The Curious Case of Mr. MaX

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disclosures and conflicts

- none

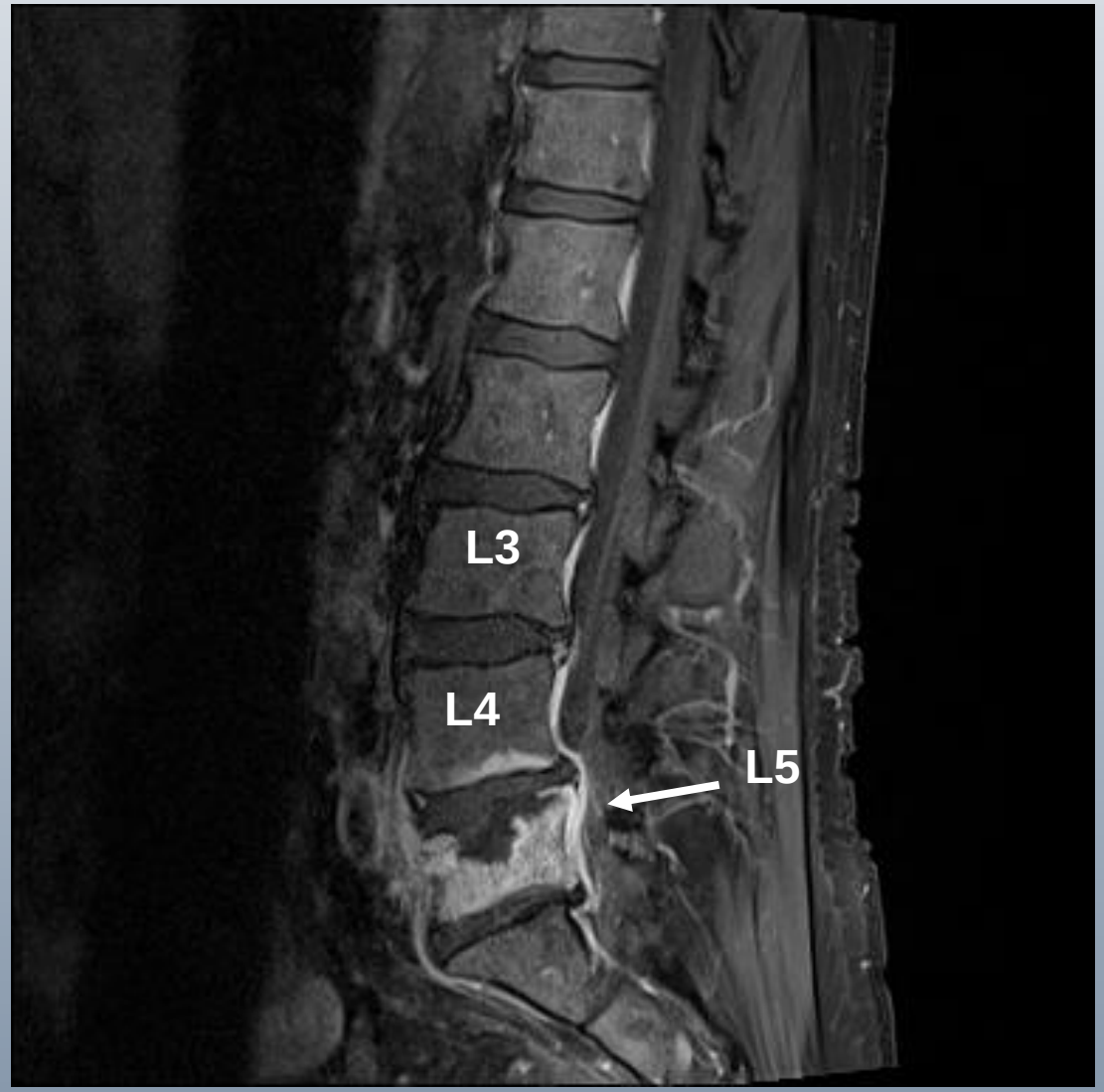
HISTORY

- 60-some year old male
- history of sarcoidosis
- long-standing low back pain.
- 5 months previously, bent over to squeegee his shower and felt the sudden onset of overwhelming pain in his lower back. There was a “popping sensation.”
- had to recover by sitting in a hard back chair for a period of time. “Thought I had thrown my back out.”

- Three days later, went to see his chiropractor.

- Saw the chiropractor 9 or 10 times over the next three months but continued to have 5/10 to 6/10 pain when flexing spine (for example, bending to pick something up off the floor or squeegeeing his shower, etc.). No or minimal pain when sitting upright or standing.

- 3 1/2 months after symptom onset, MRI of the spine revealed: extensive avid enhancement in the L5 vertebral body, enhancement of L4 inferior endplate and S1 superior endplate, soft tissue enhancement around the spine with small fluid collections

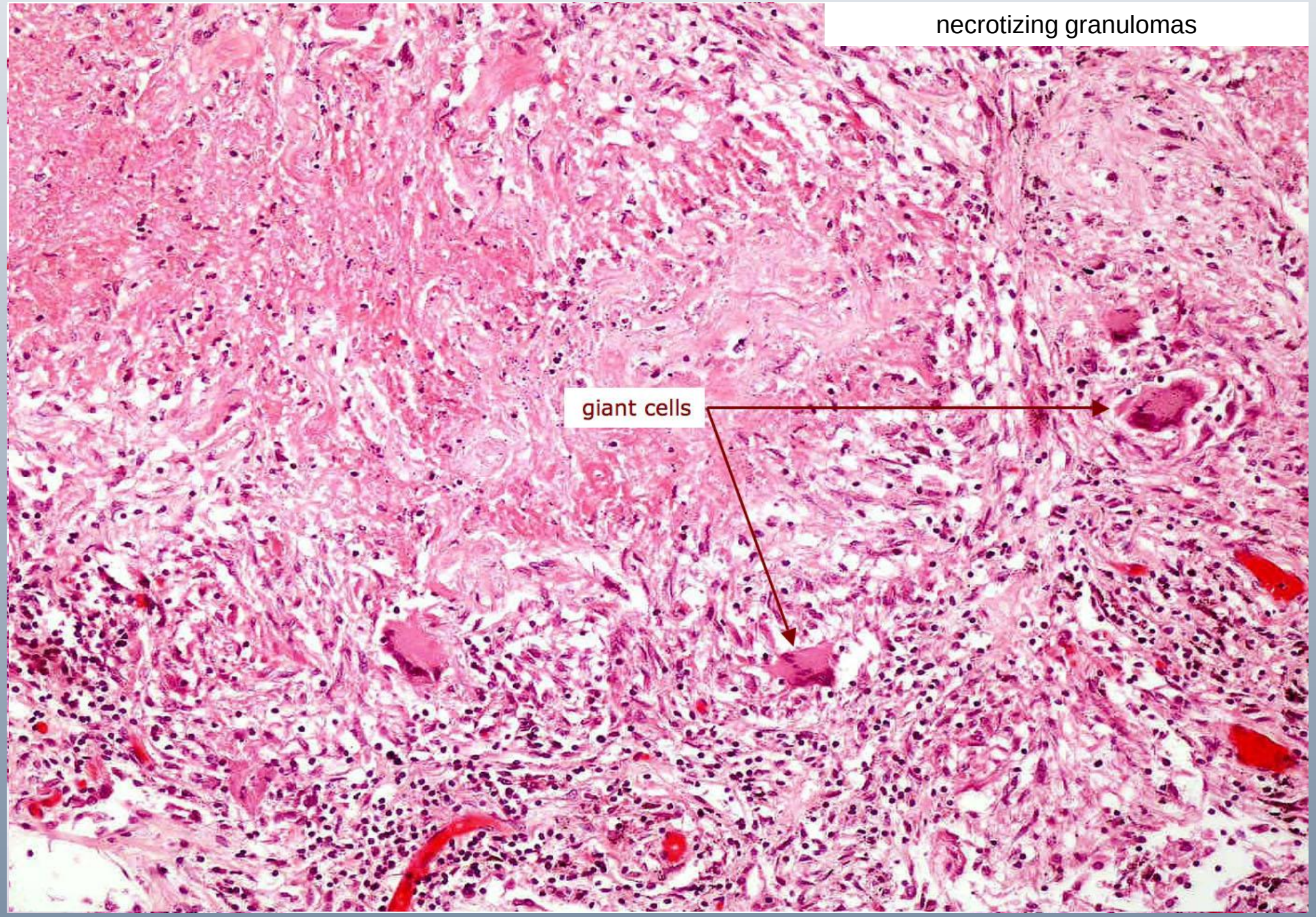


3/14/2018

- Radiology-guided biopsy
- sampled abscess/ fluid collection and bone
- Pathology: necrotizing inflammation of the L5 vertebral body (special stains negative).
- Bacterial, fungal and AFB stains and culture: negative
- 16S PCR (for bacterial DNA): negative.

early April 2018

necrotizing granulomas



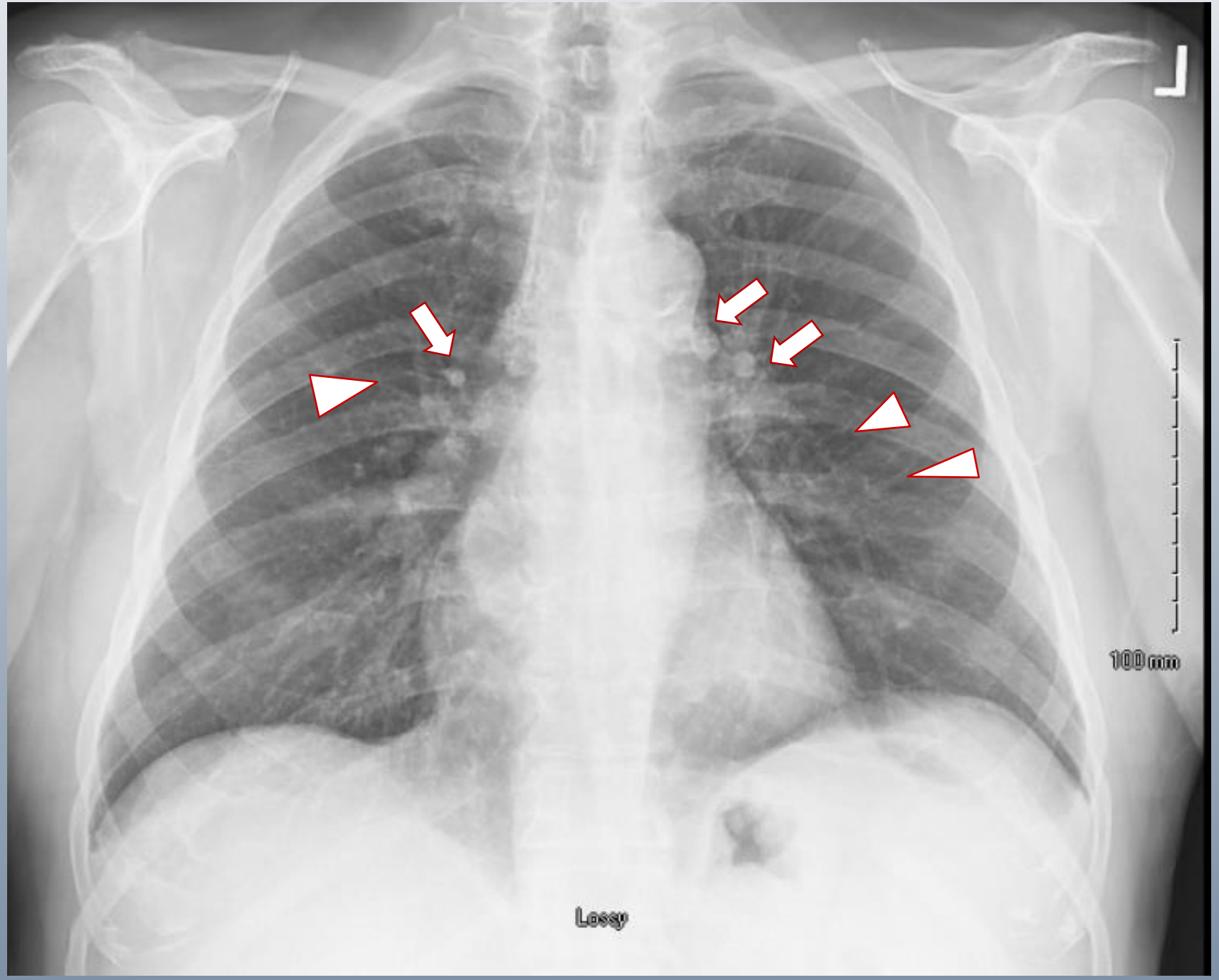
- **sees Infectious Diseases specialist** mid-April 2018
- ID review of systems: no fevers, chills, night sweats, weight loss. gets hot at night during the wintertime, which he attributes to winter bedding, and sometimes can sweat a little bit.
- chronic dry cough for a number of years. Wife notes voice less forceful. coughs and spits up mucus in night often
- Denies headache, blurry vision, double vision, or vertigo. No imbalance, clumsiness, or falling.
- No lymph node enlargement.
- quantiferon gold: negative

Past Medical History

- Sarcoidosis involving the lung, diagnosed 16 years ago by lung biopsy. Received a prednisone course twice, once around the time of diagnosis and again one to two years later. Not followed by a pulmonologist now and told that his sarcoid is "inactive."
- gastro-esophageal reflux disease
- Obstructive sleep apnea.
- prior pneumonia
- seasonal allergies

geographic and other exposures

- born in Illinois. As a boy, had a pet parakeet
- Travel in the Grand Canyon, Utah, Mexico (Cancun)
- industrial arts teacher at Junior High school in Illinois, then graphics arts teacher at another high school in Iowa. some students from disadvantaged backgrounds
- spent a lot of time canoeing on Wisconsin River during previous summer
- no known TB contacts. No fam history of TB



- multiple dense small, likely calcified hilar and mediastinal lymph nodes
- mild diffuse interstitial prominence, somewhat perihilar in distribution

- chest CT: Numerous bilateral mediastinal and hilar calcified lymph nodes.
- Nodular configuration of the liver with splenomegaly.
- Severe three-vessel coronary artery calcifications and aortic valve calcifications.

- **second** Radiology-guided biopsy
- sampled abscess/ fluid collection and bone
- Pathology: necrotizing inflammation of the L5 vertebral body (special stains negative).
- Bacterial, fungal and AFB stains and culture: negative
- 16S PCR (for bacterial DNA): negative.

June 2018

- in the interim, essentially completely symptoms.
- no fevers, chills, night sweats, or unintentional weight loss.
- may have a slight decrement in appetite
- lost 15 lbs of weight intentionally
- pain only with bending at the waist or back tightness with more prolonged walking

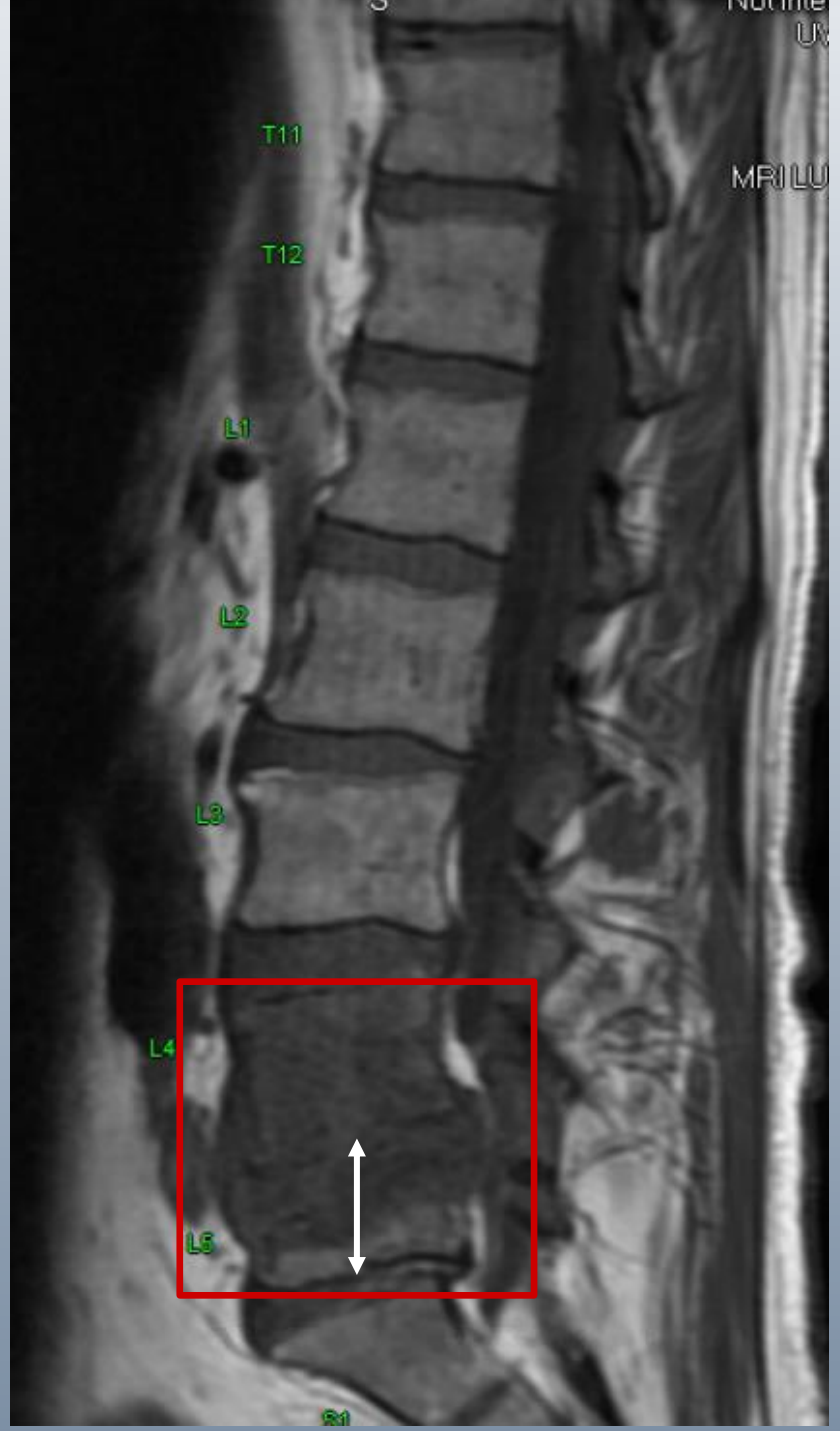
- sees GI specialist for cirrhosis, diagnosed incidentally during workup
- found to also have large spleen, esophageal varies, and portal hypertension (all signs of advanced liver disease)
- undergoes liver biopsy --
  - non-necrotizing granulomas seen
  - AFB stain/culture, fungal stain/culture, bacterial stain/culture all negative
  - PCRs for bacteria, fungi and mycobacteria all negative

presumptive diagnosis: liver and bone sarcoidosis

- continued to have mild low back pain (3/10). Pain free while sitting. Pain worse with forward bending, lifting, rising from seated position, walking for more than half an hour. Improves when he sits to rest. Difficulty taking out the garbage and mowing the lawn.
- new right buttock and posterior thigh pain at times, and rare numbness to the right great toe.
- started a steroid trial for sarcoidosis with rheumatologist

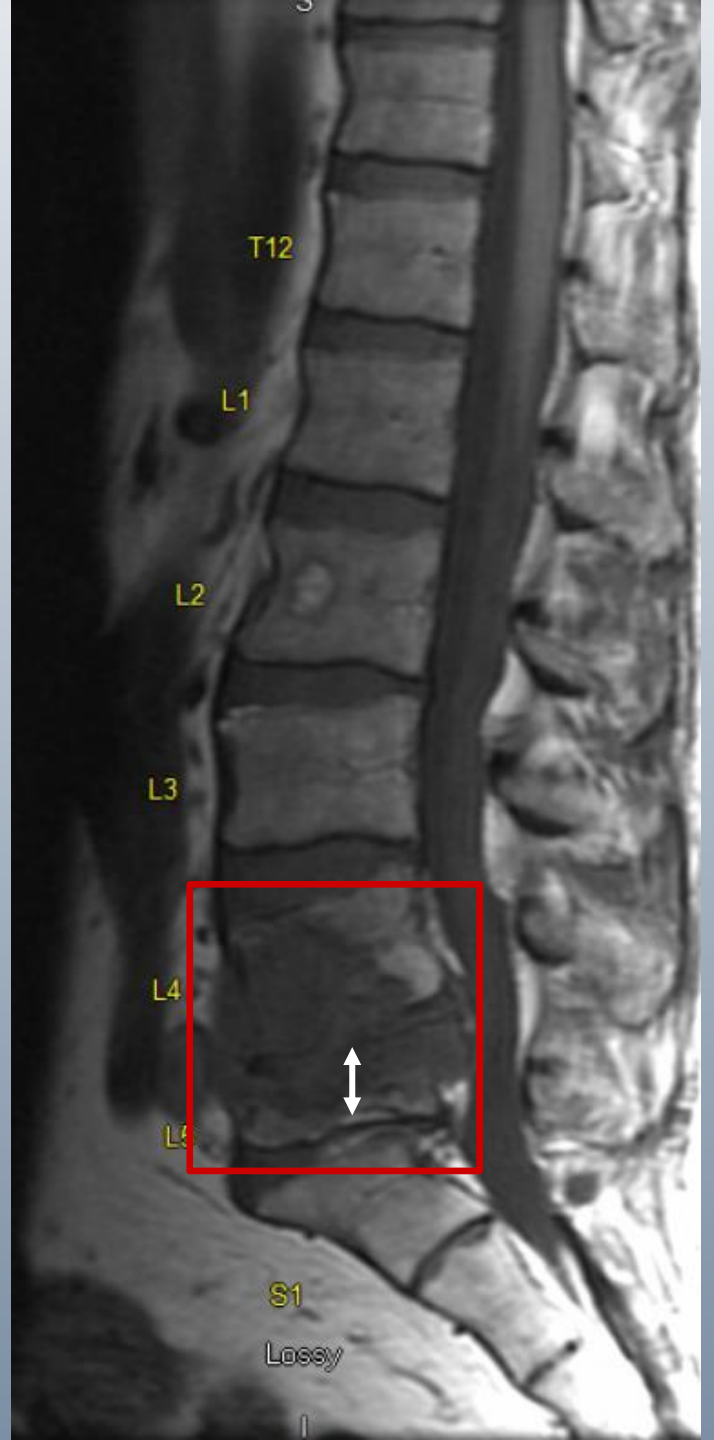
  →pain improved

  → imaging got worse



Nov 2018

T1 FSE



Feb 2019

T1 FSE

further developments …

- loses another 20-25 lbs, this time unintentionally
- admitted for spinal surgery to stabilize spine
- undergoes rod/screw placement, fusion, laminectomy, corpectomy, discectomy of L4-L5
- AFB smear of operative tissue: rare AFBs seen
- cuture: no growth
- PCR: *M. xenopi*

TABLE 2. CLINICAL DISEASE CAUSED BY NONTUBERCULOUS MYCOBACTERIA (ALPHABETICAL ORDER BY SPECIES)

Common	Page	Comment	Uncommon	Page	Comment
Pulmonary Disease					
M. abscessus	396	Worldwide; may be found concomitant with MAC	*M. asiaticum**		Rarely isolated
M. avium complex	386	Worldwide; most common NTM pathogen in U.S.	*M. celatum**		Cross-reactivity with TB-DNA probe
M. kansasii	395	U.S., Europe, South Africa, coal-mining regions	*M. chelonae*	398	
M. malmoense	399	U.K., northern Europe; uncommon in U.S.	*M. fortuitum*	398	Associated with aspiration
			M. haemophilum	399	Rarely isolated
M. xenopi	402	Europe, Canada; uncommon in U.S.; associated with pseudoinfection	*M. scrofulaceum*	400	South Africa; uncommon in U.S.
Disseminated Disease					
M. avium complex	386	Worldwide; AIDS; most common NTM pathogen in U.S.	*M. abscessus*	396	Non-AIDS immunosuppressed
			*M. celatum**		AIDS
M. chelonae	398	U.S.; non-AIDS immunosuppressed skin lesions	*M. conspicuum**		AIDS, non-AIDS immunosuppressed
			M. fortuitum	398	Non-AIDS immunosuppressed
M. haemophilum	399	AIDS; U.S., Australia; non-AIDS immunosuppressed	*M. genavense*	399	AIDS
M. kansasii	395	AIDS; U.S., South Africa	*M. immunogenum*	399	Rare, associated with pseudo-outbreaks
			M. szulgai	401	Rarely isolated
			M. xenopi	402	Europe, Canada, associated with pseudoinfection

Griffith DE (2007) Am J Respir Crit Care Med 175: 367–416

epidemiology of M. xenopi

- municipal water supply (incl hot water taps)
- hospital water supply
- showerheads
- soil, sewage sludege
- slow growing (> one week on culture, often > 4 wks)
- thermophilic: grows well at 45°-55° C
- resist disinfectants, such as chlorine and formaldehyde

epidemiology of M. xenopi

- second most common cause of NTM lung disease in Canada, UK, parts of Europe; less frequent in U.S
- lung disease often with apical cavity
- host often has COPD (emphysema) or other “structural lung disease”
- nosocomial spine infections reported as result of contamination of surgical instruments with tap water
- “pseudo-outbreaks” have been caused by contaminated fiberoptic bronchoscopes
- reported as cause of otitis media

Griffith DE (2007) Am J Respir Crit Care Med 175: 367–416; Astagneau P (2001) Lancet 358:747–51; Wallace RJ (1998) Annu Rev Microbiol 52:453–90; Costrini AM (1981) Am Rev Respir Dis 123: 104–109. Jenkins PA (2008) Thorax 63:627–634.

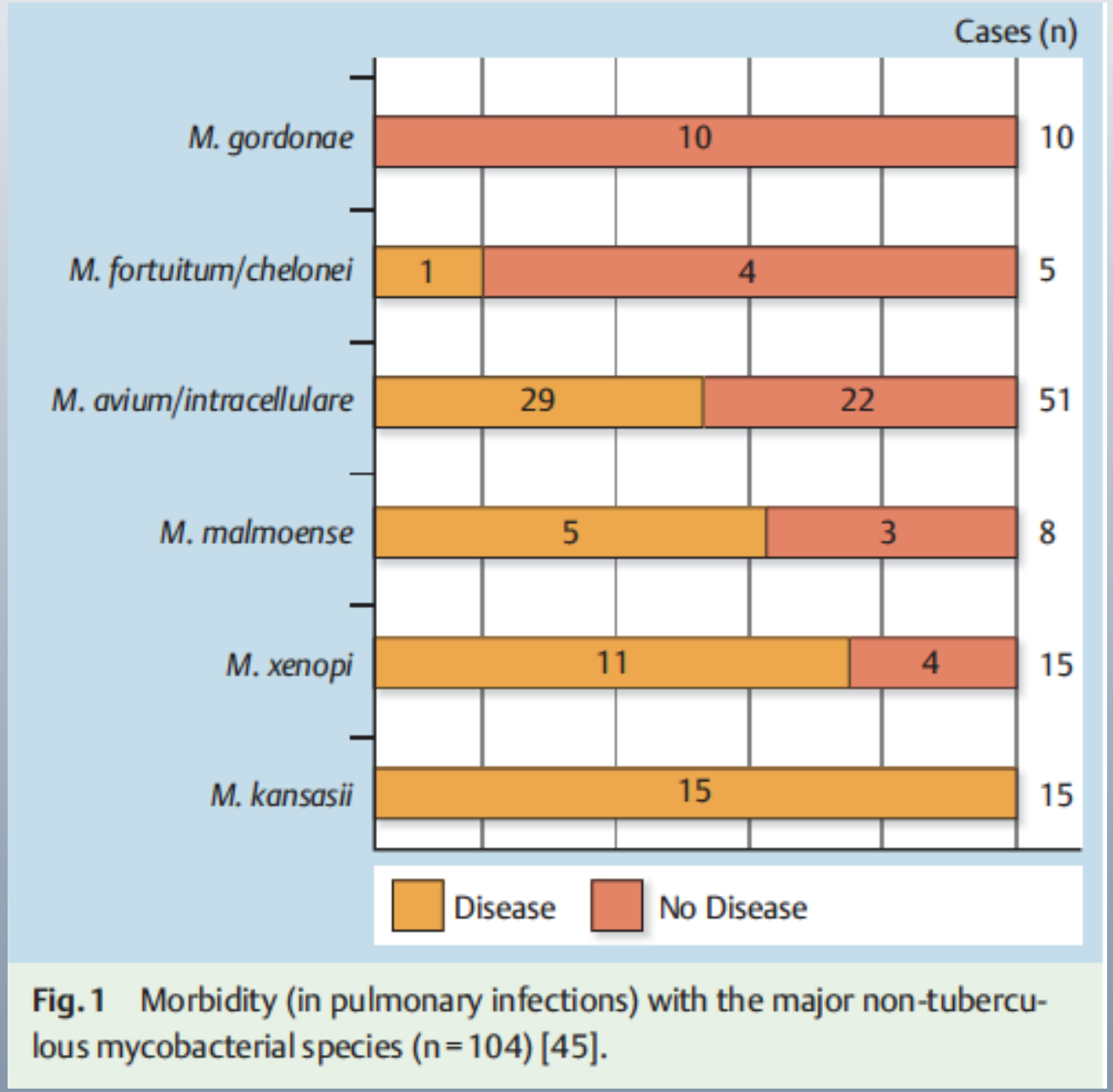


Fig. 1 Morbidity (in pulmonary infections) with the major non-tuberculous mycobacterial species (n = 104) [45].

Schoenfeld N (2016) Pneumologie 70: 250-76

TABLE 1. CHARACTERISTICS OF PATIENTS WITH NONTUBERCULOUS MYCOBACTERIA COLONIZATION, POSSIBLE NONTUBERCULOUS MYCOBACTERIA DISEASE, AND DEFINITE NONTUBERCULOUS MYCOBACTERIA DISEASE

	Colonized Patients (*n* = 709)	Possible NTM Disease (*n* = 238)	Definite NTM Disease (*n* = 335)
NTM species			
Mycobacterium gordonae (n = 485)	392 (55.3)	75 (31.5)	18 (5.3)
Mycobacterium avium complex (n = 425)	137 (19.3)	97 (40.7)	191 (57.0)
Mycobacterium xenopi (n = 52)	14 (1.9)	12 (5.0)	26 (7.8)
Mycobacterium malmoense (n = 46)	12 (1.7)	7 (2.9)	27 (8.1)
Others NRGM (n = 110)	46 (6.5)	25 (10.5)	39 (11.6)
Mycobacterium celatum (n = 25)	11 (1.6)	2 (0.8)	12 (3.6)
Mycobacterium szulgai (n = 12)	0	5 (2.2)	7 (2.1)
Others RGM (n = 164)	108 (15.2)	22 (9.2)	34 (10.1)
Mycobacterium abscessus (n = 58)	28 (3.9)	7 (2.9)	23 (6.9)
Mycobacterium fortuitum (n = 42)	34 (4.8)	4 (1.2)	3 (1.3)

81%
32%
27%
15%
23%
23%
4%
45%
50%

Andréjak C (2010) Am J Respir Crit Care Med 181: 514–21

susceptibility testing for M. xenopi

"Because too few isolates of each species have been studied, no specific susceptibility method can be recommended at this time … Until further data are available, testing should be performed as for rifampin-resistant *M. kansasii (*i.e., rifampin and secondary agents should be tested)"

<u>secondary agents</u>:
isoniazid
clarithromycin, azithromycin
ciprofloxacin, moxifloxacin
ethambutol
rifabutin
streptomycin, amikacin
sulfonamides

"the response of this organism to therapy is variable and does not always correlate well with the results of in vitro susceptibility."

Griffith DE (2007) Am J Respir Crit Care Med 175: 367–416

treatment recommendations: M. xenopi

- U.S. guidelines: Isoniazid (INH), rifabutin/rifampin, ethambutol, and clarithromycin +/- initial streptomycin
  - a quinolone may be substituted for one of the anti-tuberculosis drugs
  - duration: continue therapy until patient has maintained negative sputum samples for 12 months
- German guidelines: same as U.S. “Isoniazid *in vivo* is considered effective, similar to the situation in *M. kansasii.”*

Griffith DE (2007) Am J Respir Crit Care Med 175: 367–416; Schoenfeld N (2016) Pneumologie 70: 250-76

treatment recommendations: M. xenopi

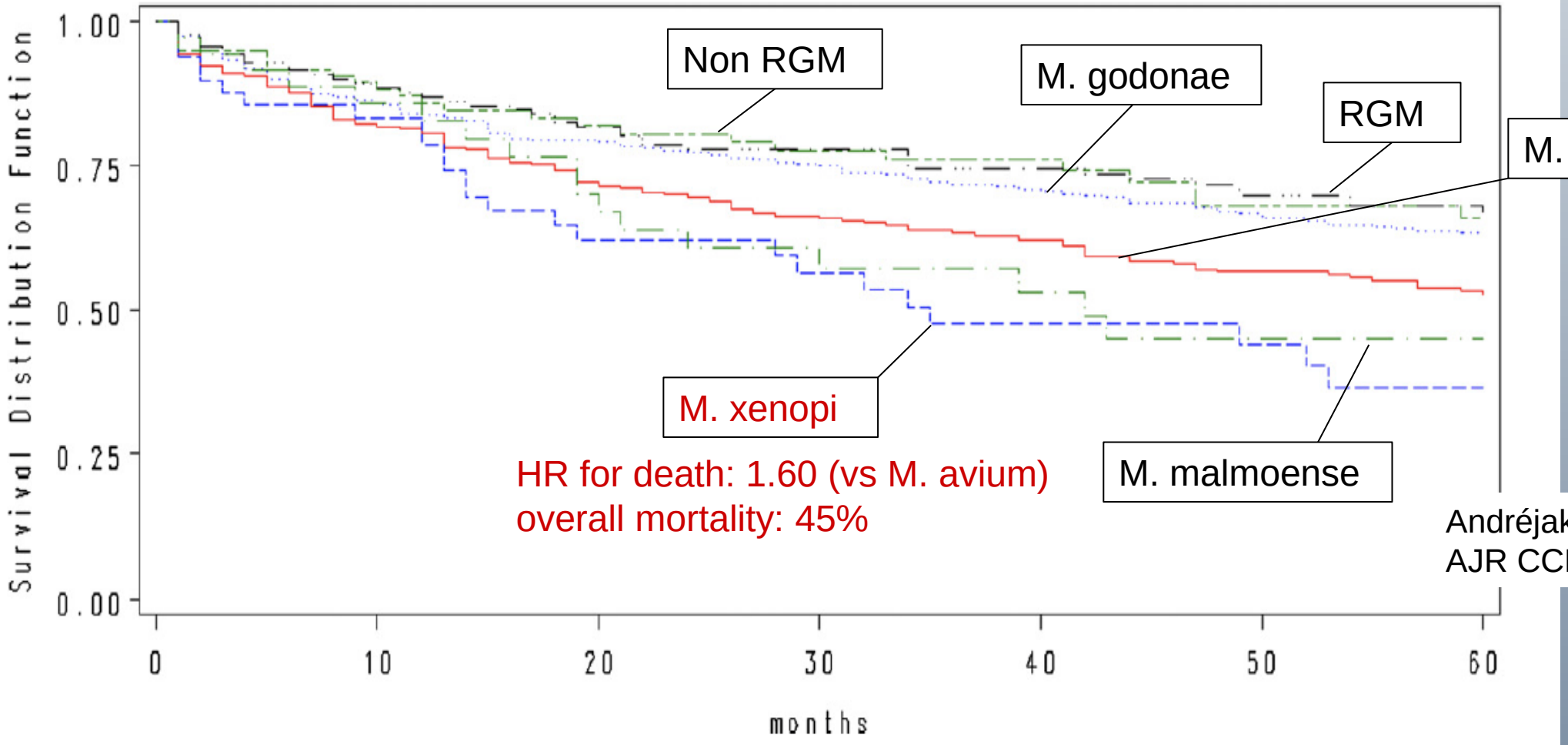
- British Guidelines: four-drug regimen (where tolerated) of rifampicin, ethambutol, macrolide (clarithromycin or azithromycin), and a quinolone (ciprofloxacin or moxifloxacin) or isoniazid.

- injectable aminoglycoside (amikacin or streptomycin) *should be considered* in severe pulmonary disease (ie, AFB smear positive, cavity, severe lung or systemic illness).
  - alternatively, nebulised amikacin may be used

- continue for a minimum of 12 months after culture conversion.

outcomes: M. xenopi

- most data from studies of pulmonary disease



Andréjak C *et al* (2010)
AJR CCM 181: 514–21

outcomes: M. xenopi

- mortality: 51% to 69% within 5 years of diagnosis.
- non-controlled study of 80 patients
- only 2 RCTs
  - BTS RCT #1 published in 2001
    - 42 HIV-negative patients treated with RHE or RE only.
    - 18% failure/relapse with RE vs 5% with RHE (not significant)
    - RHE associated with increased death
  - BTS RCT #2 published in 2008
    - 32 HIV-neg patients treated with RE+ clarithromycin or RE+ ciprofloxacin.
    - all-cause **mortality higher in those on cipro** (47% vs 29%)
    - overall cure rates dismal (35%)

Research Committee of the BTS (2001) Thorax 56: 167–72; Andréjak C (2009) Thorax 64:291–6; Andréjak C *et al* (2010) AJR CCM 181:514–21; Jenkins PA (2008) Thorax. 63:627-34.

Table 5 Comparative outcomes of four regimens in the treatment of lung diseases caused by MAC, *M malmoense* and *M xenopi*

	MAC				*M xenopi*				
	RE	REH	REClari	RECipro	RE	REH	REClari	RECipro	Total
No of patients	37	38	83	87	22	20	17	17	594
Deviated from protocol	16%	21%	35%	43%	14%	25%	59%	47%	32%
Deaths (all causes)	32%	39%	48%	30%	55%	85%	29%	47%	42%
Deaths (due to mycobacteria)	0%	8%	2%	3%	0%	15%	0%	6%	4%
Failures of treatment and relapses	41%	16%	13%	23%	18%	5%	24%	6%	14%
Completed treatment as allocated, alive and cured at 5 years	27%	34%	24%	23%	23%	10%	18%	12%	28%

Clari, clarithromycin; Cipro, ciprofloxacin; H, isoniazid; E, ethambutol; MAC, *Mycobacterium a*
Percentages do not always add up to 100% because some patients who died had earlier bee

Jenkins PA (2008) Thorax. 63:627-34.

our patient

- started therapy with moxifloxacin, ethambutol, rifampin, Isoniazid, Azithromycin
- INH stopped 8/1/2019
- continues on moxifloxacin, ethambutol, rifampin, and azithromycin

THANKS