Heart & Vascular: Churg Strauss Vasculitis (CSS)

Background
1. General Information
   o Classically a triad of vasculitis, bronchial asthma, and eosinophilia
   o Also called
     ▪ Churg Strauss Granulomatosis
     ▪ Allergic granulomatosis
     ▪ Allergic granulomatosis angiitis

Pathophysiology
1. Pathology of Disease\(^1\)
   o Necrotizing vasculitis involving small and medium-sized vessels due to unknown etiology
   o Associated with infiltration of any organ system with eosinophils
   o Composed of 3 phases\(^2\)
     ▪ Prodromal phase:
       • Adult-onset asthma with or without allergic rhinitis
       • Preceding systemic vasculitis by several years
     ▪ Eosinophilic/tissue infiltration phase:
       • Peripheral eosinophilia and infiltration of eosinophils into organs
       • Typical organs: lung, gastrointestinal, skin
     ▪ Systemic vasculitic phase:
       • Necrotizing vasculitis that is clinically apparent
       • Any organ can be involved
2. Incidence, Prevalence\(^{12}\)
   o Mean age of onset: 48 years
   o Female to male ratio of 1.2:1
   o Estimated annual incidence of 1-3 per million
3. Risk Factors
   o History of severe asthma
   o Family history of systemic inflammatory disorders
   o Misconceptions
     ▪ Leukotriene receptor antagonists (zafirlukast, montelukast, pranlukast) can cause CSS\(^5\)
4. Morbidity
   o Morbidity\(^1\)
     ▪ Asthma almost always present
     ▪ Gastrointestinal involvement and nasal Staphlococcus may increase the risk of relapse
     ▪ Pulmonary infiltrates and granulomas\(^3\)
   o Cardiac involvement is common
     ▪ Eosinophilic endomyocarditis
     ▪ Coronary vasculitis
     ▪ Valvular heart disease
     ▪ Congestive heart failure
     ▪ Pericarditis
Neurologic involvement
- Peripheral neuropathy reported in 65-75% patients, especially mononeuritis multiplex
- CNS involvement less common

Skin involvement
- Erythematous, maculopapular or pustular lesions
- Non-thrombocytopenic palpable purpura
- Nodules

Gastrointestinal involvement
- Mesenteric ischemia
- Eosinophilic gastroenteritis leading to bloody diarrhea and intestinal perforation
- Eosinophilic peritonitis with ascites
- Rarely, pancreatitis and cholecystitis

Focal segmental glomerulonephritis is common but renal failure rare

Orbital inflammatory disease

5. Mortality
- Myocardial involvement is the most frequent cause of death
- 5 factor score at the time of initial assessment may predict 5-year mortality
  - 5 factors
    - Proteinuria > 1g/day
    - Serum creatinine > 1.58 mg/dL
    - Gastrointestinal tract involvement
    - Cardiomyopathy
    - CNS involvement
  - 5 year mortality
    - 12% if 0 factors
    - 26% if 1 factor
    - 46% if 3 or more factors

Diagnostics
1. History/symptoms
- Nonspecific systemic symptoms: fatigue, weakness, fever
- Pulmonary: dyspnea, cough, hemoptysis
- Musculoskeletal: arthralgias, arthritis
- GI: abdominal pain
- Skin: ulcers, nodules
- CNS: peripheral numbness/weakness/paresthesias
- Cardiac: chest pain, dyspnea
- Atopy found in 63.8% of patients
  - Eczema
  - Drug-induced allergy
  - Allergic rhinitis
  - Urticaria
- Can be unmasked while abruptly stopping or rapidly tapering glucocorticoids

2. Physical Examination at presentation
- Asthma most common finding (97.9-100%)
  - Usually precedes diagnosis of CSS
o Mononeuritis multiplex (77.1%)
o Weight loss (70.8%)
o Paranasal sinusitis (61.1%)
  - Usually precedes diagnosis of CSS
o Fever (57.3%)
o Myalgias (54.2%)
o Skin involvement (49%): palpable purpura, nodules, urticaria, livedo reticularis
o GI involvement (31.2%): abdominal pain, melena, hematemesis, diarrhea
o Renal involvement (26%): proteinuria (> 1 gram/day), hypertension, glomerulonephritis, renal insufficiency

3. Diagnostic Testing

o Diagnostic imaging
  - Chest Radiograph and chest CT scan
    • Abnormal in eosinophilic and vasculitic phases
    • Asymmetrical bilateral patchy migratory infiltrates, interstitial lung disease, or nodular infiltrates
    • Noncavitating lung lesions
  - Paranasal sinus films
    • Sinus opacification
  - Angiography
    • Can show mesenteric ischemia or renal involvement

4. Laboratory.

o Systemic: CBC with differential, LFTs, BUN/Cr, urinalysis, ESR, CRP, stool occult blood
  - Eosinophilia > 1000 cells/μL seen in > 80%1
o Rheumatoid factor may be positive
o ANA may be positive
o Hepatitis B and C serology
o HIV
o Plasma IgE elevated in 74% of patients

o Specific (% positive)
  • ANCA
    • Perinuclear ANCA (P-ANCA) - 60%7
    • Cytoplasmic ANCA (C-ANCA) - 10%7
    • 81% sensitivity, 98% specificity, 54% positive predictive value, 99% negative predictive value
    • ANCA testing can rule out ANCA-associated vasculitis but a positive result is not diagnostic8

5. Biopsy

o Surgical lung biopsy is the gold standard
  • Transbronchial biopsy is rarely helpful
o Skin, muscle, (sural) nerve biopsy
  • Perivascular eosinophilic inflammation
  • Necrotizing granulomas
o Renal biopsy is non-specific
6. Diagnostic Criteria
   o Clinical diagnosis
     - American College of Rheumatology: 4 of 6 features had 85% sensitivity and 99.7% specificity without features of vasculitis
       - Asthma
       - Eosinophilia or > 10%
       - Mononeuropathy or polyneuropathy
       - Non-fixed pulmonary infiltrates
       - Abnormalities of paranasal sinuses
       - Extravascular eosinophils on biopsy
   o Hammersmith criteria\(^{11}\)
     - Asthma
     - Eosinophilia > 1,500/mm\(^3\)
     - Systemic vasculities involving 2 or more extrapulmonary organs

Differential Diagnoses\(^{12,13}\)

1. Key Differential Diagnoses
   o ANCA-associated small-vessel vasculitis
     - Wegener's granulomatosis
     - Microscopic polyangiitis
     - Polyarteritis nodosa
   o Non-ANCA associated small-vessel vasculitis
     - Henoch-Schonlein purpura
     - Cryoglobulinemia
     - Hepatitis B and C
   o Allergic bronchopulmonary aspergillosis
   o Hypersesoinophilic syndrome

2. Extensive Differential Diagnoses
   o Other granulomatous arteritis: temporal arteritis, Takayasu's arteritis, seronegative spondylarthropathy
   o Other causes of eosinophilia: drug or parasite, chronic eosinophilic pneumonia, hypersensitivity pneumonia, rheumatoid arthritis
   o Vessel thrombosis: thrombotic thrombocytopenic purpura (TTP), antiphospholipid antibody syndrome
   o Sarcoidosis
   o Vessel stenosis or spasm: drug-induced vasospasm (ergotamines, cocaine), fibromuscular dysplasia
   o Goodpasture syndrome
   o HIV

Therapeutics\(^{2,12,14,18}\)

1. Treatment based on 5 Factor Score
   o Renal insufficiency (creatinine level >1.58 mg/dL)
   o Proteinuria higher than 1 gram/day
   o Gastrointestinal bleeding, perforation, infarction, or pancreatitis
   o Central nervous system involvement
   o Cardiomyopathy
   o A score of >1 benefit from steroids plus cyclophosphamide
2. Prednisone
   - Oral 1 mg/kg/day for 6 to 12 weeks and then tapered to 10 mg/day at 1 year as clinical disease resolves
   - For severe or rapidly progressive disease: methylprednisolone 1 g/day for 3 days
3. Cyclophosphamide
   - Oral: 2mg/kg/day, IV: 400-800 mg/day for 12 to 18 months
   - Intravenous pulse dosing may reduce side effects without reducing efficacy
   - Twelve cyclophosphamide vs 6 cyclophosphamide pulses has been found to decrease relapse rate
4. A drop in the patients eosinophil count and ESR indicates a response to treatment
5. The use of plasma exchange does not appear to be effective for acute treatment
6. Insufficient evidence to support the use of Azathroprine in place of cyclophosphamide
   - Interferon-alpha
   - Tumor necrosis factor (TNF)-alpha inhibitors
   - Intravenous immunoglobulin (IVIG)
7. Long-Term Care
   - Low dose steroids and immunosuppressive therapy (cyclophosphamide or azathroprine) to maintain remission
     - Oral cyclophosphamide may be replaced with azathroprine once clinical remission has occurred
     - For patients in continued remission at 12 months, the use of immunosuppressive medications may be slowly tapered
     - H2-blockers or proton-pump inhibitors may be used during long-term immunosuppressive therapy to prevent gastrointestinal ulcers
     - Consider prophylactic treatment with fluconazole orally for fungal infections
     - Trimethoprim-sulfamethoxazole 480 mg PO may be used for prophylaxis of pneumocystis carinii
   - Low dose oral or inhaled steroids may be used for persistent symptoms of asthma

Follow-up
1. Return to Office
   - Six month interval check-ups for relapse
   - While being treated with immunosuppressives, CBC and LFTs should be preformed periodically
   - While on immunosuppressives, patients should be monitored for infections
2. Referrals
   - Patients should be closely followed by a rheumatologist
   - Pulmonary referral for management
Prognosis
1. Most patients die within 1 year without treatment
2. 5 year survival > 65% with treatment
3. Clinical remission in more than 90% of patients after treatment
4. Approximately 26% of patients relapse after cessation of therapy
5. Mean survival is 9 years

Patient Education
1. Cleveland Clinic: http://my.clevelandclinic.org/default.aspx
2. Churg Strauss Syndrome Association: http://www.cssassociation.org/

References

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