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Case Report

Clostridium subterminale septicemia in a patient with esophageal cancer

Sharanjeet K. Thind [a,*], Jana I. Preis [a,b]

[a] Department of Medicine, Division of Infectious Diseases, SUNY Downstate Medical Center, Brooklyn, NY, United States
[b] Department of Medicine, Division of Infectious Diseases, Brooklyn VA Medical Center, Brooklyn, NY, United States

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ABSTRACT

Clostridium subterminale (*C. subterminale*) is a pathogenic species of *Clostridium* that has been infrequently isolated. We report a case of *C. subterminale* bacteremia causing sepsis in a patient with metastatic gastrointestinal malignancy.

Introduction

Clostridium species are known to cause a variety of diseases, such as botulism, tetanus, severe soft tissue infections and diarrhea. *Clostridium* spp. are the second most commonly isolated anaerobic bacteria in the blood, second to *Bacteroides* spp. [1]. The most commonly identified clostridial species in blood cultures is *Clostridium perfringens, often in the setting of severe soft* tissue infection [1]. *Clostridium subterminale* is another species of *Clostridium* that has been infrequently isolated. To the best of our knowledge, this species has been reported a total of eight times in the medical literature. Among the reported cases, it has been isolated only twice in the blood. We present a case of sepsis due to *C. subterminale* bacteremia in a patient with esophageal cancer.

Case

A 77 year old man with recently diagnosed esophageal cancer was admitted to another hospital for epigastric pain. He was found to be hypotensive (69/49 mm Hg), tachycardic (112 bpm) and had a leukocyte count of 15,300/μl without bandemia. A chest X-ray showed moderate bilateral effusions. The patient underwent thoracentesis, and was started on empiric cefepime, vancomycin and metronidazole for a possible health-care associated pneumonia. He had recently undergone endoscopy and placement of an esophageal stent one week prior to presentation for a partially obstructing esophageal tumor that was causing epigastric pain, odynophagia and dysphagia. Due to ongoing pain and high suspicion for stent migration, he underwent repeat endoscopy shortly thereafter, which did not reveal significant stent migration or esophageal perforation.

In the months prior to the diagnosis of esophageal cancer, the patient had symptoms of epigastric pain, weight loss, and back pain, which prompted CT and MRI imaging that revealed an esophageal mass with evidence of metastatic disease in the lungs and thoracic spine, resulting in spinal cord compression. Subsequent endoscopy and biopsy of the esophageal mass was consistent with adenocarcinoma. Following this, he underwent a minimally invasive trans-thoracic approach for T8 corpectomy, T7-9 interbody cage placement and fusion with plating without complication, and was eventually discharged home.

Several days after the most recent presentation to the other hospital, the patient was transferred to our institution for radiation therapy and the initial antibiotic regimen that had been started was continued. In the following days, a blood culture drawn on admission had growth in the anaerobic bottle of one out of the two obtained sets and revealed gram-positive rods on gram stain. A sputum culture grew *Candida albicans*, pleural fluid cultures were negative and a chest X-ray did not show infiltrates or consolidation. Three days after the hospital transfer, the blood cultures were growing *Clostridium* species. At that time, the leukocytosis had resolved and the patient continued to be hemodynamically stable

* Corresponding author at: SUNY Downstate Medical Center, 450 Clarkson Ave., Brooklyn, NY 11203, United States. Tel.: +1 718 270 1432.
E-mail addresses: sharanjeet.thind@downstate.edu, sharnthind@yahoo.com (S.K. Thind).

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with improved abdominal pain, however he developed intermittent nausea and vomiting attributed to ongoing radiation therapy. Vancomycin and cefepime were discontinued, and the patient was continued on metronidazole alone. On day 18 of his hospitalization, the *Clostridium* spp. was identified as *C. subterminale*. During his third week of hospitalization at our institution, the patient died secondary to complications related to his malignancy.

Discussion

Clostridium spp. are gram positive, anaerobic rods that are ubiquitously found in the soil and are part of the gastrointestinal flora of animals and humans [2]. Up to 70% of humans are colonized with clostridial species, most commonly harboring the spore-forming bacteria in their gastrointestinal tract, while about 10% of healthy women are colonized with the bacteria in the genital tract [2,3]. The species can cause a variety of diseases that may range from localized infection to devastating, invasive, toxin-mediated and systemic infections in the appropriate setting [4].

Clostridium subterminale, like *Clostridium botulinum*, have characteristic subterminally located endospores [5], and has been reported in a minority of *Clostridium* infections.

A review of the English literature yielded eight reported cases of infections caused by *C. subterminale*. Out of these, there were two cases of empyema, three cases of skin and soft tissue infection, one case of meningitis, and two reported cases of bacteremia.

Gorbach et al. reviewed 114 cases of *Clostridium* infections in a large city hospital in Chicago in 1975 and found that *C. perfringens* was the most commonly isolated species of *Clostridium*, both in tissue and in blood [6]. In this review, *C. subterminale* was isolated as the only organism in a patient with empyema [6]. A second reported case of empyema due to *C. subterminale* was in a man who developed the infection as complication of a pulmonary embolism and pulmonary infarct. Before these two cases, *Clostridium* spp. had been only rarely reported in thoracic infections without a preceding penetrating chest injury or procedure [7,8]. In such cases, the organism was generally a part of a polymicrobial infection and was associated with aspiration, or in some cases due to pulmonary infarction likely complicated by occult anaerobic bacteremia [7,9].

The first of the three total cases of skin and soft tissue infection was reported in the previously mentioned review by Gorbach et al. who identified *C. subterminale* amongst several other species of *Clostridium* in cultures from a patient who developed gangrene after severe frost bite [6]. Another case of *C. subterminale* skin and soft tissue infection was reported in 1997 in a middle-aged male injecting-drug user who presented with severe respiratory distress and tremors, thought to be due to heroin withdrawal. Further clinical deterioration was consistent with symptoms of tetanus, and *C. subterminale* and *Staphylococcus aureus* were eventually isolated from a wound on his arm related to injecting-drug use [10]. Another severe soft tissue infection was seen in a patient two weeks post open repositioning and plate insertion for a right forearm fracture, from which purulent discharge cultures grew *C. subterminale* [5]. A sixth case of *C. subterminale* infection resulted in meningitis in a six-year-old girl after penetrating injury to the brain [11].

Additionally, there were two cases in which *C. subterminale* was isolated in the blood. The first reported case was of a 41 year old female with a history of chronic myelogenous leukemia in the chronic phase admitted with fatigue, with a bone marrow aspirate showing 52% blasts. She was started on imatinib with good response, and eventually underwent unrelated umbilical cord blood transplantation after receiving total body irradiation, cytarabine, and cyclophosphamide. She became neutropenic and febrile during hospitalization, and was started on empiric antibiotics. Two weeks post-transplant, *C. subterminale* was isolated from the blood. Repeat blood cultures were negative, and she completed treatment with ceftazidime and vancomycin, with the presumed source of chemotherapy-related mucositis [12].

The second case of bacteremia and sepsis was of a 51 year old male with Philadelphia chromosome-positive T-cell acute lymphoblastic leukemia, treated initially with imatinib, then cyclophosphamide, vincristine, doxorubicin, and dexamethasone, in addition to intrathecal methotrexate, with failure to obtain complete remission. Several months after chemotherapy, his peripheral blood smears showed numerous circulating blasts. Imatinib had been discontinued and one month later he was started on dasatinib. Shortly thereafter, the patient was admitted with hemorrhoidal pain, and was found to have ulceration near the anal verge with erythema and induration of the right perianal area. The patient was tachycardic, febrile, and neutropenic and was started on empiric cefepime, vancomycin and metronidazole. Gram stains of blood cultures from admission showed sporulating gram positive rods, suggestive of *Clostridium* species. Amplification and sequence analysis of the bacterial 16S ribosomal RNA identified the organism as *C. subterminale*. All other aerobic cultures remained negative. Due to persistent fever, cefepime was changed to imipenem on the fifth day of admission, with minimal clinical improvement. The patient's leukocyte count continued to rise, reaching 123,000 mm^{-3}, with 28% blasts. Due to his poor prognosis hospice care was offered. After 9 days of intravenous antibiotic therapy, he was discharged to home hospice with oral amoxicillin/clavulanate, and died 1 week after discharge [13].

In several of these cases the mechanism of infection with *C. subterminale* was likely due to inoculation from the environment as was seen in the case of severe gangrene after frostbite and soft tissue infection in the setting of a forearm fracture. In the cases of meningitis and wound infection with clinical tetanus, *C. subterminale* infection was likely introduced during direct inoculation from penetrating injury. In the two reported cases of bacteremia due to *C. subterminale*, both patients were immunocompromised due to hematologic malignancies and had evidence of damage to mucosal tissue and likely disruption of mucosal barriers that may have facilitated entry of *C. subterminale* into the blood stream. Furthermore, in the case of the cord blood transplant, the patient was also neutropenic. In our case, the patient was also immunocompromised due to metastatic esophageal cancer, was likely colonized with the pathogen, and became bacteremic upon mucosal manipulation during stent placement or during repeat endoscopy.

The isolation of *Clostridium* from the blood is associated with hemodialysis, intestinal malignancy, inflammatory bowel disease and neutropenia [1]. The most often isolated species in the blood is *C. perfringens*, followed by *Clostridium septicum*, which is known to be associated with intestinal malignancy [4]. In our patient and the previously reported cases, there was clinical improvement due to treatment of the bacteremia. Despite this, in two of the three cases, the patients died, seemingly unrelated to *C. subterminale* bacteremia. Numerous antibiotic classes have activity against clostridia, including penicillins, cephalosporins, glycopeptides, carbapenems, clindamycin and metronidazole. However, there is evidence of resistance to cephalosporins, tetracyclines, quinolones and aminoglycosides [2,12]. Unfortunately, susceptibility testing on was not performed on the isolate at our institution.

In conclusion, *Clostridium* species can be found in the normal microflora and may cause indolent disease but can be associated with severe outcomes. Although this microorganism is rarely isolated in the blood, upon discovery, a potential source of infection should be sought and treated to prevent the possibility of severe disease which may be more detrimental in immunocompromised hosts.

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