Learning Objectives

- Identify significant but less recognized disease features in common forms of systemic vasculitis
- Recognize important clinical mimics of vasculitis
- Apply strategies to lessen treatment risks in vasculitis
Which of the Following Is NOT a Feature of Giant Cell Arteritis (GCA) ?

A. Cough
B. Increased liver function tests (LFTs)
C. Thrombocytopenia
D. None of the above – they are all features

Consider GCA in an older patient with unexplained cough

LFTs (alk phos, AST) occur in 25-35% of GCA patients

Leukopenia and thrombocytopenia are not disease-related features of a primary vasculitis

If present consider other causes
You have been taking care of a 76-year-old woman with polymyalgia rheumatica (PMR). She has been on the internet and is very worried about her risk of GCA and vision loss.

**True or false:**
It is very unlikely that she would develop GCA associated with vision loss.

**FALSE**
Greatest Concern in Giant Cell Arteritis: Cranial Ischemic Complications – Tissue Oschemia Due to Vessel Occlusion

- visual loss - 14% (6-42%)
- stroke - 3-8%
- tongue ischemia
- scalp ischemia


- 73 patients where PMR preceded GCA
- 20% developed ischemic complications (16 visual features, 3 stroke)

Onset of GCA can occur after PMR and may not be benign
You have been caring for a 73-year-old woman who you diagnosed with giant cell arteritis on the basis of prior headache, increased ESR, and jaw claudication. She did well on prednisone but now comes to see you with R arm pain on shampooing her hair. You note a decreased pulse.

True or false: This lesion is not compatible with giant cell arteritis and she likely had Takayasu arteritis all along.

FALSE
Large Vessel Disease Is Common in GCA

Nuenninghoff et al. A & R 2003; 48:3522 and 3532

27% of GCA patients had large vessel complications

13% large-artery stenosis
18% aortic aneurysm

Thoracic aortic aneurysms in GCA:
- 18 x more likely than the general population
- Are associated with decreased survival

Thoracic aortic aneurysms are common in GCA, they can occur late, and they are an important cause of mortality
Polymyalgia Rheumatica

Cranial Disease

Systemic / Inflammatory Disease

Large Vessel Disease

GCA
One disease
Multiple phenotypes
In Managing the 73-Year-Old Woman with GCA and Axillary Artery Stenosis

**True or false:**

You should advise her that revascularization will be necessary in the future

**FALSE**

The presence of a vascular lesion should not be the sole indication for vascular intervention

Collateral vessels commonly form around upper extremity stenoses
For What Indications Is Vascular Intervention Often Considered in Large Vessel Vasculitis?

Indications for stenotic lesions:
- Renal artery stenosis (medically uncontrolled hypertension, renal insufficiency)
- CNS: TIA / cerebral ischemia / stroke
- Angina
- Severe limb claudication affecting quality of life
- Bowel ischemia / infarction

Indications for aneurysmal disease:
- Aortic aneurysm thoracic / abdominal
- Aortic root / valve replacement

Vascular intervention for large vessel disease should be based on symptoms, signs, and location
For which of the following medications is there evidence of benefit in preventing cranial ischemic complications in giant cell arteritis?

A. Methotrexate
B. Aspirin
C. Infliximab
D. Tocilizumab

Aspirin (81 mg daily) should be given to all patients with GCA who do not have a contraindication.

175 patients retrospectively reviewed for cranial ischemic complications (CIC)
- ASA treated patients were 5x less likely to have CIC prior or after diagnosis
- CIC developed in 3% of ASA-treated patients vs 13% (P=0.02)

Only 10 patients would need to be treated with ASA to prevent one CIC

Lee et al. Arthritis Rheum 2006;54:3306

143 patients retrospectively reviewed for ischemic complications
- 16% on therapy had an ischemic event compared to 40% not on therapy
- no increase in risk of bleeding complications

In patients without contraindications, these data support the addition of ASA 81mg daily to prednisone in GCA

(Supportive data also in Takayasu – de Souza et al. Circ J 2010; 74:1236)
Methotrexate (MTX) in Giant Cell Arteritis

Methods:

Meta-analysis of:

Results:

- Have to treat 4 patients with MTX to prevent first relapse
- Have to treat 11 patients with MTX to prevent a cranial relapse
- MTX use was associated with a reduction in cumulative steroid dose
- MTX did not reduce frequency of prednisone side effects

Limitations:

- Very different study designs and relapse definitions
- Does not take into account the impact of rare but life threatening MTX toxicities

**Absolute reduction in relapse by MTX is at best very modest**
**Decision to use MTX must weigh risk against small margin of benefit**
Infliximab in Giant Cell Arteritis


- Relapse-free through week 22: infliximab = placebo (p=0.651)
- Infection: infliximab (71%) > placebo (56%)

Infliximab does not reduce relapse in GCA

Similar results also found in PMR (Salvarani et al. Ann Intern Med 2007;146:631)
## Tocilizumab in Giant Cell Arteritis

*Experience with tocilizumab based on case reports*

<table>
<thead>
<tr>
<th>Study</th>
<th>GCA</th>
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<tbody>
<tr>
<td>Christidis et al. 2011</td>
<td>1</td>
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<td>Seitz et al. 2011</td>
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<td>Beyer et al. 2011</td>
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<td>Sciascia et al. 2011</td>
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<td>Salvarani et al. 2012</td>
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<td>Unizony et al. 2012</td>
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<td>Lurati et al. 2012</td>
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<tr>
<th></th>
<th>GCA</th>
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<tr>
<td>Total</td>
<td>24</td>
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- Overall a beneficial response has been observed.
- What does reduction of acute phase reactants mean with this agent?
- 1 report of active vascular inflammation seen on histology despite treatment with tocilizumab (*Unizony et al. AC&R 2012;64:1720*).
  
30 patients with GCA (23 patients newly diagnosed)
2:1 randomization: Tocilizumab 8 mg/kg q4weeks X 1 year + prednisolone taper vs. PCB + prednisolone taper
Primary endpoint: remission at week 12 w/dose of prednisolone 0.1 mg/kg/day

Results:
85% of TCZ group vs 40% PCB reached primary endpoint
Cumulative prednisolone dose 43 mg/kg in TCZ vs. 110 mg/kg in PCB after 52 weeks
SAE for TCA < PCB

Tocilizumab in Giant Cell Arteritis
Phase 3: GiACTA RDBPCT Tocilizumab for GCA

251 patients with GCA
- 1:1:2:1 randomization: 26 wk prednisone +PCB vs. 52 week prednisone +PCB vs. TCZ 162 mg qweek +26 week prednisone vs. TCZ 162 mg q2weeks + 26 weeks prednisone
- Primary endpoint: no flares, normal CRP at week 52 with adherence to steroid taper.
- Secondary endpoint: cumulative dose of steroid

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<tr>
<th>Table. Efficacy and Safety During GiACTA Part 1</th>
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<tr>
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<tr>
<td>A) Short-course prednisone n = 50</td>
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<td>B) Long-course prednisone n = 51</td>
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<td>C) Weekly SC TCZ n = 100</td>
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<td>D) Every other week SC TCZ n = 49</td>
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<td>Patients in sustained remission at 52 weeks, n (%)</td>
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<tr>
<td>7 (14.0)</td>
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<td>9 (17.6)</td>
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<td>56 (56.0)</td>
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<td>26 (53.1)</td>
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<td>TCZ groups vs short-course prednisone</td>
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<td>Unadjusted difference in proportion of responders (99.5% CI)</td>
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<td>42.0 (18.0, 66.0)</td>
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<td>p &lt; 0.0001</td>
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<td>39.1 (12.5, 65.7)</td>
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<td>p &lt; 0.0001</td>
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<td>TCZ groups vs long-course prednisone</td>
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<td>Unadjusted difference in proportion of responders (99.5% CI)</td>
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<tr>
<td>38.4 (17.9, 58.8)</td>
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<td>p &lt; 0.0001</td>
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<td>35.4 (10.4, 60.4)</td>
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<td>p = 0.0002</td>
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<td>Cumulative CS dose, median (min-max)</td>
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<td>932.0-9777.5</td>
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<td>3817.50</td>
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<td>822.5-10697.5</td>
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<tr>
<td>1862.00</td>
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<tr>
<td>630.0-6602.5</td>
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<tr>
<td>295.0-9912.5</td>
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<td>AEs Patients with event, n (%)</td>
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<td>48 (96.0)</td>
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<td>47 (92.2)</td>
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<td>98 (98.8)</td>
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<td>47 (95.9)</td>
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<td>Withdrawals Patients withdrawn from study, n (%)</td>
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<td>5 (9.8)</td>
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<td>15 (15.0)</td>
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<td>9 (18.4)</td>
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<td>Withdrawals due to an AE, n (%)</td>
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<td>2 (4.0)</td>
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<td>7 (7.0)</td>
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<td>3 (6.1)</td>
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<td>SAEs Patients with event, n (%)</td>
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<td>11 (22.0)</td>
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<td>13 (25.5)</td>
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<td>15 (15.0)</td>
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<td>7 (14.3)</td>
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<td>Infection SAEs Patients with event, n (%)</td>
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<td>2 (4.0)</td>
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<td>6 (11.8)</td>
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<td>7 (7.0)</td>
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<td>2 (4.1)</td>
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A 23-year-old woman with Takayasu arteritis comes to the ER with profound dyspnea. She is frothing at the mouth and is in florid CHF. On examination: BP 100/60, P 120 regular, CV reveals a prominent S3, she has diminished B/L radial pulses, with full pulses elsewhere.

Which of the following should you do next:
A. Obtain an MRI of her aorta and great vessels
B. Check her ESR and CRP
C. Measure her BP in her lower extremities
D. Perform an echo

Obtain four extremity BP measurements in all patients with Takayasu arteritis (also a pearl for GCA)

Upper extremity measurement may be unreliable due to stenotic lesions
# Takayasu Arteritis

## Distribution of Vascular Lesions

<table>
<thead>
<tr>
<th>Vessel</th>
<th>USA (%)</th>
<th>India (%)</th>
<th>Symptoms / Signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subclavian</td>
<td>69</td>
<td>59</td>
<td>Arm claudication</td>
</tr>
<tr>
<td>Carotid</td>
<td>37</td>
<td>21</td>
<td>TIA, stroke, syncope, Visual symptoms</td>
</tr>
<tr>
<td>Renal</td>
<td>16</td>
<td>53</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Iliac</td>
<td>19</td>
<td>15</td>
<td>Leg claudication</td>
</tr>
<tr>
<td>Mesenteric</td>
<td>36</td>
<td>12</td>
<td>Abdominal angina (rare)</td>
</tr>
<tr>
<td>Thoracic aorta</td>
<td>46</td>
<td>19</td>
<td>CHF</td>
</tr>
<tr>
<td>Abdominal Aorta</td>
<td>37</td>
<td>72</td>
<td>Aneurysm: No symptoms, Stenosis: claudication</td>
</tr>
</tbody>
</table>
Hypertension occurs in 32-93% of Takayasu arteritis patients

- Often secondary to renal artery stenosis
- Important cause of morbidity
  - Contributes to renal, cardiac, and cerebral injury
- Can go undetected
  - BP will not be accurate when measured distal to stenotic lesions
- Treatment must balance reducing BP with flow across stenotic lesions

Hypertension is an important cause of morbidity in Takayasu arteritis
Which of the following carries the worst prognosis in EGPA (Churg-Strauss)?

A. Glomerulonephritis
B. Eosinophilic pulmonary infiltrates
C. Cardiac involvement
D. Mononeuritis multiplex

Cardiac involvement is a prominent disease feature in EGPA.

Echo should be performed at diagnosis in all EGPA patients.

Cardiac features of EGPA can include:
- Pericarditis
- Myocarditis
- Endocarditis
- Valvulitis
- Coronary vasculitis
Eosinophilic Granulomatosis with Polyangiitis (Churg-Strauss)

Prodromal phase: asthma, allergic rhinitis

Eosinophilic phase: peripheral eosinophilia, eosinophilic tissue infiltrates

Vasculitic phase: nerve, skin, lung, GI tract, heart
Eosinophilic Granulomatosis with Polyangiitis (Churg-Strauss) Outcome and Treatment

Outcome - *Guillevin et al. Medicine* 1999;78:26

- 96 patients with EGPA
- Myocardial involvement was the most frequent cause of death responsible for 9 of 23 deaths (39.1%)

Treatment strategy based upon manifestations and disease severity

Glucocorticoids
asthma often limits tapering

Cytotoxic therapy

Cyclophosphamide should be utilized for life-threatening disease involving the GI tract, CNS, glomerulonephritis, heart
A 65-year-old female with GPA (Wegener’s) recently had a renal relapse. Her creatinine is normal, UA shows 2+ protein. She is ambulating normally. At her one month visit you note painless B/L symmetric lower extremity swelling with 1+ pitting. She is taking prednisone 60 mg daily and cyclophosphamide and she has been on amlodipine for hypertension.

Which of the following should you do first:

A. Stop amlodipine
B. Prescribe B/L compression hose
C. Add an ACE to reduce her proteinuria
D. Have her get a same-day venous duplex
E. No intervention needed as you will begin tapering the prednisone

Patients with GPA (Wegener’s) are at increased risk of venous thrombotic events (DVT and PE)

(PS: So are MPA and EGPA)
• 180 patients in the Wegener’s granulomatosis etanercept trial (WGET)
• Higher rate of DVT/PE compared to other groups
• Most were during/within 2 months of active disease

<table>
<thead>
<tr>
<th>Study</th>
<th>DVT / PE rate</th>
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<tbody>
<tr>
<td>WGET</td>
<td>7.0</td>
</tr>
<tr>
<td>General Population</td>
<td>0.3</td>
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<tr>
<td>JHU Lupus</td>
<td>1.0</td>
</tr>
<tr>
<td>RA Etanercept</td>
<td>0.3</td>
</tr>
</tbody>
</table>

Remember DVT/PE in GPA (Wegener’s)
----- also -----  
If a patient with GPA has a DVT/PE – look for active disease
A 55-year-old male with MPA has had disease of the skin, lungs, nerve, and kidneys (creatinine 2.5 mg/dL, UA 2+ protein, (-) blood).

He is 4 months into treatment with cyclophosphamide and you are deciding today whether to switch him to azathioprine.

At today’s visit, chest CT is clear, creatinine 1.0 mg/dL but he has persistent:
- Fatigue
- Foot drop
- Proteinuria
- Sensory loss

**True or False:** It is OK to switch him to azathioprine as all of his current features can be seen as a result of damage

**TRUE**

Clinical features similar to active disease may be due to damage, infection, medication toxicities, or other causes.
Remember - In MPA - and really in all forms of vasculitis what looks like disease may not be

New clinical features:

Characteristic features are NOT always indicative of activity

- Pulmonary infiltrates (infection, MTX pneumonitis)
- Hematuria (cyclophosphamide bladder injury)

Always consider: infection or medication side effect

Persistent clinical features:

Differentiate active disease from chronic damage

- Renal: creatinine may not go down and proteinuria may persist
- Nerve: persistence of motor and sensory deficits is common
- Sinonasal: persistence of symptoms (GPA, EGPA)
- Persistent radiographic changes: lung, orbit, sinus (GPA, MPA, EGPA)
You are planning to treat a patient with cyclophosphamide for 3 months. You should counsel your patient that his risk of bladder cancer lasts:

A. Until he stops the cyclophosphamide
B. For 10 years
C. Lifelong

The risk of bladder cancer in cyclophosphamide treated patients should be considered lifelong.

Which of the following is the most effective test for detecting bladder cancer in cyclophosphamide treated patients:

A. Urinalysis
B. Urine cytology
C. Bladder CT

Urinalysis is the best test to identify CYC-treated patients at risk of developing bladder cancer.
Cyclophosphamide – Strategies for Toxicity Reduction

• General - limit duration of exposure to 3-4 months

• Urothelial protection
  Daily CYC - Take at once in the AM, fluids to maintain a dilute urine
  Intermittent CYC – MESNA

• Bladder cancer monitoring
  Urinalysis to detect non-glomerular hematuria and urine cytology
  Cystoscopy for non glomerular hematuria or atypia

• Cytopenia prevention - CBC every 1-2 weeks

• Pneumocystis prophylaxis
  Trimethoprim/sulfamethoxazole
  Alternative agents:
    pentamidine
dapsone
atovaquone
Your patient has switched from cyclophosphamide to methotrexate, Pneumocystis prophylaxis should be continued

Your patient relapses – methotrexate is stopped and rituximab is given, Pneumocystis prophylaxis should be continued

Pneumocystis occurs in ~10% of vasculitis patients on prednisone + another immunosuppressive and prophylaxis should be given (Yes - Including rituximab !)

What about the risk of combining trimethoprim sulfa (T/S) and methotrexate?

OK Dose to prevent Pneumocystis

T/S DS three times a week
T/S SS once a day

Can be combined with MTX with monitoring

Reports of fatal pancytopenia

Dose to treat infection (UTI)

T/S DS BID

What about the risk of combining trimethoprim sulfa (T/S) and methotrexate?
45-year-old male presents with 3 month history of cough. Otherwise feels well - no sinus symptoms, fevers, arthralgias, rash, weight loss. Examination completely unremarkable; Labs: CBC, chemistries, LFT, UA all normal. pANCA (+); Chest CT:

True or False:

There is a high likelihood that this patient has granulomatosis with polyangiitis (Wegener’s)  

FALSE
Lymphadenopathy should raise concern for:
- lymphoma
- infections (mycobacteria, histoplasmosis)
- sarcoid

So what did the patient have? 

Histoplasma capsulatum
A patient is referred to you from ENT for the question of GPA (Wegener’s). There are no other features other than the lesion pictured below. Labs are notable only for (+) PR3-cANCA.

**True or False:**

This patient is likely to have GPA (Wegener’s) **FALSE**
Erosive lesions of the hard palate are exceedingly rare in GPA (Wegener’s).

Hard palate erosions should raise concern for:
- lymphoma (extranodal NK / T-cell lymphoma)
- invasive infections (fungus, leishmaniasis)
- cocaine

ANCA can be found in cocaine-induced midline destructive lesions

Reacts to human neutrophil elastase, a serine protease which is structurally and functionally related to PR3, such that (+) PR3-ANCA can be seen (Weisner et al. A & R 2004; 50: 2954)
This same patient now comes into the ER 2 months later with this lesion.

**True or False:**
You should now conclude this patient has GPA (Wegener’s) 

**FALSE**

What does he have? 
Levamisole-induced cutaneous necrosis

Levamisole induced disease is an important mimic of vasculitis.
Levamisole-Induced Cutaneous Necrosis

- Introduced in 1960’s as an antihelminthic agent
- Found to have immunomodulatory properties
  - studied in RA, colon CA
- Since ~2004 used as a cutting agent for cocaine (found in 70-100%)
- Linked findings
  - leukopenia and specifically agranulocytosis
  - cutaneous necrosis
    - vasculitis/thrombotic vasculopathy
    - predilection for the earlobe (> 50%)
  - autoantibodies: pANCA, LAC, ACL
  - features of cocaine use

A 26-year-old non-pregnant woman was well until she developed sudden onset of a severe headache. She was exercising when this began. She is on no medications; denies recreational drug use. Her examination is non-focal. Spinal fluid reveals 0 wbc, protein 31 (normal). Brain MRI is normal but MRA is abnormal. Dye arteriogram reveals:

True or False:
This patient is very likely to have Primary CNS vasculitis FALSE
LP is almost always abnormal in CNS vasculitis (>95%)

What diagnosis does she most likely have?

**Reversible Cerebral Vasoconstriction Syndrome (RCVS)**

- Women > Men
- Sudden onset of severe “thunderclap” headache
- Associated conditions
  - Pregnancy
  - Drugs: pseudoephedrine, cocaine, amphetamines
  - Misc: exercise, intercourse
- Normal LP
- Abnormal arteriogram that demonstrates reversibility
- Can result in stroke or hemorrhage
- Treatment – calcium channel blockers - verapamil
An Abnormal Arteriogram Does **Not** Always = CNS Vasculitis

Settings Where an Abnormal CNS Arteriogram has been Reported

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<thead>
<tr>
<th>Settings</th>
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<td>Subarachnoid hemorrhage</td>
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<td>Childbirth</td>
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<td>Other causes of vasospasm</td>
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