LONG-WINDED: SUBACUTE AND CHRONIC PULMONARY INFECTIONS

Elisabeth Merchant, MD
Chief Resident
Department of Medicine
Tufts Medical Center
Boston, MA

OBJECTIVES

• List the infections that can present as subacute or chronic dyspnea or cough in an immunocompetent host
• Perform the indicated work-up to diagnose infectious causes of subacute or chronic dyspnea or cough
• Describe the first-line treatments for some of the infectious causes of subacute or chronic dyspnea or cough

• We will NOT be covering:
  • Acute pulmonary infections
  • Pulmonary infections in patients with immunocompromised hosts

DISCLOSURES

• I have no conflicts of interest or financial disclosures related to this presentation.
CASE 1
34 year old man with no past medical history presented with 5 weeks of progressive cough, initially productive of clear phlegm and now with blood-tinged sputum.

Differential diagnosis

<table>
<thead>
<tr>
<th>V</th>
<th>Vascular</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Infectious</td>
</tr>
<tr>
<td>N</td>
<td>Neoplastic/Neurologic</td>
</tr>
<tr>
<td>D</td>
<td>Drugs/toxins</td>
</tr>
<tr>
<td>I</td>
<td>Inflammatory/idiopathic</td>
</tr>
<tr>
<td>C</td>
<td>Congenital</td>
</tr>
<tr>
<td>A</td>
<td>Autoimmune</td>
</tr>
<tr>
<td>T</td>
<td>Trauma</td>
</tr>
<tr>
<td>E</td>
<td>Endocrine/Metabolic</td>
</tr>
<tr>
<td>S</td>
<td>Psychologic</td>
</tr>
</tbody>
</table>

He was seen in clinic 2 weeks prior and treated for post-nasal drip, without improvement.

Review of symptoms was positive for few pounds of weight loss and occasional chills.

He is an “occasional” tobacco smoker and alcohol drinker, but denies use of other drugs. He is from CT, but does travel, most recently to Bermuda 1 year ago.

Exam revealed a well-appearing man with normal vital signs and exam (including lungs clear to auscultation).

APPROACH TO INFECTIONS

- Viruses
- Bacteria
- Mycobacteria
- Fungi
- Parasites

Chronic
**Viruses**

- Viruses are the most common cause of respiratory infections
  - Adenovirus, enterovirus, coronavirus, human metapneumovirus, rhinovirus, influenza, parainfluenza, respiratory syncytial virus
  - Usually limited to upper airways
- Most viruses have a relatively acute time-course

---

**Chronic Viral Infections**

- **HIV**
  - Pulmonary Arterial Hypertension
    - Persons with HIV are several thousand times more likely to develop PAH
    - Increased risk for COPD and lung cancer
    - Thought to be driven by non-HIV risk factors (e.g. smoking)
- **Hepatitis C**
  - Chronic infection associated with idiopathic pulmonary fibrosis
  - HCV appears to be able to initiate or worsen COPD
  - Mixed cryoglobulinemia leads to vasculitis, pulmonary hemorrhage
  - Cirrhosis can also lead to hepatopulmonary syndrome with pulmonary hypertension
BACTERIA

- Pulmonary bacterial infections are also more typically acute, as well as being more severe, in their presentation.

- Chronic structural lung diseases (COPD, bronchiectasis, cystic fibrosis) can present with chronic bacterial infection.
  - H. influenza, Pseudomonas aeruginosa, S. pneumoniae, M. catarrhalis


BACK TO CASE 1
Sputum cultures with mycoplasma chelonae

Viruses
Bacteria
Mycobacteria
Fungi
Parasites

MYCOBACTERIA

- “Myco” is Greek for fungus – felt to appear mold-like on culture
- Acid fast, aerobic, bacilli
- Unique cell wall – thicker than other bacteria, hydrophobic,
  - Naturally resistant to many antibiotics that disrupt cell-wall biosynthesis (like Penicillin)
  - Can survive long exposures to many exposures including acids, alkalis, detergents, and complement
- Neither gram positive nor negative, some characteristics of both

NON-TUBERCULOUS MYCOBACTERIA (NTM) REFERS TO MYCOBACTERIA OTHER THAN M. TUBERCULOSIS AND M. LEPRAE

- Usually acquired by inhalation or ingestion
- No documented cases of person-to-person transmission
- Ubiquitous in the environment, including household water, natural water sources, and soil
- Resistant to commonly used water disinfectants (e.g., chlorine)
- Recent study (Gebert et al., 2018) found regional association between pathogenic NTM in showerheads and clinical NTM infections

>200 SPECIES OF NTM...

Correct speciation is important because species have differing clinical relevance:
- Some are likely pathogens when found in sputum
- While others are likely contaminants

NTM FOUND IN SHOWERHEAD BIOFILMS
IMPORTANT NTM TO KNOW, EVEN IF YOU AREN’T IN INFECTIOUS DISEASE*:

- M. avium Complex
  - Most common NTM pulmonary infection
  - Originally two species, M. avium and M. intracellulare
  - Mycobacterium chimaera spread from heating and cooling units in heart surgery

- M. kansasii
  - Considered most virulent NTM
  - Second most common etiology of NTM in much of Europe

- M. abscessus complex
  - Important source of pulmonary infections in those with chronic lung diseases
  - Divided into subspecies that have different responses to antibiotics

*Which must be sad

FOUR CLINICAL SYNDROMES

- 90% of NTM infections involve the lungs!

- Chronic productive cough
- Hemoptysis
- Fatigue
- Malaise
- Weight loss

RISK FACTORS

- Structural Lung Disease
  - Cystic Fibrosis
  - Bronchiectasis
  - Primary ciliary dyskinesia
  - COPD
  - Previous TB
- Immunosuppression
  - HIV
  - Transplant
  - TNF-α inhibitor use
  - Defects in IL-12/IFN-γ

LADY WINDERMERE SYNDROME

- Immunocompetent, otherwise healthy older women
- Particularly with thin body habitus
- Also associated with thoracic cage abnormalities like scoliosis and pectus excavatum
- Marker for underlying genetic predisposition
- Historically thought to be due to cough suppression
- May be related to lower estrogen levels, altered expression of leptin and adiponectin

“CLASSIC” PRESENTATION – FIBROCAVITARY

- Symptoms and radiographic findings similar to tuberculosis
- Nodules with predilection for apical and posterior segments
- Can develop into cavities
- Usually <2.5 cm
- Mediastinal lymphadenopathy and pleural effusions are rare

“NON-CLASSIC” – NODULAR BRONCHIECTATIC

- Bronchiectatic disease
- Centrilobular nodules; tree-in-bud pattern
- Cavitation and mediastinal lymphadenopathy are rare
DIAGNOSIS

- All patients with suspected NTM should have:
  - Chest X-ray
  - CT if normal CXR
  - ≥3 sputum samples for AFB

- Diagnostic criteria (for MAC, M. kansasii and M. abscessus):
  - Clinical
    - Pulmonary symptoms
    - Imaging with fibrocavitary or nodular bronchiectatic disease
    - Exclusion of other disorders (including TB)
  - Microbiologic
    - Positive cultures from 2 separate expectorate samples
    - Positive culture from 1 bronchial lavage
    - Lung biopsy with granulomatous inflammation or AFB AND positive culture for NTM (biopsy or sputum)

LAB TESTING

- Acid-fast staining cannot differentiate TB from NTM!
- NAAT tests need to be performed on AFB-smear positive samples
- Drug susceptibility testing - Discrepancies between in vitro susceptibilities and in vivo outcomes

TO TREAT OR NOT TO TREAT...

- Individualized decision!
- Why not?
  - Long-term treatment with multiple antibiotics that have significant toxicities
  - Microbiologic cures can be difficult to achieve
  - Nodular bronchiectatic disease
    - Tends to occur without other comorbidities and progress slowly
    - May be less utility to treatment
  - Cavitary disease
    - Higher mortality
    - Usually requires immediate treatment
- Guidelines for treatment, differs based on species/subspecies
  - Macrolides, rifampin and ethambutol are mainstays of most regimens
  - For MAC, pulmonary disease, regimen is continued until culture negative for 1 year

**CASE 1 CONTINUED**

- Symptoms had already started to improve by time M. chelonae grew
- Decision made to not treat
- Patient was followed closely in ID clinic and with periodic CXRs
- Repeat CT 1 year later showed only scar at the site of previous cavitation

**MYCOBACTERIUM TUBERCULOSIS**

- Transmitted exclusively via cough aerosol
- Necrotizing granulomatous inflammation, usually in the lung (85%), although almost any other organ can be involved
- ~1/3 of the world’s population has been infected
  - 12% actually develop disease
    - Depends on host immunocompetence
  - Still among top 10 causes of death worldwide
    - Unhealed, active tuberculosis has a mortality of 70%

**DISEASE COURSE**

- Infections may be cleared completely without risk of activation (10-20%)
  - Can have clinical manifestations from minor to fulminant infection
  - Latent TB maintained by continued sequestration by the immune system
  - Insults to immune system increase risk of reactivation
DIAGNOSIS OF LATENT TB INFECTION (LTBI)

- Interferon-γ release assay (IGRA) recommended in people >5
- Likely to be infected with TB
  - Household contacts or recent exposure to active TB
  - Mycobacteriology lab personnel
  - Immigrants from high burden countries
  - Residents and employees of high risk congregate settings

- Tuberculin skin test (PPD) is an acceptable alternative, especially if IGRA unavailable or too costly
  - Likelihood of false positive after BCG vaccine (≥10 years) ~1%
  - NTM can also cause false-positives (0.1-2.3%)

- If unlikely to be infected, testing NOT recommended
- If required, positive tests should have a confirmatory repeat to rule out false positive


CLINICAL PRESENTATION OF ACTIVE TB

- Fever
- Often in the afternoon
- Drenching night sweats
- Weight loss
- Malaise/Fatigue
- Symptoms related to involved organs
  - For lungs:
    - Cough, +/- hemoptysis
    - Pleuritic chest pain
    - Dyspnea (Late feature - usually indicates widespread involvement of the lung or airway obstruction)


IMAGING

- Cavities in 50%
- Classic teaching:
  - Primary TB with lower lobe consolidation, hilar adenopathy
  - Reactivation with upper lobe, fibronodular pattern, cavitation
- Growing evidence that there is NO RADIOLOGIC DIFFERENCE between primary and reactivation TB!
- Immunocompetent adults:
  - Cavitary upper lobe lesions with satellite nodules
- Immunocompromised or children - Lower lobe disease, adenopathy, pleural effusions

DIAGNOSIS OF ACTIVE TB

- 3 expectorated samples for
  - Acid-fast bacilli smear microscopy
  - Frequent false negatives and false positives
  - Mycobacterial cultures

- Nucleic-acid amplification (DNA) testing of ≥1 sample
  - If AFB smear positive, positive NAAT confirms diagnosis
  - If AFB smear negative but high suspicion, positive NAAT strongly suggests TB
  - If negative, test cannot exclude TB alone
    - Although with 2 samples sensitivity is 0.95 (CI 0.73-1.0) compared to culture

- If respiratory sample not able to be obtained (or if expectorated sputum negative with high suspicion)
  - Spumt Induction
  - Flexible bronchoscopic sampling

LATENT TB TREATMENT

- Reduces risk of tuberculosis development by 70%
- Possible regimens:
  - Isoniazid daily for 6 or 9 months
  - Isoniazid and rifampin daily for 3-4 months
  - Rifampin daily for 3-4 months
  - Lower hepatotoxicity
  - Isoniazid and rifapentine weekly for 3 months (DOT)
    - Not for children <2
    - Safe and effective, substantially higher treatment completion rates
    - Lower hepatotoxicity

TREATMENT OF ACTIVE TB

- RIPE: Isoniazid and rifampicin for 6 months, with pyrazinamide and ethambutol for the first 2 months
  - Assumes drug-sensitive (testing should be done first)
  - Most serious adverse reaction is liver injury, related to rifampicin, isoniazid, or pyrazinamide (5-33%)
  - Repeat sputum smears done at 2 and 3 months
Viruses

Bacteria

Mycobacteria

Fungi

Parasites

Over 1.5 years in 2012-2013. 5 cases in Montana with no recent (≤ 3 years) travel to endemic region.
• Acute pneumonia few days after substantial exposure (e.g., spelunking)
• Chronic cavitary disease (immunocompetent)
  • Frequently associated with emphysema
  • Productive cough, dyspnea, weight loss, night sweats, fevers
  • Months to years
• Disseminated disease (immunocompromise)
• Subclinical exposure can leave small calcified granulomas in lungs and/or spleen

HISTOPLASMA CAPSULATUM

COCCIDIOIDES

• Asymptomatic in 60%
• Primary infection:
  • Valley Fever - Flu-like symptoms (fever, chest pain, cough, weight loss, erythema nodosum or erythema multiforme)
  • Primary pulmonary coccidioidomycosis
    • Nodules or consolidation in lower lobes
  • Chronic pulmonary coccidioidomycosis
    • Persistent cough, weight loss, malaise
    • Usually single, thin-walled cavity, may have multiple nodules or cavities

https://www.cdc.gov/fungal/diseases/histoplasmosis/causes.html


https://www.cdc.gov/fungal/diseases/coccidiodomycosis/causes.html
**PARACOCCIDIOIDES BRASILIENSIS**
- Associated with soil where coffee grows
- Immunocompetent and immunocompromised
- Acute presentation
  - Patients younger than 30
  - Adenopathy, unilateral pleural effusion, miliary-like shadows
  - Disseminates to other organs
  - Fatal if untreated
- Chronic pulmonary paracoccidioidomycosis
  - Slowly growing granulomatous nodules that often cavitate
  - Often associated with granulomas in other organs (skin/mouth, lymph nodes, spleen, liver, adrenal glands)

**BLASTOMYCES DERMATITIDIS**
- Transmitted via inhalation of soil or bird guano
- Symptom onset in 3 weeks to 4 months
- 50% asymptomatic
- Most infections in immunocompetent adults
- Pulmonary blastomycosis
  - Ranges from subclinical to ARDS
  - Presents with cough, dyspnea, weight loss, chest pain, fever, and occasional hemoptysis
  - Can disseminate (25-40%)
  - Skin
  - Bone
  - Central nervous system
  - Genitourinary tract
- Can become chronic, with non-specific symptoms (above), and nodules, masses or cavitation on chest x-ray

**ASPERGILLUS FUMIGATUS**
- Ubiquitous
- In normal hosts most often causes acute pneumonia
- Can progress to chronic pulmonary aspergillosis
- Subacute invasive pulmonary aspergillosis in immunocompromised
- Chronic pulmonary aspergillosis
  - 2-10% of cases occur in immunocompetent hosts (mostly with obstructive lung diseases or TB)
  - Mostly older males
  - Progressive over months
  - Constitutional symptoms — fatigue, weight loss
  - Pulmonary symptoms — Cough, hemoptysis, chest discomfort, dyspnea
  - Imaging reveals one or more cavities, +/- aspergilloma, large mass lesions or extensive consolidation
  - Pleural thickening is common

---


https://www.cdc.gov/fungal/diseases/blasto.html
CASE 2

- A 21 year old man with Lynch Syndrome (predisposition to multiple cancers) is seen in clinic.
- He notes that he has had about 9-10 months of fatigue, decreased exercise tolerance, exertional dyspnea, and occasional left-sided pleuritic chest pain.
- As part of his cancer screening, he has an MRCP which shows an incidental large left pleural effusion.
- On further history, he has had significant recent travel:
  - Singapore, Indonesia and Thailand 1.5 years ago (hiked, swam in fresh water and ate raw freshwater crab)
  - Mexico 2 months ago (ate local foods, but drank bottled water)

THORACENTESIS

- Exudative fluid
- 3921 nucleated cells, with 52% eosinophils
- Gram stain and AFB smear negative
- Flow cytometry negative for malignant cells

CLINICAL COURSE

- Pigtail placed, but persistent effusion
- Taken to OR for VATS/deorticication, which showed necrotic purulent material
- Stool negative for ova or parasites
- Serologies positive for paragonimus
- Improved with Praziquantel treatment
PARAGONIMIASIS

- Paragonimus (lung fluke)
  - Ingestion of (undercooked) intermediate hosts (freshwater crabs, crayfish) in SE Asia, central Africa, or South America
  - Adult worms found in pulmonary cysts (usually in pairs)
  - Can cause pleural effusions or pneumothoraces
  - Presents with pleuritic chest pain, chronic cough, hemoptysis, fever
  - Frequently misdiagnosed as tuberculosis or malignancy


AMOEBIASIS – ENTAMOeba HISTolytica

- Protozoa found worldwide
  - Fecal-oral transmission
  - Usually lives in intestinal lumen, causes diarrhea
  - Rarely invades mucosa and can form amoebic liver abscesses (several months after initial infection)
    - Cough from diaphragm irritation
    - Serous pleural effusion
    - Atelectasis from right hemidiaphragm elevation
  - Amoebic pleuropulmonary disease (trans-diaphragm, hematogenous spread, or lymphatic spread)
    - Empyema
    - Lung abscesses
    - Pneumonia
    - Hepatobronchial fistula

**SCHISTOSOMIASIS**

- Endemic in tropics
- Infection from contact with larvae in freshwater
  - Enter circulation, pass through heart, lungs, and liver before reaching (intra-abdominal) veins where they mature and mate
  - In heavy infections, migration through the lungs can produce pneumonitis
  - Eggs that are not passed in intestines cause chronic disease - granulomas and fibrosis
  - Release of eggs results in acute schistosomiasis (Katayama fever) - cough, fever, fatigue
  - Pulmonary Hypertension
  - In severe, chronic infection with *S. mansoni* and *S. japonicum* – hepatosplenomegaly and portal hypertension can divert eggs to lung vasculature, resulting in obliterator arteritis
- Chronic presentation with dyspnea, chest pain, digital clubbing, hypoxemia

**HELMINTHS (WORMS)**

- *Echinococcus* (tapeworm) – Hydatid Cysts
  - Dogs and foxes definitive host, other livestock can be intermediate
  - Found in South America, Mediterranean, Middle East, Sub-Saharan Africa, Russia, and China
  - Most hydatid cysts form in liver, 20-30% in lungs
  - Form over several months to years
  - Often asymptomatic, can have chest pain, cough, hemoptysis
  - Cysts rupture can lead to a hypersensitivity reaction with wheezing, anaphylaxis or pneumothorax
- *Dirofilaria immitis* (dog heartworm)
  - Transmitted from dogs via mosquitoes (RARE)
  - 1-3 cm granulomatous lesion with necrotic center and fibrous wall
  - Usually asymptomatic, can have chest pain, cough, hemoptysis, wheeze, fever

**TOXOCARIASIS**

- *Toxocara canis* (dog round worm)
  - Found world-wide in young dogs
  - Fecal-oral ingestion of eggs (mostly children)
  - Migrate from intestine to multiple organs
  - Mast infections asymptomatic
  - Covert toxocariasis - cough, wheezing, fever, abdominal pain, headaches
  - Visceral Larval Migrans – diffuse inflammation of various organs
  - Pulmonary symptoms - cough, asthma, chest tightness
  - Non-pulmonary symptoms – pallor, fatigue, weight loss, fever, headache, rash, abdominal pain, nausea, vomiting
TAKE HOME POINTS

- Viral and bacterial infections are more often ACUTE, although both HIV and HCV can have pulmonary complications
- Consider non-tuberculous mycobacteria in a patient with chronic cough and constitutional symptoms, especially if they have immunocompromise or underlying lung disease, or are thin older women
- Consider TB, NTM, and fungi in cavitating lesions
- Consider fungal and parasitic infections if history of travel to endemic region
  • (Don’t forget to ask!)

MORE REFERENCES

THANK YOU!

- David Stone, MD
- Christine Nayar, MD
- Laurie Pearson, MD
- Will Whalen, MD
- Robert Merchant, MD