VASCULITIS MIMICKERS

Eugene R. Jalbert II, D.O., MBA

DISCLOSURES:

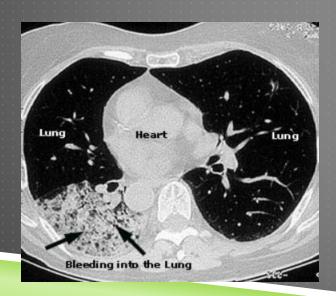
None.

EDUCATIONAL OBJECTIVES:

- Understand what vasculitis mimickers are and the importance of recognizing them.
- 2. Understand how to work-up a patient who you suspect has a vasculitis mimic.
- 3. Understand an appropriate approach to treatment of certain vasculitis mimickers.

DEFINITION OF VASCULITIS:

- "Inflammatory leukocytes in the vessel walls with reactive damage to mural structures."
- ▶ The end result of vasculitis:
 - Aneurysm with bleeding
 - Or, stenosis and ischemia





VASCULITIS:

2012 Revised International Chapel Hill Consensus Conference Nomenclature of Vasculitis:

Large vessel vasculitis (LVV)

Takayasu arteritis (TAK)

Giant cell arteritis (GCA)

Medium vessel vasculitis (MVV)

Polyarteritis nodosa (PAN)

Kawasaki disease (KD)

Small vessel vasculitis (SVV)

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV)

Microscopic polyangiitis (MPA)

Granulomatosis with polyangiitis (Wegener's) (GPA)

Eosinophilic granulomatosis with polyangiitis (Churg-Strauss) (EGPA)

Immune complex SVV

Anti-glomerular basement membrane (anti-GBM) disease

Cryoglobulinemic vasculitis (CV)

IgA vasculitis (Henoch-Schönlein) (IgAV)

Hypocomplementemic urticarial vasculitis (HUV) (anti-C1q vasculitis)

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

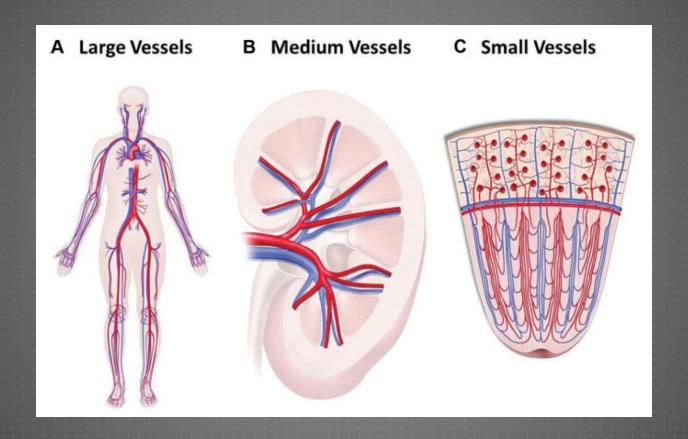
Drug-associated immune complex vasculitis

Drug-associated ANCA-associated vasculitis

Cancer-associated vasculitis

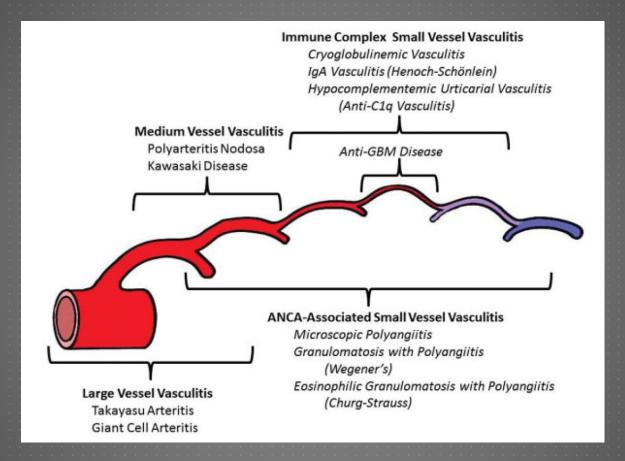
Others

VASCULITIS:



ARTHRITIS & RHEUMATISM
Vol. 65, No. 1, January 2013, pp 1–11
DOI 10.1002/art.37715
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MIMICKERS OF VASCULITIS:

- Consider a mimicker when a condition has "shared clinical, laboratory, radiographic and, sometimes, pathological features" of a vasculitis.
 - ▶ Karen Adams, MD and Simon Carette, MD
- ► Features of vasculitis:
 - **▶** Purpura
 - ► End Organ Damage
 - Vascular aneurysms
 - Vascular stenosis
 - Multi-System Disease

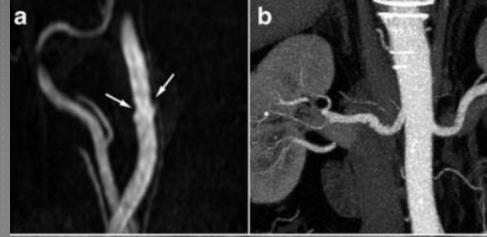
MIMICKERS:

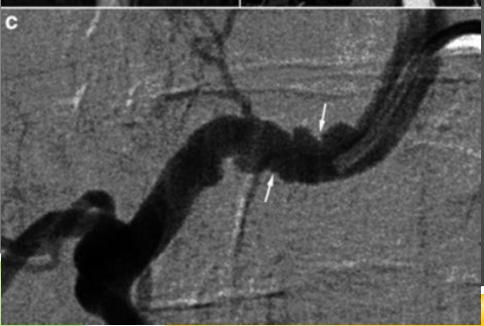
- Fibromuscular dysplasia
- Calciphylaxis
- Segmental arterial mediolysis
- Antiphospholipid syndrome
- Hypereosinophilic syndrome
- Lymphomatoid granulomatosis
- Malignant atrophic papulosis
- Livedoid vasculopathy
- ▶ Immunoglobulin G4-related disease
- Cholesterol Emboli

- ▶ Thromboembolic disease
- Congenital conditions: Aortic coarctation, middle aortic syndrome
- Hereditary Disorders: Marfans,EDS
- Atherosclerotic Disease
- Malignancy
- Infections: HBV, HCV, HIV, PML, Endocarditis
- **Drug Reactions**
- Vaso-occlusive processes: **RCVS**, Drugs
- Systemic Inflammatory Diseases:Sarcoid, Susac

42 YEAR OLD MALE WITH HTN:

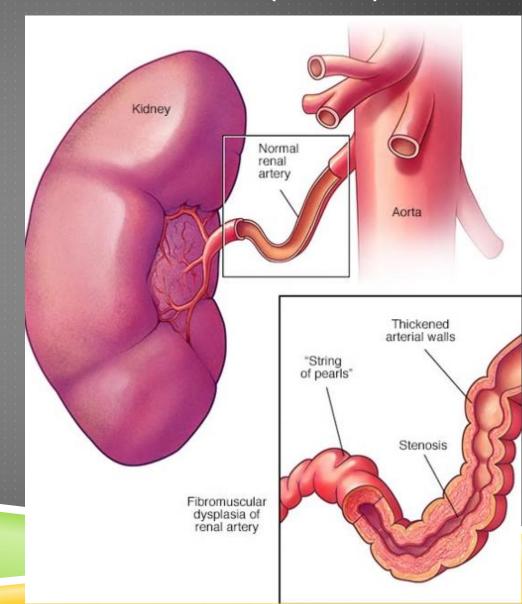
- A Neck MRA.
- B. Renal artery MRA.
- C. Renal artery angiogram.





FIBROMUSCULAR DYSPLASIA (FMD):

- Muscles and fibrous tissues in the blood vessels thicken.
- ▶ Non-Inflammatory.
- ► Non-Atherosclerotic.
- Arterial Stenosis.
- Reduced blood flow leads to organ damage.
- Characteristic findings are described as "string of pearls" or beads on a string appearance.



https://www.mayoclinic.org/diseasesconditions/fibromuscular-dysplasia/symptoms-causes/syc-20352144

FMD:

- ▶ 10% have an affected family member
- Suggesting a genetic association
- Increased risk of stroke, aneurysms and sudden death
- Increased risk of hypertension if renal arteries involved
- Advanced renal artery involvement leads to ischemic nephropathy

FMD:

► Treatment:

- Anti-hypertensives: ACEi/ARBs, Thiazides, CCBs, Beta-Blockers
- ► +/- Revascularization in only certain circumstances (Grade 2C):
 - Young with low likelihood of atherosclerosis.
 - Resistant hypertension despite 3 drugs.
 - Unable to tolerate hypertension drugs or are non-compliant with the medications.
 - Bilateral renal FMD OR unilateral FMD with one functioning kidney with ischemic nephropathy.
 - Hypertensive children with renal FMD.
- Percutaneous intervention > Surgery (Grade 2C).
 - Percutaneous intervention is WITHOUT stents.
 - Surgery: Aortorenal bypass with saphenous vein graft.
- ▶ WARNING: Steroids can harm the vascular wall, aggravating the lesions of FMD.

PAN:

Multiple
microaneurysms in the
upper pole of the right
kidney of a patient with
polyarteritis nodosa.



PAN:

- ► Treatment:
 - Steroids monotherapy if mild
 - Other DMARDS:
 - Azathioprine
 - Methotrexate
 - Cyclophosphamide
 - Mycophenolate
 - Rituximab
 - ▶ If Hep B related: Treat hepatitis B (or hep C) before immunosuppressive medications.
 - For hypertension:
 - ► ACEi and ARBs are preferred (Grade 2B).

FMD VS PAN:



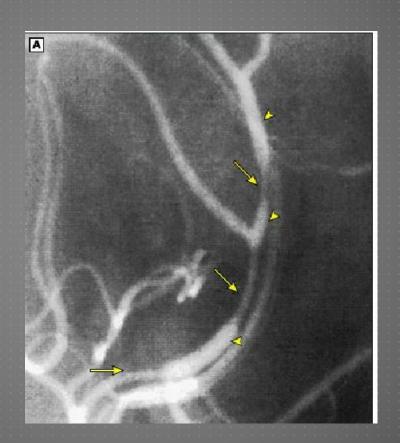


https://consultqd.clevelandclinic.org/giving-fibromuscular-dysplasia-its-due/

https://ucsfmed.wordpress.com/2017/01/25/polyarteritis-nodosa/

38 YO FEMALE WITH SUDDEN ONSET OF THE WORST HEADACHE OF HER LIFE:

- CT and MRI of the brain were normal.
- Cerebral angiogram (Right):



REVERSIBLE CEREBRAL VASOCONSTRICTION SYNDROME (RCVS):

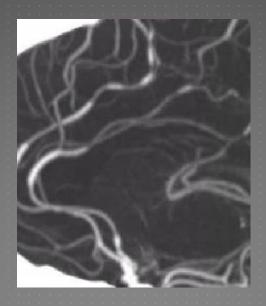
- "Thunderclap" headache with or without focal neurologic deficits.
- AKA:
 - ► Migrainous Vasospasms or angiitis
 - Call-Fleming Syndrome
 - Drug-Induced cerebral arteritis
 - Postpartum cerebral angiopathy
 - Benign angiopathy of the CNS
 - ► Central nervous system pseudovasculitis
- ▶ Mean age of onset: 42 years of age.
- Female to male ratio: 2-10:1, but in children it is more common in males.

RCVS:

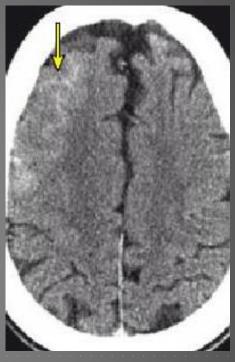
- ▶ Diagnostic Criteria (98-100% specific):
 - Recurrent thunderclap headaches. OR
 - Single thunderclap headaches with normal neuroimaging, border zone infarcts or vasogenic edema. OR
 - No thunderclap headache but abnormal angiography and no brain lesions on neuroimaging.
 - NOTE: Useful because you do not necessarily need imaging.
- Overall prognosis:
 - Benign in 95% of the cases.
 - Rarely causes severe irreversible deficits or death from progressive strokes or edema.

RCVS:

- Cerebral Angiographs:
 - "Sausage on a string" appearance of the circle of Willis and its branches.
 - These resolve spontaneously without therapy.
- ► CT:
 - Can present w/ SAH
- MRI:
 - Can lead to edema
- MRA:
 - Can be normal in 21%

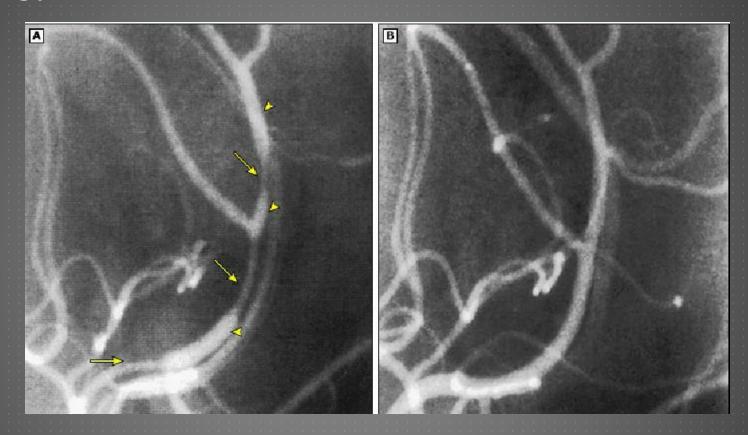






Singhal AB, Hajj-Ali RA, Topcuoglu MA, et al. Reversible cerebral vasoconstriction syndromes: Analysis of 139 cases. Arch Neurol 2011; 68:1005. Copyright © 2011 American Medical Association.

RCVS:

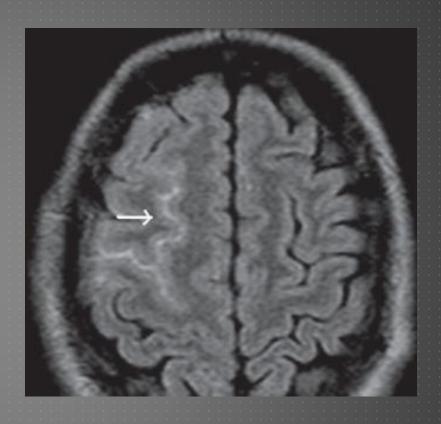


Cerebral angiogram of patient with RCVS. Left showing stenosis and dilation. Right showing resolution after 4 weeks.

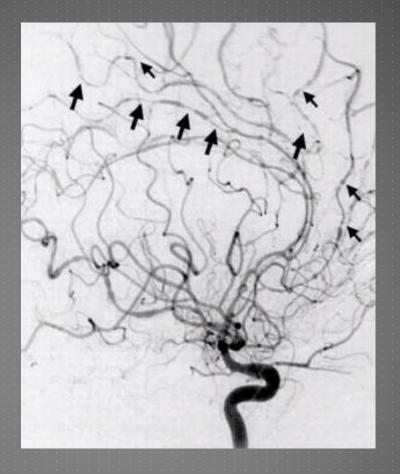
Hajj-Ali RA, Furlan A, Abou-Chebel A, Calabrese LH. Benign angiopathy of the central nervous system: cohort of 16 patients with clinical course and long-term followup. Arthritis Rheum 2002; 47:662

RCVS AND SAH:

- SAH can be aneurysmal or non-aneurysmal.
- ▶ RCVS: SAH is non-aneurysmal.
- Presentations:
 - Aneurysmal SAH: Delayed vasospasms 1-2
 weeks after the event.
 - Non-Aneurysmal SAH: Vasospasms occur at the same time as the SAH.



PACNS:



Typical angiographic findings in a patient with central nervous system vasculitis. *Arrows* point to areas of alternating stenosis and ectasia.

Hajj—Ali RA, Ghamande S, Calabrese LH, Arroliga AC: Central nervous system vasculitis in the intensive care unit. *Crit Care Clin* 2002;18:897–914.)

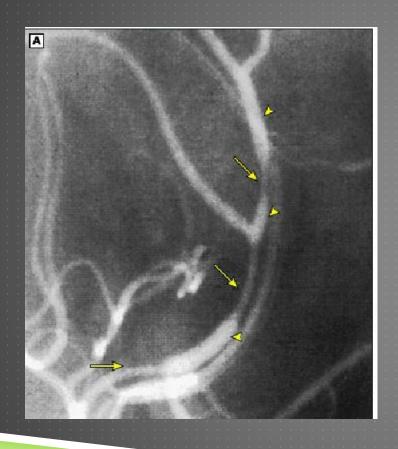
PACNS:

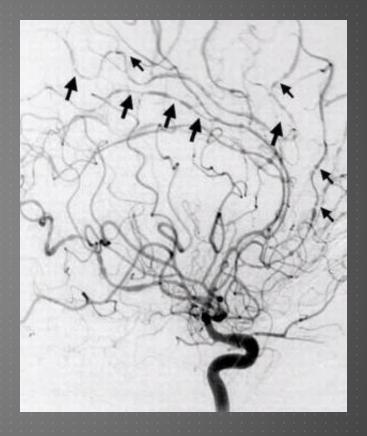
- PACNS: Primary Anglitis of the CNS:
 - Age of onset: 50
 - ► Abnormal CSF in 80-90% of the cases: increased protein/lymphocytes
 - Insidious progression to chronic headaches (not thunderclap).
 - Irregular narrowing of the cerebral arterial bed.
 - Neuroimaging: T2-hyperintence brain lesions, leptomeningeal enhancement and scattered deep infarcts.
 - Biopsy needed to diagnose PACNS definitively and rule out mimics (malignancy/infection)

TREATMENT OF RCVS/PACNS:

- Treatment of RCVS:
 - ▶ BP Control
 - Seizure Control if needed
 - Intra-arterial vasodilators
 - ▶ NOT immunosuppression
- ► Treatment of PACNS:
 - Steroids
 - Cyclophosphamide
 - F/u MRI 4-6 weeks after tx started.

RCVS VS PACNS:





Hajj—Ali RA, Ghamande S, Calabrese LH, Arroliga AC: Central nervous system vasculitis in the intensive care unit. *Crit Care Clin* 2002;18:897–914.)

45 YO MALE PRESENTS TO THE EMERGENCY DEPARTMENT:

- Abd pain and facial swelling.
- ▶ Non alcoholic
- No gallstones
- ▶ No scorpion stings.
- Normal triglycerides.
- Lipase of 4200.
- ► ESR of 102.
- \triangleright CT Abd/Pelvis \rightarrow



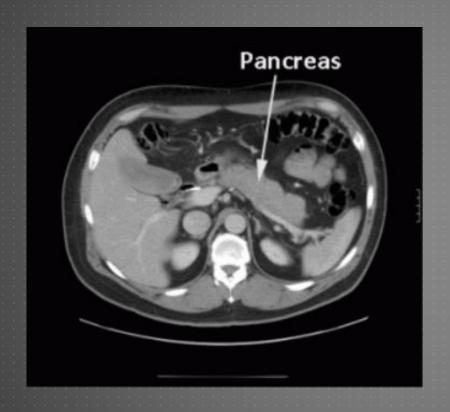
Pancreas

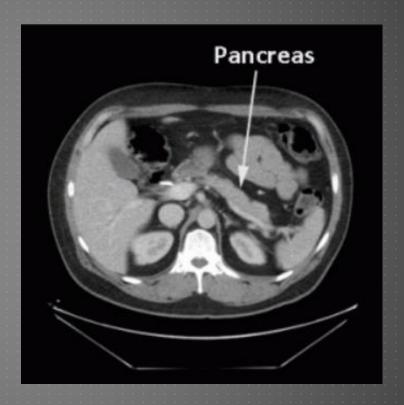
http://images.rheumatology.org/bp/#/search/?q=antiphospholipid&filters=% 257B%257D

https://pancreas.org/physicians/autoimmune-pancreatitis/

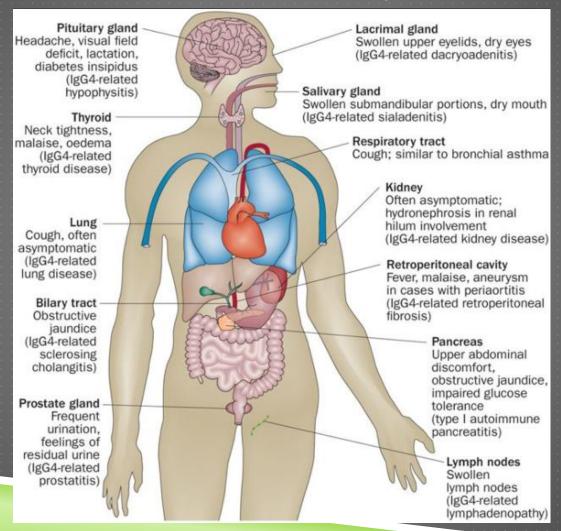
https://doi.org/10.1016/j.ehpc.2015.08.002

3 WEEKS AFTER TREATMENT:





IGG4 RELATED DISEASE (IGG4-RD):

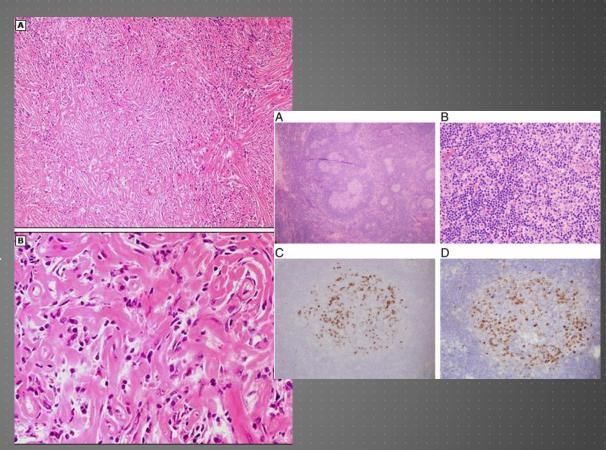


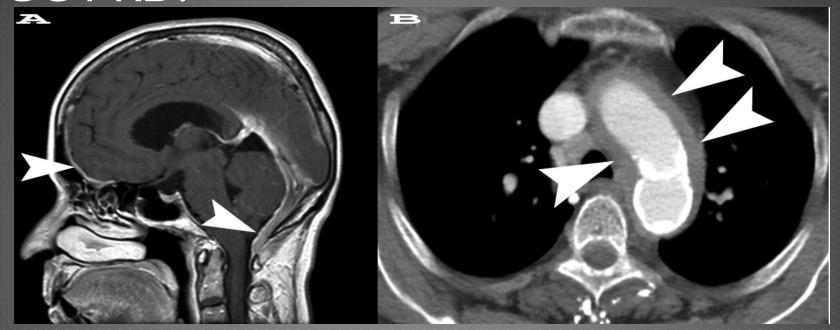
- Several previously unrelated diseases, now viewed as a syndrome/disease with various presentations:
 - Type I Autoimmune Pancreatitis (AIP) and sclerosing cholangitis
 - Mikulicz disease, Kuttner tumor, inflammatory orbital pseudotumor.
 - ► Idiopathic retroperitoneal fibrosis
 - Chronic sclerosing aortitis/periaortitis
 - Riedel's thyroiditis
 - IgG-4 Related interstitial pneumonitis and pulmonary inflammatory pseudotumors.
 - ▶ IgG-4 related renal disease, tubulointerstitial nephritis (TIN).
 - Pachymeningitis

- Diagnostic Criteria (not well established):
 - ► Histopathologic Findings:
 - Dense Lymphoplasmacytic infiltrate
 - Storiform Fibrosis
 - Obliterative phlebitis
 - At least 30-50 IgG4 Cells/HPF for most tissues
 - Some say 10 IgG4 Cells/HPF is adequate for kidney.
 - Serum IgG4 levels should NOT be used to diagnose this disease (to be discussed).

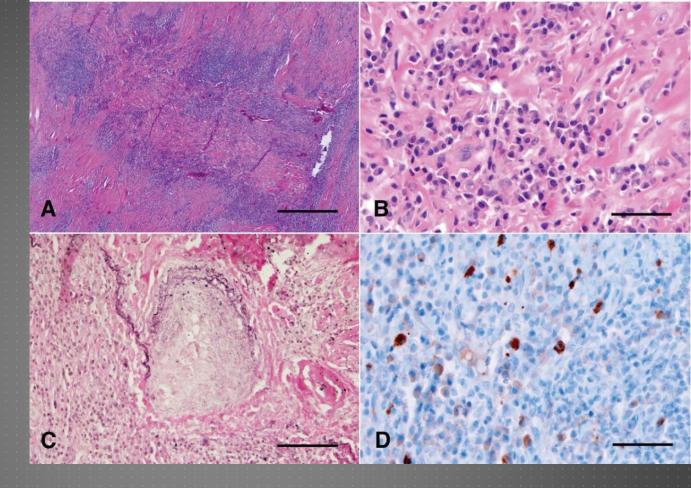
- Diagnosis:
 - ► In a study of 1,510 patients:
 - If, IgG4 was elevated, only 22.4% met the diagnostic criteria for IgG4-RD.
 - ▶ 82.5% of those with IgG4-RD had elevated IgG4.
 - The higher serum level of IgG4 was associated with higher specificity.
 - ► The higher serum level of IgG4 also predicted more severe disease.
 - IgG4 in other conditions: Malignancies, GPA, Castleman Disease
 - Diagnosis largely based on biopsy demonstrating lymphoplasmacytic IgG-4 positive cells.

- Hallmark: Lymphoplasmacytic infiltration of IgG-4 plasma cells and small lymphocytes with or without fibrosis, phlebitis and elevation of peripheral IgG-4.
- Classic findings: Fibrosis has a "storiform" pattern typified by cartwheel appearance of fibroblasts and inflammatory cells with or without eosinophils.





A. Sagittal postcontrast T1-weighted magnetic resonance scan shows diffuse pachymeningeal thickening and enhancement best seen in the anterior and posterior cranial fossa (arrowheads). The anterior cranial fossa arrowhead shows the future site of dural biopsy. The dural thickening had completely resolved on follow-up imaging 6 months after therapy was initiated. B. Axial postcontrast computed tomography image from the chest shows circumferential wall thickening surrounding the aortic arch and proximal great vessels (arrowheads) consistent with aortitis. There is a small amount of hyperattenuation in the aortic wall because of calcification. On followup imaging, the soft-tissue thickening was almost completely resolved.



A. Low-power H&E stained section showing dense inflammatory infiltrate with lymphoid nodules. B. High-power H&E stained section showing plasma cell infiltrate and fibrosis. C. Elastin stain showing obliterative phlebitis. D. IgG4 immunostain highlights increased IgG4-positive plasma cells (in brown) within and adjacent to a lymphoid nodule.

IgG4-related Disease Manifesting as Pachymeningitis and Aortitis SARAH LIPTON, GARTH WARREN, JEFFREY POLLOCK, PASCALE SCHWAB The Journal of Rheumatology Jul 2013

- ► Vasculitis mimic or actual vasculitis?
 - Non-Infectious, Lymphoplasmacytic aortitis and periaortitis
 - ▶ In a North American study of 638 patients who had thoracic aortic resection
 - 9 of the 638 had non-infectious aortitis
 - ▶ 4 of those 9 had lymphoplasmacytic aortitis
 - ▶ 3 of those 4 patients were IgG-4 positive.
 - Conclusion: 0.5% of all cases of thoracic aortitis is from IgG4-RD.
 - Similarly, a Japanese study found that 36% of patients with IgG4-RD had periaortitis or aortitis commonly at the infrarenal portion of the abdominal aorta.
- ► Conclusion: IgG4-RD is in and of itself NOT a vasculitis, but CAN present with vasculitis.
- Proposal to include it in the new Chapel-Hill Consensus.

IGG4-RD:

of TAK or GCA. Isolated aortitis can also be associated with an infection (e.g., syphilis) or systemic disease. For example, some patients with IgG4-related systemic disease develop aortitis as the only vasculitic manifestation (22).

IGG4-RD:

- ► Treatment:
 - Steroids: Prednisone 0.6 mg/kg/day, then taper to off over 2 months.
 - If not responsive to above, consider Rituximab.

28 YO MALE PRESENTS TO THE ED:

- ▶ WBC count of I.2
- ► ANC of 0.8
- Urinalysis with 2+ Proteinuria.
- ▶ UDS + for cocaine

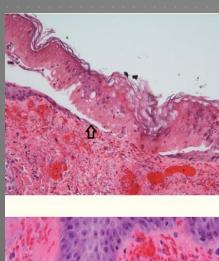


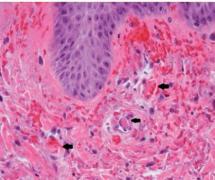


UpToDate Graphic 74436 Version 2.0 UpToDate Graphic 77067 Version 4.0 UpToDate Graphic 58626 Version 4.0

28 YEAR OLD:

- Admitted to the hospital
- On day 10:
 - ▶ pANCA with MPO is positive.
- Skin biopsy:
- Diagnosis?







COCAINE (LEVAMISOLE) VASCULOPATHY:

Levamisole:

- An adulterant in cocaine over 70% of the time.
- ► An anthelminthic agent used to treat parasitic worm infections.
- ► Known to cause positive MPO (p-ANCA), PR3 (c-ANCA) and atypical ANCA
- Nearly all have + MPO, ~50% have + PR3
- ▶ Atypical ANCAs: Human Neutrophil Elastase (HNE) and lactoferrin.
- Causes a vasculopathy associated with gangrenous skin lesions.

Presentation is variable:

- Constitutional symptoms, myalgias, arthralgias
- Leukopenia (neutropenia)
- Abnormal UA: Proteinuria, hematuria, cellular casts.
- Rarely: Pulmonary hemorrhage.

LEVAMISOLE VASCULOPATHY:

► The workup:

- ANCAs: p-ANCA, c-ANCA w/ reflex to MPO/PR3, atypical ANCAs if possible including human neutrophil elastase.
- Antiphospholipid antibody syndrome (APS):
 - Cardiolipin antibodies: Higher incidence in patients with +CL antibodies.
 - ▶ B-2-GP antibodies
 - Lupus anticoagulant
- ▶ CBC: looking for leukopenia/neutropenia
- Urine Drug Screen: Cocaine
- Urinalysis
- Detecting cocaine: Within 3 days of use
- Detecting levamisole is difficult due to short half life (5.6 hours).
- +/- Skin biopsy

LEVAMISOLE VASCULOPATHY:

► Small vessel cutaneous lesions:







UpToDate Graphic 74436 Version 2.0 UpToDate Graphic 77067 Version 4.0 UpToDate Graphic 58626 Version 4.0

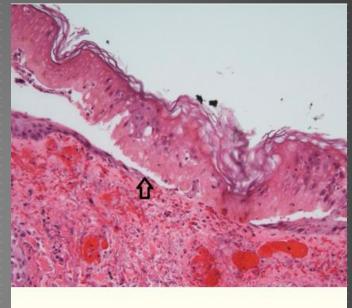
LEVAMISOLE VASCULOPATHY:

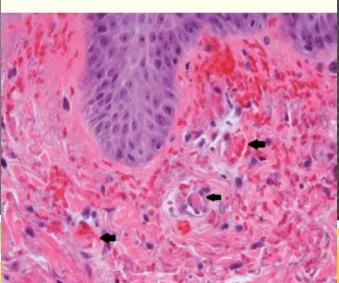
Skin biopsy:

Thrombotic vasculopathy with or without Leukocytoclastic vasculitis.

► Treatment:

- Stop cocaine use
- Usually resolves spontaneously without treatment.
- Takes about 2-14 months to resolve completely.
- In severe cases, immunosuppression is used but this is not substantiated by RCTs.





https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3603736/

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3573092/

IMAGES IN CLINICAL MEDICINE

Midline Destructive Lesions in a Cocaine User

Bianca M.L. Stelten, M.D., and Bart Post, M.D., Ph.D.

March 10, 2016

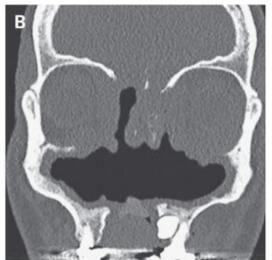
N Engl J Med 2016; 374:969

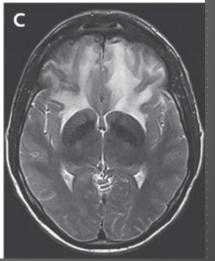
DOI: 10.1056/NEJMicm1503043

Metrics

1 Citing Article







H. S. Füeßl. (2016) Kokain-Loch im Gaumen. MMW - Fortschritte der Medizin 158:9, 33-33.

COCAINE INDUCED MIDLINE DESTRUCTIVE LESIONS (CIMDL):

- Can cause saddle nose deformities that resemble GPA
- Often the patient is ANCA +
- From the cocaine or the levamisole?
- Most are also + for HNE antibodies.
- This can be concerning for GPA (Wegner's) as well:



https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5101010/

NASAL BIOPSIES:

- ▶ In a 1991 study of 17 patients with established GPA:
 - Nasal biopsy was diagnostic in only 53% of the patients.
 - Increased yield with biopsies >5 mm (p = 0.002).
- Classic GPA Nasal biopsy:
 - Necrotizing granulomatous inflammation with small-vessel vasculitis
 - ► This is only seen in **10-20% of nasal biopsies**.
- Conclusion: Low yield but should still be done.

43 YO FEMALE WITH R-SIDED HEMIPARESIS AND RASH:

- ightharpoonup Rash ightharpoonup
- ▶ Ultrasound: +for DVT
- ▶ Plts of 90
- Elevated PTT
- CT of brain: Normal
- MRI of the brain: Small ischemic stroke on the left.



ANTIPHOSPHOLIPID ANTIBODY SYNDROME:

- Characteristics:
 - Vascular thrombosis:
 - Arterial, Venous or Small vessel.
 - Ex. Stroke, DVT, PE, Superficial thrombosis.
 - Pregnancy complications: Pre-term births, late miscarriages:
 - Pre-Term: Before 34 weeks
 - Late miscarriages: At or beyond 10 weeks
 - 3 "embryonic" miscarriages: Before 10 weeks.
 - With the presence of antiphospholipid antibodies (x2 12 weeks apart).
 - Cardiolipin Antibodies (IgM and IgG)
 - Beta-2-Glycoprotein-l antibodies (IgM and IgG)
 - Lupus Anticoagulant positivity
- Can be primary or secondary.
 - ▶ Most common secondary cause: Lupus.

APS:

- In a patient less than 50 years of age:
 - ▶ 15-20% of DVTs are due to APS
 - > 33% of Strokes are due to APS
 - ► 15% of recurrent miscarriages are due to APS

https://www.rheumatology.org/I-Am-A/Patient-Caregiver/Diseases-Conditions/Antiphospholipid-Syndrome

APS:

Non-Criteria Findings:

- Thrombocytopenia, usually mild.
- Bone-Marrow necrosis
- Thrombotic microangiopathy (TMA).
- Autoimmune hemolytic anemia
- Pulmonary hypertension, thrombosis, ARDS, and DAH.
- Cardiac valvular thickening, nodules and Libman-Sacks endocarditis.
- Livedo reticularis, splinter hemorrhages, cutaneous necrosis and infarcts.
- Digital gangrene, ulcerations and pseudovasculitis nodulosis.
- Livedoid vasculopathy (Atrophie blanche).
- Renal Failure, Adrenal insufficiency
- GI issues.

SKIN LESIONS OF APS:



SKIN LESIONS OF APS:



27 yrs old. SLE. Treated with pred 80, Cyclophosphamide and Dapsone and did not resolve. Had +Cardiolipin antibody. Ulcers completely healed with two weeks of low-dose tPA.

APS:

► Treatment:

- ► Anticoagulation with warfarin or lovenox.
- ASA is used however data are lacking.
- Hydroxychloroquine: Used for its anti-thrombotic properties.
- Statins
- Referral to rheumatology especially if considering getting pregnant.

CAPS:

- Catastrophic APS:
 - ► Involvement of 3 or more organs
 - Widespread thrombotic disease
 - Biopsy confirming microthrombus
 - ► Exclude DIC, HIT, TMA, etc
- Tx:
 - Heparin
 - High Dose Steroids
 - ► IVIG or Plasma Exchange
 - Last line: Rituximab or Eculizumab.

SOME FINAL THOUGHTS:

- Blood cultures
- ► Hepatitis screen
- ► HIV
- **UDS**
- **ECHO**
- ► ANA, ANCA, RF, CCP
- ► Complements: C3, C4 and CH50
- ► APS evaluation: B2GP, CL and LAC.
- MRA head/neck/chest/abd pelvis
- +/- Angiography
- +/- Tissue biopsy

ADDITIONAL REFERENCES:

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QUESTIONS?

