An "Atypical" Dialysis Catheter Infection

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Case Presentation

- 71 year old male with history of ESRD on HD presents to the VA with altered mental status
- Had previously been followed by community ID physician in Colorado Springs for recurrent *Mycobacterium abscessus* peritoneal dialysis catheter-associated infection
- Spouse wanted patient to be evaluated for symptoms of delirium that had been present for several months, worsening more recently

PD Catheter Infection

- Dialysis dependent for last 3 years
- Primarily on PD, had first catheter infection 7 months prior to current presentation, no cultures/treatment-related data available
- New catheter placed in same location, re-infected infected couple months later, PD exit site cx recovered *M. abscessus,* susceptibilities showed:
  - Sensitive to amikacin
  - Intermediate to cefoxitin, doxycycline, minocycline, imipenem, linezolid
  - Resistant to ciprofloxacin, moxifloxacin, TMP-SMX, clarithromycin
- Reportedly treated with topical gentamicin alone
- Replaced catheter in different site, re-infected again 6 weeks later while in Alaska, peritoneal fluid cultures again recovered *M. abscessus*

PD Catheter Infection

- PD catheter removed, patient referred to ID for further management
- Case reviewed with National Jewish, came up with treatment regimen for *M. abscessus* peritonitis:
  - Linezolid 600 mg daily
  - Cefoxitin 1 g MWF post-HD
  - Amikacin 500 mg MWF post-HD
- Plan was to treat for 8 weeks (had completed ~3 weeks upon presentation)

Other Past Medical History

- IDDM
- Legal blindness (s/p bilateral eye enucleation)
- Baseline hearing loss and tinnitus
- HTN
- COPD
- OSA on CPAP
- Depression
- Fatty liver disease
- Nephrolithiasis

VA Admission

- CC: Progressively worsening AMS, moderate L-sided abdominal pain
- Physical Exam
  - Vitals: BP 161/74, P 79, RR 18, T 98.4
  - Gen: Pleasant, NAD, extremely hard of hearing
  - Card: RRR no MRG
  - Pulm: CTAB, normal respiratory effort
  - Abd: Mild TTP in LLQ, packing in place of prior RLQ PD site
  - Skin: Discoloration/thickening of skin over LLQ of abdomen
  - Ext: RUE fistula with palpable thrill

Labs

- WBC 7.1, Hgb 8.3, Hct 25.7, plt 332
- CMP with elevated Cr
- Lactate wnl, UA bland
- ESR 99, CRP 104
- HIV neg

Imaging

- CT Head non-con: 7 mm R parietal thickness probable acute-subacute subdural hematoma with mild mass effect on the inferior R parietal gyri, no midline shift
- CT Abd/Pelvis non-con:
  - 16 x 7.5 x 12 cm fluid collection in left abdomen
  - Presumed sinus tract in RLQ abdominal wall
  - Small density in deep subcutaneous fat of left anterior abdominal wall
  - Renal cysts
  - Diverticulosis

Initial Hospital Course

- Underwent IR-guided LLQ 10F drain placement, drained 500 cc of purulent fluid, sent for studies:
  - PD fluid: opaque, green, WBC >400K (93% segs), RBC 300K
  - Sent for culture
- Evaluated by general surgery for possible surgical debridement
- Concern for progression of hearing loss prompted concern for amikacin ototoxicity

Clinical Questions

- How common is *M. abscessus* peritonitis?
- What are the treatment options for *M. abscessus* infections?
- What specific data exists for treatment of *M. abscessus* peritonitis?

Mycobacterium abscessus Complex

- One of the six groups/complexes within the rapidly growing mycobacteria (RGM) group
- Tends to be the most pathogenic of the RGM group
- Frequently causes pulmonary infection (causes 80% of cases) particularly in those with underlying pulmonary disease states

Griffith 1993

Mycobacterium abscessus Infections

- Often affects immunocompromised individuals: CF, transplant, HIV, TNFα treatment
- Appear to manifest most frequently as pulmonary disease
- Also seen in skin and soft tissue infections: tattoos, cosmetic surgery, acupuncture
- Reported in gastric lap-band surgery, endocarditis, prosthetic joint infections, pericarditis, chronic otitis media, mastoiditis, tenosynovitis, vertebral osteomyelitis, VP shunt infection, chronic meningoencephalitis, disseminated disease

NTM Peritonitis: Case Review

- 57 cases of PD-associated NTM peritonitis
- Ages 5 to 82 years
- 66.7% smear positive
- Mycobacterial species:
  - *M. fortuitum* (38.6%)
  - *M. chelonae* (14.0%)
  - *M. abscessus* (8.8%)
- Mean and median duration of treatments 4.6 and 3 months, respectively

Song et al. 2012

RGM PD Catheter-Associated Infections

- RGM is responsible for most catheter-related infections
  - More commonly *M. fortuitum* and *M. mucogenicum* groups
  - 20 reports of *M. fortuitum* PD peritonitis identified in a 2014 case series
  - Majority described in Asian countries

Jiang et al. 2012, Hamade et al. 2014

M. abscessus PD Catheter-Associated Infectio

Previously reported cases of peritoneal dialysis peritonitis and exit-site infections by *Mycobacterium abscessus*.

Article (Ref)	Country or region	Number of PD-peritonitis cases	Number of ESI cases	Number of cases with blood infection
Lo et al., Perit Dial Int 2013 [2]	Hong Kong	2	4	0
Renaud et al., Nephrology 2011 [3]	Singapore	4	3	1
Kameyama et al., Ther Apher Dial 2007 [4]	Japan	1	–	0
Ellis et al., Pediatr Nephrol 2005 [5]	USA	–	1	0
Tsai, Ther Apher Dial 2013 [6]	Taiwan	–	1	0
Yang et al., Perit Dial Int 2015 [7]	Taiwan	2	–	0
Jiang et al., Int Urol Nephrol 2013 [8]	Australia	3	–	0
Siddiqi et al., Saudi J Kidney Dis Transpl 2012 [9]	Saudi Arabia	2	–	0

Abbreviations: PD, peritoneal dialysis; ESI, exit-site infection.

Mooren et al. 2017

M. abscessus PD Catheter-Associated Infectio

- Mooren case:
  - 73yo F with ESRD on PD, developed exit-site infection after 1 year
  - Treated with flucloxacillin, no improvement after 10 days
  - Cultures grew *Corynebacterium sp.*, switched to amoxacillin-clavulanate, no improvement
  - Removed and replaced catheter on day 24, switched to HD
  - PCR revealed *M. abscessus* on day 29, did not give additional treatment
  - POD#10 developed new fevers, restarted flucloxacillin, no improvement, blood cultures later revealed *M. abscessus*
  - Both PD and HD catheters removed, started treatment with tigecycline and clarithromycin, switched clarithromycin to imipenem based on susceptibilities (imipenem-I, inducible macrolide resistance)
- Tsei case:
  - 50yo M with ESRD on PD, developed exit-site infection after 1 year
  - Treated with topical gentamicin and oral beta-lactams for 6 months, no improvement, developed an abscess
  - Culture of abscess fluid revealed *M. abscessus*, performed debridement and received 2 months of ciprofloxacin, clarithromycin, and rifampin
  - Preserved the catheter

Tsei 2013

M. abscessus Peritoneal Dialysis-Associated Peritonitis: Case Series and Review

- Case report:
  - 44yo F on PD for 8 years admitted for refractory exit-site infection
  - Catheter replaced, started HD, fever/chills after 3 days treated with piperacillin-tazobactam and vancomycin
  - AFB positive smear of ascites fluid POD #10, started TB therapy
  - MTB PCR negative at 4 weeks, switched to NTM regimen (meropenem, amikacin, clarithromycin), *M. abscessus* diagnosed during week 5 of treatment
  - Had multiple complications including adhesions/abscess, died 8 months later due to renal hemorrhage and retroperitoneal infection
- 11 cases total reviewed:
  - All except 1 sensitive to amikacin, all sensitive to clarithromycin, all quinolone resistant
  - Treatment duration varied between 4 weeks and 7 months
  - All catheters were removed

Yang et al. 2015

M. abscessus Treatment: 2007 ATS/IDSA Statement

"At present, there is no reliable or dependable antibiotic regimen, even based on in vitro susceptibilities and including parenteral agents, to produce cure for M. abscessus lung disease."

Griffith et al. 2007

M. abscessus Treatment

- Often treatment refractory
- Discordance between *in vitro* data and *in vivo* outcomes
- Lack of antimicrobial bactericidal activity: Maurer et al 2014
  - Time-kill curves generated for *M. abscessus* and *E. coli* isolates using commonly categorized bactericidal agents (amikacin, moxifloxacin) and bacteriostatic agents (tigecycline, linezolid)
  - None of the compounds showed bactericidal activity against *M. abscessus*
  - Suggested chromosomally encoded drug-modifying enzymes present
    - Chromosome of *M. abscessus* contained regions coding for aminoglycoside phosphotransferases representing homologs of aminoglycoside-modifying enzymes
      - Knocking out 2'-N-acetyltransferase in *M. smegmatis* restored bactericidal activity

M. abscessus Treatment: Non-pulmonary Disease

- Uniformly resistant to standard anti-TB agents
- Macrolides are only oral agents reliably active *in vitro*
- Most active parenteral agent is amikacin
  - Given at dose of 10-15 mg/kg daily (with normal renal function)
  - Goal peak serum levels in the low 20-mg/ml range
- Amikacin combined with high-dose cefoxitin is recommended for initial therapy
- Imipenem is a reasonable alternative to cefoxitin
- Minimum 4 months for serious disease
- Acquired mutational resistance to clarithromycin and amikacin can occur

Griffith et al. 2007

M. abscessus Resistance Mechanisms

- *erm* gene usually present in *M. smegmatis, M. fortuitum,* and *M. abscessus*
- Confers inducible macrolide resistance
- Other innate resistance mechanisms: *erm*-like gene, efflux pumps, aminoglycoside 2'-N-acetyltransferase, aminoglycoside phosphotransferases
- Can acquire additional macrolide resistance from 23S rRNA gene mutation

Griffith 2014

M. abscessus Treatment: Additional Agents

- Oxazolidinones, glycylcyclines, and ketolides have some *in vitro* activity 50% of isolates susceptible or intermediate in vitro to linezolid
  - Small number of patients treated with linezolid combined usually with a macrolide with mixed results
  - Long-term linezolid at 600mg bid dosing associated with severe side effects, but 600 daily may have significant activity with fewer side effects
  - Novel agent LCB01-0371 with similar efficacy to linezolid and inhibited strains resistant to amikacin, cefoxitin, and clarithromycin
- Tigecycline-containing regimens for salvage therapy: Wallace et al 2014
  - 52 patients on tigecycline-containing multidrug regimens for salvage treatment
  - Pulmonary represented most common presentation, 58.3% of these had CF
  - Concomitant antimicrobials most commonly were macrolides, amikacin, and linezolid
  - 61.5% overall and 75.0% of extrapulmonary infections were considered improved
  - Adverse events in >90% of cases, most commonly nausea and vomiting

Griffith et al. 2007, Brown et al 2002

M. abscessus Treatment: Additional Agents

- Combination clofazimine and tigecycline: Singh et al. 2014
  - Tested susceptibility profile for 67 strains, clofazimine and tigecycline most active
  - Combination *in vitro* showed synergistic activity in 42% of 19 isolates
- Rifabutin: Aziz et al. 2017
  - Had activity against reference strain and clinical isolates
  - Active against clarithromycin-resistant strains
- Combination carbapenems (doripenem, biapenem) and rifampin: Kaushik et al. 2015
  - High MICs as monotherapy
  - Concentrations in combination exhibited synergistic activity
- Combination avibactam and carbapenems: Kaushik et al. 2017
  - 28 multidrug resistant isolates included
  - Avibactam restored MICs of tebipenem, ertapenem, and panipenem

Clinical Questions Revisited

- How common is *M. abscessus* peritonitis?
  - *Relatively uncommon, most frequently presents as pulmonary disease, less common cause of peritonitis than other RGMs.*
- What are the treatment options for *M. abscessus* infections?
  - *Typically use 2-3 drug regimens which include macrolides, cefoxitin, imipenem, or amikacin. Linezolid and tigecycline are alternative treatment options.*
- What specific data exists for treatment of *M. abscessus* peritonitis?
  - *Data mostly exists for in vitro studies, extrapolated from pulmonary infections.*

Case Conclusion

- Audiology evaluation:
  - Mild to severe sensorineural hearing loss
  - Excessive cerumen removed, dead hearing aid batteries replaced
  - Recommended retesting in 6 months
- Repeat imaging revealed resolution of L abdominal fluid collection, surgical debridement no longer indicated
- Patient's mental status improved, abdominal pain resolved
- Cultures remained negative
- Discussed case again with National Jewish:
  - Stopped amikacin, switched to tigecycline and applied for clofazimine
  - Later developed pancreatitis and tigecycline stopped, continued linezolid and cefoxitin
  - Ultimately family decided to stop therapy due excessive to side effects

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Questions?