

VASCULITIS

Robert L. DiGiovanni, DO, FACOI

robdsimc@tampabay.rr.com

Disclosures

- **NONE**

Topics to be discussed

- Introduction
- Pathogenesis
- ANCA patterns
- ANCA associated vasculitis
- Non-ANCA associated vasculitis
- Miscellaneous

Vasculitis

- Clinicopathologic process characterized by inflammation of and damage to blood vessels.
- Vessel lumen is usually compromised → leading to possible ischemia and necrosis.
- This also leads to increased cytokine production and inflammation.
- Can be confined to one single organ (i.e skin), or it may simultaneously involve several organ systems.
- The distribution of affected organs may suggest a particular vasculitic disorder, but significant overlap is observed.
- It is often a serious and sometimes fatal disease that requires prompt recognition and therapy

Pathophysiology

- Likely that a number of factors are involved in the ultimate expression of a vasculitis syndrome.
 - Genetic predisposition
 - Environmental exposure
 - Regulatory mechanisms associated with immune response to certain antigens

Conditions that can mimic vasculitis

Infectious ds:

- Bacterial endocarditis
- Disseminated gonococcal infection
- Pulmonary histoplasmosis
- Coccidioidomycosis
- Syphilis
- Lyme ds
- Rocky Mountain spotted fever
- Whipple's ds

Coagulopathies/thrombotic microangiopathies

- Antiphospholipid antibody syndrome
- Thrombotic thrombocytopenic purpura
-

Neoplasms

- Atrial myxoma
- Lymphoma
- Carcinomatosis

Drug toxicity

- Cocaine
- Amphetamines
- Ergot alkaloids
- Arsenic

Sarcoidosis

Atheroembolic ds

Goodpasture's syndrome

Amyloidosis

Migraine

Classification

Large-sized Vessels:

- Giant Cell Arteritis
- Takayasu's Arteritis

Medium-sized Vessels

- Polyarteritis Nodosa
- Kawasaki's Disease
- Primary Central Nervous system vasculitis

Classification

Small-sized Vessels

ANCA-Associated

- Granulomatosis with polyangiitis (Wegener's)
- Microscopic Polyangiitis
- Eosinophilic granulomatosis with polyangiitis (Churg-Strauss Syndrome)

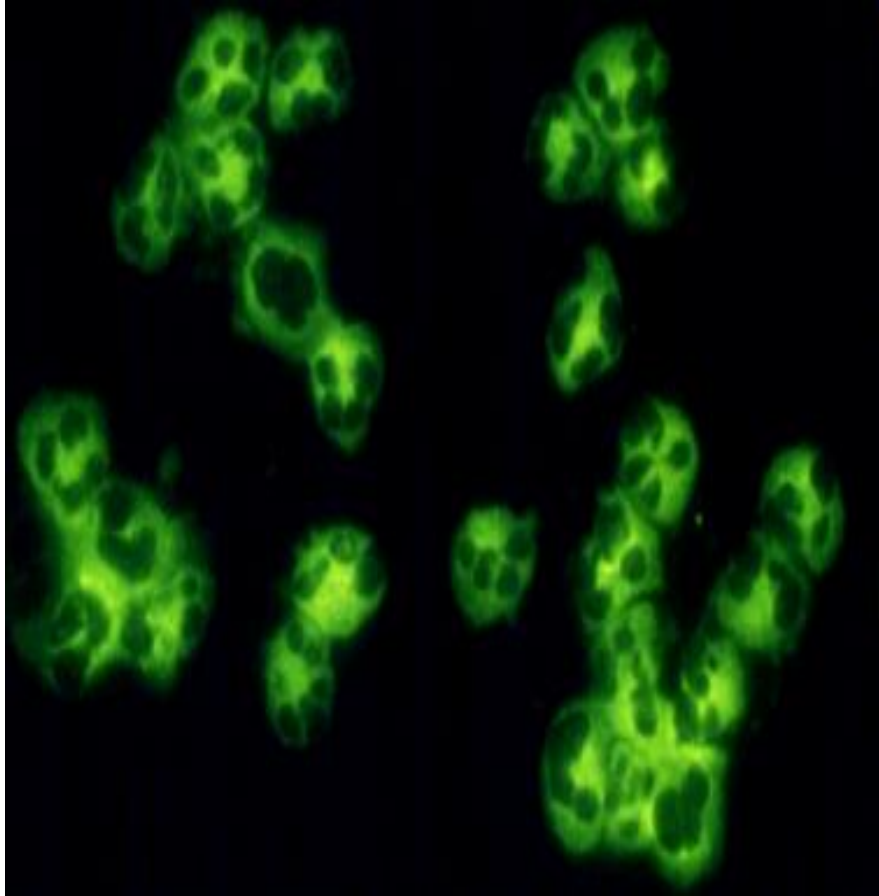
Immune-Complex mediated:

- Henoch-Schonlein purpura
- Essential cryoglobulinemic vasculitis
- Hypersensitivity vasculitis
- Vasculitis secondary to connective tissue disease
- Vasculitis secondary to viral infection

ANCA-associated antibodies

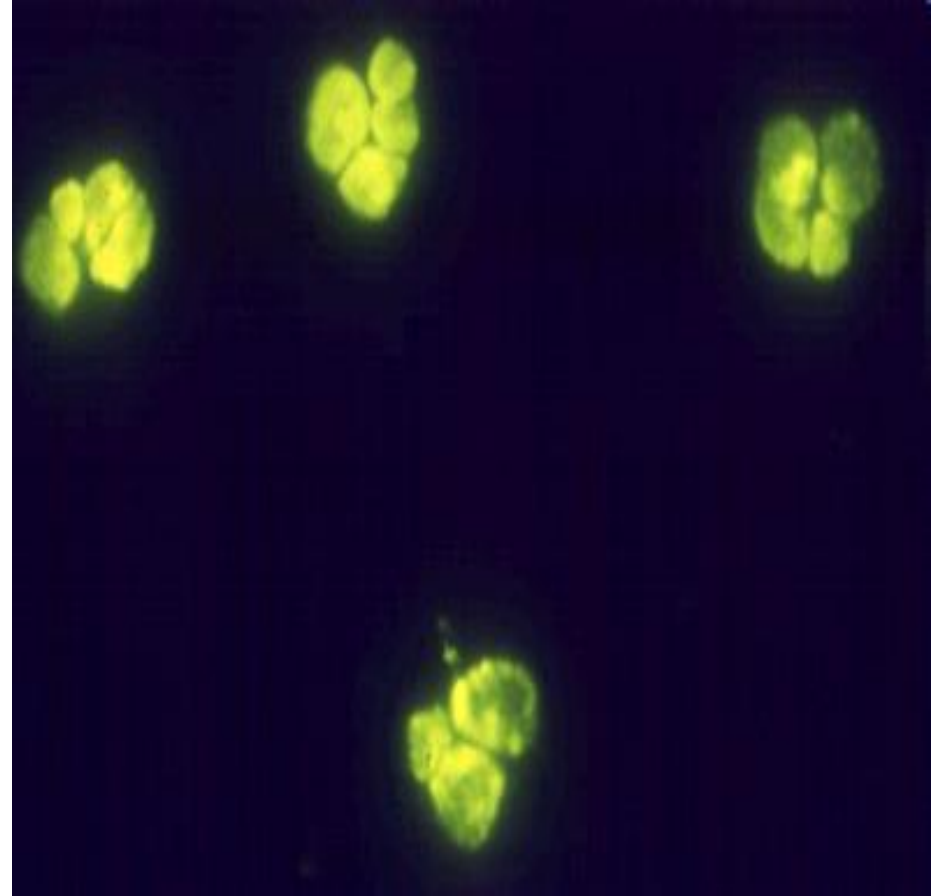
- Directed against certain proteins in the cytoplasmic granules of neutrophils and monocytes.
- Two patterns of ANCA:
 - **Cytoplasmic (C-ANCA)**
 - Major target is Proteinase-3 (PR-3)
 - **Perinuclear (P-ANCA)**
 - Major target is the enzyme myeloperoxidase (MPO).

C-ANCA



There is heavy staining in the cytoplasm while the multilobulated nuclei (clear zones) are nonreactive.

P-ANCA



Staining is limited to the perinuclear region and the cytoplasm is nonreactive.

More on P-ANCA

- P-ANCA can be associated to certain medications (drug-induced) that include:
 - Hydralazine, propylthiouracil, minocycline.
- P-ANCA pattern or atypical pattern has been associated with rheumatic diseases:
 - inflammatory myopathies, reactive arthritis, APS, autoimmune GI disorders, such as ulcerative colitis or chrons ds, also cocaine, infections.
- Typically anti-MPO antibody is helpful and if present, it is more suggestive of true vasculitis.

Churg-Strauss syndrome (EGPA)

- Allergic angiitis and granulomatosis.
- Characterized by asthma, peripheral and tissue eosinophilia, extravascular granuloma formation, and vasculitis of multiple organ systems.
- Uncommon ds with estimated annual incidence of 1-3/ 1,000,000.
- Can affect any age, except infants with mean age at onset at 48y/o.
- Female:male 1.2 :1

Churg-Strauss syndrome clinical presentation

- Fever, malaise, anorexia, weight loss (**constitutional symptoms**),
- **Most predominant: pulmonary:** severe asthmatic attacks with presence of pulmonary infiltrates.
- **Mononeuritis multiplex:** second most common manifestation (up to 72% pts).
- **Allergic rhinitis and sinusitis (up to 61% pts).**
- **Heart ds (14% pts).**
- **Skin lesions (51%):** purpura, cutaneous and subcutaneous nodules.
- **Kidney:** less common and generally less-severe than of WG or MPA.

Labs:

- Eosinophilia (>1000 cells/uL in >80%), elevated ESR, fibrinogen, Alpha2-globulins found in >81%. And then organ specific findings.
- About 48% pts have +ANCA, usually anti-MPO ab.

Churg-Strauss syndrome

Treatment

- Prognosis is poor without treatment, with reported 5-year survival of 25%.
- With treatment, prognosis is favorable, about 72%.
- Myocardial involvement is the most frequent cause of death and is responsible for 39% of pts' mortality.
- Treatment is with glucocorticoids
 - If persistent high doses of glucocorticoids are needed, then cyclophosphamide or other immunomodulatory agents are used.

Wegner's granulomatosis (GPA)

- Characterized by granulomatous vasculitis of the upper and lower respiratory tracts together with glomerulonephritis.
- Prevalence: 3/100,000,
- Extremely rare in blacks compared to whites.
- Male: female 1:1.
- 15% pts are <19 y/o, mean age of onset is approximately 40y/o.
- Rarely occurs before adolescence

Wegner's granulomatosis pathogenesis

- Necrotizing vasculitis of small arteries and veins together with granuloma formation.
- **Lung:**
 - multiple bilateral nodular cavitary infiltrates (on biopsy almost always show necrotizing granulomatous vasculitis).
- **Upper airway:**
 - sinuses and nasopharynx reveal inflammation, necrosis, granuloma formation, with or without vasculitis.
- **Kidneys:**
 - earliest form presents with focal and segmental glomerulonephritis that may evolve into rapidly progressive crescentic glomerulonephritis.
 - Granuloma formation is rarely seen on renal biopsy.
 - No immune complex deposition is found.

Wegner's granulomatosis

Clinical presentation-1

Upper airway (95% pts):

- paranasal sinus pain and drainage, purulent or bloody nasal discharge
- nasal mucosal ulceration
- nasal septal perforation → can lead to saddle nose deformity
- serous otitis media from eustachian tube blockage
- subglottic tracheal stenosis from active ds or scarring in up to 16% of pts (can lead to severe airway obstruction).

Lower airway (85 to 90%):

- Cough, hemoptysis, dyspnea, chest discomfort (present in 85-90%).
- Endobronchial ds (active or as a result of fibrous scarring, can lead to obstruction with atelectasis).

Eye involvement (up to 52%): may range from mild conjunctivitis to dacryocystitis, episcleritis, scleritis, granulomatous sclerouveitis, ciliary vessel vasculitis, and retroorbital mass lesions, leading to proptosis.

Wegner's granulomatosis saddle nose deformity



Wegner's granulomatosis ground glass opacities and cavitory nodule



Wegner's granulomatosis

Clinical presentation-2

Skin lesions (46% of pts) appear as papules, vesicles, palpable purpura, ulcers, or subcutaneous nodules (biopsy shows vasculitis, granuloma or both).

Cardiac involvement (8% of pts) as pericarditis, coronary vasculitis or cardiomyopathy.

Nervous system manifestations (23%) include cranial neuritis, mononeuritis multiplex, or cerebral vasculitis and/or granuloma.

Renal ds (77% of pts) presents with glomerulitis with proteinuria, hematuria, red blood cell casts, but if untreated, then rapidly progressive renal failure ensues.

Constitutional symptoms

Labs:

- Elevated ESR, mild anemia, leukocytosis, mild hypergammaglobulinemia (mostly IgA class), could have mildly elevated RF, thrombosis.
- 90% of pts have +anti-PR3 ANCA.
- In the absence of active ds, the sensitivity drops to approximately 60 to 70%.

Wegner's granulomatosis

Treatment

- Mortality reaches 90% in 2 years if untreated.
- With proper treatment, more than 75% remission.
- The most effective therapy for life-threatening disease, typically with pulmonary-renal involvement is cyclophosphamide with high dose glucocorticoids
 - Cyclophosphamide-related toxicities include: cystitis (at least 30%), bladder cancer (6%), myelodysplasia (2%), high risk of infertility.
- Following induction of remission: maintenance therapy with methotrexate, azathioprine or cellcept.
- TMP-SMX for PJP prophylaxis and also to prevent upper respiratory relapse.

Wegner's granulomatosis

Treatment

- **For mild ds:** consider methotrexate.
- **For pulmonary hemorrhage:** plasma exchange
- **For subglottic stenosis:** intralesional injection of glucocorticoids in combination with endoscopic dilation may avoid the need for more invasive surgical procedures
- **FDA approved 2011: rituximab** (B-cell depletion anti-CD20 monoclonal Ab) for ANCA-associated vasculitis in non-inferiority study compared to cyclophosphamide

Microscopic polyangiitis

- Pts have equivalent vasculitic lesions to those observed in GPA, but, at least at presentation, do not typically have symptomatic or histologic respiratory involvement.
 - Such individuals are considered to have microscopic polyarteritis.
- ANCA are typically present with anti-MPO ab.
- Absence of granulomatous inflammation differentiates it from GPA.
- Renal lesion is identical to that of GPA.

Microscopic polyangiitis clinical manifestation

- **Constitutional symptoms**
- **Glomerulonephritis occurs in 79%** pts and can be rapidly progressive, leading to renal failure.
- **Hemoptysis** may be the first symptom of alveolar hemorrhage, which occurs in 12% of pts.
- **Mononeuritis multiplex.**
- **GI tract.**
- **Cutaneous vasculitis.**
- Upper airway ds and pulmonary nodules are **not** typically found in microscopic polyangiitis (and if present, suggest GPA).

Labs:

- Elevated ESR, anemia, leukocytosis, thrombocytosis,
- ANCA is present in 75% pts (typically with anti-MPO ab).

Microscopic polyangiitis treatment

- Treatment is similar to GPA, depending on severity.
- 5-year survival rate is about 74%.
- Disease-related mortality occurs usually from alveolar hemorrhage or GI, cardiac, or renal ds.
- Relapse is lower than GPA with about 34% pts relapsing.
- Limited studies. Most information comes from GPA treatment trials.

Difference between GPA and MPA

- On histologic examination, the absence of granulomatous inflammation in MPA.
- Both disorders are typically ANCA-positive, but GPA is primarily associated with PR3-ANCA, while MPA is primarily associated with MPO.
- According to some experts, a lower rate of significant upper respiratory tract involvement in MPA.
- After induction of remission with initial immunosuppressive therapy, a lower rate of relapse in MPA is seen.

Does negative ANCA exclude small vessel vasculitis?

- Up to 40% pts with limited GPA and up to 10% of severe GPA have negative ANCA.
- Up to 30% of MPA and up to 50% of CSS could have negative ANCA

Does increased ANCA titers predict a disease flare?

- Studies have shown that elevations in titers in ANCA do not predict disease flares.
- If a pt was ANCA-positive during a period of active disease, a persistently ANCA-negative status is consistent with, but not absolutely proof of remission.
- Absolute height of antibody titers does not correlate well with disease activity.

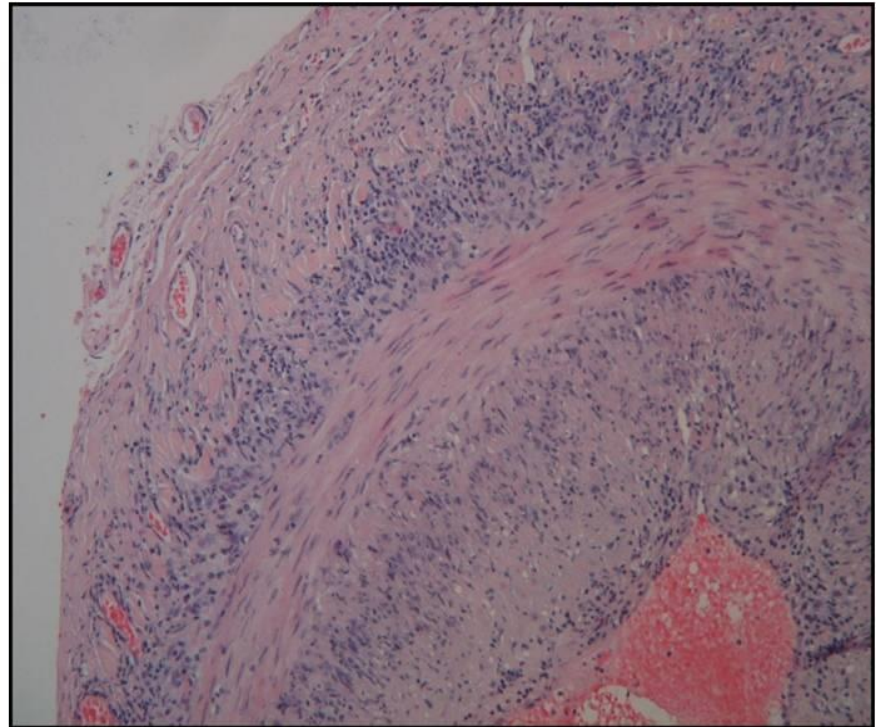
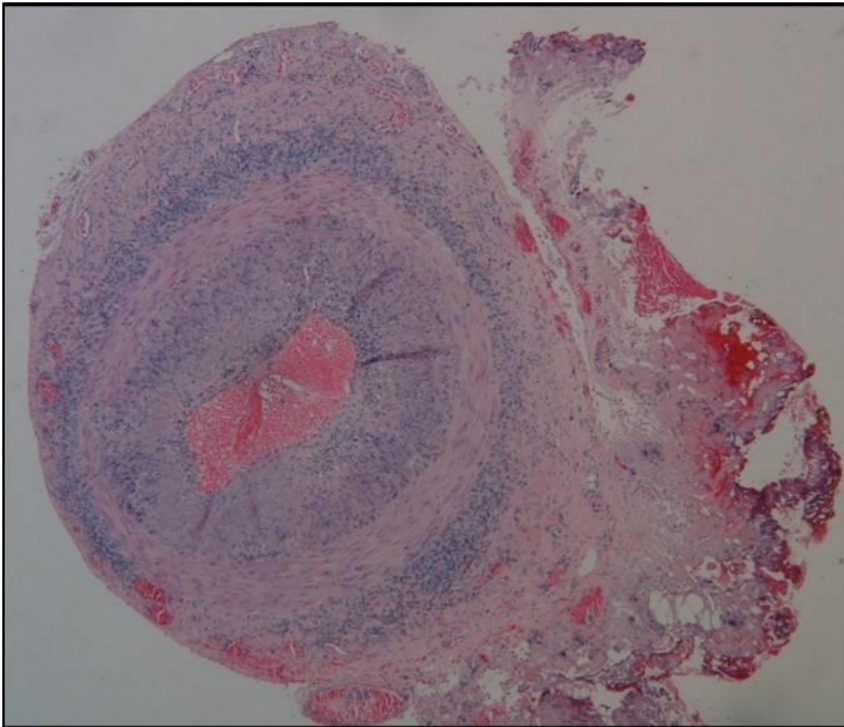
Should tissue biopsy be done?

- It depends on the clinical presentation.
- Predictive value of ANCA testing depends heavily upon clinical presentation of the pt.
- If the presentation is highly suggestive of WG for example, and C-ANCA with anti PR3 ab is present, tissue biopsy is not necessary before initiation of treatment.
- However, the recommendation per ACR states that the biopsy should be obtained whenever possible, and it should be a biopsy of involved organ before starting pt on long-term potentially toxic therapy.

Giant Cell Arteritis

- Affects the second- to fifth-order aortic branches, often in the extracranial aa of the head
 - AKA temporal arteritis, cranial arteritis
- Aged 50+ years, mean age is 72
- Women>men
- Epidemiology
 - Scandinavian countries/N Eur (15-25 cases/100,000)
 - Southern Europeans (6/100,000)
 - Blacks, Hispanics (1-2/100,000)
 - US-Olmsted County, Minnesota (17.8/100,000)

Giant Cell Arteritis

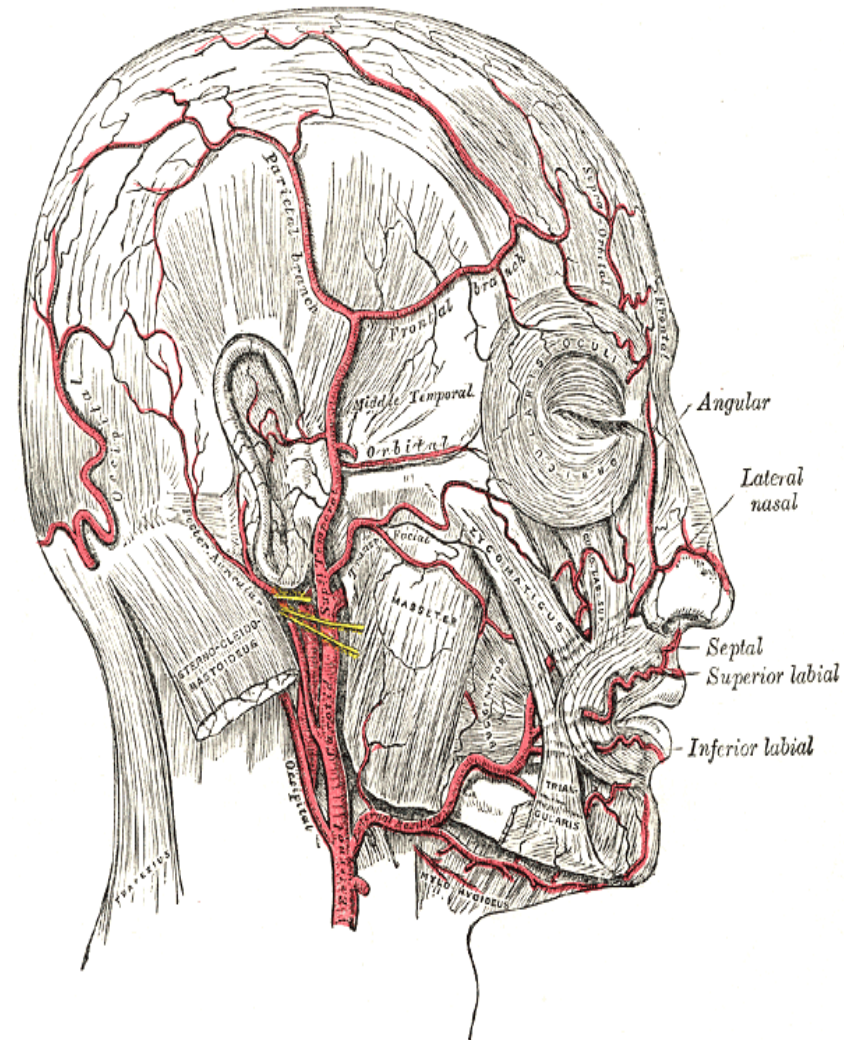


GCA-Clinical Features

- Two major symptomatic complexes
 - Vascular insufficiency
 - Usually occlusion, aorta-arterial wall dilatation
 - Systemic inflammation
- Multiple variants/GCA-PMR syndrome
 - Cranial arteritis
 - Large-vessel GCA/aortitis
 - Fever/wasting syndrome
 - Isolated PMR

Cranial Arteritis

- Headaches- throbbing, sharp, or dull; unilateral or back of head
- Scalp tenderness
- Ischemic optic neuropathy→blindness (sudden, painless, irreversible)
 - Amaurosis fugax-intermittent visual blurring or diplopia with heat, exercise or postural changes
- Jaw claudication-talking, chewing illicit pain (50%)
- CNS ischemia→TIA, CVA (20-30%)
- PMR



Large-vessel GCA/Aortitis

- Large-vessel in 10-15% of pts, prefers carotid, subclavian, and axillary aa > femoral aa
 - Usually lack cranial involvement, 50% TA bx-neg
 - Aortic arch syndrome-claudication of the arms, absent or asymmetrical pulses, parasthesias, digital ischemia
- Aortitis-Aortic valve insufficiency, aortic aneurysm and dissection
 - Risk thoracic aortic aneurysm increased 17-fold
 - Ranges from silent aneurysm to dissection and rupture

Fever/Wasting Syndrome

- Fever and chills (occult presentation-GCA is cause of FUO in up to 15% elderly)
 - Need to exclude infection, malignancy
- Malaise, fatigue, anorexia, weight loss
- Night sweats
- Weakness
- Depression

Isolated PMR

- Pain and stiffness in shoulder and pelvic girdle muscles
- Peripheral synovitis (uncommon)
- Malaise, weight loss, sweats, and low-grade fever
- Elevated ESR and/or CRP, anemia
- 2-3x more common than GCA, same population
- Exclude other diagnoses but if Signs of vascular insufficiency i.e. claudication, bruits over aa, and discrepant BP readings → high index of suspicion for GCA

GCA-Diagnosis

- Temporal artery Bx:
 - False-negative bx in 10% of pts
- Short-term steroids (up to 2 weeks) is unlikely to interfere with results
- Labs: elevated ESR, CRP, IL-6, normochromic or hypochromic anemia, thrombocytosis, elevated Alk phos
 - 25% of patients w/ + temporal bx had normal ESR
- Imaging-angiography (MRA, CTA, Doppler US)

GCA-Treatment

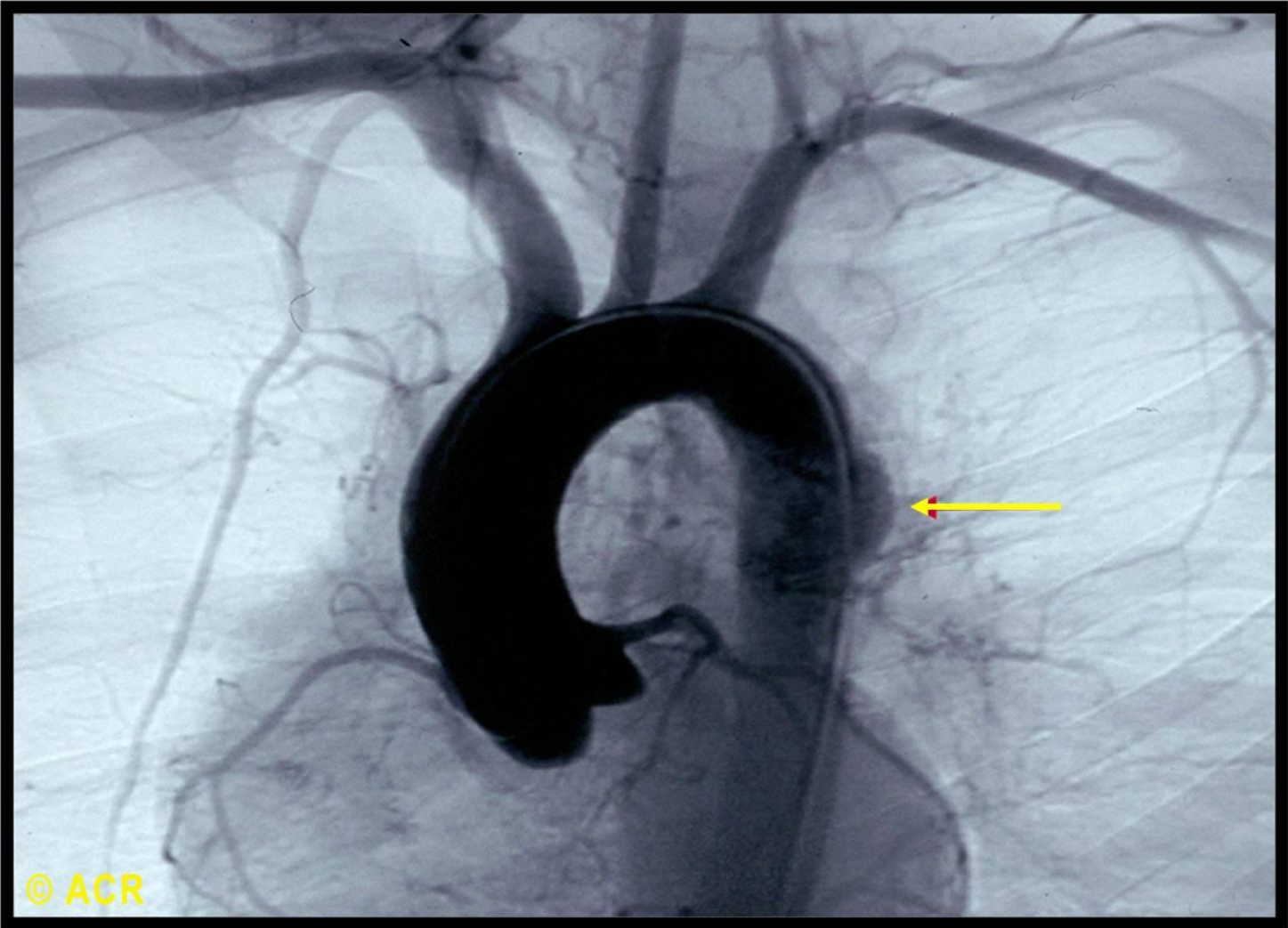
- Glucocorticoids
 - 60mg of prednisone or equivalent
 - Relief within 12 to 48 hours
 - Cannot reverse intimal hyperplasia, may decrease ischemic complications by decreasing edema
 - Once clinically stable, decrease dose by 10% q 1-2wks
- DMARDs, TNF blockers-results vary
- Tocilizumab and Abatacept
- ASA 81-325mg/day may decrease risk of visual loss and CNS ischemia

PMR

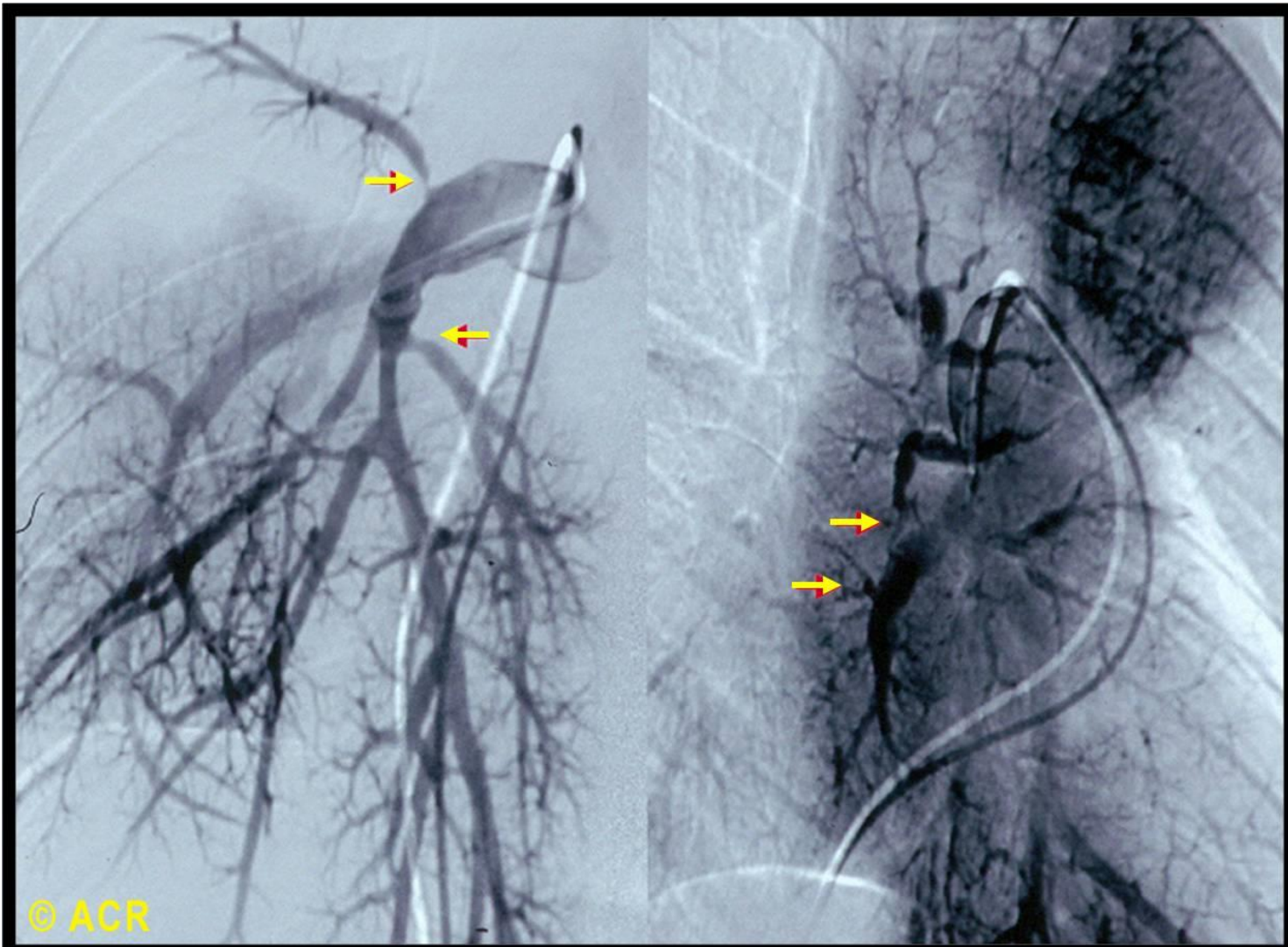
- Very steroid responsive which may help in diagnosis
- Treatment: steroids, 2/3 respond to prednisone < 20mg/day
 - Decrease by 2.5mg q 10-14 days until 8mg then slower tapering may be required
 - Higher required doses may indicate risk of developing GCA
- Prognosis good, disease self-limiting
- Some may develop seronegative RA-type picture requiring DMARDs

Takayasu's Arteritis

- Chronic granulomatous vasculitis characterized by stenosis, occlusion, and sometimes aneurysm of the large elastic arteries, especially aorta and its main branches
 - May also affect coronary and pulmonary arteries
 - AKA Pulseless disease-complete occlusion of upper extremities
 - AKA Aortic arch syndrome
- Primarily affects adolescent girls and young women <40yo, can start >40 esp. in Asians
- Incidence highest in Asia followed by South Americans but occurs in all races



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TA-Clinical Features

- Generalized inflammatory syndrome with fever, night sweats, malaise, anorexia, weight loss, diffuse myalgias
- Late consequences-ischemic complications
 - Carotid and vertebral- dizziness, tinnitus, HA, syncope, CVA, visual disturbances; facial muscle atrophy
 - Brachiocephalic and subclavian-arm claudication, pulselessness, and discrepant blood pressures, bruits
 - Aorta-Ischemic CAD, arrhythmia, CHF, AR
 - Coronary aa-angina pectoralis
 - Renal-renovascular HTN
 - Mesenteric aa-N/V, ischemic bowel disease

TA-Diagnosis

- High index of suspicion-vaso-occlusive disease and systemic inflammation in a young pt
- Dx: Angiography-long, smooth taperings of involved vessels, with collateralization in advanced cases
 - MRI/MRA for serial assessments
 - Doppler US for cervical vessels
 - CTA for aorta and proximal vessels

TA-Treatment

- Some cases TA “burn out” while others have progressive or relapsing/remitting course
- Glucocorticoids: prednisone 40-60mg/day then taper 5mg/day q2wks until 10mg/day
 - Monitor ESR, CRP but 50% of patients had progressing disease despite normal values
- ASA or other antiplatelet agent
- MTX up to 25mg/wk help improve remission and decrease steroids (no randomized trials)
 - Azathioprine, MMF, cyclosporine, TNF-blockers also success but no controlled studies
- Stenotic lesions are irreversible-no tx if collaterals
- Prognosis much improved; death d/t CHF, ischemic HD

Polyarteritis Nodosa

- Systemic vasculitis affects medium-sized arteries that supply the skin, gut, nerve, and kidney, but may affect multiple organs
- Incidence 2-9 cases per million annually
- M=F, all races and ages (mostly 40-60)
- May be p-ANCA positive but PR3- and MPO-ANCA negative
 - Not associated with glomerulonephritis or pulmonary involvement

PAN

- Presents insidiously with nonspecific symptoms
 - Fever, fatigue, malaise, myalgias, arthralgias
 - Cutaneous involvement possible
 - Diagnosis made when other systemic manifestations occur
- Associated w/ Hepatitis B infection and possibly hairy cell leukemia
 - 77 per 1 million in a Hep B-hyperendemic Alaskan Eskimo population

PAN-Diagnosis

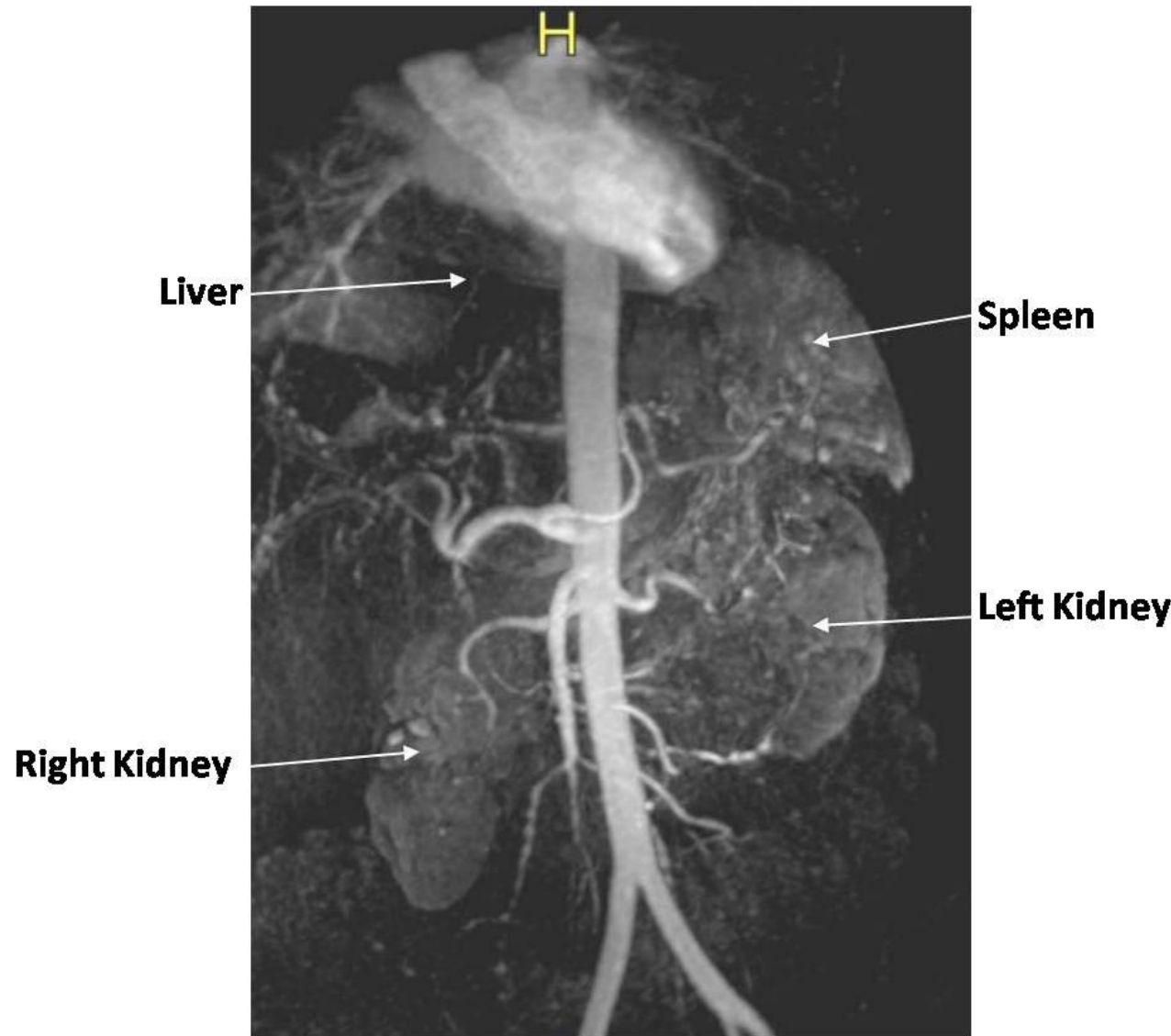
- Based on characteristic symptoms, PE findings, and lab, angiography and pathologic findings
 - Abdominal angiography or biopsy recommended
 - abdominal arteriography reveals strictures and aneurysms (beading)
- Differentiate from ANCA-associated vasculitis, cryoglobulinemia, and Buerger's disease
 - R/O viral hepatitis, bacterial endocarditis, or other embolic disease; CTD-SLE, RA, SSc
- Lab-nonspecific: elevated acute phase reactants, anemia, renal insufficiency
- EMG/NCV-useful for confirming mononeuritis multiplex

PAN-1990 ACR Criteria

- Weight loss >4kg
- Livedo reticularis
- Testicular pain or tenderness
- Myalgias, weakness, or leg tenderness
- Mononeuropathy or polyneuropathy
- Diastolic BP>90mm Hg
- Elevated BUN (>40 mg/dL) or creatinine (>1.5 mg/dL)
- Hepatitis B virus
- Arteriographic abnormality-aneurysms or occlusions
- Biopsy of small or medium-sized vessel-granulocytes or leukocytes in the artery wall
 - +PAN if 3 of 10 criteria are present
 - Sensitivity-82.2%, specificity-86.6%

PAN

- Predelection for certain organs:
 - Arteries to the kidney (70-80%)
 - GI tract (50%)
 - Peripheral nerves (50%)
 - CNS (10%)
 - Skin- livedo reticularis, nodules, ulcerations, ischemia of digits
 - Cutaneous PAN-nodules and ulcers, primarily of lower legs, in crops and very painful



This 37 year old woman presented with low-grade fever, abdominal pain, arthralgia, myalgia, anemia, and elevated ESR and C-reactive protein. There are numerous aneurysms in the hepatic, splenic, renal, celiac, superior mesenteric and inferior mesenteric arteries.

PAN-Treatment

- Glucocorticoids-prednisone 1 mg/kg/day
 - Will treat milder forms of the disease
- Rapidly progressive or organ-threatening cyclophosphamide is added to steroids
 - Daily oral or monthly pulsed IV for 6 to 12 months
 - Maintenance with azathioprine or MTX x 18 mos

Hypersensitivity Vasculitis

- AKA leukocytoclastic vasculitis, hypersensitivity angiitis
- Small-vessel vasculitis localized to the skin or may manifest in other organs, most commonly the joints, GI tract and kidneys
 - Can be acute or chronic
- 10-30 persons per million persons per year
- M=F, whites more common, any age (HSP in children)

LCV-Etiology

- Drugs: antibiotics, NSAIDs, and diuretics; foreign proteins such as streptokinase and those found in vaccines
- Infections: URIs, viral hepatitis, HIV, bacterial endocarditis, HCV (?virus or cryoglobulins)
- Foods, additives
- CVD in 10-15% of vasculitis cases
 - RA, Sjögren syndrome and SLE; may indicate active dz
- Inflammatory bowel disease: Crohn's, UC
- Malignancy (< 1%) lymphoproliferative diseases are more common, esp. hairy cell leukemia; however any tumor type
 - Treatment of malignancy improves
- No cause is identified in up to 50% of patients

LCV-PE

- Cutaneous vasculitis-itching, burning, or pain, or they may have asymptomatic lesions
 - May occur in the absence of systemic disease
- Palpable purpura-most common
 - Round and 1-3 mm or coalesce to form plaques and may ulcerate
 - Symmetric, dependent areas
- Urticarial lesions can burn more than itch
- Other rashes: Livedo reticularis, nodular lesions or ulceration
- Dx: skin biopsy

LCV-Treatment

- Removal of inciting agent, usually resolves in 1-2 weeks
 - May need to stop many meds simultaneously then re-start them gradually
- Reserve glucocorticoids for patients with fulminant systemic disease
- May have relapsing/remitting course but restricted to the skin not requiring immunosuppressive tx

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