Case 1: History

- A 45-year-old man presents with severe dyspnea and cough. He was in excellent health until 4 weeks ago when he developed a sore throat and fever. Over the past 2 weeks, he has noticed reddish ulcers on his legs, episodes of dark urine, and migratory arthralgias. He reports a past history of heavy alcohol use and acknowledges occasional “recreational” drug use.

Case 1: Objective Findings

- Diffuse pulmonary rales and rhonchi
- No detectable heart murmurs or \( S_3 \)
- Palpable ulcerative rash over the legs
- No synovitis
- Hgb = 9.8; WBC = 23,000; ESR = 68; Creatinine = 2.8
- UA = 50 RBCs with casts
- Oximetry = 85% \( O_2 \) saturation
Approach to Multisystem Inflammatory Disease

- How should you approach a patient who presents with multisystem inflammatory disease?

Diagnostic Considerations in Patients With Multisystem Inflammation

- Systemic lupus erythematosus (SLE)
- Systemic vasculitis
- Vasculitis mimics

Systemic Lupus Erythematosus

- Inflammatory multisystem disease primarily seen in females
- Highly variable course and prognosis
- Often has significant constitutional symptoms
- Associated with characteristic autoantibodies
Systemic Lupus Erythematosus (cont’d)

- Clinical symptoms related to the degree of inflammation in various organs
  - Skin and mucous membranes
  - Synovium (joints)
  - Serosal membranes
  - Kidneys
  - Central nervous system
  - Lungs
  - Heart
  - Hematopoietic system

Autoantibodies in SLE

- ANA
  - Seen in 95% of SLE
  - Not specific for SLE
  - Seen in many inflammatory, infectious, and neoplastic diseases
  - Seen in 5% to 15% of normal persons

- Anti-ds DNA
  - Seen in 60% of patients with SLE
  - Highly specific for SLE
  - Low titer rarely seen in other inflammatory conditions
  - Strongest clinical association is with nephritis

- Anti-Sm (Smith)
  - Seen in 10% to 30% of SLE patients
  - Highly specific for SLE
When to Consider a Diagnosis of SLE

- Usually seen in women of childbearing age with:
  - Constitutional symptoms of fever, weight loss, malaise, and severe fatigue
  - Skin rash and/or stomatitis
  - Arthritis
  - Renal disease
  - Cytopenias
- Although 90% of patients are female, SLE can be seen at any age in either sex

Diagnostic Classification of Vasculitis—I

- Large-vessel involvement
  - Giant cell arteritis
  - Takayasu's arteritis
- Medium-vessel involvement
  - Polyarteritis nodosa
  - Kawasaki disease of childhood

Diagnostic Classification of Vasculitis—II

- Small-vessel involvement with immune complex deposition
  - Hypersensitivity vasculitis
  - Henoch-Schönlein purpura
  - Behçet's syndrome
  - Cryoglobulinemia
  - Vasculitis of rheumatic diseases (SLE, RA)

Diagnostic Classification of Vasculitis—III

- Small-vessel involvement without immune complex deposition (pauci-immune)
  - Wegener’s granulomatosis
  - Churg-Strauss vasculitis
  - Microscopic polyangiitis

Clinical Features Suggesting Vasculitis

- Multisystem inflammatory disease
- Rapidly progressive major organ dysfunction
- Constitutional symptoms (fever, weight loss)
- High ESR, severe anemia, thrombocytosis
- Evidence of small-vessel inflammation:
  - In the kidneys = active urinary sediment
  - In the lungs = hemoptysis, dyspnea
  - In the skin = palpable purpura/hemorrhage
- Acute neurologic changes
  - Footdrop
  - Altered mental status

Diagnostic Approach to Patients With Suspected Vasculitis

- Consider tissue biopsy of affected organ to determine
  - Vessel size
  - Histologic features of vessel inflammation
    - Vessel wall necrosis
    - Granulomas/giant cells
    - Immune complex and/or C3 deposition
- Consider angiography of mesenteric or cerebral vessels as clinically indicated
Laboratory Tests That Are Helpful in the Diagnosis of Vasculitis

- Tests suggesting immune complex formation and/or deposition
  - Rheumatoid factor and cryoglobulins
  - Antinuclear antibodies (ANA)
  - Low C₃ or C₄ levels
- Tests suggesting necrotizing vasculitis without immune complex deposition
  - Antineutrophil cytoplasmic antibodies (ANCA)
- Tests suggesting systemic inflammation
  - Erythrocyte sedimentation rate (ESR)
  - C-reactive protein (CRP)

Antineutrophil Cytoplasmic Antibodies

- ANCA by immunofluorescence methods
  - c-ANCA = Wegener’s disease (60% to 90%)
  - p-ANCA = microscopic polyangiitis (MPA) (50% to 80%), UC (40% to 80%), Crohn’s (10% to 40%)

Antineutrophil Cytoplasmic Antibodies

- ANCA by ELISA methods
  - Proteinase 3 (PR3) = Wegener’s disease
  - Myeloperoxidase (MPO) = MPA

## Diseases That Can Present as Vasculitic Syndromes

<table>
<thead>
<tr>
<th>Vasculitis</th>
<th>Vasculopathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infectious diseases</td>
<td>Cholesterol emboli syndrome</td>
</tr>
<tr>
<td>Bacterial endocarditis</td>
<td>Toxic drug effects</td>
</tr>
<tr>
<td>HIV infections</td>
<td>Ergots</td>
</tr>
<tr>
<td>Viral hepatitis</td>
<td>Cocaine</td>
</tr>
<tr>
<td>Paraneoplastic syndromes</td>
<td>Amphetamines</td>
</tr>
<tr>
<td>Atrial myxoma</td>
<td></td>
</tr>
</tbody>
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## Studies Useful in Diagnosing Vasculitis Mimics

- Blood culture
- Viral hepatitis antigen/antibodies
- HIV test
- Urine toxicology screen
- Angiography
- Echocardiogram

## When to Consider Vasculitis Mimics (the Red Flags)

- Presence of a heart murmur
- Necrosis of lower extremity digits
- Splinter hemorrhages
- Prominent liver dysfunction
- History of recreational drug use
- History of high-risk sexual activity
- Prior diagnosis of neoplastic disease
- Unusually high fevers
Case 2: History

- A 36-year-old female is seen for migratory arthritis of 6 months’ duration. She also reports some fatigue and a photosensitive skin rash.
- ROS notes:
  - Patchy hair loss 4 months ago that regrew
  - Aphthous-like mouth ulcers every 4 to 6 weeks
  - A diagnosis of “walking pneumonia” made last month based on symptoms of pleuritic chest pain

Case 2: Objective Findings

- Pain with mild synovitis over the MCPs and PIPs
- Rash over her face, legs, and trunk
- Hgb = 12.1; ESR = 33
- UA = 3+ protein
- ANA = 1:640 titer

Case 2: Question

- With this clinical history, what is the most important thing to do now?
  A. Start an NSAID for the joint pain
  B. Start hydroxychloroquine to treat the rash and prevent recurrent pleurisy
  C. Fully evaluate her renal status and initiate appropriate therapy
  D. Start prednisone at 80 mg qd
Case 2: Answer

- C. Fully evaluate her renal status

Don’t Wait

- Aggressively evaluate renal status if the urinalysis is abnormal in SLE patients

Case 3: Clinical Findings

- A 26-year-old woman presents with progressive weight loss, fevers to 103.5°F, arthralgias, and ischemic ulcers on the fingers
- Physical examination reveals an enlarged spleen and a harsh midsystolic murmur
- Hgb 9.3 mg%, ESR 82 mm/s
- Urinalysis shows 15 to 20 RBCs

Case 3: Question

- Which of the following would you do first?
  A. Echocardiogram and blood cultures
  B. Renal biopsy
  C. Anti-ds DNA antibody levels
  D. C-reactive protein level
Case 3: Answer

- A. An echocardiogram and blood cultures
  - Echocardiogram showed vegetations on the valves
  - Blood cultures were positive for Staph aureus

Don’t Guess

- ALWAYS look for mimics of vasculitis that have specific treatments

Case 4: Question

- A 43-year-old woman has a presumptive diagnosis of Wegener’s granulomatosis based on sinusitis with bone destruction, abnormal chest x-ray, skin rash, and active urinary sediment. Which biopsy would provide the highest diagnostic return?
  A. Sinus mucosal biopsy
  B. Renal biopsy
  C. Open lung biopsy
  D. Skin biopsy
Case 4: Answer

C. Open lung biopsy

Principles of Tissue Biopsy in Vasculitis

- Obtain tissue immediately
- Obtain tissue from most significantly involved organ
  - Lung = usually diagnostic
  - Kidney = often diagnostic
  - Skin = sometimes diagnostic, but always easy to obtain
  - Nasal/sinus mucosa = easy to obtain but may be nondiagnostic

Principles of Tissue Biopsy in Vasculitis (cont’d)

- Obtain an adequate specimen
- Obtain immunofluorescence studies
  - Immunoglobulin deposition
  - C₃ deposition
Don’t Forget

- TISSUE is the ISSUE for diagnosis!

Case 5: Question

- A 59-year-old male with chronic sinusitis and no other clinical findings is referred to you because of a positive c-ANCA test. The chest x-ray, ESR, and UA are normal. What would you recommend?
  A. Start prednisone at 80 mg/d and arrange a sinus mucosal biopsy
  B. Arrange a “blind” lung biopsy
  C. Start no specific therapy, but evaluate at 4-month intervals
  D. Start prednisone at 80 mg/d and follow the c-ANCA titers

Case 5: Answer

C. Start no specific therapy, but evaluate at 4-month intervals

Don’t treat lab tests
Case 5: Answer (cont’d)

- ANCA tests alone are rarely diagnostic
  - With chronic sinusitis, pulmonary infiltrates, and active urine sediment, a positive c-ANCA means Wegener’s granulomatosis 98% of the time
  - With only chronic sinusitis, a positive c-ANCA predicts Wegener’s granulomatosis in only 12% of cases


Case 6: History

- A 32-year-old woman comes in Friday morning with intermittent skin rash over the legs for 2 months. Lesions are not painful and resolve with minimal discoloration
  - PMH is positive for chronic sinusitis requiring antibiotics 3 to 4 times per year
  - ROS is negative except for a 15-lb weight loss over the past 2 months

Case 6: Objective Findings

- Nonulcerating palpable purpura over the lower extremities
- Remainder of the examination is unremarkable
Case 6: Action

- You order a chest x-ray, CBC, urinalysis, ESR, and metabolic panel
- She is scheduled to return next Tuesday

Case 6: Follow-Up

- You receive the following results in the afternoon:
  - Hgb 8.9; ESR 115; creatinine 1.6
  - UA = 20 to 30 RBC; 3+ protein; no casts
  - Chest x-ray = multiple infiltrates

Case 6: Question

- What should you do now?
  A. Order an ANA, ANCA, and anti-ds DNA to be drawn on Tuesday
  B. Have her seen immediately by your rheumatology consultant
  C. Schedule a rheumatology consult for Monday
  D. Call in a prescription for prednisone at 40 mg bid until she is seen on Tuesday
Case 6: Answer

- B. Have her seen immediately

DON’T HESITATE

- For significant major organ dysfunction of unknown duration in suspected vasculitis
- Evaluate immediately
- Therapy will depend on obtaining a specific diagnosis
- Patients can clinically deteriorate suddenly

Case 7: Clinical Findings

- A 51-year-old man is seen for complaints of hives, skin rash, and ulcers over his shins
- Physical exam reveals
  - Palpable purpura, ulcers, and urticarial lesions over the arms and legs
  - Palpable cervical and axillary adenopathy
  - Hepatosplenomegaly

Case 7: Diagnostic Studies

- Laboratory studies
  - ESR = 64; RF = 489 IU;
  - C3 = 24; AST = 876;
  - ALP = 234
  - UA shows 20 to 30 RBCs, negative protein, no casts
  - Cryoglobulins = positive
- Skin biopsy reveals leukocytoclastic vasculitis
Case 7: Question

- What is the most probable etiology for this vasculitic syndrome?
  A. Parvovirus infection
  B. Drug reaction
  C. Hepatitis C infection
  D. Staph sepsis

Case 7: Answer

C. Hepatitis C infection

“Essential cryoglobulinemic vasculitis is not so essential anymore”

Hepatitis C Virus-Associated Vasculitis

- The cause of most cryoglobulinemic vasculitis
- Cryoglobulins lead to tissue damage
- Patients are rheumatoid factor positive
- Prednisone and/or cytotoxic agents may increase virion load
- Alpha interferon may improve vasculitis and infection
- Despite therapy, relapses are common

Hepatitis B Virus-Associated Vasculitis

- Seen in 10% to 50% of polyarteritis nodosa cases
- Presents as a systemic vasculitis with abnormal liver function tests
- Tissue damage is due to immune complexes
- Therapy includes steroids, antiviral agents, and occasionally apheresis

HIV Virus-Associated Vasculitis

- Masquerades as many rheumatic syndromes
- Polyarteritis nodosa
- Churg-Strauss vasculitis
- Hypersensitivity vasculitis
- Systemic lupus erythematosus
- Sjögren’s syndrome
- Primary CNS vasculitis
- Primary therapy is antiviral
- Careful use of immunosuppressive agents may be considered

Don’t Miss It

- Viral infections can mimic many rheumatic and vasculitic syndromes
- Key associations
  - Hepatitis B—polyarteritis nodosa
  - Hepatitis C—cryoglobulinemia
  - HIV—“seronegative” rheumatic syndromes

General Concepts About Vasculitis Treatment

- Tissue damage with vasculitis requires early diagnosis and treatment
- Combinations of high-dose steroids and cytotoxic drugs are commonly used
- Effective treatment can improve outcome
- There is a delicate balance between treatment efficacy and toxicity
- Well-defined clinical outcomes are needed to guide the intensity and duration of treatment

Points to Remember

- When a patient has a complex multisystem inflammatory picture—think vasculitis
- If a vasculitic disorder is considered, search for its cause
- Employ tests and biopsies when indicated, but remember to treat the patient, not the test
- Rapid diagnosis and treatment is often organ or lifesaving
- Consider viral associated rheumatic/vasculitis syndromes when the autoantibody results are not typical