Applications of Radiologic modalities in the understanding and management of Pulmonary Sarcoidosis

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Sarcoidosis: Introduction

* Multisystem Granulomatous Disease of unknown etiology
* Characterized pathologically by the accumulation of noncaseating epithelioid granulomas in involved organs
* Multiple organ systems usually affected:
  * Pulmonary involvement occurs in >90% of patients
  * Extra-pulmonary disease seen in up to 30% of patients
* Frequently presents with bilateral hilar adenopathy, pulmonary infiltration, and ocular and skin lesions
* Lymph nodes, liver, spleen, sinuses, salivary glands, heart, kidney, nervous system, bones, and other organs may also be involved
Epidemiology

- Commonly affects young and middle-aged adults
  - Onset usually in third or fourth decade
  - Slightly higher incidence in females
- Geographic and ethnic clustering seen in distribution of disease
  For instance, highest incidence noted in:
  - Northern Europe
  - Countries with temperate climates; springtime especially
  - Black Americans; annual incidence is ~three times that of white Americans (35.5 vs 10.9/100,000)
- In carriers of “susceptibility” genes on chromosomes 3p and 5q11.2 vs. carriers of “protective” genes on 5p15.2
- Epidemiologic data highlights potential role of environmental and immunogenetic factors
Clinical Presentation

- Clinical presentation widely varies on patient specific factors as well as extent of organ involvement.
- Cough, dyspnea and chest pain are frequent complaints.
- 30-60% of patients with pulmonary sarcoidosis evident on chest radiograph are asymptomatic.
- Fever, night sweats, malaise, and weight loss are also common and may relate to cytokines associated with inflammation.
- Extra-pulmonary manifestations may occur before, coincide with, or after pulmonary manifestation.
  - For instance, Skin lesions with or without concomitant pulmonary symptoms, right upper quadrant abdominal pain, or peripheral lymphadenopathy may be seen at presentation.
Diagnosis

* No single test confirms the diagnosis of Sarcoidosis; Sarcoidosis is thus usually a diagnosis of exclusion.

* Relevant diagnosis include:
  * Clinical Evidence
  * Histopathology showing non-caseating granuloma
  * Radiographic Evidence
Patient
Demonstration

Ms. J
Introduction to our patient: Ms. J

- Ms. J is a previously healthy 33 year old African American woman who presents with discrete subcutaneous nodules in her trunk and extremities. She also has had fatigue and mild subjective fever.
- Review of system is otherwise negative; No dyspnea, or cough. Physical exam reveals no other lesions or organomegaly.
- Biopsy of a nodule reveals noncaseating granuloma.
Ms. J: Diagnostic workup

- Clinical Evidence for Sarcoidosis
- Histopathology showing noncaseating granuloma
- Radiographic Evidence
  - What are the radiologic test available?
Menu of Radiologic Tests

- Plain Radiograph, PA & Lateral
  - Initial test of choice; inexpensive; used for staging
  - Limitations: not sensitive to early interstitial process

- High Resolution Computerized Tomography
  - Detailed assessment of pulmonary parenchyma
  - Limitations: expensive, increased dose of radiation

- Gallium 67 scan & PET scan
  - Assessment of disease activity
  - Diagnosis of extra-pulmonary involvement
  - Very sensitive, Not specific
Let's review the relevant features of a normal chest x-ray (CXR)
Companion Patient #1: Normal CXR, frontal

Features

- Thin Right Paratracheal stripe
- Aortic arch
- Main pulmonary artery
- Normal Right and Left Hilum
- Well defined heart borders

Fig. 1a – Features of CXR

BIDMC “PACS”
Companion Patient#1: Normal CXR, frontal

**Features**

- Thin Right Paratracheal stripe
- Aortic arch
- Main pulmonary artery
- Normal Right and Left Hilum
- Well defined heart borders

*Fig. 1b – Features of CXR*

*BIDMC “PACS”*
Ms. J: Initial CXR, frontal

Features

Thick Right Paratracheal stripe

Left, Right Hilar enlargement

Triad:
“1, 2, 3” sign of lymphadenopathy

Fig. 2 –Ms. J’s CXR, frontal

BIDMC “PACS”
Ms. J: Initial CXR, frontal

**Features**

- Thick Right Paratracheal stripe
- Left, Right Hilar enlargement

**Triad:**

- “1, 2, 3” sign of lymphadenopathy
- Normal Pulmonary vasculature
- No lung mass or consolidation
- No pleural effusions

Fig. 2 – Ms. J’s CXR, frontal

BIDMC “PACS”
Ms. J: Initial CXR, Lateral

Findings

* Hilar Lymph node enlargement

Fig. 3 – Ms. J’s CXR, Lateral

BIDMC “PACS”
Ms. J: Laboratory workup

Laboratory workup:

- CBC count with differential and platelets: within normal limits
- ASO titer Negative
- Non reactive RPR
- Hepatitis B and C serologies: Negative
- ANCA: Negative
- PPD: negative
Ms. J: diagnostic assessment

- Patient has subcutaneous nodules and bilateral adenopathy on chest radiograph; workup is otherwise unremarkable
- No evidence of malignancy or infection
- Most likely diagnosis is Sarcoidosis
- Next step is to assess the pulmonary parenchyma for involvement using CT with intravenous contrast
- Parenchymal involvement in Sarcoidosis usually manifests as diffuse reticular infiltrates, but focal infiltrates, acinar shadows, nodules, and rare cavitation are also seen
- Pleural effusion occurs in <10% of patients
Ms. J: Initial CT scan, soft tissue

Findings

- Bilateral hilar lymph nodes enlargement is evident adjacent to bronchiole tree
- 15.7 x 26.6 mm node

Fig. 4 – Ms. J’s + C, axial chest CT scan, soft tissue window

BIDMC “PACS”
Ms. J: Initial CT scan, lung window

Findings

- Bronchial wall thickening
- Nodular opacities

Fig. 5 – Ms. J’s + C, axial chest CT scan, Lung window

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Pulmonary Sarcoidosis

Idiopathic Interstitial Lung Disease

www.nhlbi.nih.gov
Pathogenesis: delayed hypersensitivity

1. Unknown antigenic stimulus triggers an immunologic and inflammatory response in susceptible individuals.

2. Initial reaction leads to activation T-lymphocytes.

3. Activated T-lymphocytes secrete lymphokines and attract more lymphocytes and macrophages.

4. Inflammatory cells accumulate in the alveolar septa and spaces, resulting in "Alveolitis".

5. Persistent alveolitis attracts blood monocytes to the lung, with ultimate granulomata formation.

Lymphocytic Alveolitis

Granuloma
Pulmonary Sarcoidosis: Staging

- **Stage 0**: Normal chest radiograph
- **Stage I**: Hilar adenopathy alone
- **Stage II**: Hilar adenopathy with parenchymal involvement
- **Stage III**: Parenchymal involvement alone
- **Stage IV**: Pulmonary fibrosis
Laboratory Tests

- Common Laboratory tests:
  - Leukopenia
  - Elevated ESR
  - Hypercalcemia in 5%
  - Hypercalciuria in 20%
  - Angiotensin-converting enzyme (ACE) levels
    - Commonly elevated in active disease
    - Neither sensitive nor specific enough to be of diagnostic value
**Diagnostic tools**

- **Transbronchial biopsy**
  - Noncaseating granuloma
  - has a yield of 75–90%
  - Biopsy may be unnecessary in stage I disease with a presentation highly suggestive of sarcoidosis

- Pulmonary function tests may show obstruction or restriction, with diminished diffusion capacity

- Bronchoalveolar lavage: increase in lymphocytes with a high CD4/CD8 ratio; used to follow disease activity, but not for diagnosis
Pulmonary Manifestations

- Abnormal chest radiograph in asymptomatic patient

- Acute/Subacute pulmonary sarcoidosis:
  - Progressive dyspnea, dry cough and chest discomfort
  - +/- constitutional symptoms: fatigue, malaise, night sweats

- Chronic pulmonary Sarcoidosis
  - Pulmonary fibrosis leading to worsening dyspnea with potentially fatal respiratory failure

- Airway obstruction: wheeze, +/- stridor, cough, dyspnea, hemoptysis
Let’s continue following our patient’s clinical course ...
Ms. J: Interim Clinical Course

**Uveitis**

- Ms. J later developed decreased vision in her right eye, and was diagnosed with uveitis.
- She was seen by ophthalmology and treated with corticosteroids drops.
- Uveitis resolved without complications.
- She continued to be seen on an outpatient basis in Pulmonary clinical.
Extrapulmonary Manifestations

- Dermatologic (~20%):
  - Lupus pernio, Erythema nodosum, subcutaneous nodules, maculopapular rash

- Ophthalmic (~20%)
  - Uveitis, retinal vasculitis, keratoconjunctivitis

- Reticuloendothelial:
  - Peripheral Lymphadenopathy, hepatomegaly, splenomegaly

- Musculoskeletal:
  - Acute arthritis, chronic arthritis with periosteal bone resorption

- Renal and electrolytes:
  - Hypercalcidiuria, hypercalcemia, nephrocalcinosis

- Cardiovascular:
  - Arrhythmias, chronic pulmonary hypertension and core pulmonale

- Nervous system:
  - Meningitis, cranial nerve palsies (facial palsy), central DI, hypothalamic hypopituitarism

- Exocrine glands:
  - Enlarged salivary glands, xerostomia
Ms. J: New symptoms

- Ms. J later came to the pulmonary clinic with complaints of progressive respiratory symptoms over the past 1-2 months.

- She complained of dyspnea on exertion with inability to walk a flight of stairs without stopping to catch her breath.

- She also complained of polyarthralgias and fatigue, worse than previously.
Ms. J: Follow-up CXR, frontal

**Features**

- Thick right **paratracheal stripe**
- Mediastinal & Hilar lymph node enlargement (nodular contours)
- Diffuse reticular pattern in the lungs periphery bilaterally

Fig. 6 – Ms. J, Follow-up frontal CXR

BIDMC “PACS”
Ms. J: Follow-up CT scan, coronal

**Findings**

- Marked Mediastinal Adenopathy

Fig. 7 – Ms. J, Followup coronal CT

BIDMC “PACS”
Ms. J: Follow CT scan, axial - trachea

Findings

- Large paratracheal lymph node
- Reticular and Nodular pattern
- Groundglass opacities in peribronchiole region

Fig. 8 – Ms. J, Followup axial CT, lung window at the level of trachea

BIDMC “PACS”
Ms. J: Follow CT scan, axial - carina

Findings

- Reticular and Nodular pattern
- Groundglass opacities in peribronchiole region

Fig. 9 – Ms. J, Followup axial CT, lung window at the level of carina

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Companion patient #3: HRCT

Findings

Bronchial wall thickening

Fig. 10 – HRCT, lung window at the level of the carina

Courtesy of Dr. Cantin
Companion patient #4: HRCT

Findings

- Bronchial wall thickening
- Lymphadenopathy

Fig. 11 – HRCT, lung at the level of the bronchioles

Courtesy of Dr. Cantin
Companion patient #5: HRCT

Findings

Reticular nodular opacities with right upper field predominance typical for sarcoidosis

Fig. 12- HRCT, lung at the level of the corina

Courtesy of Dr. Boiselle
Prognosis

- 20% of patients with lung involvement suffer irreversible lung impairment, with progressive fibrosis, bronchiectasis, and cavitation.
- Outlook is best for patients with stage I disease.
- Outcome is worse with radiographic parenchymal involvement.
- Erythema nodosum is associated with a good outcome.
- Death from pulmonary insufficiency occurs in about 5% of patients.
Corticosteroids

Oral prednisone are indicated for:

- Constitutional symptoms
- Hypercalcemia
- Iritis
- Arthritis
- CNS involvement
- Cardiac involvement
- Hepatitis
- Cutaneous lesions other than erythema nodosum
- Symptomatic pulmonary lesions

Long-term therapy is usually required over months to years depending on extent of disease.

Immunosuppressive drugs and cyclosporine have been tried when benefits of corticosteroid therapy have been exhausted.

Anti-TNF therapy with infliximab has shown some promise in extrapulmonary sarcoidosis.
Ms. J: Great Treatment Outcome

Ms. J ultimately responded very well to systemic steroids. She had symptomatic relief of dyspnea, resolution of subcutaneous nodules and some reversal of parenchymal involvement of Sarcoidosis as well as diminished adenopathy!!!!

Fig. 12- HRCT, lung at the level of the corina

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Summary

- Multisystem granulomatous disorder of Unknown etiology
- Hallmark: Noncaseating epitheloid granulomas
- Heterogeneous Disease
  - Variable presentation & prognosis from asymptomatic to death from respiratory failure
  - Accurate diagnosis, appropriate treatment and proper followup is essential
- Radiologic evaluation is a requirement of diagnosis and facilitated management of patients with Sarcoidosis
References

- Up-to-date: Clinical Manifestations of Sarcoidosis
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