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 S3
- 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% O2 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%)
  - ANCA by ELISA methods
  - Proteinase 3 (PR3) = Wegener’s disease
  - Myeloperoxidase (MPO) = MPA

Diseases That Can Present as Vasculitic Syndromes

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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