Disseminated *Mycobacterium fortuitum* Infection Associated with Venous Access Device

Premamalini Thayanidhi¹, Shanthi Mariappan², Uma Sekar³, Kopula Sathyamurthy Sridharan², Aruna Rajendran⁴

¹Assistant Professor, Department of Microbiology, Sri Ramachandra Medical College and Research Institute, Sri Ramachandra University, Porur, Chennai, Tamil Nadu, India, ²Associate Professor, Department of Microbiology, Sri Ramachandra Medical College & Research Institute, Sri Ramachandra University, Porur, Chennai, Tamil Nadu, India, ³Professor and Head, Department of Microbiology and Director, Sri Ramachandra Laboratory Services, Sri Ramachandra Medical College & Research Institute, Sri Ramachandra University, Porur, Chennai, Tamil Nadu, India, ⁴Assistant Professor, Department of Pediatric Hemato-oncology, Sri Ramachandra Medical College & Research Institute, Sri Ramachandra University, Porur, Chennai, Tamil Nadu, India

*Mycobacterium fortuitum* is an important opportunistic pathogen among the rapidly growing Mycobacteria. Disseminated disease occurs as a consequence of bacteremia linked to vascular catheters, which carry high morbidity and mortality when they occur in immuno-compromised patients. Conventional culture methods often miss these organisms since they may grow more slowly (after 48 h) and are dismissed as skin contaminants because of their morphological resemblance to diphtheroids on grams staining. We report a case of 10 months old child with primitive neuroectodermal tumor who developed disseminated disease with *M. fortuitum* that was related to an indwelling intravascular device. The isolates were confirmed as *M. fortuitum* by polymerase chain reaction based DNA sequencing targeting heat shock protein 65 gene. The child was treated with, rifampicin, ethambutol and azithromycin. The patient improved remarkably and became afebrile 2 days after institution of therapy and removal of the catheter. The treatment was given for 3 months.

**Keywords:** DNA sequencing, Intravascular device, *Mycobacterium fortuitum*

### INTRODUCTION

*Mycobacterium fortuitum* is an important opportunistic pathogen among the rapidly growing Mycobacteria. It is saprophytic, ubiquitous in nature and considered of low virulence.¹ In 1905 it was first isolated from an amphibian and in 1938 it was identified as a cause of human cutaneous infection.² Precise data regarding its prevalence is lacking especially from the developing countries. This species is associated with a wide spectrum of infections of which the major types are skin, soft tissue infections, post-surgical infections and respiratory infections.²,³ Other reported infections are keratitis, endocarditis, lymphadenitis, meningitis, hepatitis, peritoneal dialysis related peritonitis, catheter-related sepsis and disseminated infections.²,⁴-⁷ Infections carry high morbidity and mortality when they occur in immuno-compromised populations, in patients with serious comorbid conditions and when they disseminate to deep organs.² We report a case of 10-month-old child with primitive neuroectodermal tumor who developed disseminated disease with *M. fortuitum* that was related to an indwelling intravascular device.

### CASE REPORT

A 10-month-old female child who had been diagnosed with primitive neuroectodermal tumor underwent therapeutic resection of mass. Following surgery, chemotherapy was initiated with four cycles of vincristine, actinomycin D and cyclophosphamide. On completion of 8 cycles of chemotherapy, the child presented with high grade fever with rigors lasting for the preceding 8 days. On examination, the child was alert and febrile with fair hydration. The cardiovascular, respiratory and central nervous system examination did not reveal any abnormal findings. Abdomen was soft and hepatosplenomegaly was noted. There was an indwelling *in-situ* port-for chemotherapy, which had been placed 6 months prior. It had been observed that every time the port was accessed the child developed bouts of increased fever with rigors. Paired blood cultures, chest radiograph and ultrasound abdomen were done as part of the work up. Chest radiograph was normal but...
for minimal right pleural effusion. Ultrasound abdomen revealed hepatomegaly, moderate splenomegaly of 8.8 cm and minimal ascites. Patient was started empirically on parenteral piperacillin - tazobactam and amikacin. Since the febrile episodes continued without abating for 48 h, the therapy was switched over to meropenem, vancomycin and azithromycin. 3 days after submission, the aerobic blood cultures on BACTEC revealed the presence of rapidly growing Mycobacteria. Confirmation with acid fast staining was performed (Figure 1). It was identified as 
\textit{M. fortuitum} based on rapid growth both at 25°C and 45°C with no pigment production, nitrate reduction, growth on MacConkey agar, utilization of citrate and tolerance to 5% sodium chloride. The isolate was \textit{in-vitro} susceptible by disc diffusion testing to amikacin, ciprofloxacin, clarithromycin, doxycycline, imipenem and sulfamethoxazole.\textdagger Following this, azithromycin (160 mg/day) was continued and treatment with, rifampicin (70 mg/day) and ethambutol (100 mg/day) was initiated. The port-a-catheter was removed and the tip was submitted for culture. This also yielded growth of \textit{M. fortuitum}. The isolates were confirmed as \textit{M. fortuitum} by polymerase chain reaction based DNA sequencing targeting heat shock protein (hsp) 65 gene. The patient improved remarkably and became afebrile 2 days after institution of therapy and removal of the catheter. There was regression of hepatosplenomegaly and resolution of ascites and pleural effusion. The patient was discharged after 11 days and remained afebrile on follow-up. The treatment was given for 3 months.

**DISCUSSION**

There are more than 100 species of rapidly growing Mycobacteria today. With the recent widespread use of 16SrRNA gene sequencing additional species are being described worldwide.\textsuperscript{9} \textit{M. fortuitum}, in particular, is classified into three biovars and several biovariants based on 16S rRNA gene. They belong to Group 4 (Runyon’s classification) of rapidly growing non-tuberculous mycobacteria (NTM).\textsuperscript{9} They have been isolated from a number of natural sources including soil, dust and water. The capability of NTM to survive with low nutrients, in low pH and temperature extremes make them ideal opportunistic pathogens. Biofilm formation is a successful strategy adopted for their persistence. Due to its hydrophobic nature, biofilm formation facilitates the development of catheter-related blood stream infections resulting in difficulty of eradication.\textsuperscript{3}

\textit{M. fortuitum} bacteremia in patients with cancer and long term venous catheters has been described before. In 1987, 4 such cases were reported but none of them had evidence of disseminated disease.\textsuperscript{5} A few years later, a report from a single cancer center described 15 cancer patients who developed catheter related \textit{M. fortuitum} infections. Among them, 11 had bacteremia and 7 had insertion site infections. It was noted that the patients recovered when catheters were removed and antibiotics instituted, but persisted when catheters were left \textit{in-situ}. The patients with catheter insertion site infection and tunnel infection responded only after surgical excision of the tissue surrounding the infected tunnel.\textsuperscript{6} A case report from India in 2005, described \textit{M. fortuitum} bacteremia in a patient with acute lymphoblastic leukemia on intensive chemotherapy. This patient was successfully treated with clarithromycin and amikacin along with the removal of the catheter. \textit{M. fortuitum} endocarditis can occur as a result of bacteremia.\textsuperscript{7} In peritoneal dialysis-related infections, catheter removal and antibiotic therapy for at least 6 months results in eradication of bacteria.\textsuperscript{4} Healthcare acquired infections due to NTM have been linked to procedures such as injections, liposuction, plastic surgery, breast implant surgery and laser-assisted \textit{in-situ} keratomileusis. A case of soft tissue infection by \textit{M. fortuitum} has been traced to improperly sterilized acupuncture needle.\textsuperscript{10}

Disseminated disease occurs as a consequence of bacteremia linked to vascular catheters, prosthetic valves and sternal wounds. Clinical features of disseminated NTM infection may be non-specific and include fever, weight loss, sweating, diarrhea, generalized lymphadenopathy, generalized cutaneous lesions, diffuse abdominal tenderness, hepatosplenomegaly. Bacteremia may be intermittent and low grade, and hence multiple blood cultures are required for diagnosis.\textsuperscript{11} In a retrospective 5 years study on cancer patients conducted at the children’s hospital of Philadelphia on NTM infections, it was observed that 13 children developed bacteremia due to NTM. All children had a central venous catheter and were lymphopenic at the time of first positive culture. It was surmised that when children with cancer who have long-term venous catheters experience fever, NTM should be thought of as an etiological

![Figure 1: Acid fast staining of the smear from BACTEC blood culture](image-url)
agent.12 As environmental reservoirs are the primary source, foreign bodies and medical devices play a prominent role in facilitating and perpetuating such infections.6 Contrary to the disseminated cutaneous form of the infection, catheter related infections do not exhibit cutaneous manifestations.6 Appropriate management of catheter-related M. fortuitum infection must be based on an accurate diagnosis of the source of infection and prompt source control.6

Conventional culture methods often miss these organisms since they may grow more slowly (after 48 h) and are misdiagnosed as skin contaminants because of their morphological resemblance to diphtheroids on grams staining. Confirmation with acid-fast or Ziehl-Neelsen staining is therefore mandatory. M. fortuitum has been successfully isolated from BACTEC 9240 blood culture system.13 In our case, it was isolated from BACTEC 9120 in 96 h. Use of automated culture systems shortens the time to recovery and increases the predictive value especially when multiple cultures are obtained. Identification of rapidly growing Mycobacteria to the species level is important because there are predictable antimicrobial susceptibility patterns. M. fortuitum is generally more drug susceptible to oral regimens. It is inhibited with therapeutic doses of tetracycline, sulfamethoxazole and quinolones. When there is a large burden of organisms, single drug regimen is contraindicated, since M. fortuitum resistance to macrolides is known to occur. A recent report has described a new rRNA methylase gene (erm) in M. fortuitum that is capable of induction and brings to a great concern, the use of a single drug therapy with macrolides. In-vitro susceptibility testing and guidelines of the Clinical Laboratory Standards Institute by microbroth dilution for antimicrobial agents such as macrolides, aminoglycosides, fluoroquinolones, imipenem, linezolid, doxycycline and trimethoprim-sulfamethoxazole should guide therapy. There are no results of controlled trials of treatment for rapidly growing Mycobacteria. Although spontaneous resolution without antibiotics especially of skin infections has been reported, most experts recommend antibiotics in combination to avoid the emergence of resistance.3 The clinical significance of M. fortuitum in respiratory infections remains controversial. In the respiratory tract, it may colonize or cause transient infection especially in patients with underlying lung diseases such as bronchiectasis or tuberculosis. Isolation from multiple serial cultures is required for the institution of treatment. Prolonged antibiotic therapy is not required in a majority of M. fortuitum associated respiratory infections.3 Molecular confirmation of this isolate was performed by the sequencing of the hsp 65 gene. Unlike the 16S rRNA sequence analysis, the hsp 65 sequence analysis can easily differentiate Mycobacterium abscessus, Mycobacterium chelonae, Mycobacterium perigrinum, Mycobacterium fortuitum, Mycobacterium senegalense and M. fortuitum as distinct species.14

For children with disseminated NTM disease, treatment with at least three drugs to which the isolate is susceptible is suggested for 3-6 months or till clinical improvement is noted. A typical regimen may include macrolide (azithromycin or clarithromycin); Ethambutol; Rifamycin (rifampin or rifabutin). Amikacin, streptomycin or a fluoroquinolone may be a substitute for the macrolide or added as the fourth drug for patients who develop breakthrough infection while on prophylaxis or for patients in whom there is a concern about macrolide resistance. The total duration of therapy is usually 3-6 months.11

**CONCLUSION**

To conclude, M. fortuitum still remains an uncommon cause of device-related disseminated infection. In cancer patients on chemotherapy, febrile episodes should initiate a high index of suspicion of infection with NTM related to the long-term indwelling vascular access device. Multiple blood cultures performed by automated methods increase the sensitivity and yield of cultures. Laboratory should have the expertise not to misidentify them as diphtheroid and also be trained to accurately identify NTM up to species level including susceptibility testing. Apart from 16SrRNA, sequencing of hsp 65 gene offers a useful tool for identification up to species level.

**REFERENCES**

Thayanidhi, et al.: Disseminated *Mycobacterium fortuitum* infection


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