Case Reports

**Clostridium subterminale** infection in a patient with diffuse large B-cell lymphoma and haemophagocytic syndrome: A case report and literature review

Ying Zhou¹,², Sheng Wang³ and Xing-bei Weng³

**Abstract**

Although uncommon, infection caused by Clostridium subterminale may be life threatening particularly in immunocompromised patients. We report here a rare presentation of a patient with diffuse large B-cell lymphoma and haemophagocytic syndrome associated with C. subterminale bacteraemia. The management of the patient is described as well as a review of medical literature. Infection by Clostridium species, including C. subterminale, should be considered in a febrile patient with a haematologic malignancy. The case highlights the importance of using gene sequencing for identification of this anaerobic organism.

**Keywords**

Clostridium subterminale, 16S rRNA, Bacteraemia, Large B-cell lymphoma, Hemophagocytic syndrome

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**Background**

Over recent years there has been an increase in infections caused by anaerobic bacteria.¹ Anaerobic bacteria account for 1–17% of all positive blood cultures, among which Bacteroides spp. are the most common anaerobes followed by Clostridium spp.² Pathogenic Clostridia with the greatest

¹School of Medicine, Ningbo University, Ningbo, China
²Birth Defects Prevention Laboratory, Ningbo Women’s and Children’s Hospital, Ningbo, China
³Department of Medical Laboratory, Ningbo First Hospital, Ningbo, China

**Corresponding author:**
Xing-bei Weng, Guangji Street 31, Haishu District, Ningbo 315010, China.
Email: wxb6006@hotmail.com
impact on human and animal health include C. difficile, C. perfringens, C. tetani, and C. botulinum. Reports of infections caused by C. subterminale are rare. We present a case of C. subterminale bacteraemia in a patient with diffuse large B-cell lymphoma and haemophagocytic syndrome.

Methods

We retrospectively reviewed the medical records of a patient who was diagnosed with diffuse large B-cell lymphoma and haemophagocytic syndrome associated with C. subterminale bacteraemia. In addition, we searched the PubMed database for similar case reports of infections caused by C. subterminale. Our literature search identified 13 articles that described 14 case studies (Table 1). The case study was approved by Ningbo First Hospital Ethics Committee (2021RS117) and signed informed consent was obtained from the patient for publishing his anonymised data. The reporting of this study conforms to CARE guidelines.17

Case report

A 56-year-old man with an unexplained fever (maximum temperature 38.4°C) which had lasted for a week, presented to his local clinic. He had a mild dry cough, fatigue and a swollen left calf. Results of outpatient laboratory tests were as follows: white blood cells (WBC), 3.03 × 10^9/l; highsensitivity C-reactive protein (hs-CRP), 38.40 mg/l; platelets, 37.0 × 10^9/l. Infectious fever was considered and he was started on intravenous (IV) ceftriaxone 2 g qd. However, after 3 days he had failed to improve and was admitted to hospital.

On admission, routine examination indicated abnormal liver and kidney function and an electrolyte disorder. His HIV test result was negative. Indices of cellular immune function (including lymphocyte subsets) were decreased and suggested that the patient’s immune function was impaired. Result were as follows: CD4⁺ T cells, 28%; natural killer (NK) cells, 4%; CD3⁺CD25⁺T cells, 0.2%; CD4⁺CD25⁺T cells, 0.05%; CD3⁺/HLA-DR⁺ cells, 1.9%; CD8⁺/HLA-DR⁺ cells, 0.6%. Magnetic resonance imaging (MRI) of the left calf suggested an inflammatory response. The patient was treated with IV piperacillin/tazobactam 4.5 g every 8 h and oral tenofovir 300 mg qd. To maintain electrolyte balance, the patient also received IV 0.9% sodium chloride 100 ml qd and oral potassium chloride 0.5 g tds. However, after three days, symptoms had not improved.

On the day of admission, a blood sample was taken and cultured using BD BACTEC Plus Aerobic and Anaerobic blood culture bottles with BD BACTEC FX (BD Diagnostics, Sparks, MD). The colonies on the blood plate were observed to be flat and transparent, with irregular edges and tiny haemolysis rings. Gram staining was performed and Clostridium gram-positive bacilli were observed. The strain 10798 was isolated from colonies and identified as C. fallax by the bioMerieux MALDI-TOF mass spectrometry (MS) (VITEK MS, bioMerieux, France) system. However, bacterial 16S rRNA gene sequencing was performed to confirm identification (specific primers: 27F: AGAGTTTGATCTGGCTCAG, 1492R: GGTACCTTGTTACGACTT) and the 10798 strain was identified as C. subterminale (GenBank NR_113027).

On Day 4, following the results of the blood culture, the patient was started on IV levofloxacin 0.5 g qd. Antiviral therapy, piperacillin/tazobactam and fluid rehydration were continued. On Day 9, a second blood culture was negative suggesting that the antibiotic treatment had been effective but the patient’s serum ferritin was 1467 μg/l. A few phagocytes without obvious bone marrow involvement were found on bone
| Study              | Country | Sex | Age | Diagnosis                                      | IC | Treatment                                                                 | Source of infection                  | Prognosis | Susceptibility testing |
|--------------------|---------|-----|-----|-----------------------------------------------|----|---------------------------------------------------------------------------|---------------------------------------|-----------|------------------------|
| Grobach et al., 1975$^4$ | USA     | N/A | N/A | Empyema                                       | N/A| N/A                                                                       | Pulmonary embolism and infarct       | N/A       | No                     |
| Grobach et al., 1975$^4$ | USA     | N/A | N/A | Empyema                                       | N/A| N/A                                                                       | Skin and soft tissue injury          | N/A       | No                     |
| Gubler et al., 1989$^5$  | CZ      | M   | 63  | Pleuropulmonary infection and empyema          | No | Amoxycillin; amoxycillin/clavulanic acid; penicillin; chest tube drainage  | Left calf swelling                    | Death     | Yes                    |
| Denny et al., 1994$^6$   | USA     | M   | 16  | Multiple injuries sustained in a motor vehicle accident. | No | Ceftriaxone; penicillin; cefazolin; clindamycin; gentamicin; surgery and tracheostomy | Facial fractures and soft tissue injuries | Discharged | No                     |
| Neal et al., 1996$^7$    | USA     | F   | 6   | Meningitis                                    | No | Penicillin; cefotaxime; spinal tap; chloramphenicol                        | Penetrating brain injury             | Discharged | No                     |
| Miyazaki et al., 2003$^8$| Japan   | F   | 41  | Septicaemia; chronic myelogenous leukaemia    | Yes| Ciprofloxacin; fluconazole; piperacillin, gentamicin; vancomycin; cef-tazidime; bone marrow aspiration | Damaged mucosa                        | Discharged | No                     |
| Tappe et al., 2009$^9$   | Germany | M   | 18  | Fracture of right forearm                     | No | Sulbamicillin (ampicillin/sulbactam); clindamycin; surgery and drainage tube insertion | Traumatic injury                      | Discharged | No                     |
| Haussen et al., 2011$^{10}$ | USA    | M   | 51  | Septicaemia; acute lymphoblastic leukaemia    | Yes| Cefepime; vancomycin; metronidazole; cefepime switched to imipenem; amoxicillin/clavulanate; peripherally inserted central catheter | Damaged mucosa (ulceration near the anal verge) | Death     | No                     |
| Thind et al., 2014$^{11}$ | USA    | M   | 77  | Septicaemia; oesophageal cancer               | Yes| Cefepime; vancomycin; metronidazole; stent placement or repeat endoscopy | Damaged mucosa (stent placement or repeat endoscopy) | Death     | No                     |
| Daganou et al., 2016$^{12}$ | Greece | M   | 50  | Septicaemia; spontaneous oesophageal rupture (Boerhaave syndrome) | No | Imipenem; vancomycin; metronidazole; thoracotomy; puncture of oesophageal effusion | Acute mediastinitis caused by greens contaminated with C. subterminale | Discharged | No                     |
### Table 1 Continued.

| Study                        | Country | Sex | Age | Diagnosis                                                                 | IC  | Treatment                                                                                                           | Source of infection                                                                 | Prognosis       | Susceptibility testing |
|------------------------------|---------|-----|-----|---------------------------------------------------------------------------|-----|---------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------|----------------|------------------------|
| Carrasquillo et al., 2018    | USA     | M   | 58  | Bacteraemia; acute onset bulbaryds function                              | No  | Vancomycin, piperacillin/tazobactam; clindamycin; levofloxacin; metronidazole; exploratory laparotomy and endotracheal intubation | Damaged mucosa (endotracheal intubation)                                        | Discharged      | No                     |
| Davis et al., 2018           | USA     | F   | 59  | Left masticator, submandibular and parapharyngeal space infections        | Yes | Piperacillin/tazobactam; clindamycin; incision and drainage, surgical debridement; vancomycin; piperacillin/tazobactam; carbapenem; doripenem; fluconazole; extraction of teeth and intubation; peripherally inserted central catheter | Multifascial space odontogenic infection                                        | Discharged      | No                     |
| Trapani et al., 2018         | USA     | M   | 72  | Septicaemia; metastatic gastrointestinal adenocarcinoma; aspiration pneumonia | Yes | Nitrofurantoin; cefepime; vancomycin; piperacillin/tazobactam; metronidazole; endotracheal intubation | Damage to the gastric mucosa                                                    | Death           | No                     |
| Grodzin et al., 2022         | USA     | M   | 72  | Sepsis, small pericardial effusion, moderate bilateral pulmonary effusions, and multiple organ dysfunction syndrome | No  | Piperacillin-tazobactam; vancomycin; ampicillin-sulbactam; amoxicillin-clavulanate; sulfamethoxazole-trimethoprim; bilateral chest tubes | Dental abscess                                                                  | Discharged      | Yes                    |

Abbreviations: CZ, Switzerland; F, female; IC, immunocompromised; M, male; N/A, not available
marrow biopsy. Enhanced computed tomography (CT) showed space occupying lesions in the adrenal gland, without lymph node lesions. Antibiotics were discontinued in consideration of lymphoma.

On Day 11, the patient’s fever had not improved, and so the patient was prescribed IV infusion of 20 g gamma globulins and 10 units of platelets. With the exception of fluid rehydration, all other treatments were stopped. Following the infusion, platelets increased from $37 \times 10^9/l$ to $48 \times 10^9/l$. On Day 13, gamma globulin was discontinued. On Day 14, haemophagocytic syndrome was considered because its five diagnostic criteria had been established. These were: fever; haemophagocytosis in the bone marrow; decreased NK cell activity (decreased by 1.1%); serum ferritin $\geq 500 \mu g/l$ (1467 $\mu g/l$), elevated soluble CD25 $\geq 2400$ U/ml (8850 U/ml). Therefore, combined treatment of IV dexamethasone $10 \text{mg/m}^2$ with etoposide (VP-16) $150 \text{mg/m}^2$ was initiated and fluid hydration continued. The patient’s temperature returned to normal the next day. Blood work showed WBC, $7.0 \times 10^9/l$ and CRP:10.32 mg/l. The treatment appeared to be effective and so IV dexamethasone $15 \text{mg/qd}$ and routine fluid rehydration were continued. On Day 17, adrenal biopsy indicated diffuse large B-cell lymphoma with bilateral adrenal involvement. After evaluation, R-CEOP (i.e., rituximab, cyclophosphamide, etoposide, vincristine and oral prednisolone) chemotherapy was initiated. The patient developed paroxysmal supraventricular tachycardia during chemotherapy, which was restored to normal rhythm using electric cardioversion. The patient was diagnosed as having diffuse large B-cell lymphoma with bilateral adrenal involvement, haemophagocytic syndrome, bacteraemia and left calf swelling. The patient’s condition stabilised following treatment and his blood results were: WBC, $6.20 \times 10^9/l$; CRP, <0.5 mg/l; platelets, $150 \times 10^9/l$. The patient was discharged from hospital on Day 27.

**Discussion**

To the best of our knowledge, this is the first reported case of a patient with diffuse large B-cell lymphoma and haemophagocytic syndrome associated with *C. subterminale* bacteraemia. Initially, using MALDI-TOF MS we identified the strain 10798 as *C. fallax*. In recent years, MALDI-TOF MS has been widely used as a rapid and reliable method for the identification of microorganisms. Microbial identification is achieved by searching databases containing mass spectra of peptides and proteins extracted from microorganisms of interest, using scoring algorithms to match analysed spectra against reference spectra.\(^{18}\) The accuracy of MALDI-TOF MS in identifying clinical pathogenic anaerobes is 84% for species, and 92% for genus. Moreover, the identification accuracy of MALDI-TOF MS is 98% for *Clostridium* spp. However, the accuracy of MALDI-TOF MS is related to many factors, including, growth of bacteria, stability of the instrument, and capacity of the database. The rarity of this present case, may have led to an inadequate database comparison which may have led to the inaccurate identification of *C. subterminale* as *C. fallax*. Bacterial 16S rRNA gene sequencing is widely used for the identification of microbes because of advantages in sample throughput, cost, and sensitivity.\(^{19,20}\) In this present case, the strain 10798 was correctly identified as *C. subterminale* by sequence-based bacterial analysis.

Susceptibility testing was not performed on the isolate which is a limitation of this case. However, although resistance to cephalosporins, clindamycin, aminoglycosides and quinolones has been reported, most *Clostridium* spp are sensitive to penicillin, carbapenems, glycopeptides and...
metronidazole.\textsuperscript{14,16} In this present case, following identification of \textit{C. subterminale} in blood culture, levofloxacin was initiated and used empirically to fight infection. After three days blood culture was negative for the bacilli and so demonstrated that the antibiotic treatment had been effective. However, the fever had not improved and haemophagocytic syndrome was suspected. After the diagnosis was confirmed, combined treatment of dexamethasone with etoposide was administered and on the following day the patient’s temperature had returned to normal.

There is little available information about \textit{C. subterminale}. It is an anaerobic, spore-forming Gram-positive bacterium usually found in soil.\textsuperscript{11} We conducted a review of medical literature and found 13 articles that described 14 cases of infections caused by \textit{C. subterminale} (Table 1).\textsuperscript{4–16} The cases were reported from 1975 to 2022. Of the 14 cases, seven (50\%) were reported after 2011, suggesting that detection rate has increased significantly over the last decade. Ten reports were from the USA, and one each in Switzerland, Japan, Germany, and Greece. Data on sex and age were available for 12 patients, of whom nine (75\%) were male and ages ranged from 6–77 years. Although data are limited, the findings of the review suggest that men are more susceptible to \textit{C. subterminale} infection and that the bacilli can affect all age groups. In terms of prognosis, five patients (42\%) died, three of whom were immunocompromised and seven cases (50\%) were diagnosed as bacteraemia or septicemia. With regard to treatment, incision, drainage, or surgical debridement were essential for bacterial clearance, and so these procedures were performed in a majority of cases. Unsurprisingly, antibiotics were administered in all cases, although susceptibility testing was only performed in two cases.\textsuperscript{5,16}

An overview of the 14 cases suggests that one of the most important risk factors for \textit{C. subterminale} infection is deep tissue injury. Indeed, sources of \textit{C. subterminale} infection include abscesses, wounds and blood.\textsuperscript{15} Detection of \textit{C. subterminale}, particularly in an immunocompromised patient, should trigger an immediate investigation into the potential source of the infection which may require surgical debridement and appropriate antibiotic coverage.\textsuperscript{16} The patient in this present case was diagnosed with diffuse large B-cell lymphoma, a haematological malignancy that severely affects immunity and is a major risk factor for infection. In addition, the patient had a swollen left calf which could have also been the source of the infection.

Although uncommon, infection caused by \textit{C. subterminale} may be life threatening particularly in immunocompromised patients and should be considered together with other \textit{Clostridium} spp in a febrile patient with a haematologic malignancy. The case also shows the importance of using gene sequencing for identification of this anaerobic organism.

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**Declaration of conflicting interests**

The authors declare that there are no conflicts of interest.

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