Overview of Pulmonary Sarcoidosis

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Objectives

- Review epidemiology, pathophysiology and manifestations of sarcoidosis
- Describe patterns of pulmonary involvement
- Outline diagnostic findings
- Describe approaches to management

Background

- First described by Norwegian dermatologist, Caesar Boeck in 1889
- Named sarcoidosis due to similarity in appearance to sarcoma
- 90% of patients with sarcoidosis will have pulmonary manifestations
- 50% of patients have only pulmonary disease

Pathophysiology

- Immune mediated/ inflammatory condition
- Thought to follow a “two hit” model
  - Genetic predisposition
  - Possible environmental or infectious trigger
- Multisystem non-caseating granuloma formation
- Theories regarding granuloma formation being protective of an unknown agent to prevent dissemination and/or local damage

Epidemiology

- Increased incidence in Afro-Caribbean, Middle Eastern and Scandinavian ethnic groups
- Different diagnostic yields and prognoses among ethnic groups
  - Higher yield in bronchoscopic mucosal biopsies shown in African ethnicity
  - More severe symptoms and course in African ethnicity
Presentation

- Acute sarcoidosis (Lofgren syndrome)
  - Fever, malaise, arthralgia, erythema nodosum, cough, uveitis
  - Typically self-limiting

- Chronic sarcoidosis
  - Often asymptomatic
  - May be incidental finding on imaging or hypercalcemia on labs
  - Symptoms depend on system involved
  - Does not have to be preceded by acute phase

Patterns of pulmonary sarcoidosis
Tissue is the issue

Non-caseating granuloma
Bronchoscopic options

- Flexible bronchoscopy
  - Transbronchial biopsy, endobronchial biopsy, cryobiopsy, bronchoalveolar lavage (culture, lymphocytosis, d-dimer, CD4:8 ratio)
  - Helpful for diffuse disease process
  - Rule out alternative diagnoses

- Endobronchial ultrasound
  - Transbronchial needle aspiration
  - Direct visualization of enlarged thoracic lymph nodes

Surgical options

- Superficial lymph node excision (always biopsy the most accessible location)
- Subcutaneous nodules
- Enlarged parotid gland
- Skin biopsy
- Mediastinoscopy
- VATS

When can we avoid biopsy

- Asymptomatic: stage 1 with low risk for malignancy
- Reasonable to monitor for 12-24 months
- Classic: Lofgren syndrome (rheumatid arthritis)
- Do not biopsy erythema nodosum, false negative
Differential and mimics

- Active TB: rule out sputum AFB x3 (or 1 with PCR via BAL)
- Latent TB: skin test or interferon-gamma release assay (quantiferon)
- Histoplasmosis
  - Antigen 6A via blood, sputum, BAL (if performed), fungal culture, pathology
- Blastomycosis
  - Spores, 6A, tissue culture and pathology, antigen sensitivity urine > blood but careful of cross-reaction
- Lymphoma (e.g. Hodgkin disease), lymphoproliferative disorders, germ cell tumors, breast cancer, renal cell carcinoma, leiomyosarcoma
  - Pathology in addition to clinical presentation
- SCLC/NSCLC
  - Risk stratification, tissue analysis
- Hypersensitivity pneumonitis
- Pattern of granulomas, clinical presentation
- Pneumocystis (e.g. Berylliosis)
  - Co-occupational history, BAL analysis if applicable

Pulmonary hypertension in sarcoidosis

- Categorically falls into WHO Group IV
- Incidence between 5-25% of patients with sarcoidosis
- Found in nearly 75% of patients referred for lung transplantation
- Increased all-cause mortality when compared to sarcoidosis patients without PH
- When to suspect?
  - Dyspnea out of proportion to spirometry
  - Low DLCO with normal spirometry/lung volumes
  - Any cases of advanced stage IV parenchymal involvement especially with chronic oxygen dependence
  - Cardiac sarcoidosis
  - If available refer to pulmonary hypertension specialty clinic

Management

- Serial monitoring
- Watchful waiting
- Lifestyle modifications
- Immunosuppression
- Pulmonary rehabilitation
- Lung transplantation

Monitoring

- Vitals
  - Bp 3-4 months and then yearly if stable/improved
  - Review of systems and physio or more detailed for nolake side, peripheral pulses, pulmonary

- Routine blood work
  - Initial workup: complete blood count (CBC), uric acid, autoimmune markers, liver function tests, renal function tests, activated partial thromboplastin time (APTT), prothrombin time (PT), international normalized ratio (INR), albumin, cholesterol, triglycerides, creatinine, blood urea nitrogen (BUN), uric acid, liver function tests, renal function tests, activated partial thromboplastin time (APTT), prothrombin time (PT), international normalized ratio (INR), albumin, cholesterol, triglycerides, creatinine, blood urea nitrogen (BUN), uric acid

- Pulmonary function tests
  - Every 6 months initially then every 2 to 4 years

- Serial imaging
  - Chest X-ray yearly
  - HRCT/PET as needed

- ECG
  - Yearly and prn new symptoms

- Eye exam
  - Asymptomatic patients: every 6 months
  - Patients on hydroxychloroquine: every 3 months

Lifestyle modifications

- Smoking cessation
- Weight reduction
- Exercise
- Good sleep habits
- Screen for sleep disordered breathing
- Avoidance of alcohol (in setting of certain therapeutic)
- Healthy nutrition including minimizing processed foods
When to treat?

- Severe symptoms
- Progressive course (symptoms, PFTs, radiographic)
- Pulmonary involvement stage III (not an absolute indication but less likely to resolve spontaneously than stage I or II; stage IV or fibrosis less likely to be steroid-responsive)
- Life or limb threatening extra-pulmonary manifestations
  - E.g., cardiac sarcoidosis with ventricular arrhythmias, severe ocular manifestations, neurosarcoidosis
- Infectious mimics have been ruled out

Therapeutic options

- Systemic glucocorticoid
  - First-line therapy
  - Start with short course
  - Goal is always to use lowest effective dose and discontinue if able

- Inhaled glucocorticoid
  - Conflicting results regarding efficacy
  - May be helpful in borderline cases

- Steroid sparing agents
  - Reserve for severe, progressive, relapsing cases
  - Use in steroid-intolerant patients
  - Use if unable to taper steroids to below 10-15 mg/day

Fun fact: There are no FDA-approved treatment options for the management of sarcoidosis.
**Controversies regarding chronic steroid use**

- No evidence to show decrease in progression to fibrotic disease when compared to placebo
- Minimal improvement in FEV1/FVC as well as radiographic evaluation
- Possibly increased rate of relapse when compared to placebo

**Systemic glucocorticoid therapy**

- **Dosing**
  - Starting with prednisone 0.3-0.6mg/kg (20-40mg daily) for 1-3 months, then when improved slow taper by 5-10 mg every 1-3 months for a total course of 6-12 months
  - If resolved can discontinue and enter monitoring phase
  - If relapsed resume lowest effective dose
  - Higher dosing may be considered for extra-pulmonary manifestations

- **Prophylaxis**
  - Consider ppi if significant symptoms
  - Consider PJP prophylaxis if on dual immunotherapy or other immunodeficiency

- **Monitoring**
  - Consider FRAX and DEXA scan at initiation
  - Careful with vitamin D calcium supplementation (vitamin D production by granulomas, risk of hypercalcemia)

**Inhaled glucocorticoid therapy**

- **Conflicting data**
- May provide symptomatic benefit, unlikely to affect PFTs
- Budesonide, fluticasone have been tried
- May be reasonable to trial for 1-2 months in symptomatic patients in whom the indications for systemic therapy are not strong
- Consider as an aide to weaning in patients who have responded to systemic glucocorticoids
Steroid sparing agents

- **Methotrexate**
  - Most commonly used second line agent
  - Monitor hepatic labs, co-administer folic acid, contraception in childbearing age
  - Concern for associated ILD which can be difficult to distinguish from progression of sarcoid

- **Leflunomide**
  - Causes hepatic impairment, avoid alcohol, contraception in childbearing age
  - Concern for associated ILD which can be difficult to distinguish from progression of sarcoid

- **Leflunomide**
  - Rarely used as single drug, avoid alcohol, contraception in childbearing age
  - Consider checking TPMT activity prior to initiation, contraception in childbearing age

- **Azathioprine**
  - Rarely used as single drug, avoid alcohol, contraception in childbearing age
  - Consider checking TPMT activity prior to initiation, contraception in childbearing age

- **Mycophenolate**
  - Relatively well tolerated symptomatically, less data than the agents above

- **TNF-a antagonists**
  - Eg infliximab or adalimumab
  - Limited data, consult your friendly rheumatologist

  - More myelosuppression, immunosuppression

Interventional therapeutic approaches

- Bronchoscopic balloon dilation
- Bronchoscopy balloon dilation
- Tracheobronchial stents

Pulmonary rehabilitation

- Trials have shown increased exertional capacity and fatigue
- Qualifying indications:
  - Pulmonary fibrosis/interstitial lung disease with exacerbation
  - Interstitial lung disease with change in respiratory symptoms
  - Pulmonary hypertension with change in respiratory symptoms
Lung transplantation

- When to consider
  - Stage IV pulmonary involvement
  - Associated pulmonary hypertension with NYHA Class IV
  - Oxygen dependence
  - Severe cardiac and pulmonary involvement (heart-lung transplant)

- Recurrence considerations
  - Asymptomatic non-caseating granulomas frequently identified
  - Clinically significant organ dysfunction due to sarcoidosis rare
  - Survival rates similar to other indications

References