Autoimmune diseases and the Heart

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Overview of Presentation

- **Vasculitis**
  - Takayasu arteritis
  - Giant Cell arteritis
  - Kawasaki disease

- **Vasculitis of Small or Medium-Sized Vessels**
  - Churg-Strauss Syndrome

- **Systemic Rheumatological Disorders**
  - Rheumatoid Arthritis
  - HLA-B27–Associated Spondyloarthropathies
  - Systemic Lupus Erythematosus
  - Antiphospholipid Antibody Syndrome
  - Scleroderma
  - Sarcoidosis
Presenting Cardiac Symptoms of Autoimmune Disease

- Pericarditis
- Myocarditis or myocardial fibrosis due to myositis or vasculitis with rhythm and conduction disturbances and diastolic or systolic heart failure
- Ischemic heart disease (coronary arteritis)
- Endocardial involvement with valvular disease and formation of thrombi
- Pulmonary hypertension secondary to concomitant lung disease or recurrent lung embolism
- Unexplained arterial thrombosis
- Syncope
- Arterial hypertension (Malignant)

Prevalence of Cardiac involvement in Autoimmune Disease

- Variable
- In general, clinical symptoms are uncommon
- Initial autopsy studies suggested high incidence of cardiac involvement
- Transesophageal echocardiogram and MRI done routinely show prevalence approaching that of autopsy
- Cardiac findings are uncommon at initial diagnosis but do increase in frequency over followup time

Takayasu Arteritis
“The pulseless disease”

- Large vessel vasculitis
- Incidence
  - 1-3 per million in US and northern Europe
  - As high as 1 in 3000 in Japan (features at autopsy)
  - Women affected 10 times more than men
  - Median age 25
- Pathogenesis
  - Exact cause unknown
  - Mononuclear cells infiltrate vessel wall
Aortic root dilation in Takayasu Arteritis
Features of Takayasu Arteritis

- Stenosis 3-4x more common than aneurysms
- Upper (and lower) extremity claudication
- Asymmetric pulses
- Aortic valve regurgitation due to aortic root aneurysms
- Hypertension associated with renal artery stenosis
- Coronary vasculitis in <5% of cases
- Mortality estimates of 3-35% in 5 years
Diagnosis of Takayasu Arteritis

- Suspect in young patient with hypertension
  - Very common cause of hypertension in adolescents in Asia, India, and Mexico
  - Asymmetric pulses
  - Vascular bruits
- Malaise, myalgias, arthralgias, night sweats, and fever
- ESR usually elevated with active disease but may be normal
- No single diagnostic test
Imaging Takayasu Arteritis

- MRI, CT
  - Visualize vessel aneurysm/stenosis
- PET
  - Visualize inflammatory activity in vessel wall
- Echocardiography
  - Left ventricular dysfunction in 20%
- Angiography
Treatment of Takayasu Arteritis

- High dose (1 mg/kg/day) prednisone
  - Tapering dose
- Refractory cases
  - cyclophosphamide (2 mg/kg) or
  - methotrexate (20 mg weekly)
- Relapse/Remission cycles common
- Long term immunosuppression often needed
- TNF blockade may be helpful
Mechanical therapy for Takayasu Arteritis

- Consider intervention for clinically important vascular stenosis
  - Stents more prone to restenosis than bypass grafts
- Aortic surgery with or without valve surgery for aortic aneurysm
Giant Cell arteritis

- Incidence of 18 in 100,000 in US
- Mean age 74
- Females > Males by 2-3:1
- 50% have features of polymyalgia rheumatica
Pathophysiology of Giant Cell arteritis

- Inflammation in Adventitial layer
- Initially high concentration of proinflammatory cytokines in vessel wall
  - IL-1
  - IL-6
  - TNF
  - Interferon-gamma
- High concentration of T cells
- Later stages demonstrate growth factors, promoting intimal growth and stenosis
Clinical features of Giant Cell Arteritis

- Severe headaches of new onset
- Temporal tenderness
- Visual loss
- Pain with chewing

- With elevated ESR, treatment should be initiated
  - If symptoms not improved in 1-3 days then alternative diagnosis should be considered
Cardiac Involvement of Giant Cell Arteritis

- 15% may involve aorta, subclavian artery
  - Similar features as Takayasu
  - Thoracic and abdominal aortic aneurysms
- Half of patients have cardiac disease
  - Secondary to aging vs Giant Cell arteritis?
Treatment of Giant Cell Arteritis

- Prednisone 0.7-1.0 mg/kg/day
  - Symptom improvement 1-3 days
  - Symptom resolution 1 week
  - Taper 2-4 weeks after ESR and Clinical symptoms resolved
- Low dose aspirin reduces incidence of blindness and stroke
- Anti-TNF monoclonal antibodies have not demonstrated efficacy
Kawasaki Disease

- Main cause of acquired heart disease in children in the US and Japan
- Mainly affects children <5 years of age
  - Rare after 8 years of age
- Male to Female predominance 1.5:1
- Incidence in Asian children 50-200/100,000
- Incidence in US 6-15/100,000
- Siblings have higher incidence (2%) than general
Pathogenesis of Kawasaki Disease

- Possible infectious cause?
  - Fever, rash, conjunctivitis, adenopathy

- Acute phase
  - Widespread inflammation
  - Macrophages, T lymphocytes
  - Increased levels of many cytokines
Clinical Definition of Kawasaki Disease

- Fever ≥5 days, without other explanation, plus at least four of the following:
  1. Bilateral conjunctival injection
  2. Mucous membrane changes— injected or fissured lips; injected pharynx or “strawberry” tongue
  3. Extremity abnormality—erythema of palms, soles, edema of hands, feet, or generalized or peripheral desquamation (hands, feet)
  4. Rash (polymorphous)
  5. Cervical lymphadenopathy (usually a single node >1.5 cm)

- Associated manifestations
  - Irritability
  - Sterile pyuria, meatitis
  - Perineal erythema and desquamation
  - Arthralgias, arthritis
  - Abdominal pain, diarrhea
  - Aseptic meningitis
  - Hepatitis
  - Obstructive jaundice
  - Hydrops of gallbladder
  - Uveitis
  - Sensorineural hearing loss
  - Cardiovascular changes

Cardiac manifestations of Kawaskai disease

- Pericardial effusion (30%)
- Mitral regurgitation (30%)
- Coronary aneurysms
- Myocarditis
- Aortitis
- Congestive heart failure
- Arrhythmias
- EKG changes
  - ST depression, T wave flattening/inversion
  - PR and/or QT prolongation
Coronary aneurysms

- Develop in 20-25% if untreated for 2 weeks
  - Usually appear 1-4 weeks after symptoms
  - Proximal artery > Distal
  - Half of the aneurysms will regress in 2 years
  - Giant aneurysms (>8mm) rare, but persist
  - Overall 2% mortality
    - Death occurs due to thrombosis and occlusion
- IVIG treatment decreases incidence to 5%
- May be clinically silent until 3rd or 4th decade!

Braunwald’s Heart Disease, 8th ed.

Coronary Aneurysm in Kawasaki Disease

Kane GC, Keogh KA. Involvement of the heart by small and medium vessel vasculitis. Curr Opin Rheumatol. 2009 Jan;21(1).
Treatment of Kawasaki Disease

- Early identification!
- IVIG 2g/kg single IV infusion
- Aspirin 80-100mg/kg/day until afebrile
  - Then 3mg/kg/day for about 8 weeks
  - Low dose aspirin indefinitely for coronary aneurysms?
- Steroids? Controversial!
- Consider bypass, percutaneous intervention in cases of giant aneurysms or stenosis
Churg-Strauss Syndrome

- Incidence of 2.4/1,000,000
- Peak age 35-50
- Allergic angiitis and granulomatosis
  - Asthma
  - Eosinophilia
  - Pulmonary infiltrates
  - Upper airway inflammation
- May involve
  - Kidneys
  - Neurologic system
  - Cutaneous lesions
  - Cardiovascular system
- Eosinophilic granulomatous infiltrates and vasculitis.
Pathogenesis of Churg-Strauss

- Not well understood
- May be precipitated by environmental exposure?
- P-ANCA more common than C-ANCA
- Th1 and Th2 lymphocytes
- Eosinophils
Cardiovascular involvement of Churg-Strauss

- Most common cause of death in Churg-Strauss
- 15-55% of Churg-Strauss cases
- Pericarditis
- Myocarditis
- Coronary arteritis
- Congestive heart failure (15-30%)
- Mesenteric ischemia
Treatment of Churg-Strauss

- **Acute phase**
  - Prednisone 1mg/kg/day
  - Consider IV methylprednisolone 1 gm/day if kidney, cardiac, or neurologic involvement
  - Also cyclophosphamide 2mg/kg/day (watch renal function)

- **Chronic**
  - Azathioprine (daily) or
  - Methotrexate (weekly)
Rheumatoid Arthritis

- Most common form of chronic inflammatory polyarthritis
- 1-3% incidence in general population
- Female to Male ratio 2:1
- Genetic predisposition but unknown cause

Braunwald's Heart Disease, 8th ed.
Clinical features of Rheumatoid Arthritis

- Symmetric polyarthritis
- Small and large joints
  - Metacarpophalangeal joints and wrists
  - Spares lumbar and thoracic spine and distal interphalangeal joints
Pericarditis in Rheumatoid Arthritis

- Symptomatic involvement in 0.5%
  - But may see activity in up to 40%
- Coexistent pericardial effusion common
  - Usually blood tinged fluid with neutrophils
- Can evolve into constrictive pericarditis
- Treated with NSAIDS, steroids, pericardiocentesis, pericardial window as needed
Other cardiac involvement of Rheumatoid Arthritis

- Frequent involvement of mitral and aortic valves
  - Rarely causes clinical problems
- Secondary pulmonary hypertension can develop from rheumatoid lung disease
- Heart block is rare
Prognosis of Rheumatoid Arthritis

- Decreased life expectancy
- Main cause of death is cardiovascular
  - Chronic inflammation
  - Chronic NSAID use
  - Atherogenic HDL production
Survival in Rheumatoid Arthritis

Incidence of CHF in Rheumatoid arthritis

Treatment of Rheumatoid Arthritis

- Anti TNF agents
  - Careful in patients with CHF
- Methotrexate
- Sulfasalazine
- Leflunomide
- Hydroxychloroquine
- Low-dose prednisone
- NSAIDS increase cardiovascular risk
HLA-B27–Associated Spondyloarthropathies

- Ankylosing spondylitis
- Psoriatic arthritis
- Inflammatory bowel disease–associated arthritis
- Postinfectious reactive arthritis

Most people with HLA-B27 gene (10% of US caucasian population) do not have spondyloarthropathy!
Clinical features of Spondyloarthropathies

- Entire spine involved
- Frequent sacroiliac joint involvement
- Large joint involvement asymmetric
- “Sausage digits”
Cardiovascular involvement in Spondyloarthropathies

- Frequent Aortic root disease
  - Dilatation
  - Aortic valve regurgitation
- Conduction disease in up to one third
  - Generally progressive
- Very rare involvement of pericardium, coronary arteritis
Treatment of Spondyloarthropathies

- Anti TNF agents
- NSAIDS
- Physical therapy

- Unclear whether these influence cardiovascular complications
Systemic Lupus Erythematosus

- Serositis
- Arthritis
- Glomerulonephritis
- Neurologic dysfunction
- Hemolytic anemia
- Thrombocytopenia
- Leukopenia
- 20% have antiphospholipid antibodies
  - Arterial and venous thrombosis
  - Pulmonary hypertension
  - Miscarriage
Pericarditis in SLE

- Clinically significant pericarditis in 25%
  - Autopsy series have shown 60-80% involvement
  - Tamponade <2%
  - Constrictive pericarditis is rare

- Pericardial effusion
  - Neutrophils
  - Elevated protein level
  - May occur as complication of renal failure

Braunwald's Heart Disease, 8th ed.
Coronary involvement in SLE

- Coronary arteritis infrequent
- But coronary atherosclerosis is prevalent
  - Chronic inflammation
  - Immune complex deposition
  - Antiphospholipid antibodies
- Acute coronary syndrome
  - Thrombosis related to antiphospholipid antibody
  - Embolism from Libman-Sacks endocarditis
Conduction problems in SLE

- Unusual in patients with SLE
- But infants born to mothers with SLE have higher incidence of complete heart block
  - Occurs in small number of mothers with anti-RO/SSA and anti-LA auto-antibodies

Braunwald's Heart Disease, 8th ed.
Valvular disease in SLE

- **Sterile vegetations**
  - Libman-Sacks endocarditis
  - Seen in up to 60% of patients by TEE
  - Not related to disease severity, disease activity, or disease duration
- **Most commonly mitral valve**
- **Valvular regurgitation**
- **Valvular thickening**
  - May lead to stenosis

Braunwald's Heart Disease, 8th ed.
Treatment of SLE

- Systemic treatment courses vary
- Pericarditis
  - NSAIDS
  - Steroids
- Pericardial effusions
  - Pericardiocentesis for large effusions or tamponade
  - Pericardial window for recurrent effusions
Antiphospholipid Antibody Syndrome

- Recurrent venous or arterial thrombosis (or miscarriage) combined with Antiphospholipid Antibody or Lupus anticoagulant
- Most commonly venous thrombosis
- Cardiac involvement similar to SLE
Cardiac Involvement in Antiphospholipid Antibody Syndrome

- Valve abnormalities
  - Thickening of leaflets
  - Irregular nodular excrescences
  - Vegetations (sterile)
  - Valve dysfunction
- Thrombotic and atherosclerotic coronary occlusion
- Intracardiac thrombus
- Pulmonary hypertension
- Ventricular hypertrophy and dysfunction

Treatment of Antiphospholipid Antibody Syndrome

- Longterm secondary prevention
- Coumadin for venous thrombosis
  - INR 2.0-2.5
- Aspirin for arterial thrombosis
Scleroderma

- Progressive systemic scleroderma
- CREST syndrome
  - Calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia
- Initially inflammatory, fibrosis in later stage
- Cutaneous and parenchymal fibrosis
  - Microvascular occlusive disease
  - Vasospasm
  - Vascular intimal proliferation
- Average age of onset 45-65 years
- Female predominance
Clinical Features of Scleroderma

- Raynaud phenomena in 90%
- Arthralgias (>90%)
- Proximal weakness (>60%)
- Esophageal dysmotility (>80%)
- Telangiectasias (90% in CREST, 60% in generalized disease)
- Pulmonary fibrosis (70% in generalized, 35% in CREST)
Cardiovascular involvement in Scleroderma

- Pulmonary hypertension
- Renal crisis
  - Hypertension, LV dysfunction
  - Treatment with ACE inhibitors
- Pericarditis
- Pericardial effusion
- Coronary vasospasm
- Coronary microvascular disease
Treatment of Scleroderma

- ? Cyclophosphamide may slow progression of pulmonary hypertension
- Endothelin antagonists and prostanoids improve pulmonary hypertension
  - Bosentan/Ambrisentan
  - Epoprostenol/treprostinil/iloprost
- Steroids can precipitate renal crisis
Sarcoidosis

- Noncaseating granulomatous inflammatory disease
  - Lung parenchyma
  - Adenopathy
  - Arthropathy
  - Myositis
  - Fever
  - Renal, liver, skin, eye, and cardiac disease

- Incidence
  - 10 per 100,000 in whites
  - 35 per 100,000 in African Americans
  - 50 to 60 cases per 100,000 in Scandinavians

Cardiovascular Involvement in Sarcoidosis

- Granulomatous infiltration of heart (25%)
  - Often asymptomatic (up to 95%)
  - Endomyocardial biopsy may miss patchy infiltrates
  - Nuclear imaging can detect fibrosis/scar

- Clinically heterogeneous effects
  - Dilated cardiomyopathy
  - Congestive Heart Failure
  - Pericarditis
  - Conduction system disease
  - Pulmonary artery hypertension (due to pulmonary fibrosis)

Braunwald’s Heart Disease, 8th ed.
## Incidence of Cardiac Findings in Sarcoidosis

<table>
<thead>
<tr>
<th>Condition</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>AV block</td>
<td>26%-62%</td>
</tr>
<tr>
<td>Bundle Branch Block</td>
<td>12%-61%</td>
</tr>
<tr>
<td>Supraventricular Tachycardia</td>
<td>0%-15%</td>
</tr>
<tr>
<td>Ventricular Tachycardia</td>
<td>2%-42%</td>
</tr>
<tr>
<td>Congestive Heart Failure</td>
<td>10%-30%</td>
</tr>
<tr>
<td>Sudden Cardiac Death</td>
<td>12%-65%</td>
</tr>
</tbody>
</table>

Diagnosing Cardiac Sarcoidosis

- History, EKG nonspecific
- Endomyocardial biopsy has low sensitivity (due to patchy granulomas) but high specificity
- Echocardiography nonspecific
  - Wall motion abnormality in non-coronary distribution is suspicious
- Gallium-67 Scintigraphy detects inflammation, but has a low sensitivity
- FDG-PET demonstrates hypermetabolic activity in cardiac granulomas
- MRI with Gadolinium delayed enhancement
  - Myocardial necrosis and wall motion abnormalities in noncoronary distribution
  - High sensitivity and specificity

Treatment of Sarcoidosis

- Corticosteroids
- Methotrexate can be added
- Some studies suggest stabilization of cardiac findings with therapy
- Questionable duration of therapy
- Imaging with MRI or PET to guide therapy?
- No data on cardiac outcomes

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Summary

- **Chronic inflammatory diseases have variable cardiac sequelae**
  - Autopsy/imaging involvement greater than clinical expression
- Generally treatment targeted to underlying autoimmune disease as well as cardiac issues
- Unclear what effect treating autoimmune disease has on cardiac disease
- No clear guidelines on followup for most autoimmune diseases
References

- Kane GC, Keogh KA. Involvement of the heart by small and medium vessel vasculitis. *Curr Opin Rheumatol.* 2009 Jan;21(1).