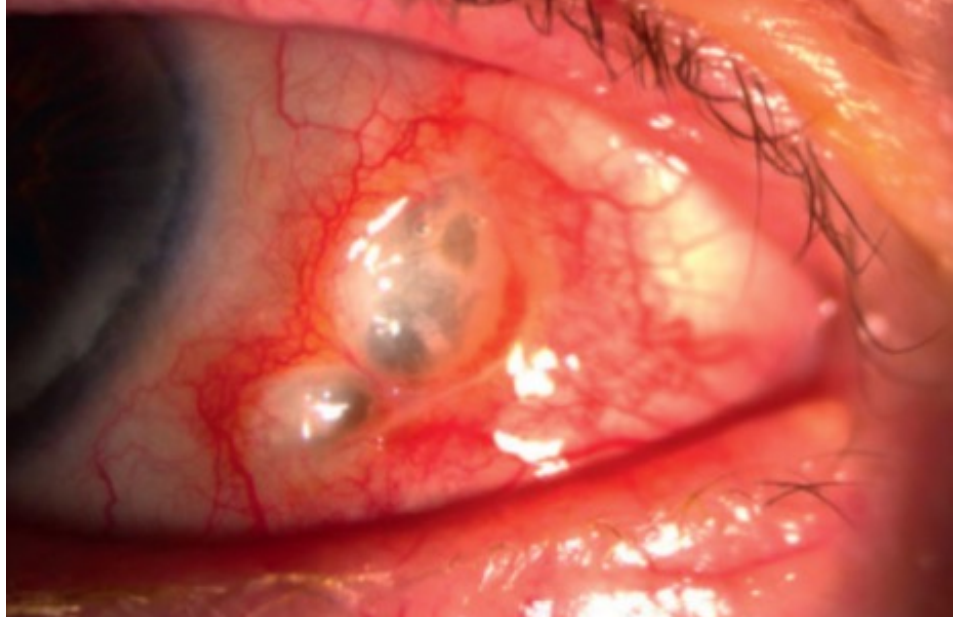
- 38 year old woman
- 3 mo history of malaise and gradual weight loss
- 2 mo history of progressive sinusitis and nasal congestion unresponsive to antibiotics
- 1 mo history of bloody nasal discharge, lower extremity petechial rash.
- Presents to hospital with hemoptysis and boring eye pain.

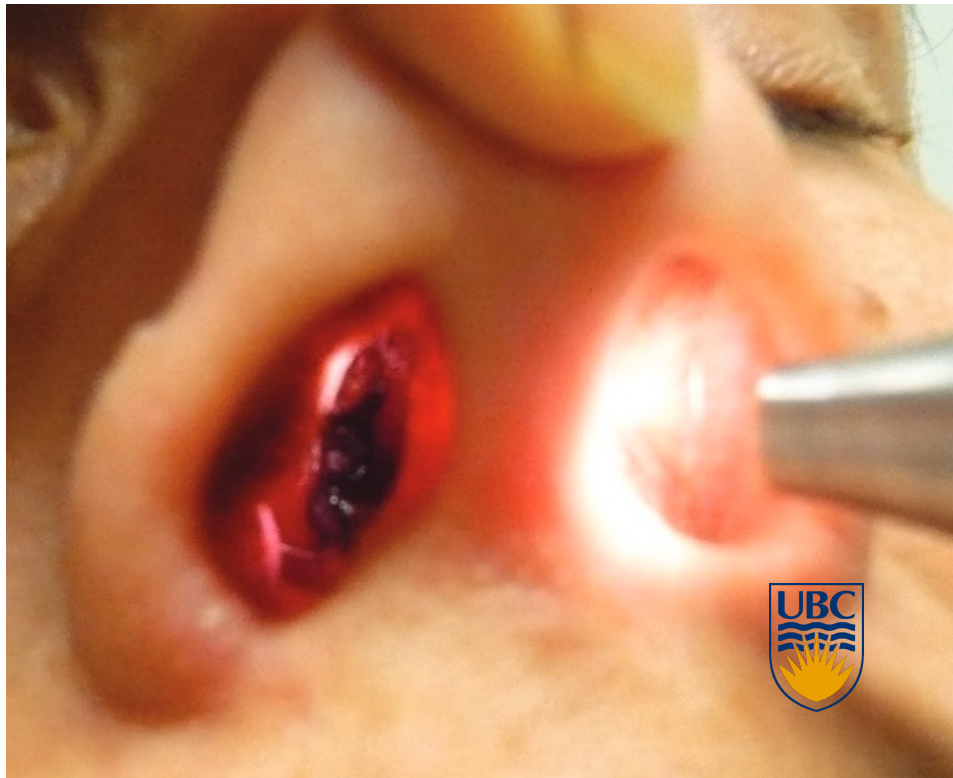




Exam

- HEENT: nasal septal defect. Ulcerating eye lesion
- Cardio: normal heart sounds, no bruits or abnormal pulses
- Resp: course crackles throughout
- Peripheral vascular: normal pulses
- Derm: mixture of palpable pin-point, non-blanching, mildly tender lesions with erythematous/violaceous coalescing macules.



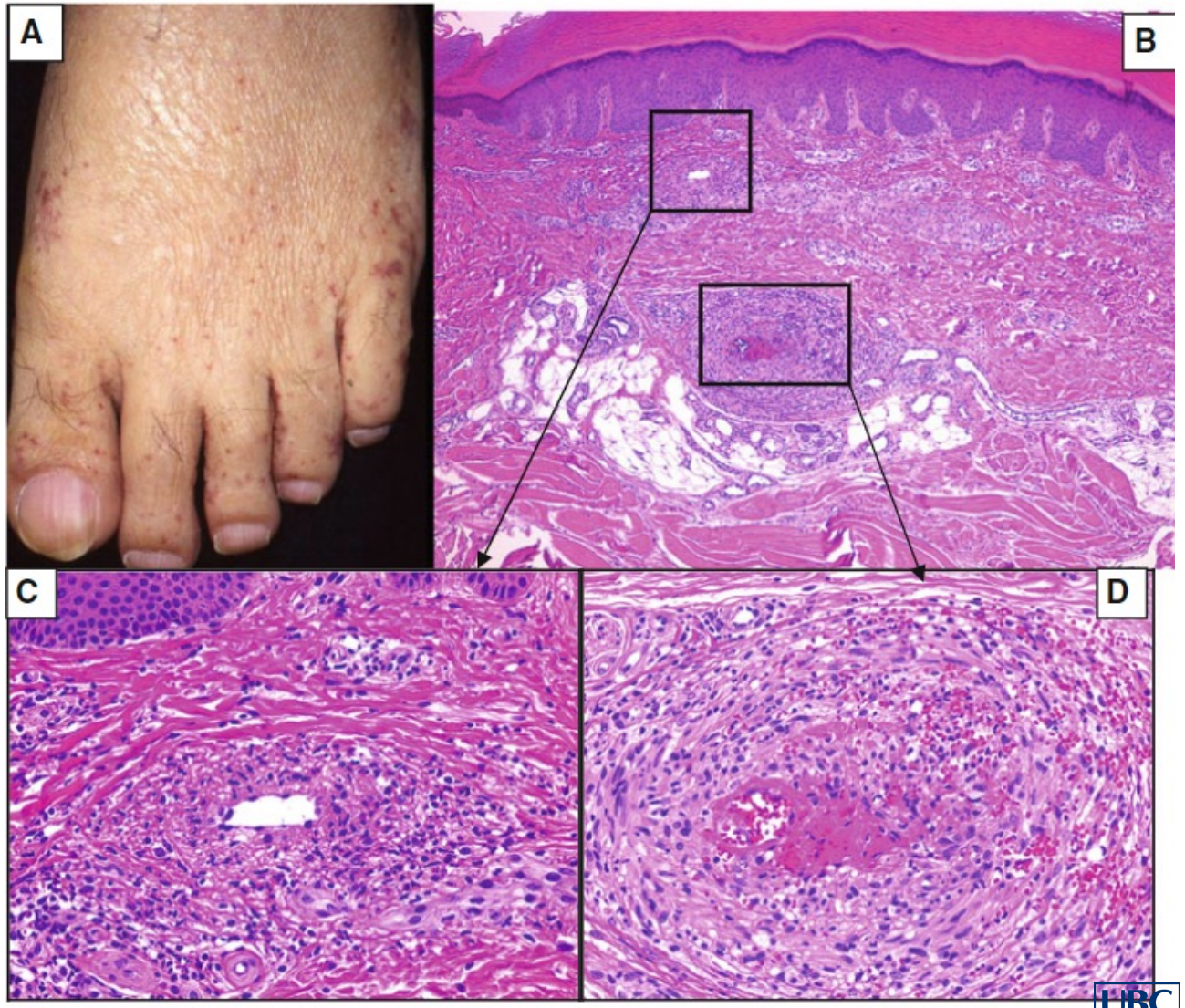


Approach to Diagnosis

What is this rash called?	→	Palpable Purpura Palpable Petechiae
What size vessel causes this rash?	→	Commonly seen in SMALL vessel vasculitis
What types of vasculitis routinely affect this vessel size	→	ANCA vasculitis Immune Complex vasculitis

Diagnosis

- This is Leukocytoclastic Vasculitis in a patient with ANCA vasculitis!
- Skin findings consistent with involvement of **small vessels** include:
  - **Leukocytoclastic vasc.**
  - **Small artery/arteriolar vasculitis**
  - **Granulomatous inflammation**



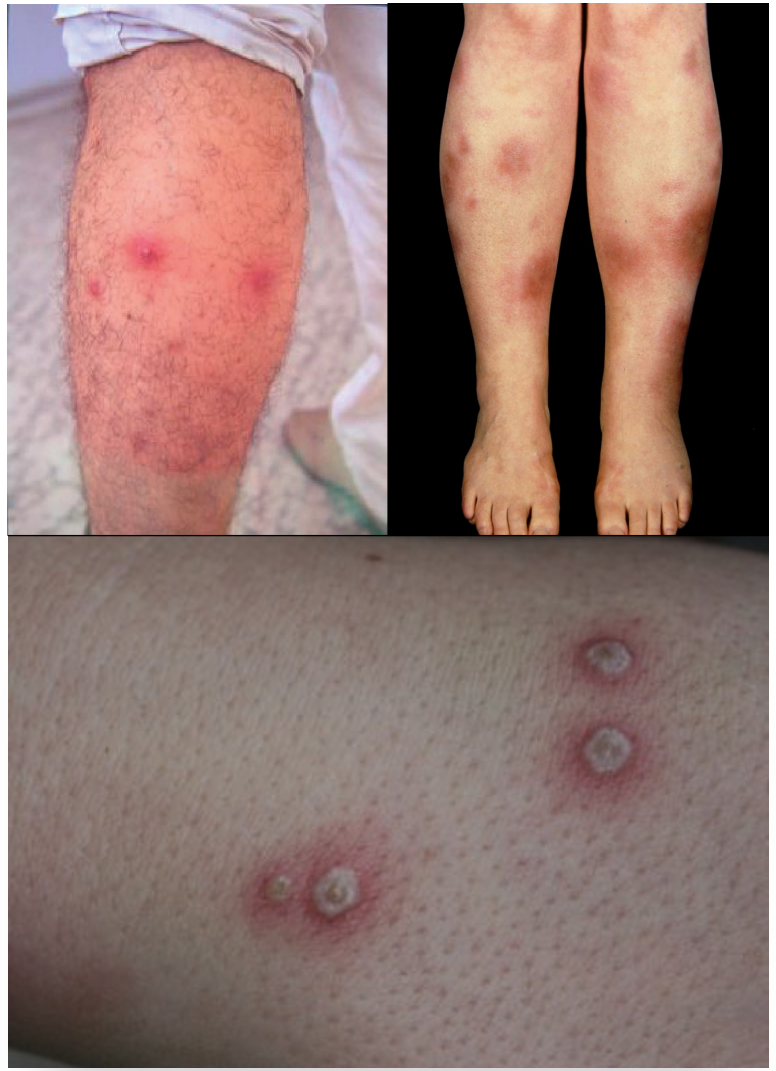
Sunderkotter, A&R. 2018; Chen, Clin Exp Nephrol. 2013

What you should do

- **2 x 3mm punch biopsy of fresh lesions**
- 1 sample for standard H&E staining (the usual formalin fixation is fine)
- 1 sample for Immunohistochemistry
  - This helps us determine if the vasculitis is an Immune Complex Vasculitis vs. an ANCA vasculitis
  - Requires special medium – Michel's or Zeus Medium

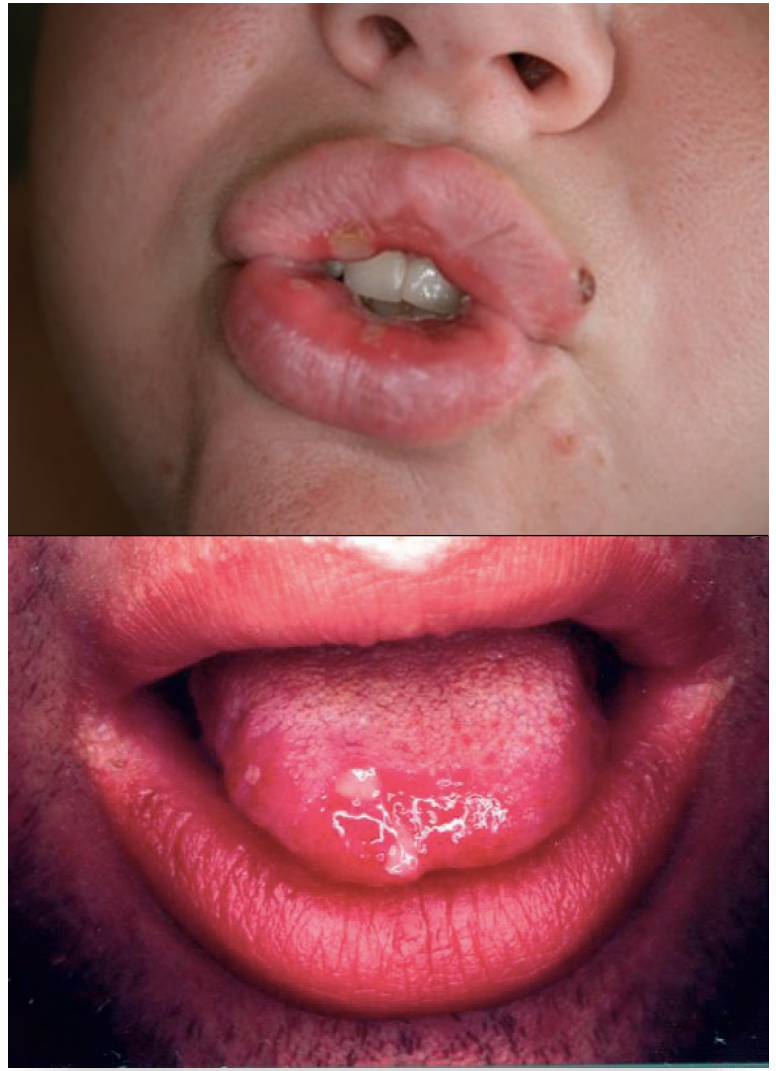
Case #3

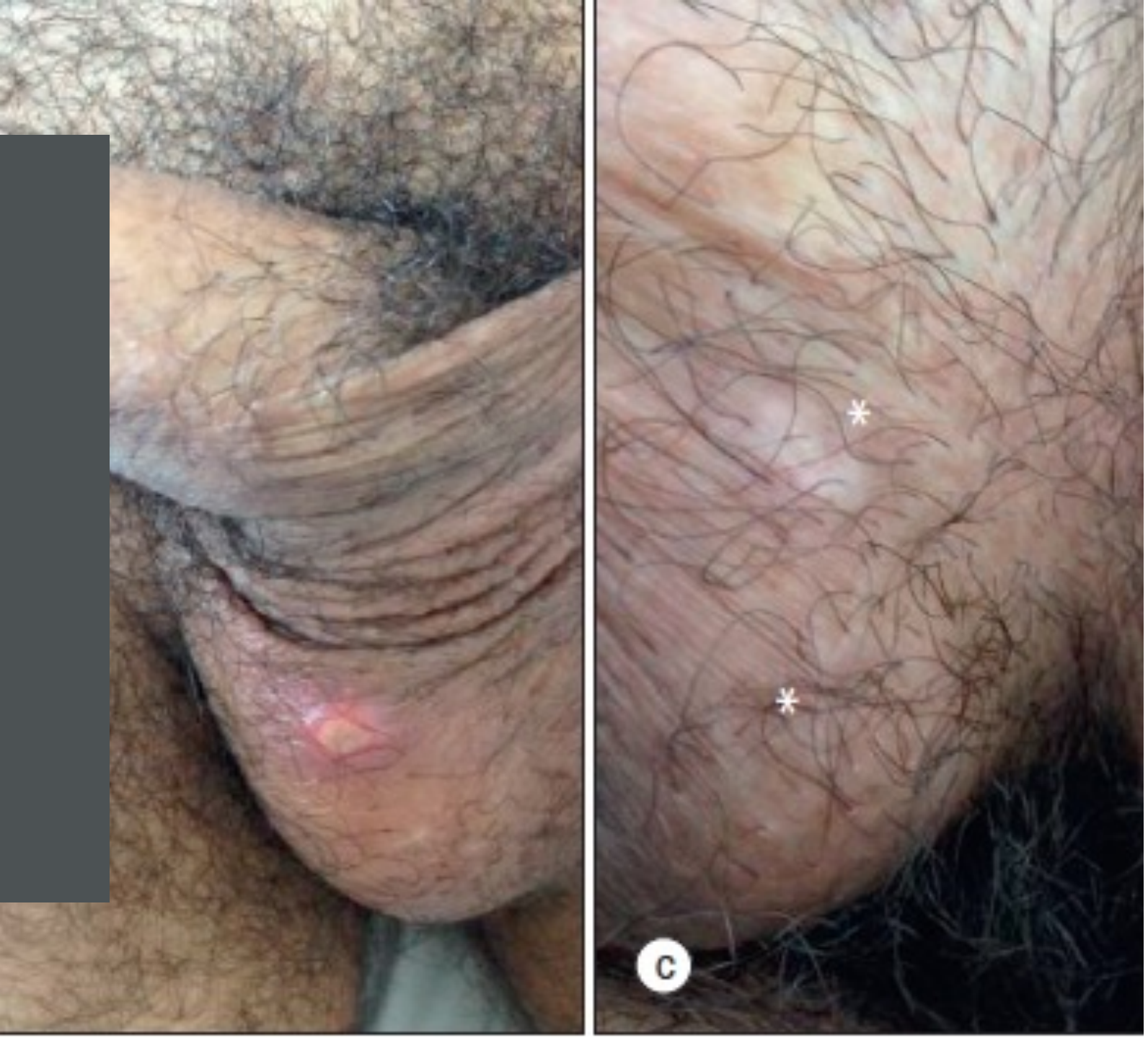
- 35 year old Korean gentleman
- Recurrent papulo-pustular rash and erythematous nodular skin lesions
- Recurrent episodes of painful red eye with blurry vision
- On review of systems you find that he has recurrent aphthous ulcers and genital ulcers



Exam

- HEENT: Apthous ulcers over the inner aspects of the lips, tongue, hard palate
- Cardio: normal heart sounds.
- Resp: Lung fields clear
- Peripheral vascular: some areas of phlebitis
- Derm: Erythematous, tender nodules over the shins bilat. Papulopustular lesions over forearms.
- GU: ulcers over penis and scrotum





Exam

- Genital ulcers
- Scars from past ulcers also identified.
- Spares the glans

Approach to Diagnosis

What is this rash called?

→ Oral and genital aphthous ulcers
Erythema Nodosum-like lesions
Papulo-pustular eruption

What size vessel causes this rash?

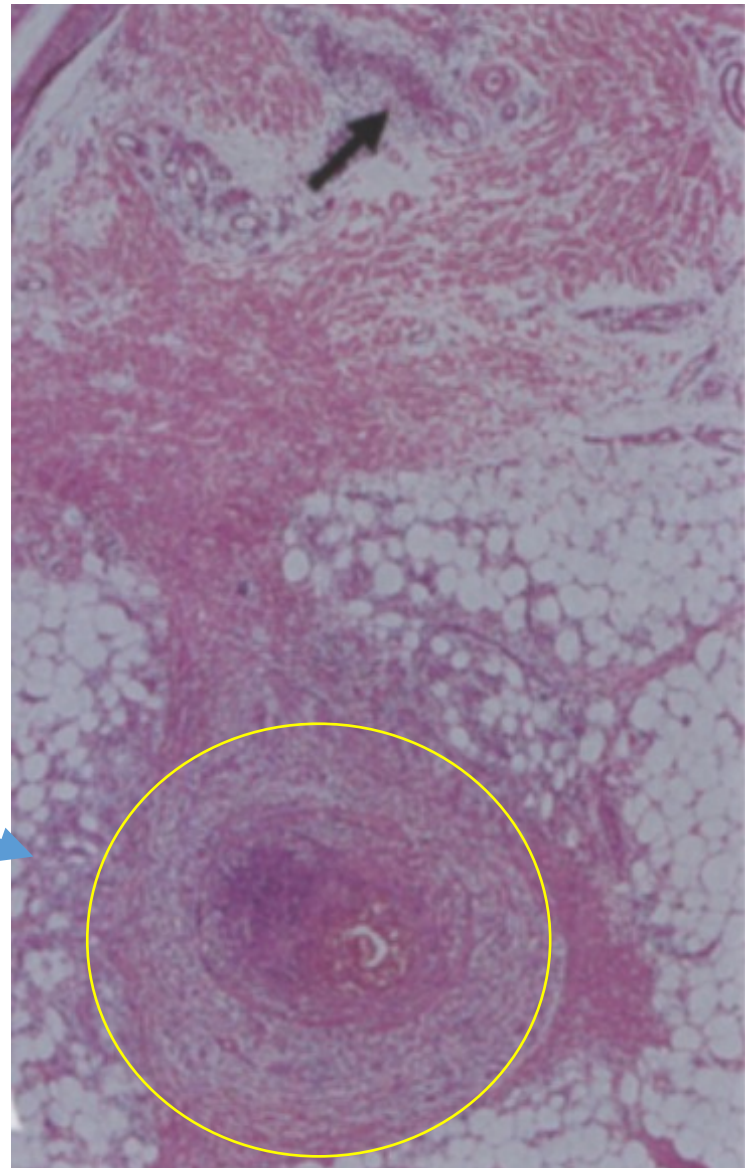
→ A bit of a mixed picture here!

What types of vasculitis routinely affect this vessel size

→ Behcet's?
Inflammatory Bowel Disease?
Celiac?
Sarcoid?

Diagnosis

- This is Behcet's!
- Mucocutaneous findings consistent with involvement of **variably sized vessels** are:
  - **Oral and genital aphthous ulcers**
  - **Erythema Nodosum-like lesions**
  - **Superficial thrombophlebitis**
  - **Papulopustular lesions (acneiform)**



Sunderkotter, A&R. 2018; Chen, J Am Acad Derm. 1997

DDX: Oral Ulcers

- **Rheum** → Lupus, SpA, RA
- **GI** → IBD, Celiac
- **Fever Syndromes** → HIDS, TRAPS, PFAPA
- **ID** → HSV, HIV
- **Derm** → SJS, Pemphigoid, Pemphigus, Lichen Planus
- **Heme** → Cyclic Neutropenia
- **Other** → Medication induced and nutritional deficiency (B12, Iron, Folate)

#1: Recurrent aphthous stomatitis (affects 10% of gen pop)

Recurrent Aphthous Stomatitis

- Not associated with systemic disease
- Ulcers are identical to those of Behcet's
- Affect buccal/labial mucosa, soft palate, tonsils, pharynx and tongue
- Typically, ulcers begin to appear in childhood and improves in adulthood
- May also cause genital or scarring ulcers (Complex Aphthosis)

Keogan, Clin Exp Imm, 2008

DDX: Genital Ulcers

Chancroid – H. Ducreyi

Chancre – Syphilis

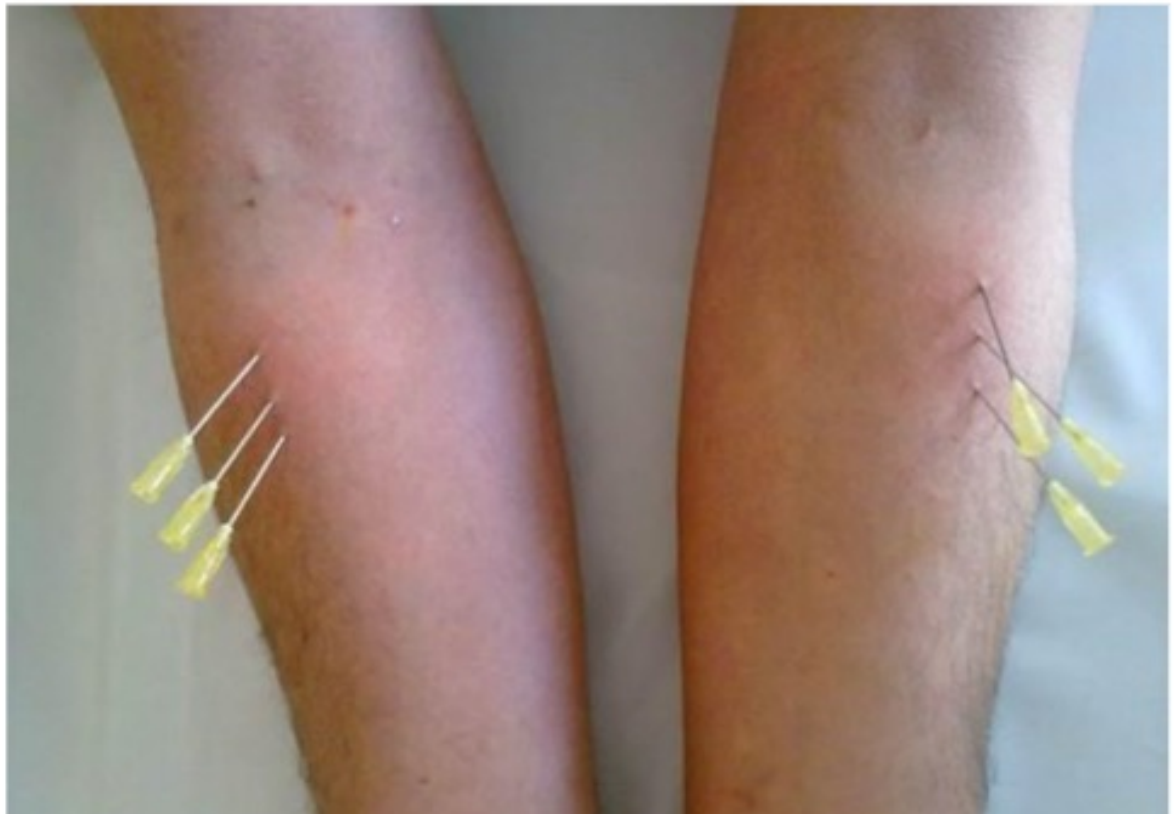
SUMMARY TABLE

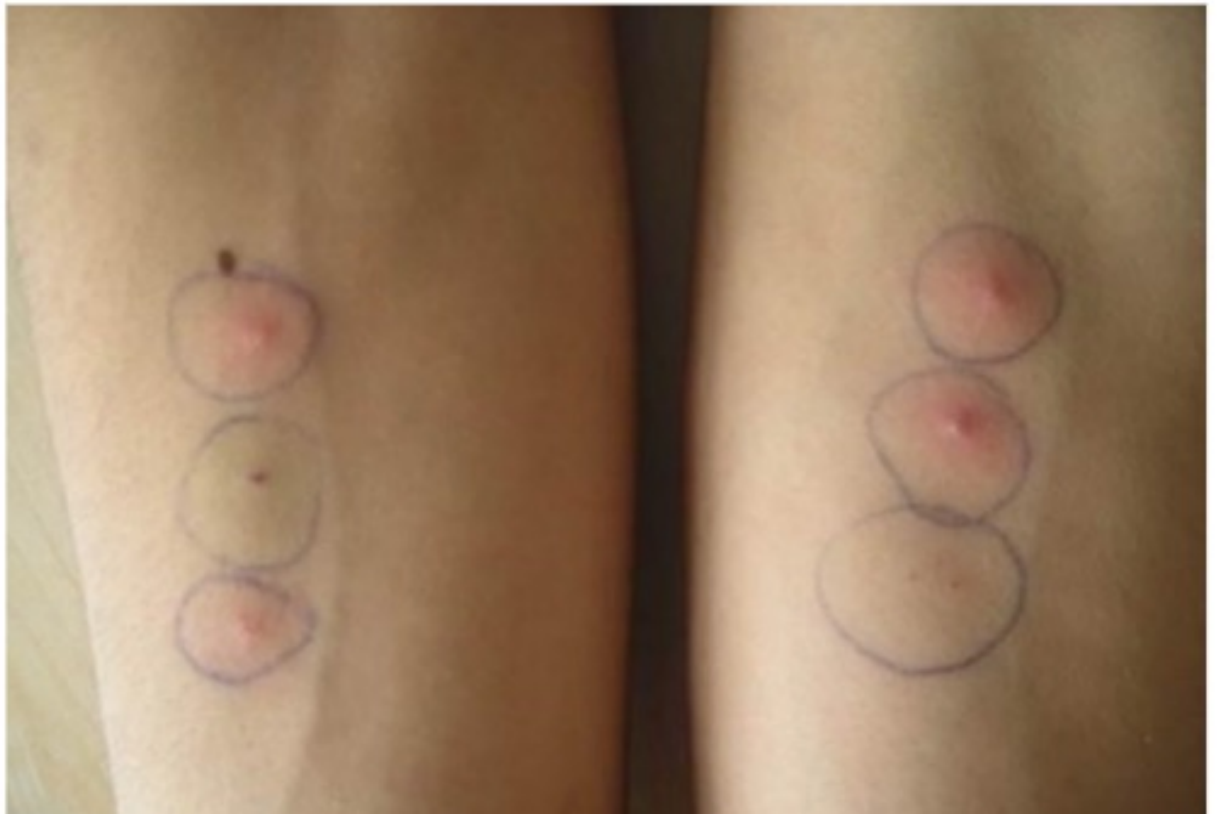
Condition	Characteristics
Aphthous ulcer	Discrete, painful, shallow, circular ulcers with an erythematous edge located on the oral mucosa
Chancroid	Painful necrotizing genital ulcer with an erythematous base and ragged edges; associated painful lymphadenopathy progressing to abscesses
Herpes labialis	Painful vesicular lesions at the vermilion border
Pemphigus vulgaris	Multiple irregularly shaped, painful ulcers on the oral mucosa that rapidly progress to ulceration
Primary syphilis	Firm ulcer with raised border and mild to no pain, sometimes with regional painless lymphadenopathy

- Lake, Am Fam Phys, 2018

What you should do

- Lesional skin biopsy of Erythema Nodosum-like lesion.
- Immunofluorescence not necessary
- No need to biopsy the ulcers unless concerned about malignancy/infection → these are indistinguishable from idiopathic oral aphthous ulcers.





Pathergy Testing

- 6 x 20-G hypodermic needle inserted into forearm at 45 degrees to 2mm below skin
- Reassess 24-48 hours later to look for 2mm erythematous papulopustular lesion
- **DDx**: Sweet Syndrome, Pyoderma Gangrenosum

Keogan, Clin Exp Imm, 2008; Gul, Rheumatology, 2019 ed


Questions

Thank you!

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