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Mycobacterium fortuitum catheter-related sepsis in acute leukaemia

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ABSTRACT

We report *Mycobacterium fortuitum (M. fortuitum)* catheter-related sepsis in a five-year-old boy with acute lymphoblastic leukaemia (ALL). This is the first reported case of *M. fortuitum* infection seen in our paediatric oncology patients. The patient was in haematological remission and receiving maintenance chemotherapy via an indwelling central venous catheter (Port-a-Cath). He was febrile, toxic-looking and was in respiratory distress. Clinically, he had a right pleural effusion and gross hepatomegaly. The patient was lymphopaenic and had deranged liver function test. Repeat paired blood cultures were positive for *M. fortuitum*. The catheter was promptly removed and he was treated aggressively with intravenous amikacin, cefoxitin, ciprofloxacin, trimethoprim-sulfamethoxazole and oral clarithromycin, with good clinical response. The patient remained well without further complications while on chemotherapy. *M. fortuitum* is an uncommon cause of catheter-related infection in patients with malignancies. Removal of an infected catheter is necessary for complete control of atypical mycobacterial infection in an immunosuppressed patient.

Keywords: acute lymphoblastic leukaemia, immunocompromised host, indwelling catheters, *Mycobacterium fortuitum*, sepsis

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INTRODUCTION

Mycobacterium fortuitum (M. fortuitum), a non-tuberculous mycobacterium (NTM) is an uncommon cause of infection in the paediatric population. In children, it is implicated in a wide spectrum of infections, which include skin and soft tissue[1,2], lymphadenitis[3] and pulmonary disease[4-5]. Rare occurrences have been described in immunocompromised children with acquired immunodeficiency syndrome (AIDS) or malignancies[6-12]. In the latter group of patients, where the use of indwelling central venous catheters (CVCs) for anti-neoplastic therapy has become standard management, NTM is increasingly recognised as another pathogen in a growing list of organisms causing catheter-related infections[9-13]. We describe a case of catheter-related septicaemia secondary to *M. fortuitum* in a paediatric oncology patient undergoing chemotherapy.

CASE REPORT

Our patient is a five-year-old Asian boy with acute lymphoblastic leukaemia (ALL) that was diagnosed two years prior to this infective episode. He was in haematological remission and was on maintenance chemotherapy via a subcutaneously implanted central venous catheter (Port-a-Cath) comprising monthly intravenous vincristine, oral prednisolone at 40 mg/m^2/day, daily 6-mercaptopurine and weekly oral methotrexate. He had no prior line-related complications. He presented with a fever of ten days' duration associated with headache. Systemic examination was essentially normal. The Port-a-Cath site was not inflammed. However, he remained febrile despite being on empiric intravenous antibiotics. He was not neutropaenic at the time of presentation. His blood counts were: white blood cell (WBC) 4.46 × 10^9/L, absolute neutrophil count (ANC) 3.5 × 10^9/L, haemoglobin (Hb) 10.4 g/dL, and platelets 39 × 10^3/L. However, he had lymphopaenia of 540 × 10^6/L. C-reactive protein was 65.5 mg/dL and initial blood cultures were negative for bacterial growth at 48 hours.

On day five of admission, he became tachypnoeic and desaturated in room air. He also developed abdominal pain and an enlarged liver that was palpable 6 cm below the costal margin. Chest radiograph confirmed a right-sided pleural effusion with underlying patchy non-cavitatory parenchymal consolidation. Computed tomography

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(CT) of the abdomen showed moderately-severe hepatomegaly. No focal parenchymal lesions or abscesses within the peritoneal cavity were found. CT of the head and a lumbar puncture were normal. His blood counts at this point were: WBC 1.61×10^9/L; ANC 1.45×10^9/L; lymphocytes 0.16×10^9/L; haemoglobin 12.4 g/dL; platelets 100×10^3/L. C-reactive protein was 65.5 mg/dL. Liver dysfunction was also noted, with total bilirubin 65 μmol/L, direct bilirubin 45 μmol/L, ALP 846 U/L, GGT 384 U/L, ALT 109 U/L, and AST 164 U/L. Paired central and peripheral blood cultures grown on Radiometric Bactec media showed gram-positive beaded bacillus, later identified as *M. fortuitum* after five days of incubation. It was isolated from three separate specimens from both the peripheral and port sites before anti-NTM therapy was commenced.

The Port-a-Cath was removed and a right pleural paracentesis was performed which drew 180 ml of straw-coloured exudate. No organism was isolated from the catheter tip. The pleural fluid was also found to be sterile and negative for *M. tuberculosis*. He was started on empiric anti-NTM therapy for presumed dissseminated atypical mycobacteria catheter-related sepsis. This included intravenous amikacin, ciprofloxacin, cefoxitin, trimethoprim-sulfamethoxazole and oral clarithromycin for two weeks. He was then switched to oral triple therapy consisting of clarithromycin, trimethoprim-sulfamethoxazole and ciprofloxacin for another 12 weeks. The *M. fortuitum* isolated was sensitive to all of the above antibiotics. The patient responded well to treatment as evidenced by fever defervescence within 72 hours of the appropriate antibiotic therapy and resolution of the pleural effusion. The hepatomegaly and liver function normalised after two weeks of antibiotic therapy. Blood cultures were repeatedly negative within one week of appropriate antibiotic therapy. Maintenance chemotherapy was restarted one month after antibiotic therapy and patient has remained well.

DISCUSSION

M. fortuitum, together with *M. chelonae* and *M. abscessus*, belong to the Runyon Group IV NTM. It is a rapidly growing NTM with an incubation period of three to seven days. It is ubiquitous in distribution; it can be isolated from environmental sources such as water, soil and dust. Under gram-stain microscopy, NTM appears as a gram-positive beaded bacillus and is not uncommonly misidentified as *Nocardia* or *Corynebacteria* species, the latter often being passed off as a contaminant. Acid-fast stain is often positive.

NTM can be cultured from Lowenstein-Jensen medium and routine blood culture media. In our institution, the Radiometric Bactec System (Becton-Dickinson, Shannon, County Clare, Ireland) – Pedoplus 6B and 7B were used. In our patient, *M. fortuitum* bacteraemia was diagnosed based on three sets of positive blood culture results obtained from both central and peripheral venous samples, collected at different times. In the first set of specimens, we were able to demonstrate a differential time to positivity of at least 24 hours between the centrally-obtained blood specimen and the peripheral venous sample, thus supporting the diagnosis of catheter-related bacteraemia[14]. The catheter tip culture, however, was negative for *M. fortuitum*. This could be attributed to appropriate antibiotic treatment prior to its removal and/or the use of roll-plate technique of isolation that was adopted in our institution. This technique has been shown to be less sensitive compared to the sonication method and is generally not recommended for culturing catheter tips of indwelling catheters that has been in-situ for more than a week[15].

Our patient had disseminated NTM infection with liver and lung involvement. The patient had acute anicteric hepatitis, presenting as tender gross hepatomegaly with elevated transaminases, and a significant pleural effusion with underlying patchy pulmonary consolidation. This is in contrast to most reported cases of disseminated *M. fortuitum* sepsis described in immunocompromised patients. Two forms of infections occur commonly in the immunocompromised patients: the disseminated cutaneous form[16] (cellulitis, skin abscess, tender nodules) and the catheter-related bacteraemia[17] which is often not associated with cutaneous manifestation or deep-seated infections other than around the catheter site. In our patient, there was no sign of inflammation or discharge at and around the catheter site; and the dissemination involved the visceral organs rather than the skin. Evidence of dissemination in *M. fortuitum* bacteraemia involving bone marrow and visceral organs including lungs, liver, spleen and kidneys, is rarely seen.

M. fortuitum infections occur in cancer patients with and without neutropaenia. Several authors described neutropaenia as a risk factor for NTM infections and the return to normal counts usually heralds impending recovery[8]. Levendoglu-Tugal

et al, however, cited lymphopaenia (absolute lymphocyte count <600/ml) in children with leukaemia, as a predisposing factor[7]. Lymphocytes are an integral part of cellular immunity and is important in the control of mycobacteria infections. In the three cases reported by Levendoglu-Tugal et al, all of the patients had absolute lymphocyte counts (ALC) between 0.224 and 0.54×10^9/L at the time of the NTM infections. Similarly, Rodgers et al reported two patients with lymphopaenia but without neutropaenia[9]. In our patient, the ALC plunged to a nadir of 0.16×10^9/L at the peak of the illness, while absolute neutrophil count maintained mostly above 1.0×10^9/L throughout the course of the illness. The ALC normalised when the infection resolved.

Management of *M. fortuitum* catheter-related bacteraemia is two-pronged: removal of the infected catheter and appropriate antibiotic therapy. Institution of either one alone has been shown to be inadequate in controlling the infection. Raad et al, in his series of *M. fortuitum* complex catheter-related bacteraemia, reported clinical response only in the group managed with both prompt removal of catheter and antibiotic therapy, whereas all patients whose catheters remained in -situ, had either persistent bacteraemia or recurrent skin sepsis[10]. Our patient was aggressively treated for disseminated catheter-related sepsis in view of the acute deterioration which required intensive care monitoring. The catheter was promptly removed and he was empirically treated with appropriate antibiotics. Our patient had good response to the above instituted measures.

A controlled clinical trial defining the optimal antibiotic therapy for *M. fortuitum* sepsis is not available owing to the infrequency of such infections. The choice of antimicrobial therapy and its duration are based on the susceptibility pattern of the organism, immunosuppressed state of the patient, clinical and bacteriological response to therapy. *M. fortuitum* is generally resistant to conventional anti-tuberculous drugs. Hence, combination antibiotic therapy consisting of amikacin and cefoxitin has been suggested and shown to be efficacious[10,12]. The duration of antibiotic therapy is variable ranging from two weeks to two years[7]. Generally, this should be guided by the severity of the infection and its complications, and the clinical as well as bacteriological response to the antibiotics. A minimum of four to six weeks of antibiotic therapy after removal of the infected catheter has been suggested[13].

M. fortuitum is increasingly recognised as an opportunistic pathogen causing disseminated disease in immunocompromised hosts. There must be a high index of suspicion for NTM infections in febrile cancer patients with lymphopaenia. NTM infections should be treated promptly with combination antibiotic therapy and catheter removal as such infections tend to be disseminated in immunosuppressed patients.

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