CASE REPORT

Fatal outcome of catheter-related bloodstream infection caused by Multidrug-Resistant Mycobacterium mucogenicum

Faridah Sulung, MD1,2, Siti Asma’ Hassan, MPath1,3, Zeti Norfidiyati Salmuna, MPath1,3, Tuan Noorkorina Tuan Kub, PHD1,3, Intan Baiduri Badri, MSc1,3, Azura Hussen, MPath1

1Department of Medical Microbiology and Parasitology, School of Medical Sciences, Universiti Sains Malaysia, Kubang Kerian, Kelantan, 2School of Health Sciences, Universiti Sains Malaysia, Health Campus, Kelantan, 3Hospital Universiti Sains Malaysia, Health Campus, Kubang Kerian, Kelantan, ‘Department Pathology, Hospital Raja Perempuan Zainab II, Kota Bharu, Kelantan

SUMMARY
Mycobacterium mucogenicum (M. mucogenicum) is a rarely isolated pathogen. It has emerged as a significant pathogen in immunocompromised patients including those with cancer, organ transplant, or patients on immunosuppressive medication. Chemotherapy may reduce the ability of the bone marrow of these to respond to infection, and patients will be at risk for neutropenic sepsis, which leads to fatal complications. Here, we report a case of a 18-year-old boy was diagnosed with B-cell acute lymphoblastic leukaemia due M. mucogenicum for clinical management and hopefully (ALL) two years earlier was seen at Hospital Raja Perempuan Zainab II. A chemophor was inserted before the initiation of this chemotherapy. During the admission he was on the consolidation phase of chemotherapy, on week 66, with modified German ALL protocol. He has never had a chemotherapy-related infection and was relatively well in between the admission.

For the current admission, he was electively admitted for the continuation of chemotherapy. On day-3 of admission, he developed a spike in temperature (38.5°C). It was associated with chills and rigors. He was normotensive and tachycardic. Chemoprot site was clean, no purulent discharge, non-tender, and not erythematous. His white blood cell (WBC) was 8.22 x10^9/L, haemoglobin of 12.6g/L, platelet of 144 x10^9/L and absolute neutrophil count (ANC) was 7.96x10^9/L with raised in C-reactive protein (CRP) (147mg/L; Lung auscultation and his chest x-ray were normal. Blood was taken for culture before the initiation of antibiotics. Intravenous (IV) cefepime 1gm 12 hourly was given empirically for the sepsis. However, the source of infection was still unknown.

The sample from the patient grew small, whitish colonies on blood sheep agar (Figure 1). It appears as gram-positive bacilli on gram staining. Acid-fast bacilli stain was also positive. Identification of the organism was performed by matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF MS, Bruker Daltonik, Bremen, Germany), and M.mucogenicum was identified with a score of 1.98 using the MALDI Biotyper reference library. The sample was sent to the national referral laboratory (Makmal Kesihatan Awam, Sungai Buloh, Selangor, Malaysia), confirmed that the organism was M.mucogenicum, and proceeded with sensitivity testing. However, in HRPF ILsetting, the sensitivity testing took about two weeks for the result to be available.

Antibiotic was changed to IV ciprofloxacin 400mg 12 hourly and IV amikacin 800mg once a day as the preferred treatment of choice for NTM. The second blood culture was taken from his chemophor (central sample) and peripheral site. M.mucogenicum was isolated from both samples. The central sample grew 2 hours earlier than the peripheral sample, which fulfilled the criteria of catheter-related bloodstream infection (CRBSI) based on IDSA guidelines.

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Corresponding Author: Dr Siti Asma’ Hassan
Email: sitiasmakb@usm.my
After a few days of treatment, his condition showed no sign of improvement. He developed neutropenic sepsis with acute liver injury possible secondary to drug-induced. Full blood count showed; WBC 0.99x10^9/L, ANC of 0.56x10^9/L and single-digit platelet. There was derangement in the liver enzymes; aspartate transferase was 263U/L (normal value: <50 U/L), alanine transferase of 3041/U/L (normal value: <50U/L), and alkaline phosphatase of 74U/L (normal value: 52-171U/L). IV ciprofloxacin was discontinued as it may contribute to acute liver injury. He was started on subcutaneous Neupogen, IV methylprednisolone, and IV imipenem 1gm 6 hourly.

Despite appropriate therapy given to him, his condition further deteriorated. He developed type 1 respiratory failure secondary to nosocomial pneumonia. His ANC remained below 0.5x10^9/L with worsening of aspartate transferase and alanine transferase more than 2000U/L. He succumbed on day 14 of admission. The cause of death was severe neutropenic sepsis secondary to pneumonia. The anti-tuberculosis sensitivity testing result from the referral laboratory showed resistance to ciprofloxacin, doxycycline, clarithromycin, and tobramycin.

**DISCUSSION**

*M. mucogenicum* belongs to a rapidly growing RGM group of non-tuberculous mycobacteria (NTM). It is an unusual cause of human infections, but the cases are higher among immunocompromised patients. Infection caused by *M. mucogenicum* results in various spectrum of disease, either pulmonary or extrapulmonary disease like skin and soft tissue infection (STI), bacteremia, CRBSI, meningitis, and peritonitis. The prevalence of pulmonary NTM infection was reported to be 8.6 episodes per 100,000 people in the United States of America (USA). However, the prevalence in Southeast Asia countries, including Singapore and Malaysia, is limited. The incidence rate for pulmonary NTM in Japan and Taiwan was higher than the USA, 14.7 and 46.0 cases per 100,000 population, respectively. The earliest outbreak of *M. mucogenicum* was discovered in 1976 from intermittent peritoneal dialysis, which developed peritonitis. The investigation of the outbreak reported that it was caused by ineffective disinfection and colonisation of the machine by *M. mucogenicum*. Implanted central venous port devices or chemopорт are used in oncologic patients for chemotherapy access, delivery of parenteral nutrition, or blood transfusions. Infections are the most common complication of chemopорт compared to catheter thrombosis, vessel stenosis, or catheter fracture with embolisation of catheter materials. Port-related infections are commonly seen in haematological malignancies, probably due to prolonged neutropenia, and intensive chemotherapy compared to solid tumors. The incidence rate for port-associated infection was 2.5%. In Malaysia, a 4 year-study showed that out of 102 chemopорт insertions, 5 (4.9%) had port-related infection. In our patient, his chemopорт was inserted two years earlier. He had never experienced any complication relating to his central line until this episode where he developed CRBSI caused by *M. mucogenicum*. Several studies reported that water from taps may be contaminated with this organism or suboptimal water chlorination was the source of *M. mucogenicum* infection. During showering, the catheter was exposed to tap water, resulting in contamination of the catheter. Given this information, the source of infection in this patient is still unestablished. There was no additional environmental sampling done for this case to confirm the source of infection. Our patient had an episode of neutropenic fever with chills and rigors, high in CRP, no signs of infection at the chemopорт site, and *M. mucogenicum* was isolated from paired blood culture. CRBSI is diagnosed in patients with signs and symptoms of exit-site infection like pain and tenderness at the catheter site, erythematous skin, and purulent discharge. Fever with or without rigors in 30-60 minutes of commenting infusion is a typical symptom of CRBSI. It can be misdiagnosed when patients have atypical presentations like non-specific malaise, hyperbilirubinemia, hypoalbuminemia and raised in inflammatory markers like CRP, erythrocyte sedimentation rate, and procalcitonin. *M. mucogenicum* CRBSI are seen more likely in long term intravenous catheters. A case report of the external ventricular drain (EVD)-associated with *M. mucogenicum* meningitis was reported recently. The patient developed meningitis after day 5 of EVD placement.

Our isolate was a rapid grower (grew on blood agar within seven days) NTM, which was identified as *M. mucogenicum* by MALDI-TOF. Mycobacterium organisms need to be identified up to species level as it helps to predict in vitro susceptibility and gives a guide for antibiotic therapy. Today, molecular methods like PCR sequencing (16s RNA gene sequencing) and PCR hybridisation are the new gold standard in the identification of mycobacterium. The standard conventional tests that we used previously were laborious, time-consuming, and gave a significant challenge in identifying the Mycobacteria species. However, DNA sequencing test is only available in some of the laboratories. MALDI-TOF mass spectrometry is another method that can be used to identify Mycobacteria species accurately. It is cost-effective, has a short turn-around time, and easily implemented in a routine laboratory.

![Fig 1: Mucoid whitish small colonies of *M. mucogenicum* on blood sheep agar.](image-url)
**Case Report**

*M. mucogenicum* was reported as the most susceptible organism among RGM species. They are susceptible to aminoglycoside, fluoroquinolones, tetracyclines, macrolides, carbapenem, cefoxitin, and trimethoprim-sulfamethoxazole. Non-tuberculous MDR is defined when the isolates are resistant to at least four different classes of antimicrobials. Non-tuberculous multidrug-resistance (MDR) is rarely reported due to the limited number of isolates. Our isolate was *M. mucogenicum* MDR with susceptibility to trimethoprim/sulfamethoxazole, amikacin, moxifloxacin, linezolid, and imipenem, intermediate to cefoxitin but appears resistant to four different classes of antibiotics, which were ciprofloxacin, doxycycline, clarithromycin, and tobramycin (fluoroquinolone, tetracycline, macrolide, and aminoglycoside). Other than multiorgan involvement, the possibility of fatality in this patient was due to treatment failure. It is learned that he developed acute liver injury induced by ciprofloxacin, despite treatment escalation using imipenem was in place. His chemoport was kept in-situ since his first insertion about 66 weeks earlier. It was only 2 weeks later that when the final sensitivity revealed resistance to fluoroquinolone. The initiation of appropriate antibiotics and removal of the catheter may have increased the likelihood of recovery. On the other hand, catheter salvage may result in treatment failure. There is no specific guideline regarding the ideal duration of treatment for RGM CRBSI. Intravenous antimicrobial may be given at least 2 weeks, followed by oral therapy for another two weeks. Total antimicrobial treatment varies from 4 to 24 weeks. CDC guidelines recommend covering the catheters during bathing to prevent *M. mucogenicum* catheter-related bloodstream infection.

**CONCLUSION**

Delayed diagnosis and treatment of MDR NTM may lead to the fatality of a patient. A modern microbiological machine-like MALDI-TOF can identify NTM within hours compared to the culture method. The timely and reliable result is important to aid the clinician in treating patients, hence reducing the mortality rate.

**REFERENCES**

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