IDCases 32 (2023) e01801

Contents lists available at ScienceDirect

IDCases

journal homepage: www.elsevier.com/locate/idcases

Case report

# Development of multidrug-resistant *Mycobacterium tuberculosis* in the biofilm of a peritoneal-venous shunt

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ARTICLE INFO

*Keywords:*
Tuberculosis
Multi-drug resistance
Biofilm
Foreign body
Denver catheter
Relapse

ABSTRACT

A patient with ascites received a peritoneal-venous shunt for presumed cirrhosis, however surgical specimens grew *Mycobacterium tuberculosis* (MTb) sensitive to all anti-tuberculous drugs. Directly-Observed-Therapy (DOT) led to improvement followed by relapse with multidrug resistant MTb (MDRTB). We discuss pathways for selection of MDRTB within mycobacterial biofilm. This case illustrates the potential for development of MDRTB in patients with long-term indwelling catheters. We emphasize catheter removal and if not possible continuing follow-up for symptoms and signs of relapse.

## Introduction

We encountered a patient with multidrug-resistant tuberculosis (MDRTB) who had received recommended directly-observed-therapy (DOT). The patient had a peritoneal-venous shunt in place at the time of tuberculosis (TB) diagnosis. The presence of this foreign body may have allowed for selection of MDRTB. We address possible mechanisms for development of MDRTB in a patient harboring a peritoneal-venous catheter.

## Case

A 45-year-old divorced homeless man was admitted to our hospital with abdominal pain. He was a Vietnam veteran. Medical history was significant for MDRTB, chronic hepatitis C, and alcohol use disorder with associated complications including liver cirrhosis with ascites, bleeding from esophageal variceal veins and pancreatits.

Five years previously he presented to an outside hospital with incarcerated inguinal hernia and worsening ascites. He underwent surgery with herniorrhaphy and placement of a Denver shunt catheter from the peritoneal cavity to the superior vena cava for management of ascites presumed secondary to cirrhosis and portal hypertension. Histopathology of the hernia sac revealed caseating granulomas. Cultures of tissue and ascitic fluid grew *Mycobacterium tuberculosis* (MTb). At this time chest x-ray showed no evidence of pulmonary involvement. A four-drug regimen with isoniazid (INH), rifampin (RMP), pyrazinamide (PZA) and ethambutol (EMB) was begun. Susceptibility testing at Utah State Health Laboratory (USHL) revealed isolates were susceptible to all drugs tested. DOT was managed by Salt Lake County Health Department (SLCHD). DOT log showed perfect compliance with his regimen (Supplement Fig. 1). He received four drugs for the first four months and continuation of INH and RMP for a total of ten months. Monthly visits to the SLCHD TB clinic documented clinical response to treatment. The patient gained weight, had no fever and abdominal pain resolved.

Near completing treatment, he began to have fever, chills, weight loss and cough. He was admitted to an outside hospital where his chest x-ray suggested pulmonary tuberculosis. Sputum smear showed rare acid-fast bacilli (AFB); culture was positive for Mtb. His isolate was resistant to INH and RMP, and to PZA on one sputum sample but susceptible on another (Supplement Figure 2). INH and RMP were

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https://doi.org/10.1016/j.idcr.2023.e01801
Received 4 April 2023; Received in revised form 13 May 2023; Accepted 16 May 2023
Available online 18 May 2023

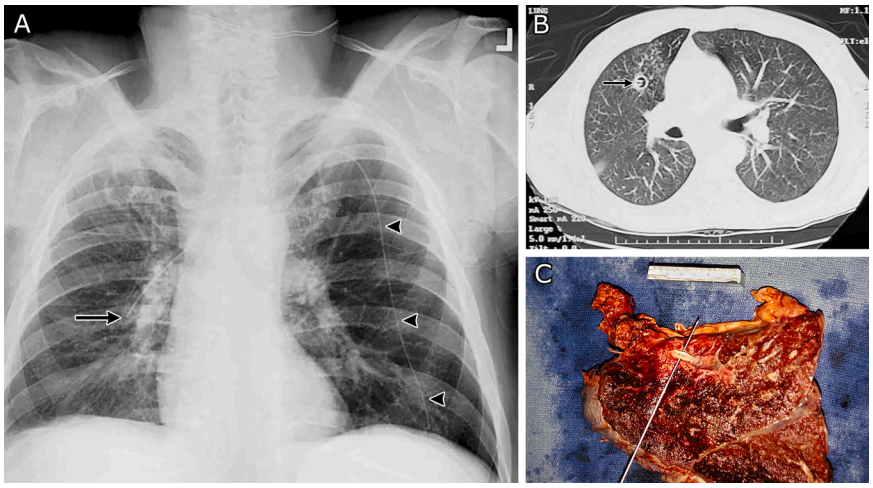


**Fig. 1. Pulmonary findings at last admission and at autopsy.** *Panel A*, PA view showing Denver shunt coursing upward along the posterior-lateral chest wall (arrowheads) and extending across the midline to end in the right mid-lung field (arrow). *Panel B*, Chest CT scan showing catheter tip (arrow) protruding into a cavity in the right upper lobe at the level just caudal to the bifurcation of the mainstem bronchi. *Panel C*, Gross pathology at autopsy with the Denver shunt catheter tubing exposed above an underlying probe. The photo is of the right upper lobe, which had been bread-knifed to examine lung parenchyma. Note the extensive surrounding hemorrhage and marked pleural thickening.

discontinued, PZA was continued, and streptomycin, ofloxacin and cycloserine were begun. DOT records again showed excellent compliance with a good clinical response. After 9 months of treatment, he felt well, and his chest x-ray had improved. At this time, he was lost to follow-up.

After a hiatus of almost three years (Supplement Figure 3) he presented to a local emergency room complaining of recurrent abdominal pain. He was referred to our hospital and admitted. He was cachectic with a protuberant abdomen. Vital signs were normal. Denver shunt tubing was visible through a skin defect of the left chest wall with expressible fluid. The abdomen had a doughy consistency. Chest x-ray showed the course of the shunt catheter, which appeared to terminate within the right lung (Fig. 1**A**). Chest and abdominal CT demonstrated multiple pulmonary cavities including one into which the tip of his shunt catheter protruded (Fig. 1**B**). There were extensive inflammatory changes of the peritoneal cavity including loculated fluid collections. Sputum, peritoneal fluid and chest wall fluid grew MTb, confirming disseminated infection. All isolates were resistant to INH but susceptible to RMP. A multidrug regimen recommended by the CDC-sponsored TB Hotline was begun.

His hospital course was complicated by recurrent emesis due to small bowel obstructions. Attempts at nutritional replacement were unsuccessful, inanition worsened, and aspiration occurred which was fatal.

At autopsy the Denver shunt catheter was visible within the lung parenchyma (Fig. 1**C**) but determining the site of entry into the right lung was obscured by caseous inflammation. It was impossible to "run the intestines" due to their incasement within caseous material. His course is summarized in Supplement Figure 3.

## Discussion

We discuss possibilities for development of MDRTB during DOT: 1) compliance failure, 2) drug malabsorption, 3) laboratory error failing to identify MDRTB in initial isolates, 4) reinfection with a new MDRTB strain, and 5) selection for MDRTB within catheter biofilm.

DOT record (Supplement Fig. 1) showed complete compliance. TB Control Program staff verified this and noted his friendly and consistent cooperation throughout DOT. He lived in a private apartment through the Salt Lake County Housing authority to ensure treatment compliance.

Malabsorption of TB drugs is rare. In this case with peritoneal involvement intestinal malfunction should be considered. However, experience with treatment for both peritoneal and ileal TB strongly supports efficacy for standard treatment of susceptible isolates [1]. Microbiological records showed a positive response to treatment during therapy, and this correlated with clinical improvement. Thus, drug malabsorption was not likely.

We investigated laboratory error for susceptibility testing of his initial isolates. The source document from USHL showed pan-susceptibility (Supplement Figure 2). During the same year thirty-three MTb isolates from Utah were sent to the VA Medical Center in Little Rock, AK for DNA fingerprinting using restriction fragment length polymorphisms (RFLP). Of 33 samples from 22 patients, three isolates bore an identical 10-band electrophoretic pattern (Supplement Figure 4). These were our patient's initial isolate, his MDRTB isolate, and a third isolate from a patient who died of pulmonary tuberculosis one year previously. The latter was pan-susceptible, and the deceased man was a close companion of our patient. Since the two men likely shared the same strain, microbiological data corroborates pan-susceptible MTb. Further, the patient's susceptible and MDRTB isolates were sent to CDC for spoligotyping. The strains had identical patterns confirming RFLP results. This excluded laboratory error or reinfection with a new MDRTB strain.

We considered the role of his shunt as a nidus for relapsing infection and environment for selection of multi-drug resistance. Relapsed TB is described in the presence of foreign bodies, including bone/joint prosthetics, ventricular shunts and plombage for collapse-therapy with Lucite or resin balls [2–4]. We found no reports of foreign body associated-risk for MDRTB. In the case of our patient his medical record gave no clue as to the time when the catheter fistulated from the superior vena cava into his right lung. We found no reports describing this complication.

Resistance to individual anti-tuberculous drugs requires *de novo* random chromosomal mutations within a large population of bacterial cells [5]. Event frequency for a single drug is roughly $10^{-6}$ to $10^{-9}$ per bacterium per replication. The probability for selection of double or triple mutants is diminishingly small. However, the presence of the Denver shunt as a focus for cell attachment within mycobacterial biofilm could alter the dynamics of sterilizing drug treatment [6]. It is well established that mycobacteria form biofilm [7]. This requires cell attachment, intercellular aggregation with quorum sensing and architecture maturation [8]. Unlike planktonic cells, MTb within biofilm attain a so-called "persister" or "elite" state becoming tolerant to drug bactericidal activity [6]. Susceptibility to drugs decreases [9]. Spontaneous *de novo* mutants could arise within biofilm. However single mutants do not provide a mechanism for multi-drug resistance. However, if presence within biofilm substantially increased random spontaneous mutation rates, selection for MDRTB cells might occur. We searched for literature evidence of such phenomena in mycobacterial species but found none.

Horizontal gene transfer (HGT) by conjugation could select for MDRTB [10]. A unique type of conjugation called "distributive conjugal transfer" (DCT) has been extensively studied [10–12]. It involves

transfer of multiple random unlinked DNA sequences giving rise to recipient cells bearing mosaic chromosomes by homologous recombination events. Such genetic exchange can potentially enhance fitness [11]. Two factors limit DCT involvement: 1) DCT has not been reported in MTb. 2) MTb strains from human cases are clonal and therefore would lack either donor or recipient genotypes [10,13]. RFLP results from our patient's initial and first relapse isolates indicated clonal infection.

While the genetic pathway to MDRTB remains unknown, it seems likely that MTb biofilm played an important role in development of drug resistance [14,15]. Our report emphasizes the necessity for removal of permanent catheters. In retrospect the Denver shunt should have been removed at the time of TB diagnosis. If catheter removal is impossible, based on our experience from this case, patients should be followed monthly and then long-term for any symptoms or signs of relapse once treatment is completed.

## Funding

This report did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

## Author Statement

All Authors have read and agree with the revised version of our manuscript and Supplemental Materials. I have received approval from all Authors for the submission of the revised manuscript and Supplemental Materials. No part of our revised submission has been submitted or published elsewhere. Donald L. Granger, M.S., M.D.

## Conflicts of interest

All authors must disclose any financial and personal relationships with other people or organisations that could inappropriately influence (bias) their work. Examples of potential conflicts of interest include employment, consultancies, stock ownership, honoraria, paid expert testimony, patent applications/registrations, and grants or other funding.

## Acknowledgements

We thank Alfonso Ramirez, Dan Andrews, Kyle Cannon (deceased), Christie Chester, Larry Niler and June Oliverson from the Salt Lake County and Utah State Health Departments for their dedicated assistance in managing the patient's infection. Dr. Elizabeth Jensen, Pathology Service, Salt Lake Veterans Affairs Medical Center performed the autopsy and exhibited the gross findings. Dr. Don Cave, Little Rock, AR VA Hospital kindly shared the RFLP data on MTb isolates from Utah. We thank Mary McFarland and Lydia Howes, Eccles Health Sciences Library, Spencer Fox Eccles University of Utah School of Medicine, for assisting with manuscript preparation. Tod Peterson, Communications Service, Salt Lake VA Medical Center, generously aided with reproductions of the Figures.

### *Patient consent statement*

We were unable to obtain patient consent for this case report. The patient expired before our report was prepared. We were unable to identify next of kin from hospital records. Ethics committee approval was not required for this case report. All patient records have been de-identified for this report.

### *Authorship contribution statement*

DLG, PFC and CBS cared for the patient during his final admission. DLG collected the data from Public Health Departments in Davis and Salt Lake Counties, from the Utah State Public Health Laboratory, and from the hospital of the patient's previous admissions. RMR, TDM and DLG wrote the manuscript. Layout for Supplement Figure 4 was inspired by CBS.

## Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.idcr.2023.e01801.

## References

[1] Jullien S, Jain S, Ryan H, Ahuja V. Six-month therapy for abdominal tuberculosis. Cochrane Database Syst Rev 2016;(11).
[2] Massard G, Thomas P, Barsotti P, Riera P, Giudicelli R, Reboud E, et al. Long-term complications of extraperiosteal plombage. discussion 4-5. Epub 1997/07/01 Ann Thorac Surg 1997;64(1):220–4. https://doi.org/10.1016/s0003-4975(97)00344-5.
[3] Shibolet S, Dan M, Jedwab M, Goldhammer Y, Baum GL. Recurrent miliary tuberculosis secondary to infected ventriculoatrial shunt. Epub 1979/09/01 Chest 1979;76(3):328–30. https://doi.org/10.1378/chest.76.3.328.
[4] Veloci S, Mencarini J, Lagi F, Beltrami G, Campanacci DA, Bartoloni A, et al. Tubercular prosthetic joint infection: two case reports and literature review. Epub 2017/11/01 Infection 2018;46(1):55–68. https://doi.org/10.1007/s15010-017-1085-1.
[5] Eldholm V, Balloux F. Antimicrobial resistance in mycobacterium tuberculosis: the odd one out. Epub 2016/04/14 Trends Microbiol 2016;24(8):637–48. https://doi.org/10.1016/j.tim.2016.03.007.
[6] Ojha AK, Baughn AD, Sambandan D, Hsu T, Trivelli X, Guerardel Y, et al. Growth of Mycobacterium tuberculosis biofilms containing free mycolic acids and harbouring drug-tolerant bacteria. Epub 2008/05/10 Mol Microbiol 2008;69(1):164–74. https://doi.org/10.1111/j.1365-2958.2008.06274.x.
[7] Esteban J, García-Coca M. Mycobacterium biofilms. Epub 2018/02/07 Front Microbiol 2017;8:2651. https://doi.org/10.3389/fmicb.2017.02651.
[8] Yang Y, Thomas J, Li Y, Vilchèze C, Derbyshire KM, Jacobs Jr WR, et al. Defining a temporal order of genetic requirements for development of mycobacterial biofilms. Epub 2017/06/20 Mol Microbiol 2017;105(5):794–809. https://doi.org/10.1111/mmi.13734.
[9] Richards JP, Cai W, Zill NA, Zhang W, Ojha AK. Adaptation of mycobacterium tuberculosis to biofilm growth is genetically linked to drug tolerance. Epub 2019/09/11 Antimicrob Agents Chemother 2019;63(11). https://doi.org/10.1128/aac.01213-19.
[10] Derbyshire KM, Gray TA. Distributive conjugal transfer: new insights into horizontal gene transfer and genetic exchange in mycobacteria. Mgm2-0022-2013. Epub 2014/02/01 Microbiol Spectr 2014;2(1). https://doi.org/10.1128/microbiolspec.MGM2-0022-2013.
[11] Gray TA, Derbyshire KM. Blending genomes: distributive conjugal transfer in mycobacteria, a sexier form of HGT. Epub 2018/04/19 Mol Microbiol 2018;108(6):601–13. https://doi.org/10.1111/mmi.13971.
[12] Nguyen KT, Piastro K, Gray TA, Derbyshire KM. Mycobacterial biofilms facilitate horizontal DNA transfer between strains of Mycobacterium smegmatis. Epub 2010/08/03 J Bacteriol 2010;192(19):5134–42. https://doi.org/10.1128/jb.00650-10.
[13] Clark RR, Lapierre P, Lasek-Nesselquist E, Gray TA, Derbyshire KM. A polymorphic gene within the Mycobacterium smegmatis esx1 locus determines mycobacterial self-identity and conjugal compatibility. Epub 2022/03/18 mBio 2022;13(2):e0021322. https://doi.org/10.1128/mbio.00213-22.
[14] Chakraborty P, Bajeli S, Kaushal D, Radotra BD, Kumar A. Biofilm formation in the lung contributes to virulence and drug tolerance of Mycobacterium tuberculosis. Epub 2021/03/13 Nat Commun 2021;12(1):1606. https://doi.org/10.1038/s41467-021-21748-6.
[15] Ma F, Zhou H, Yang Z, Wang C, An Y, Ni L, et al. Gene expression profile analysis and target gene discovery of Mycobacterium tuberculosis biofilm. Epub 2021/06/15 Appl Microbiol Biotechnol 2021;105(12):5123–34. https://doi.org/10.1007/s00253-021-11361-4.