52 – Nocardiosis Rhodococcus equi Melioidosis & Actinomycosis

Speaker: David M. Aronoff, MD, FIDSA, FAAM

2020 INFECTIOUS DISEASE BOARD REVIEW

Nocardiosis, Rhodococcus, Melioidosis, and Actinomycosis

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Disclosures of Financial Relationships with Relevant Commercial Interests

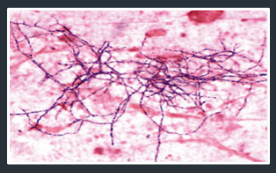
- None

Case

54 year old man with 4 weeks of cough, low grade fevers, & left-sided chest pain. Received a liver transplant 11 months ago, complicated by rejection, requiring high dose steroids 4 months ago. He receives TMP/SMX three times a week. On exam, he is stable, chronically-ill appearing, febrile (101.1ºF), has clear lungs and benign abdomen. Labs reveal a normal white blood cell count, slight anemia, & normal creatinine. Chest radiograph reveals hazy opacity in left lower lung zone. Chest CT reveals nodular air-space consolidation in the left lower lobe with central cavitation (image). Gram strain of bronchoalveolar lavage fluid reveals beaded gram positive filamentous organisms (image).

Chest CT

BAL



CT Image from J. Bargehr, *et al. Clinical Radiology*, 2013-05-01, Volume 68, Issue 5, Pages e266-e271.
Gram stain image from Murray, *et al.* Medical Microbiology, 7E. 2013 Saunders, Elsevier.

What is the most likely cause of this patient's pneumonia?

A. Cryptococcus neoformans
B. Histoplasma capsulatum
C. Actinomyces israellii
D. Nocardia farcinica
E. Aspergillus fumigatus

What are the most appropriate next steps in this patient's care?

A. Initiate therapy with intravenous TMP/SMX
B. Obtain a needle biopsy of the lung nodule to confirm the diagnosis
C. Obtain a brain MRI & start amikacin, imipenem, & TMP/SMX
D. Defer therapy until antimicrobial susceptibilities return

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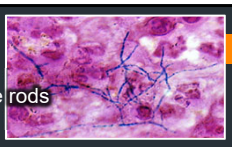
Nocardia Infections



- **Microbiology:**
  - Beaded & branching gram-positive rods
  - Partially acid-fast
  - Aerobic (unlike anaerobic Actinomyces)
  - More than 80 species & >40 cause disease in humans
    - New phylogeny based on DNA sequence (*formerly*, *N. asteroides* complex): **species names are *lookups***.
- **Pathogenesis:**
  - **Inhalation** (most common)
  - **Direct inoculation** through the skin

Photo: http://path.upmc.edu/cases/case226/dx.html; Good reference: Restrepo A & Clark NM. *Clinical Transplantation*. 2019:e13509.

Images of *Nocardia*

- **Beaded**
- **Branching**
- **Gram positive**
- **Partially acid-fast**

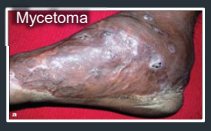
Images from http://thunderhoused.wur.blogspot.com/2010/06/nocardia-species.html

Clinical Features of *Nocardia*

- **Immunocompromised**
  - **Solid organ transplant**, hematopoietic transplant, chronic steroids, alcoholism, diabetes, CGD, CF, anti-TNF therapy, AIDS (less common)
    - *PJP prophylaxis may not prevent nocardiosis*
  - Months to years after transplantation
- **90%**: **slowly progressive pneumonia** with cough, dyspnea, & fever
  - *Aspergillus* similar; co-infections occur
  - Similar to cryptococcal disease & actinomycosis
  - Can disseminate to any organ (**brain** in particular: get MRI)

Clinical Features of *Nocardia*

- **10%**: Skin infections from direct inoculation:
  - Immunocompetent host in tropical region (*N. brasiliensis*)
  - Immunocompromised patient who gardens or walks barefoot
  - **Sporotrichoid** lesions
  - **Mycetomas**: chronic, progressive, lower limbs, draining sinuses (similar to Actinomycetes)

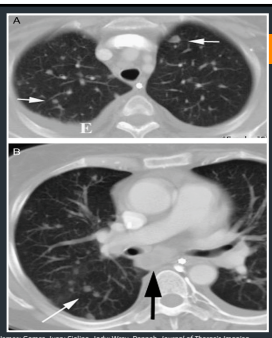


Baradkar V P, *et al. Indian J Pathol Microbiol* 2008;51:432-4 Sharma NL, *et al. Indian J Dermatol Venereol Leprol* 2008;74:635-40

Nocardia Diagnosis

- **Diagnosis**:
  - Suggestive **radiology**
    - Chest imaging: **nodules**, cavities, infiltrates with consolidation, effusions, ground-glass opacities
    - MRI brain: single or multiple **abscesses**
  - Blood **culture**, BAL, biopsy
    - Gram stain, modified acid-fast stain, culture
  - Species identification with nucleic acid sequencing or MALDI: **predictive of drug susceptibility**

- 56-year-old woman post kidney-pancreas transplant & *N. brasiliense*s
- Small lung nodules (white arrows), small right pleural effusion & subcarinal lymphadenopathy (black arrow)



Pulmonary Nocardiosis: Computed Tomography Features at Diagnosis. Blackmon, Kevin; Ravenel, James; Gomez, Juan; Ciolino, Jody; Wray, Dannah. *Journal of Thoracic Imaging*. 26(3):224-229, August 2011. DOI: 10.1097/RTI.0b013e3181f45dd5

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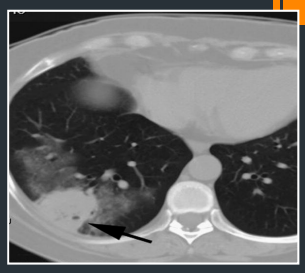
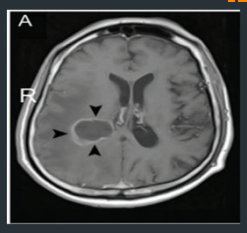
- 55-year-old woman with acute myelogenous leukemia & *N. nova*
- Axial CT image without contrast = solitary RLL **mass** with single focus of **cavitation** (arrow) & surrounding **ground-glass opacity**



Pulmonary Nocardiosis: Computed Tomography Features at Diagnosis. Blackmon, Kevin; Ravenel, James; Gomez, Juan; Ciolino, Jody; Wray, Dannah. *Journal of Thoracic Imaging*. 26(3):224-229, August 2011. DOI: 10.1097/RTI.0b013e3181f45dd5

- Right frontoparietal subcortical ring lesion with a central dark signal & bright peripheral contrast enhancement (black arrowheads) in postcontrast T1-weighted image.



Nandhagopal, Ramachandiran, Zakariya Al-Muharrmi, and Abdullah Balkhair. "Nocardia brain abscess." *QJM* 107.12 (2014): 1041-1042.

Nocardia Treatment

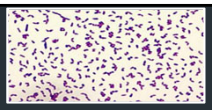
- **Susceptibility testing**
  - Important because of drug resistance
- **TMP/SMX** is mainstay (skin = monotherapy)
- Empiric combination therapy:
  - Amikacin + imipenem/meropenem + TMP/SMX
  - Ceftriaxone & linezolid as alternate agents

Restrepo A & Clark NM. *Clinical Transplantation*. 2019:e13509.

Nocardia **Buzzwords**

- **B**eaded
- **B**ranching
- **B**rain (+ lung)
- **B**actrim

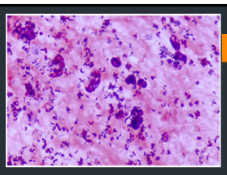
Rhodococcus



- **Clinical findings**:
  - Indolent pneumonia (80%) in **immunocompromised** host
  - **Fever, cough, hemoptysis**, fatigue, subacute, pleuritic CP
  - Nodules, thick-walled **cavities**, infiltrates, effusions possible
  - Extrapulmonary dissemination possible (**skin & brain**)
  - Mimic of TB, NTM, *Aspergillus*, *Nocardia*

Photo: microbe canvas

Rhodococcus



- **Typical patient**:
  - T cell immunosuppressed
    - HIV+ & CD4<100; organ transplant
  - Inhalation or ingestion
  - Farm, soil, manure or horse exposure in some patients
- **Microbiology**: *R. equi* is the most common
  - Gram positive, **aerobe**, **coccobacillary**
  - Colonies can be **salmon pink**
  - Weakly acid fast: can be mistaken for *Nocardia* but **no branching**

Image from W.V. Lin *et al. / Clinical Microbiology and Infection* (2019)

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Rhodococcus

33 year-old HIV+ male (CD4 = 20) who lived on a cattle & horse farm

Presented to hospital with 1 month of fever, dry cough, 13# weight loss, sweats & anorexia

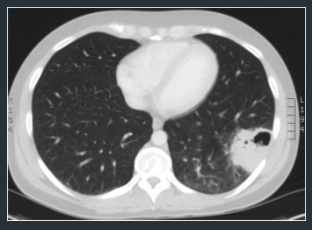

Image from Stewart A., *et al. IDCases.* (2019)

Rhodococcus

- **Diagnosis:**
  - **Culture** followed by 16S rRNA, MALDI-TOF
  - Tissue: gram stain, **necrotizing granulomatous** reaction; microabscess
  - Blood cultures may be positive (>25%)
- **Treatment:**
  - Combination therapy
  - 2 or 3 drug regimens: vancomycin + imipenem/meropenem + fluoroquinolone or rifampin 2-3 wks then oral FQ + azithro/clari or rifampin
    - Linezolid an alternative

Lin WV, *et al. Clin Micro Infect* (2019), Stewart A., *et al. IDCases.* (2019)

Rhodococcus Buzzwords

- **Short** Gram positive rod (coccobacillus)
- **Cavitary** pneumonia (hemoptysis)
- **Salmon pink** colonies
- Advanced **HIV**
- **Horse** / manure exposure

Case

- A 62 yr old sheep rancher from Northern Australia was referred to a West Coast hospital because of refractory pneumonia that had failed to respond completely to multiple, prolonged courses of antibiotics over 3 months, leaving him with continued low grade fever, productive cough & asthenia
- Gram negative rods noted in moderate abundance on Gram stain of sputum & in sputum culture. Identification by automated system failed & isolate sent to referral lab

Question

- Which of the following would have been a likely source of this infection?

A. Hospital nebulizer while hospitalized in Australia (nosocomial superinfection)
B. Water or soil from his ranch
C. Coughing worker on his ranch
D. Sick sheep on his ranch.

Melioidosis Take-Aways

- Microbiology lab:
  - Facultative intracellular gram-negative rod, *Burkholderia pseudomallei*
  - Oxidase positive
  - Characteristic bipolar staining with a "safety pin" appearance
- Typical patient:
  - SE Asia, northern Australia, South Asia (+ India), & China
    - *Esp.* Northeastern Thailand & northern Australia

Chakravorty A, Heath CH. *Australian Journal of General Practice* (2019)

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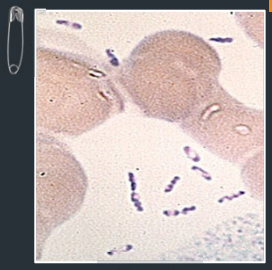
Bacteria with "safety pin" appearance

- *Yersinia pestis*
- *Vibrio parahemolyticus*
- *Burkholderia mallei & pseudomallei*
- *Haemophilus ducreyi* (chancroid)
- *Klebsiella granulomatis* (granuloma inguinale)



Y. pestis

Melioidosis Take-Aways

- **Clinical findings:**
  - **Acute** or chronic pneumonia or sepsis
  - Transmission via percutaneous inoculation, **inhalation**
  - Risk factors = **diabetes**, alcoholism, chronic renal & lung disease
  - Acute infection more common than chronic infection

Chakravorty A, Heath CH. *Australian Journal of General Practice* (2019)

Melioidosis Take-Aways

- **Clinical findings:**
  - Acute infection can present with **pneumonia, bacteremia & septic shock**
  - Metastatic abscesses: skin ulcers or abscesses more common than bone, spleen, brain, prostate
  - Chronic infection presents like TB (cough, hemoptysis, night sweats)
  - Can become latent & reactivate like TB (rare)

Wiersinga WJ, *et al. Nat Rev Dis Primers*. 2018

Melioidosis Take-Aways

- **Diagnosis: Culture**
- **Treatment: Treat all cases**
  - Mild disease: initial intensive **IV therapy for two weeks** followed by eradication therapy **orally for 3-6 months**
  - *B. pseudomallei* resistant to penicillin, ampicillin, 1st/2nd generation cephalosporins, polymyxin, aminoglycosides
  - **Meropenem or ceftazidime** then **tmp/smx for 3-6 months**

Wiersinga WJ, *et al. Nat Rev Dis Primers*. 2018

For the most up-to-date recommendations by the International Melioidosis Society: http://www.melioidosis.info

Melioidosis: **Buzzwords**

- **SE Asia** (Thailand)/Australia
- **Soil/water exposure** (inhalation/inoculation/rainy season; post-tsunami injury)
- Pneumonia + **severe sepsis**/shock or multiple abscesses
- Can be **years after exposure** (not usually)
- **Safety pins** on Gram stain; Gram negative rods

Le Tohic, s., *et al. European Journal of Clinical Microbiology & Infectious Diseases* (2019)

Glanders

- Caused by *Burkholderia mallei* & is rare in humans
- Requires close contact w/ infected animals (horses, donkeys, mules)
- Bacteria enter through the eyes, nose, mouth, or skin wounds
- *B. mallei* is an obligate mammalian pathogen & must cause the disease to be transmitted between hosts
- Africa, Asia, Middle East, Central America, South America
- Similar presentation to melioidosis

Smith ME, Gossman WG. Glanders And Melioidosis. [Updated 2017 Oct 6]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2018 Jan.

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Glanders

- Incubation period usually 1 to 21 days but can be months or years
- 1st symptom usually fever, followed by pneumonia, pustules & abscesses
- The acute form is highly lethal without treatment
- Treatment = imipenem + doxycycline for 2 weeks, then azithromycin + doxycycline for 6 months

Smith ME, Gossman WG. Glanders And Melioidosis. [Updated 2017 Oct 6]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2018 Jan.

Actinomyces Take-Aways

- Microbiology lab:
  - Gram-positive, **anaerobic**, non–spore-forming bacteria
  - Part of the normal mucosal flora of the oral, gastrointestinal, respiratory, & genital tracts
  - *Actinomyces israelii* most common species
  - Produce **sulfur granules**
- Typical patient:
  - Recent dental procedures
  - Aspiration (thoracic)
  - IUD (pelvic)

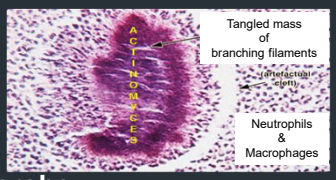
Photos: http://intranet.tdmu.edu.ua/ & webpathology.com

Actinomyces Take-Aways

- Clinical findings:
  - Oral-cervicofacial more common>abdominal & thoracic infection
  - **Lumpy jaw**
  - Slow growing mass, **ignores tissue planes**, can necessitate, form sinuses, fistulas
  - DDx: Cancer, TB, Nocardia
- Diagnosis:
  - Culture, histopathology (sulfur granules)
- Treatment:
  - **Penicillins** (PCN, ampicillin) x weeks to months

Actinomyces: **Buzzwords**

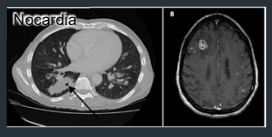
- **Sulfur granules**
- **Dental work**
- **IUD**
- **Erosive mass**
- **Filamentous anaerobe**



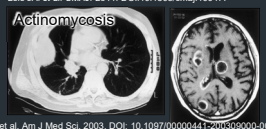
If you see this CXR think of which infection?

Lesions in the Lungs & Brain

- Actinomycosis
- *Aspergillus, Zygomycetes*
- *Blastomyces, Coccidioides, Cryptococcus, Histoplasma*
- *Mycobacterium tuberculosis*
- *Nocardia*
- Infectious emboli (SBE)
- Lemierre syndrome (*Fusobacterium*)
- *Toxoplasma*
- Tumors



Leis JA. *et al. CMAJ.* 2011. DOI:10.1503/cmaj.100477



Colmegna I, et al. Am J Med Sci, 2003. DOI: 10.1097/00000441-200309000-00010

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Causes of Sporotrichoid Lesions

Nodular lymphangitis

Organism	Exposure
Sporothrix schenckii	Gardening, soil, splinters, animal bites/scratches
Nocardia brasiliensis	Gardening, soil, splinters
Mycobacterium marinum	Aquarium, fish handling, water exposure
Leishmania brasiliensis	Living/traveling in endemic regions

Photo: eScholarship

THANK YOU

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