Pulmonary Coccidioidomycosis

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Clinical Manifestations of Coccidioidomycosis

- Asymptomatic (60%)
- Symptomatic Primary Pneumonia (35%)
- Erythema multiforme, erythema nodosum ("Valley Fever") (5%)
- Disseminated or Chronic Management (5%)

adapted from Kirkland and Fierer, Emerging Infect Dis, 1996
Common presenting symptoms of pulmonary coccidioidomycosis

- Cough
- Pleuritic chest pain
- Fever
- Usually acute (over days)
- May be difficult to distinguish from community-acquired pneumonia (“CAP”) that is due to bacterial etiology
Primary coccidioidal pneumonia is a common cause of community-acquired pneumonia or “CAP” in Arizona

- 54 patients in a primary care and urgent care clinic in Tucson, AZ diagnosed with CAP during 2 time periods:
  - December 2003 through February 2004
  - May 2004 through August 2004
- 16 (30%) were seropositive for coccidioidomycosis (CI 16 - 45%)

Valdivia et al, Emerg Infect Dis, 2006; 12:958
Coccidioidal pneumonia, Phoenix, Arizona USA, 2000–2004

- Evaluated patients with acute pneumonia at Mayo Clinic, Scottsdale
- 59 subjects accrued
  - 35 completed paired serology
- 6 (17%) seroconverted
  - 95% confidence interval (7-34%)
  - rash more common ($p = 0.002$)
  - no other factors associated with coccidioidomycosis

Kim et al, Emerg Infect Dis, 2009;15:397
Symptoms suggestive of pulmonary coccidioidomycosis

- Night sweats
- Fatigue
- Rash
- Headache
- Weight loss
- Symptoms persisting for weeks
Rashes and pulmonary coccidioidomycosis

- Toxic erythroderma
  - diffuse, red, scaly

- Erythema nodosum
  - over lower extremities
  - violaceous
  - painful
  - usually in women

- Erythema multiforme
  - target lesions
  - often in a “necklace” distribution
Rashes associated with primary pulmonary coccidioidomycosis

- Toxic erythema
- Erythema multiforme
- Erythema nodosum

(from D. Pappagianis)
“Desert Rheumatism”

- Arthralgias and arthritis associated with primary pulmonary coccidioidomycosis
- Usually occurs in association with erythema nodosum in women
- Ankle, wrist, knee, most common
- Usually symmetric
Coccidioidomycosis as a cause of chronic fatigue

- 48 subjects with symptomatic coccidioidomycosis were studied
- 65% had significant fatigue as measured by a validated scale
- Associated with a low body mass index (BMI)
- Over 4 months, fatigue significantly improved

Bowers et al, Med Mycol 2006; 44:585
The chest radiograph in pulmonary coccidioidomycosis

• Usually focal
• May be upper or lower lobe
Distinctive radiographic features

• Dense infiltrate
• Upper lobe
• Associated hilar or mediastinal adenopathy
Characteristic X-ray

January 12, 2008

March 13, 2008
Another example
Diffuse or “miliary” pulmonary coccidioidomycosis

- Occurs in highly immunocompromised patients
  - presentation of AIDS in coccidioidal endemic region
  - manifestation of fungemia
- May also occur from high inoculum exposure
  - archeology
Diffuse pulmonary coccidioidomycosis in an AIDS patient

from JN Galgiani, PPID 2009
High-inoculum exposure

Day 1

Day 4

Larsen et al, Am Rev Respir Dis 1985; 131:797
When to suspect coccidioidal pneumonia

- Fatigue
- Headache
- Night sweats
- Weight loss

- Upper lobe infiltrate
- Dense pulmonary infiltrate
- Hilar or mediastinal adenopathy

- Failure to improve with antibiotics
- Peripheral blood eosinophilia
Complications of primary pulmonary coccidioidomycosis
Pulmonary residua

• Nodules
• Cavities
• Pyopneumothorax
• Chronic pulmonary coccidioidomycosis
Nodules

• Resolution of initial pulmonary infiltrate
• Usually benign course
  - may cavitate
  - generally resolve over 1-5 years
• Unless evolution from infiltrate observed, difficult to distinguish from pulmonary malignancy
Example: infiltrate into nodule

Oct 1, 2008

Oct 10, 2008

Oct 31, 2008
Solitary coccidioidal pulmonary nodule
Diagnostic approach to nodules

• Observation
  - non-smoker
  - positive serum coccidioidal serology positive
  - obtain plain chest radiograph every 3 months

• PET scans are frequently positive
  - see Reyes et al, Lung 2014; 192:589

• Biopsy
  - smoker
  - negative coccidioidal serology
PET scan in pulmonary coccidioidomycosis
Modalities available for biopsy of pulmonary nodules

- Bronchoscopy with transthoracic biopsy
- Percutaneous fine-needle aspirate - false negative result in ~25-50%
- Video-assisted thoracotomy biopsy
- Open thoracotomy
Cavities

• Cavitations of previous nodules
• May be asymptomatic or symptomatic
  - Cough
  - Hemoptysis
  - Pleuritic chest pain
  - Positive sputum culture
• Less likely to close if >4 cm or present >1-2 years
• May become secondarily infected
Chest radiographs of coccidioidal cavities
Pyopneumothorax

• Occurs when a subpleural cavity ruptures into the pleural space
• Results in lung collapse with pleural fluid collection
• Sudden dyspnea and pleuritic chest pain most common presentation
Radiographic appearances of coccidioidal pyopneumothorax
CT scan of cavity associated with pyopneumothorax
Chronic pulmonary coccidioidomycosis

- Uncommon
- Occurs in patients with chronic lung disease
- Monitor course with sputum culture and serology
Chronic pulmonary coccidioidomycosis
Diagnosis
Issues of diagnosis

• Most cases are diagnosed based on positive serology
  - some patients, particularly with primary pneumonia, are never positive

• Sputum culture is may be positive if obtained
  - KOH is insensitive

• There is a need for more organism-based diagnostic tests
  - antigenic, genomic
Approach to the patient with suspected primary pulmonary coccidioidomycosis

- Obtain chest radiograph
- Obtain serology
- Obtain sputum for fungal culture
  - first morning specimen
  - obtain even if production is scant!
  - Alert the laboratory!
    - *Coccidioides* is a major laboratory hazard
- Follow and repeat testing
Treatment
Treatment of primary pulmonary coccidioidomycosis

• Most patients with primary pulmonary coccidioidomycosis will not require therapy

• Consider therapy if:
  - symptoms are on-going and not improving after 8 weeks
  - intense night sweats for 3 weeks
  - there has been a >10% loss of weight
  - infiltrate >1/2 lung or both lungs
  - prominent or persistent hilar adenopathy
  - IgG titer ≥1:16
  - inability to work
  - age > 55 years

Galgiani et al., Clin Infect Dis 2005; 41:1217
Treatment vs non-treatment of primary pulmonary coccidioidomycosis

- We performed a prospective, observational study of 105 patients with primary pulmonary coccidioidomycosis
- 54 were prescribed antifungals
- 51 were not
- Patients prescribed therapy had higher clinical severity scores
  - based on symptoms, coccidioidal IgG titer and culture

Ampel et al., Clin Infect Dis 2009; 48:172
Results

• There was no difference in rate of improvement between those treated and those not treated

• None of the untreated patients had any complications

• Two of the treated patients developed disseminated infection after prolonged courses of azole therapy
• 36 patients with primary pulmonary coccidioidomycosis followed for 24 weeks. Twenty received antifungal therapy.
Conclusions

• If a patient with primary pulmonary coccidioidomycosis is already improving when seen, no antifungal therapy is indicated.

• Therapy is indicated in those with persistent signs and symptoms of active pulmonary infection:
  - should be continued at least 6 months
  - patients should be followed for at least 1 year after therapy is discontinued

• Antifungal therapy has not been shown to prevent subsequent dissemination and is not recommended.
Primary pulmonary coccidioidomycosis in special hosts

- Patients with suppressed cellular immunity are at ↑ risk for severe or disseminated disease
  - HIV infection
  - 2nd & 3rd trimester of pregnancy
  - Patients on corticosteroids
  - Patients with allogeneic transplants
  - Patients on TNF-α inhibitors

- Most clinicians would treat
Sex, age, and race

• Males > females for symptomatic coccidioidomycosis
• Risk for symptomatic coccidioidomycosis increases as age > 60 years
• Black men are at increased risk for disseminated disease
  - Filipino men appear to also be at increased risk
  - There is no obligation to start therapy but close follow-up is advised
    • every 6 - 12 weeks for the 1st year

Nodules and cavities

- Nodules are generally benign sequellae of primary pulmonary infection
  - do not require therapy
  - they do not enlarge over time
    - if they do, work-up for malignancy

- Cavities are more problematic
  - consider therapy if
    - persistent cough
    - hemoptysis
    - pleuritic chest pain
  - be aware of secondary infection
    - air-fluid level
  - consider surgical extirpation if
    - non-closure after 1-2 years
    - >4 cm
Which antifungal?

• Oral azoles have supplanted amphotericin B in all but the most severe cases

• Fluconazole or itraconazole?
  - fluconazole well tolerated, well absorbed, fewer adverse reactions
  - but itraconazole may be more active
    • Galgiani et al, Ann Intern Med 2000; 133:676

• Newer azoles
  - Posaconazole and voriconazole reserved for non-responsive cases