Polyarteritis Nodosa

Background

1. Definition
    - Systemic necrotizing vasculitis that typically affects medium-sized muscular arteries, without occasional involvement of small muscular arteries
2. General info
    - Unlike similar vasculitides, polyarteritis nodosa (PAN) is not typically associated with anti-neutrophilic cytoplasmic antibodies (ANCA)
    - Presents with systemic Sx including:
        - Peripheral nervous system
        - Skin
        - GI
        - Joints
    - Lungs often spared
    - Often associated with Hepatitis B virus infection

Pathophysiology

1. Pathology of disease
    - Poorly understood
    - Most likely a spectrum of disease rather than single entity
    - Subset of cases associated with Hepatitis B, immune complexes thought to play a role
    - Characterized by segmental transmural inflammation of muscular arteries by polymorphonuclear leukocytes and mononuclear cells, with no involvement of veins
    - Luminal narrowing caused by thickening of inflamed vessel walls and intimal proliferation, reducing blood flow and predisposing to thrombosis and resultant ischemia
    - Vessel inflammation can cause structural wall weakness leading to aneurysm with possible rupture
2. Incidence/prevalence
    - Incidence 0.7/100,000
    - Prevalence 6.3/100,000
    - Variation in these numbers exist in part due to differences in Dx criteria, and existence of regional variations
    - 1.5:1 male predominance
3. Risk factors
    - Most cases of PAN are idiopathic
    - Hepatitis B infection, particularly in IV drug users, can impart incr risk of developing PAN, represent 30% of cases
    - Hairy cell leukemia carries association with PAN
4. Morbidity/mortality
    - Morbidity
        - Consistent with multisystem involvement:
            - Hypertension
            - Renal insufficiency
            - Neurologic dysfunction
            - Abdominal pain

- Mortality
  - Untreated PAN has poor prognosis
  - 13 % 5-yr survival, with:
    - Renal failure and mesenteric
    - Cardiac or cerebral infarction
      - Major causes of death

Diagnostics

1. Dx based on Sx, PE and labs
   - Dx should be confirmed by Bx whenever possible
2. History
   - Multisystemic Sx:
     - Skin
     - Neurologic
     - GI
     - Cardiac
     - Musculoskeletal
     - Eye
   - S/Sx
     - Low-grade fever
     - N/V
     - Dyspnea on exertion
     - Fatigue,weakness, malaise
     - Weight loss
     - Headache
     - Rash or urticaria
     - Myalgia, arthralgia, arthritis
     - Abdominal pain
     - Melena
     - Peripheral neuropathy
   - Hepatitis B infection
     - Particularly in pts with Hx of IV drug exposure
     - Can be specifically associated with development of PAN
3. Physical exam
   - PAN should be considered in pts with constellation of musculoskeletal Sx, constitutional Sx and multisystem involvement
   - Neurologic findings
     - Asymmetric sensory and motor neuropathies
     - Multiple mononeuropathies
     - CNS involvement rare, <10% cases
     - Severe depression in 8% of pts
   - Renal findings
     - Occur in 30-60% of pts
     - Hypertension, may be severe
   - GI findings
     - Generalized abdominal tenderness
     - Hepatomegaly
     - Signs of:
       - Appendicitis

- Cholecystitis
- Hemorrhagic pancreatitis
- Hepatic or splenic infarction

- Skin findings
  - Painful skin ulceration
  - Livedo reticularis
  - Papules and nodules
  - Ischemia and gangrene
    - Most common skin manifestations
- Musculoskeletal findings
  - Asymmetric arthritis
    - Usually involving larger joints of lower extremities
- Cardiac findings
  - Pericarditis with friction rub
  - Signs of CHF
  - Arrhythmias
- Ophthalmologic findings
  - Retinal vasculitis
  - Retinal detachment
  - Cotton-wool spots

4. Diagnostic testing:
   - No definitive test for PAN
   - Laboratory evaluation:
     - Basic labs:
       - Can help determine extent and degree of organ involvement
       - Some findings, although nonspecific, can be helpful in initial evaluation
     - CBC:
       - Leukocytosis, normochromic anemia, thrombocytosis urinalysis: proteinuria, hematuria
     - Serum creatinine:
       - Elevated
     - Liver function studies:
       - Elevated transaminases, decreased serum albumin
     - ESR: >50 mm/h
     - CRP: increased
     - Hepatitis serologies:
       - Presence of hepatitis B surface antigen
     - ANCA: rarely found in PAN
   - X-ray:
     - Can exclude other conditions, particularly forms of vasculitis more often involving lung
   - Baseline ECG
   - Blood cultures:
     - Exclude endovascular infection
   - Additional labs:
     - Valuable in narrowing differential diagnosis when results are found to be negative
       - Antinuclear antibodies Rheumatoid factor

- Antibodies to cyclic citrullinated peptides
- Antibodies to double stranded DNA
- Antibodies to extractable nuclear antigens (anti-Smith, anti-Rl/SSA, anti-La/SSB, and anti-RNP)
- Cryoglobulins
- Lyme testing in endemic areas
- Complement components (C3 and C4)

o Tissue Bx:
  - Should be obtained from affected organ to confirm Dx
  - Histology reveals focal necrotizing arteritis of mixed cellular infiltrate within vessel wall

o Angiography:
  - Alternative to Bx if involved tissue not accessible, Dx studies demonstrate multiple aneurysms and irregular constrictions in larger vessels, and occlusion of smaller arteries

5. Diagnostic criteria
   o American college of Rheumatology
     - 10 criteria for classification of PAN in pts with vasculitis, sens 82%, spec 87% for Dx of PAN in pts with documented vasculitis and $\geq$3 of the following:
       - Otherwise unexplained wt loss >4 kg
       - Livedo reticularis
         - Reddish blue netlike mottling of skin that can be caused by changes in underlying blood vessels
       - Testicular pain or tenderness
       - Myalgias (excluding that of shoulder and hip girdle), weakness of muscles, tenderness of leg muscles, or polyneuropathy
       - Mononeuropathy or polyneuropathy
       - New onset diastolic blood pressure >90 mmHg
       - Elevated BUN (>40 mg/dL or 14.3 mmol/L) or creatinine (>1.5 mg/dL or 132 umol/L)
       - Evidence of Hepatitis B infection via serum antibody or antigen serology
       - Characteristic arteriographic abnormalities not resulting from noninflammatory disease processes
       - Bx of small or medium-sized artery containing polymorphonuclear cells

Differential Diagnosis

1. Vascular diseases
   o Wegener's granulomatosis
     - Vasculitis affecting small arteries of lungs and kidney, ANCA positive
   o Henoch-Schönlein purpura
     - Vasculitis caused by immune complex deposition, purpuric rash on buttocks or extensor surfaces, children
   o Cryoglobulinemia
     - Cutaneous vasculitis, palpable purpura, digital vessel occlusion
   o Churg-Strauss syndrome

        - Necrotizing granulomas of small arteries of lungs, associated w/asthma, eosinophilia, ANCA positive) microscopic polyangiitis (necrotizing arteritis of capillaries, venules, arterioles, ANCA positive
    - Giant cell arteritis
        - Temporal artery affected, headaches, visual disturbances, associated with polymyalgia rheumatica
    - Takayasu's arteritis
        - Granulomatous inflammation of aorta and major branches, pts usually <50 yrs
    - Kawasaki disease
        - Involves coronary arteries, fever is common, usually in children
    - Hypersensitivity vasculitis
        - Affects small vessels of skin, triggered by allergen
2. Other autoimmune conditions
    - Rheumatoid arthritis
        - Systemic polyarthritis, deforming arthropathy
    - SLE
        - Systemic disease, rash, joint involvement, pericardial rub and heart murmurs
    - Behçet's syndrome
        - Oral aphthous ulcer, genital ulcers, uveitis
3. Infectious conditions
    - Infective endocarditis
        - Fever, changing heart murmur, splenomegaly
    - Hepatitis B or C
        - Hepatitis B surface antigen positive, Antihepatitis C virus antibody positive, progression to cirrhosis
4. Malignancy
    - Lymphoma
        - Vague constitution symptoms, fever, weight loss, night sweats, hepatomegaly, splenomegaly
5. Extensive DDx
    - Cholesterol embolization
        - Purpura, skin ulcers and kidney disease seen
    - Rickettsial infection
        - Constitutional Sx, skin rash, serologies may help confirm diagnosis
    - Lyme disease
        - Constitutional Sx, lymphadenopathy, rash, serologies may be helpful in Dx
    - Left atrial myxoma
        - Constitutional Sx, skin rash, echocardiogram diagnostic
    - Ergotism
        - Poisoning can cause vessel constriction, leading to extremity numbness or gangrene

Therapeutics

1. Develop Tx plan focusing on pt's symptoms, reducing pain, and preventing dz progression and end-organ damage
2. Medical therapy:

- Based on severity of dz
- Mild PAN:
  - Constitutional Sx, arthritis, anemia, but normal renal function, no GI involvement, and no neurologic deficits; isolated cutaneous dz
  - Glucocorticoid monotherapy
  - Prednisone 1 mg/kg per day (max 60-80 mg/day) for 4 wks
    - Once improvement is noted taper prednisone slowly for overall treatment course of 9 months
- Moderate and Severe PAN
  - Renal insuff or GI, cardiac or neuro involvement: combination Tx of glucocorticoids and cyclophosphamide
  - Prednisone 1 mg/kg per day (max 60-80 mg/day) given concurrently
    - Initial dose continued for 2-4 wks, until improvement seen, then taper slowly for overall course of 6 months
  - Oral Cyclophosphamide 1.5-2 mg/kg per day
    - Limited data on optimal duration of Tx, but most studies use 12 mo of cyclophosphamide
    - WBC count must be closely monitored and cyclophosphamide dose adjusted if need be to avoid severe leucopenia

Follow-Up

1. Return to office
   - Follow-up in person to monitor immunosuppressive Tx and observe for any Dx exacerbations
2. Refer to specialist
   - Referral to rheumatologist indicated for long term care of these pts
3. Admit to hospital
   - If Dz becomes rapidly progressive referral to hospital should be immediate with early consultation by rheumatologist

Prognosis

1. Untreated PAN
   - Poor prognosis: 13% 5-yr survival
2. Outcomes improved with Tx: 80% 5-yr survival
3. Hepatitis B -associated PAN: 73% 5-yr survival

References

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