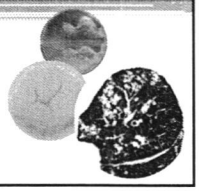
Cases in Non-Tuberculous Mycobacteria



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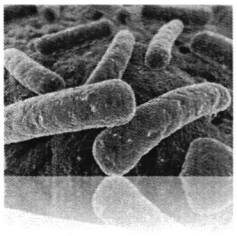
Overview

- Review of NTM
- Case 1
- Case 2



Non-Tuberculous Mycobacteria (NTM)

- Ubiquitous organisms
  - Found in soil and water
  - Need to correlate with clinical picture
- Opportunistic infection
  - Most patients are immune compromised or have preexisting damage

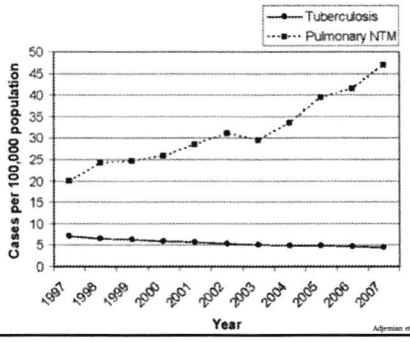
Non-Tuberculous Mycobacteria

- Over 125 different species
  - ~40% documented to cause disease in humans

Species names	This study [N. %]	[7] [N. %]	[12] [N. %]
M. avium complex	106 (62.2)	138 (42.1)	34 (29.0)
M. avium	68 (39.5)	62 (18.9)	10 (8.5)
M. intracellulare (type I, II)	39 (22.7)	76 (23.2)	24 (20.5)
M. abscessus	33 (19.2)	37 (11.3)	4 (3.4)
M. fortuitum complex	7 (4.1)	64 (19.5)*	1 (0.9)
M. scrofulaceum	5 (2.9)	-	-
M. nonchromogenicum	4 (2.3)	-	-
M. asiaticum	3 (1.7)	-	-
M. mucogenicum	3 (1.7)	3 (0.9)	-
M. scrofulaceum	3 (1.7)	-	-
M. shimoidi	2 (1.2)	-	-
M. kansasii	2 (1.2)	13 (4.0)	33 (28.2)
M. gordonae	1 (0.6)	33 (10.1)	31 (26.5)
M. peregrinum	1 (0.6)	-	2 (1.7)
M. pulveris	1 (0.6)	-	-
M. terrae complex	-	28 (8.5)	-
M. chelonae	-	7 (2.1)	-
M. celatum	-	2 (0.6)	-
Others	-	3 (1.2)†	12 (10.3)‡
Total	172 (100.0)	328 (100.0)	117 (100.0)

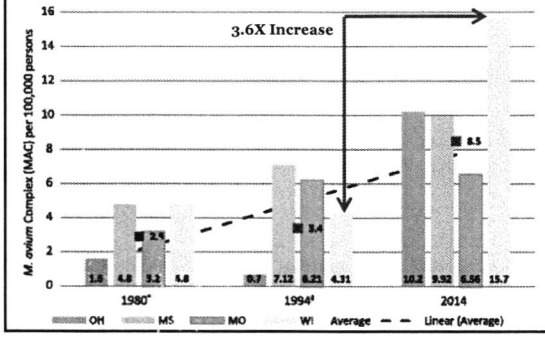
Park, Chul Min, et al. Kor J Lab Med. 2006

NTM Rates are increasing



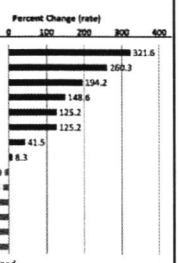
Adjemian et al. 2010 and CDC 2011

MAC rates have greatly increased in WI



The change in rate is species specific

NTM Species	1994 Number	1994 Rate[$]	2014 Number	2014 Rate[$]	P Value
M. chelonae-abscessus Group*	94	0.40	440	1.67	P = <0.001
M. smegmatis	1	0.00	4	0.02	NS[‡]
M. fortuitum Group	105	0.44	343	1.30	P = <0.001
M. avium Complex	816	3.43	2252	8.53	P = <0.001
M. malmoense	2	0.01	5	0.02	NS
M. szulgai	4	0.02	10	0.04	NS
M. simiae	14	0.06	22	0.08	NS
M. gordonae	573	2.41	689	2.61	P = <0.001
M. vaccae	1	0.00	1	0.00	NS
M. xenopi	57	0.24	54	0.20	P = <0.001
M. kansasii Clade	128	0.54	100	0.38	P = <0.001
M. terrae	42	0.18	28	0.11	P = <0.001
M. scrofulaceum	6	0.03	3	0.01	NS
M. flavescens	6	0.03	0	0.00	P = 0.002

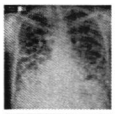


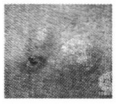
* 2014: *M. chelonae-abscessus* Group plus *M. mucogenicum-phocaicum* report numbers were combined.
‡ NS=Non-significant
$ per 100,000 persons: 1994 population 23,795,000 (as reported by Butler and Crawford), 1999; 2014 population 26,414,700

Donohue, M. Increasing nontuberculous mycobacteria reporting rates and species diversity identified in clinical laboratories. BMC Infec. Dis. 2018

Clinical Syndromes

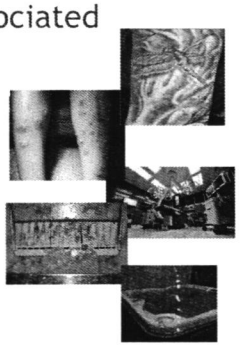
- Progressive pulmonary disease
- Lymphadenitis
- Disseminated disease
- Skin and soft tissue infections



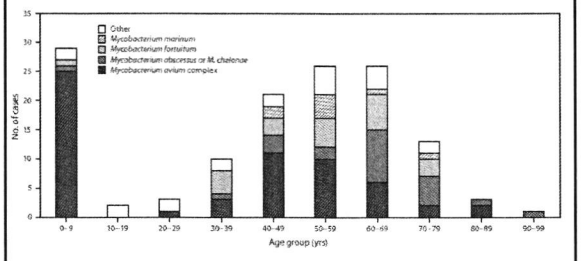


Can Be Outbreak Associated

- Tattoos
- Foot baths and Nail Salons
- Surgery
- Ice makers
- Hot tubs



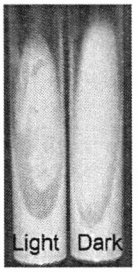
Young Children and Middle Aged at greatest risk



Shij, David, et al. **Extrapulmonary Nontuberculous Mycobacterial Disease Surveillance – Oregon, 2014–2016.** MMWR *Weekly* / August 10, 2018 / 67(31):854–857

Runyon Classification

- Rapid growers (5-7 days)
  - *M. fortuitum*
  - *M. chelonae*
  - *M. abscessus*
- Slow growers (10+ days)
  - Non-chromogens
    - *M. avium* complex (MAC)
  - Scotochromogens
    - *M. gordonae*
  - Photochromogens
    - *M. marinum*



Case 1

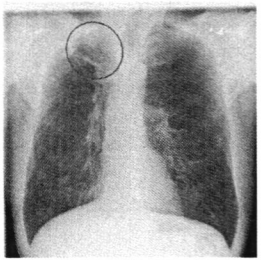
Mix it up

Patient History

- 52 year old man presents after a few months of productive cough and a 40 lb unintentional weight loss.
- Asthma and a 2.5 pack/day smoking history.
- Smoked since he was 14 and both parents died of lung cancer.
- No significant travel history, animal exposure, or sick contacts.
- No history of steroids use or other immune suppressants
- Otherwise healthy man with remote medical history of a knee surgery and back surgery more than 10 years prior.

On presentation

- Patient feels he is "drowning in phlegm".
- He's seen blood in his sputum on several occasions.
- He did not improve on routine antibiotics.
- Cavitary lesion seen on X-ray.
- Despite a lack of exposure history he is presumed to have TB



The next 3 months

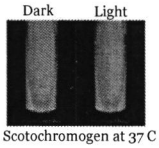
- He is started on RIPE therapy
  Rifampin
  Isoniazid
  Pyrazinamide
  Ethambutol
- Laboratory Testing
  - Sputum smear **positive** for AFB
  - PCR **negative** for Tuberculosis
  - Quantiferon Gold **negative**
- RIPE therapy stopped
- Sputum culture eventually identifies ***Mycobacterium szulgai***
  - RIPE therapy restarted
- Referred to Infectious Disease team for management

Mycobacterium szulgai

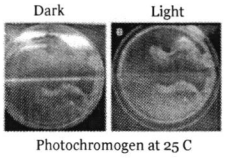
- Unusual cause of disease
- Very rarely isolated from environmental sources
- Nearly always clinically relevant
- First described in 1972 by Marks and Jenkins and named after Dr. Szulga who developed the lipid identification method that helped to describe this pathogen.

In the Lab

- Colonies are slow growing, 14-25 days
- Scotochromogen at 37 C
- Photochromogen at 25 C
- Only Mycobacteria to do this
- Does not grow at 42 C



Scotochromogen at 37 C



Photochromogen at 25 C

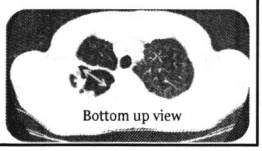
Margie Morgan. Mycobacteriology 2016
Marks J, Jenkins PA, Tsukamura M. *Mycobacterium szulgai*—a new pathogen. Tubercle 1972;53:210-4

CT Scan

Front view

Side view

- Large cavitary lesion on upper right lobe


Bottom up view

Mycobacterium szulgai

- Often present like pulmonary Tuberculosis
- Seen in wounds less frequently
- Most common: upper lobe cavitation in older men with some kind of lung damage
- Generally susceptible however, they tend to be more resistant to isoniazid than other NTMs

Next Steps

- Antimicrobial susceptibility testing is ordered
- Patient worked up for immune defects.
  - No apparent immune defect
    - Negative for HIV, normal T cell counts, no unusual illness as a child.
  - Damage from heavy smoking and asthma
- Patient is given resources to assist with smoking cessation.
- Patient instructed to continue antibiotics until susceptibilities return.

Susceptibility testing

Drug	Results
Amikacin	Susceptible
Capreomycin	Susceptible
Ciprofloxacin	Susceptible
Clarithromycin	Susceptible
Cycloserine	Susceptible
Ethambutol	Susceptible
Ethionamide	Susceptible
Isoniazid low	Resistant
Isoniazid high	Susceptible
Kanamycin	Susceptible
PAS	Susceptible
Rifampin	Susceptible
Streptomycin low	Susceptible
Streptomycin high	Susceptible

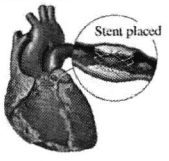
Key
Susceptible
Intermediate
Resistant

6 months later. . .

- Has decreased smoking
- Feeling better
- Gaining weight
- Less phlegm
- Less hemoptyses
- Repeat sputum cultures remain positive for *M. szulgai*

- Patient is lost to follow-up for the next 6 months

1 year from presentation



- Patient has a heart attack
  - Has stent placement
  - Started on blood thinners
  - Diagnosed with coronary artery disease
- Sputum cultures repeated
  - They remain positive for *M. szulgai*
- Patient indicates he does not always take his antibiotics. Is not interested in changing his antibiotic regimen.

In the 1 year interview

- Patient has resumed smoking 1.5-2.5 pack/day
- Reports regular headaches and stomach pain he attributes to the antibiotics.
- Admits to only taking antibiotics when he feels OK and not as prescribed.

Susceptibility Testing take 2

Drug	At presentation	1 year later
Amikacin	Susceptible	Susceptible
Capreomycin	Susceptible	Susceptible
Ciprofloxacin	Susceptible	Intermediate
Clarithromycin	Susceptible	
Cycloserine	Susceptible	Susceptible
Ethambutol	Susceptible	Susceptible
Ethionamide	Susceptible	Susceptible
Isoniazid low	Resistant	Resistant
Isoniazid high	Susceptible	Intermediate
Kanamycin	Susceptible	Resistant
Levofloxacin		Susceptible
Linezolid		Susceptible
Moxifloxacin		Susceptible
Ofloxacin		Susceptible
PAS	Susceptible	Resistant
Rifampin	Susceptible	Susceptible
Streptomycin low	Susceptible	Resistant
Streptomycin high	Susceptible	Susceptible

Key

Susceptible
Intermediate
Resistant
Increased resistance

Infection is getting worse

- Imaging shows persistent infection and increasing nodularity prompting discussion of lung lobe resection
- Due to blood thinners and recent heart attack the patient declines surgery.

1.5 years from presentation

- The patient has worsening GI discomfort and trouble eating.
  - He blames the antibiotics and stops therapy
  - The Doctor stresses the importance of therapy and he agrees to take his meds.
- Over the next 6 months. . .
  - He intermittently takes his antibiotics off and on for about 4 days at a time.
  - Stops again when he feels stomach discomfort

2 years from presentation

- Patient returns to the clinic
- Clinician stresses the importance of antibiotics
- Recommends changes to therapy to help with tolerance and circumvent new resistance patterns.
- Patient refuses to change his antibiotic regimen
- Surgery is again discussed and declined by the patient
- Sputum is collected remains positive for *M. szulgai*
- New susceptibilities run

Susceptibility Testing

Drug	At presentation	1 year later	2 years later
Amikacin	Susceptible	Susceptible	
Capreomycin	Susceptible	Susceptible	
Ciprofloxacin	Susceptible	Intermediate	Intermediate
Clarithromycin	Susceptible		
Cycloserine	Susceptible	Susceptible	
Ethambutol	Susceptible	Susceptible	
Ethionamide	Susceptible	Susceptible	
Isoniazid low	Resistant	Resistant	
Isoniazid high	Susceptible	Intermediate	
Kanamycin	Susceptible	Resistant	
Levofloxacin		Susceptible	Intermediate
Linezolid		Susceptible	Susceptible
Moxifloxacin		Susceptible	Susceptible
Ofloxacin		Susceptible	Resistant
PAS	Susceptible	Resistant	
Rifampin	Susceptible	Susceptible	
Streptomycin low	Susceptible	Resistant	
Streptomycin high	Susceptible	Susceptible	

Key
Susceptible
Intermediate
Resistant
Increased resistance

At next appointment. . .

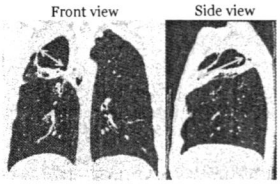
- Patient indicates he stopped taking his antibiotics all together a few weeks back.
- He has stopped coming in for testing.
- States he understands that stopping treatment may lead to death
- Patient does not follow up with testing or clinic visits

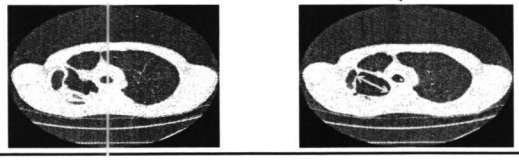
3 years from presentation

- Patient presents at ED with worsening symptoms
  - Cough
  - Sputum production that is bloody
  - Shortness of breath affecting his ability to work
  - Recent diagnosis of COPD and type 2 diabetes
  - Says he has not taken antibiotics for several months

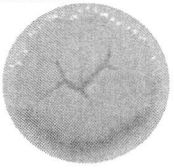
Chest CT at 3 years from presentation

- Worsening cavitary lesion
- Several nodular frond-like opacities
- Patient says he is ready to try for a cure
- Restarts antibiotics
- New cultures grow *M. abscessus*





M. abscessus



- Rapid grower (nonchromogenic)
  - Growth on blood agar on day 5
- *M. abscessus* complex
  - *abscessus* (common)
  - *massiliense* (common)
  - *bolletii* (rare)
- Second most common NTM after MAC
- First isolated from a knee abscess in 1952
- Usually causes skin and soft tissue or pulmonary infections
- Found in water and soil
- Can be harder to treat than other NTMs
  - May need longer therapy

Jeon K, et al. Am J Respir Crit Care Med. 2009
Kil-Soo Lee, et al. J Bacteriol Virol. 2008

Susceptibility testing

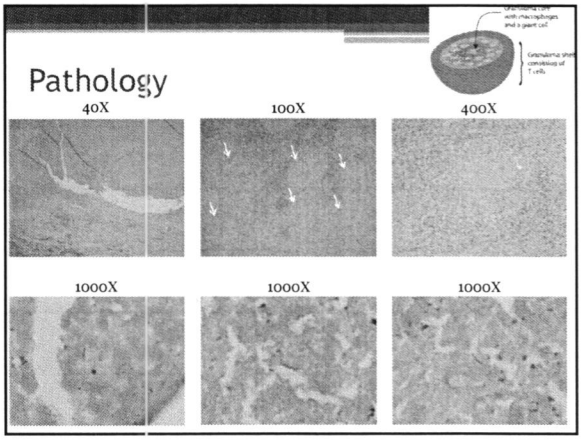
M. abscessus	
Drug	**Result**
Amikacin	Susceptible
Augmentin	Resistant
Azithromycin	Susceptible
Cefoxitin	Susceptible
Ciprofloxacin	Resistant
Clarithromycin	Susceptible
Clofazimine	Susceptible
Doxycycline	Resistant
Imipenem	Intermediate
Kanamycin	Susceptible
Linezolid	Intermediate
Moxifloxacin	Resistant
Tigecycline	Susceptible
Tobramycin	Intermediate
Trimethoprim/sulfa	Resistant

M. szulgai	
Drug	**Most Recent**
Amikacin	Susceptible
Capreomycin	Susceptible
Ciprofloxacin	Intermediate
Cycloserine	Susceptible
Ethambutol	Susceptible
Ethionamide	Susceptible
Isoniazid low	Resistant
Isoniazid high	Intermediate
Kanamycin	Resistant
Levofloxacin	Intermediate
Linezolid	Susceptible
Moxifloxacin	Susceptible
Ofloxacin	Resistant
PAS	Resistant
Rifampin	Susceptible
Streptomycin low	Resistant
Streptomycin high	Susceptible

3.5 years- Ready for Treatment

- Chronic cough
  - 2-3 blood clots a day
- Recently quit his job due to chronic shortness of breath
- Agrees to Surgery
  - Resection of right upper, middle lobes, and involved ribs
- Discharged home with a PICC line for IV antibiotics
  - Amikacin, Cefoxitin, Rifampin, Ethambutol, and Clarithromycin
- Culture grows *M. abscesses* again

Pathology



M. abscessus susceptibility testing

Drug	Sputum	Tissue
Amikacin	Susceptible	Susceptible
Augmentin	Resistant	Resistant
Azithromycin	Susceptible	Susceptible
Cefepime		Resistant
Cefotaxime		Resistant
Cefoxitin	Susceptible	Intermediate
Ceftriaxone		Resistant
Ciprofloxacin	Resistant	Resistant
Clarithromycin	Susceptible	Susceptible
Clofazimine	Susceptible	Susceptible
Doxycycline	Resistant	Resistant
Gentamicin		Intermediate
Imipenem	Intermediate	Intermediate
Kanamycin	Susceptible	Susceptible
Linezolid	Intermediate	Resistant
Moxifloxacin	Resistant	Resistant
Tigecycline	Susceptible	Susceptible
Tobramycin	Intermediate	Intermediate
Trimethoprim/sulfa	Resistant	Resistant

Key
- Susceptible
- Intermediate
- Resistant
- Increased resistance

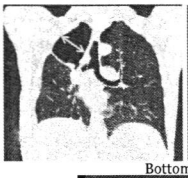
One month later (~3.5 years)

- In the next few weeks he feels worse
  - Fever, chills, vomiting
- Discontinue his all antibiotics including the IV
- The next day his chest wound opens and large amounts of chunky, discolored, purulent material drains
- He then feels much better
  - Resumes oral antibiotics only
- On exam a large amount of thick purulent material is draining from his chest tube site
  - IV antibiotics restarted
  - Culture or drainage grows *M. abscessus*

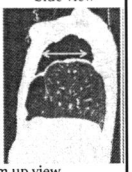
Post Surgery Imaging

6 months prior to surgery

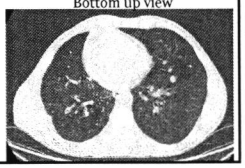
Front view



Side view

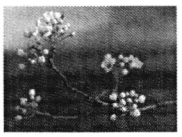


Bottom up view



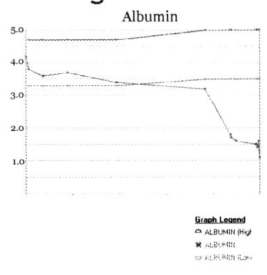
- Chest wall thickening
- Emphysema
- "Tree-in-bud" opacities in remaining right lung

Tree-in-bud opacities



3.75 years- He is not doing well

- Blood draining from wound site
- Albumin dropping (1.5 g/dL)
- White blood cell count rising (14 K/uL)
- Bronchopulmonary fistula identified
- Undergoes second surgery for debridement, flap repair and endobronchial stent placement



One month later (~4 years)

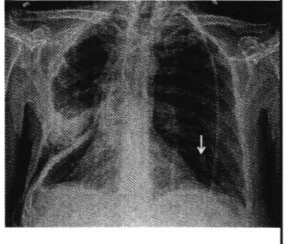
- Wound continues to drain pus and bleed.
- Heavy lifting at home resulted in sudden large amount of bleeding.
- Albumin at 1.1 g/dL in clinic
- Patient initially refuses to be admitted despite warnings he may have a heart attack
- Wife convinces him to get a transfusion
- Sputum cultures sent

M. peregrinum

- Nonpigmented Rapid grower
- Very rare cause of pulmonary infections
- *M. fortuitum* complex
  - *Fortuitum, peregrinum, senegalense, setense, septicum, porcinum, houstonense, boenickei, brisbanense, neworleansense*
- Case reports of disease in previously healthy people (Nihon Kokyuki Gakkai Zasshi. 2010)

Two months later (4 years)

- Salvage therapy recommended by National Jewish
  - amikacin, cefoxitin, tigecycline and clofazimine
- Improves initially then represents with air and pus leaking from chest wound.
- Undergoes another surgery to debride and close multiple fistulas.
- Samples sent for culture. . .



M. fortuitum

- Common mycobacterial pathogen
- Rapid grower
  - Non-pigmented
- Quirk: Does not grow at 45 C
- Usually in skin and soft tissue infections
- Often nosocomial
- Macrolide and cephalosporin resistance is common
- 4-6 months of therapy recommended

Culture Summary

M. szulgai	*M. abscesses*	*M. peregrinum*	*M. fortuitum*
Slow grower	Rapid grower	Rapid grower	Rapid grower
Rare	Common	Uncommon	Common
Fairly susceptible (except isoniazid)	Fairly resistant	Fairly susceptible	Some resistance is common
Pigment in light only when grown at 25			No growth at 45C

The patient continues to decline and passes away.

Final Thoughts

- It is possible to be multiply infected with NTMs
- *M. szulgai* is a slow grower and may have been overgrown by the rapid growers.
- Development of drug resistance can happen quickly.
- Despite our best efforts we can't force treatment compliance.

Case 2

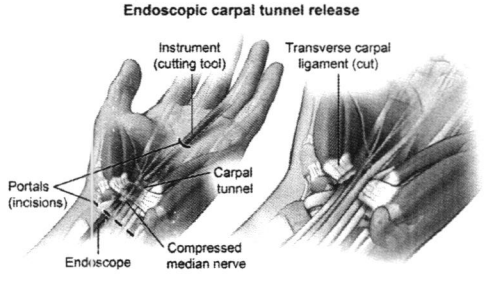
Foreign bodies

History

- 64 year old dairy farmer
- Past appendectomy and knee repair surgery post trauma
- Animal exposure to cows and cats
- Non-smoker, light drinker

- Diagnosed with Carpal tunnel syndrome

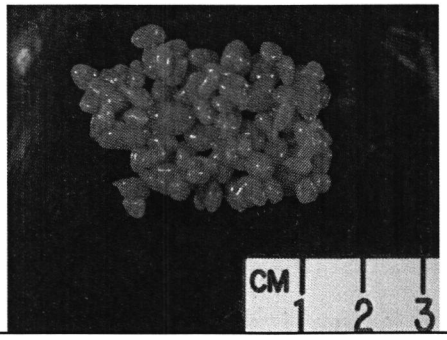
Carpal Tunnel Surgery



Case History

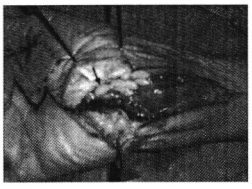
- In May he had carpal tunnel surgery on his left wrist
- Debrided tissue sent for analysis
  - Pathology report noted "small non-necrotizing granulomas"
- Persistent redness and swelling led to second procedure in August for tendon debridement
  - Unusual finding during surgery. . .

Rice Bodies removed from his wrist



Rice Bodies

- Tenosynovitis
- Fibrin nodules
- Causes:
  - Rheumatoid arthritis
  - Chronic synovitis
  - Chronic bursitis
  - Systemic lupus
  - Mycobacterial infection
- Path report "Organized fibrin with inflammatory cells and rare histiocytes and lymphocytes along with rare multinucleated giant cells"

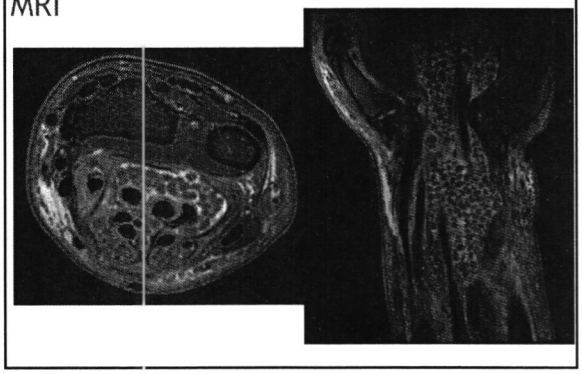


Chau et al. AJR:180, May 2003

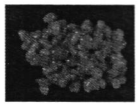
Case History

- Further pain and swelling led to a 3rd surgery for wound debridement in October
  - More rice bodies
  - No organisms seen on histology
- Recurrent swelling and discomfort led to another debridement a year later
  - More rice bodies
  - Histology described as "Granulomatous" but no organisms seen.

MRI



History Continued



- Infectious Disease Team consulted
  - Special stains of histology requested
    - No AFB seen on slide
  - 16S PCR for bacterial identification
    - No organism detected
  - AFB smear of rice bodies negative
  - *M. avium* complex grows after 15 days
    - First non-Tb case of rice bodies described in 2003
  - No respiratory symptoms, negative chest X-ray
  - No known exposures, maybe cows?

Susceptibility

- Cipro- S
- Clofazimine- S
- Rifabutin- I
- Rifampin- S
- Kanamycin- R
- Cycloserine- S
- Ethionamide- R
- Ethambutol- I
- Streptomycin- R
- Amikacin- R
- Clarithromycin- S
- Moxifloxacin- S
- Rifampin/Ethambutol combo- S

Treatment: Moxifloxacin, azithromycin, rifampin, doxycycline

History Continued

- Recurrent swelling led to another debridement a year later (3 years total)
  - More rice bodies
  - AFB smear and histology still negative
  - More MAC in culture
  - Susceptibilities
    - Rifampin now Intermediate
    - Rifampin/ethambutol combo still Susceptible
  - Treated for another year with ethambutol, rifampin, levofloxacin

- Rice bodies continue to return needing additional surgeries (4 years total)

Summary

- MAC infections can occur independent of the lungs in healthy people.
- Consider mycobacteria when rice bodies are identified.
- Rice bodies caused by Mycobacteria are usually negative for AFB by histology and smear, send cultures.
- Prolonged therapy with susceptible drugs is not always effective.

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