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Case report

An unusual odontogenic infection due to *Clostridium subterminale* in an immunocompetent patient: A case report and review of the literature

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ABSTRACT

Clostridium subterminale is an anaerobic spore-forming bacterium usually associated with infections in patients who are immunocompromised. This case report focuses on a rare presentation of a multifascial space odontogenic infection associated with the bacterial isolate *Clostridium subterminale*. The management of an odontogenic infection associated with an isolate of *Clostridium subterminale* in an immunocompetent female is described, as well as a review of the literature.

Introduction

Typical odontogenic infections are polymicrobial in nature and are comprised mostly of facultative anaerobes, such as the alpha-hemolytic streptococci, *Streptococcus anginosus* group and strict anaerobes, such as anaerobic cocci, *Prevotella*, and *Fusobacterium* species [1]. *Clostridium* species are anaerobic spore-forming gram-positive bacilli most often isolated from soil, as well as the gastrointestinal tract of animals and humans. Tetanus, sepsis and soft tissue infections can be the result of infection by a variety of Clostridial species [2,3]. Isolates of *Clostridium subterminale* have been documented in humans suffering from a variety of immunocompromised conditions with rare occurrence in patients who are immunocompetent [2,3]. There are a paucity of cases that have isolated *Clostridium subterminale* in head and neck infections [4]. We present an unusual case of a multifascial odontogenic infection in an immunocompetent female patient with a *Clostridium subterminale*.

Case

A 59-year-old Caucasian female patient presented to the emergency department with a chief complaint of pain and swelling of the left cheek for one week duration. The patient denied generalized dental pain, headaches, vomiting, fever, chills, dyspnea or dysphagia. The patient did complain of trismus (a limited opening of the jaw) and dysguesia (an unpleasant alteration of taste). Past medical and surgical histories were non-contributory. She denied any medications and allergies to drugs or food. The patient provided a social history of drinking about 6 ounces of alcohol per week, but her family revealed a history of chronic alcohol abuse.

Vital signs were blood pressure 126/85, pulse 118 beats per minute, respiratory rate of 20 and temperature of 98.7° Fahrenheit. Extraoral examination revealed left-sided middle, lower facial, and left-sided neck asymmetry. No open wounds, abrasions, or contusions were evident. Mild tenderness, erythema and induration were appreciated upon palpation of the left lower face and superior aspect of the left lateral neck. No discrete lymphadenopathy was noted and all cranial nerves were intact. Intraoral exam revealed a fetid odor with maximal incisal opening of 15 mm. The posterior oropharynx was erythematous with edema of the left tonsil, the uvula was midline and in close proximity to the left lateral pharyngeal wall. Left-sided edema, erythema, and deviation of the left posterior soft palate was also noted with a small collection of purulent drainage present in the left mandibular buccal vestibule. The floor of the mouth was soft, with no elevation or distention of the tongue.

Radiologic imaging included a panoramic x-ray and computed tomography (CT) maxillofacial scan with and without contrast. The panoramic image (Fig. 1) revealed mandibular condyles in the fossa and clear maxillary sinuses. Periapical radiolucencies were observed on

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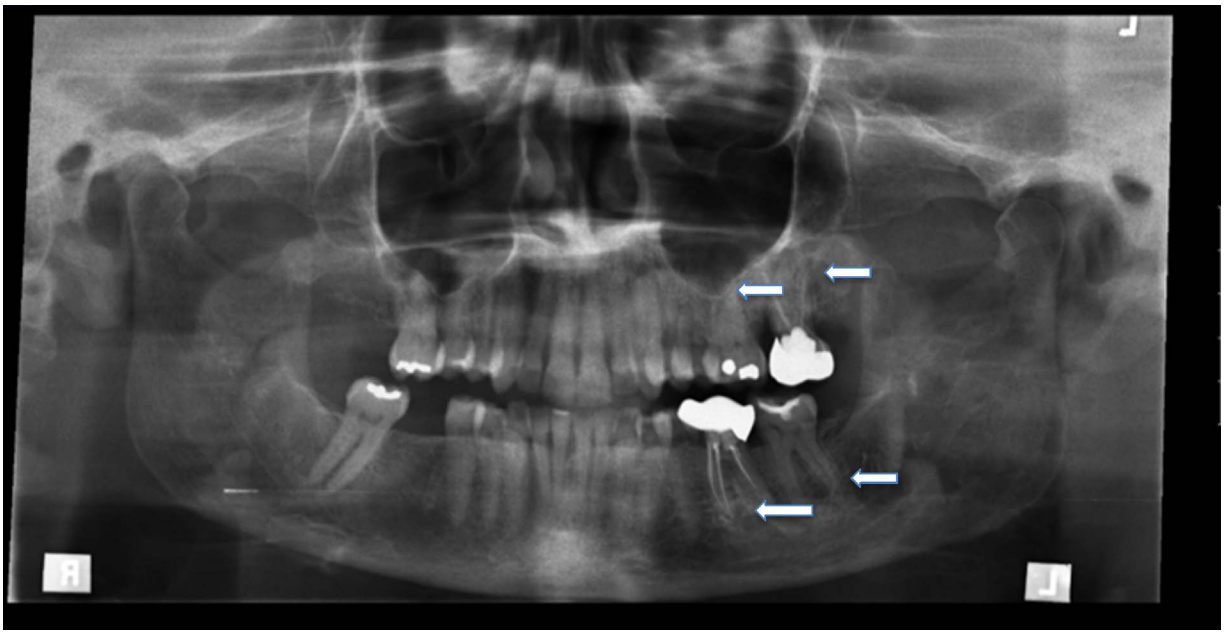

Fig. 1. Fig. 1 depicts the panoramic x-ray taken on admission to the hospital. Periapical radiolucencies are evident within teeth numbers 14, 15, 18, and 19 (white arrows).

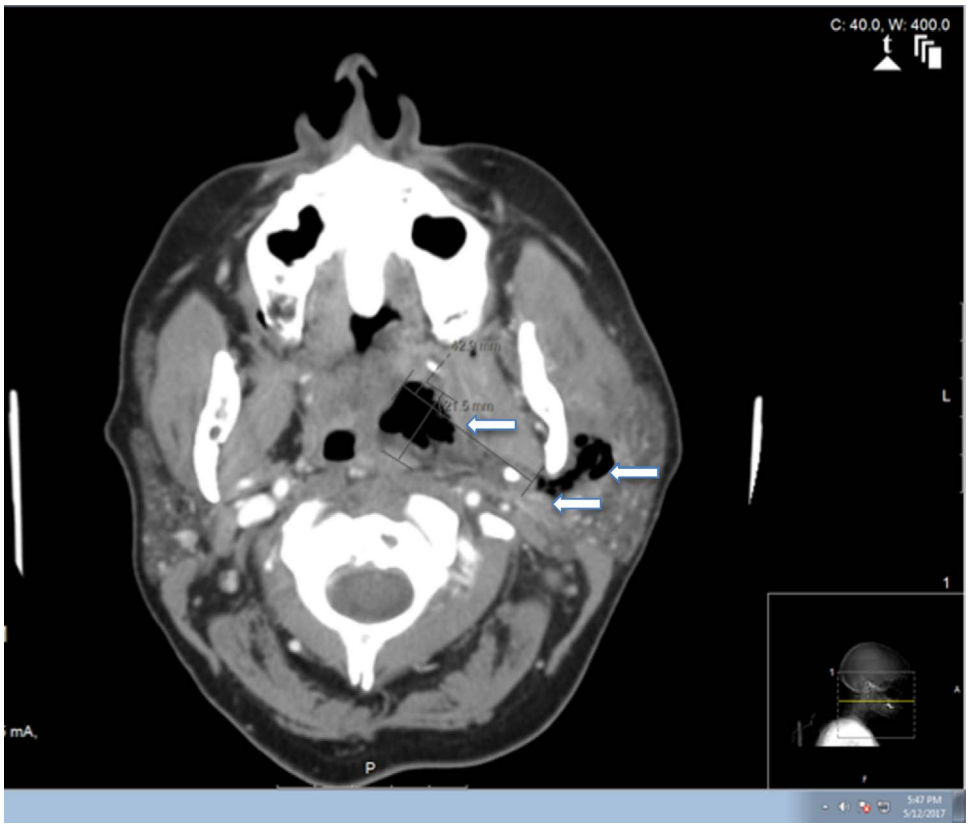

Fig. 2. Fig. 2 depicts a maxillofacial CT in axial view that identifies multifocal fluid collections with diffuse gas associated with the submasseteric, pterygomandibular, and lateral pharyngeal spaces (white arrows).

teeth numbers 14, 15, 18 and 19 (see arrows). The maxillofacial CT scan (Figs. 2 and 3) showed multifocal abscesses of the left masseteric, parotid, submandibular and parapharyngeal spaces with reactive left cervical lymphadenopathy and enlargement of the left submandibular gland. The airway was patent and unobstructed.

Laboratory work-up included a basic metabolic panel (BMP) and complete blood count with differential. The BMP results showed hyponatremia and hyperglycemic and on the following day the fasting plasma glucose was 87 mg/dL. The white blood cell count was 25.3, and neutrophil percentage 79.9%, respectively. The patient was admitted to the oral and maxillofacial surgery service with a diagnosis of left masticator, submandibular and parapharyngeal space infections. The patient was started on intravenous piperacillin-tazobactam 3.375 g every 8 h and clindamycin 600 mg every 6 h. Blood cultures were

Fig. 3. Fig. 3 depicts a CT in the coronal plane identifying gas in the left sub-masseteric, submandibular and lateral pharyngeal spaces (white arrows).

obtained and the patient was made NPO for incision and drainage, surgical debridement, and extraction of teeth with specimen collection for culture and sensitivity.

While in the operating room, a gram stain was ordered and specimens for aerobic, anaerobic, and fungal cultures were obtained. Anaerobic cultures were sent to an outside hospital lab. The patient remained intubated postoperatively and was transferred to the ICU due to airway edema and failure of a cuff leak test. At Post op day 1, the patient was hypokalemic, anemic and hypotensive. The hypokalemia was corrected with intravenous infusions of potassium chloride. The anemia was attributed to hemodilution. The hypotension was treated by femoral line placement for administration of vasopressors. A white blood cell increase occurred on Post-op day 2 and 3. A new CT scan taken showed residual fluid in the left sub-masseteric space. 48 h results of the blood cultures showed no bacterial growth and gram stain showed no organisms. An Infectious Disease (ID) consult was requested for alternative antibacterial recommendations. Clindamycin was replaced by vancomycin, 1 g every 12 h and patient remained on piperacillin-tazobactam. At Post-op day 4: the patient was afebrile, vital signs were stable, the white cell count decreased and cultures grew gram (+) cocci. The patient was extubated, the femoral line discontinued, and a PICC line placed for intravenous antimicrobials. The anaerobic cultures, however, were still pending and the gram-positive cocci grew out Streptococci species and gram-positive Bacilli.

On Post-op day 5, the white blood cell count increased again and a repeat CT scan showed residual fluid collections in the left sub-masseteric and submandibular spaces, with new enhancement of fluid in buccal and submental spaces. The patient was taken back to the operating room for repeat incision and drainage and all penrose drains were replaced (Fig. 4). Following surgery, the patient remained in the ICU intubated.

Over a 24 h period following surgery, the patient became agitated

Fig. 4. Fig. 4 is a sagittal CT view that identifies the location of penrose drains placed into the spaces mentioned in Fig. 3 above (white arrows).

and hypotensive. In an effort to increase the blood pressure and combat her agitation, patient was given fentanyl, and a benzodiazepine. These adjustments helped to reestablish a normotensive state. The patient also again became hypokalemic with an increase in the BUN/creatinine ratio suggesting an acute kidney injury (AKI) which may have been attributed to either the elevated vancomycin trough levels of 31.3 (normal 10–20ug/ml) and/or repeated use of contrast for CT. The vancomycin was discontinued and clindamycin 600 mg was restarted with the piperacillin-tazobactam. The hypokalemia was again treated with IV potassium chloride. Since patient's history of alcohol use was significant, a consult was obtained from the psychiatry service and thiamine, folic acid, and a multivitamin added to the medication regimen to treat possible delirium tremens. Anaerobic cultures were still pending at Post-op day 8.

At Post op day 9, white blood cell count spiked to 19.8 with a fever of 101.3 °F. Sputum cultures and a urinalysis were obtained, the IV site rotated, and Foley catheter changed out. Carbapenem was added to the antibacterial regimen on Post op day 10. Piperacillin-tazobactam and clindamycin were discontinued and patient was extubated.

On Post op day 11, the patient again became agitated and experienced episodes of delirium, developed stridor, and was re-intubated. A radiograph taken showed "mixed areas of ground glass/airspace opacities" in bilateral lung zones, causing concern for pneumonitis or pulmonary edema. Two days later, a repeat chest x-ray showed persistence of opacities with partial obscuration of the left hemi-diaphragm (see arrow) suggesting pulmonary edema and low-dose furosemide was started. A cardiac enzyme panel, B-type natriuretic peptide levels (BNP), and cardiology consult was obtained for evaluation of cardiac function. All labs were negative. A chest CT was taken to evaluate pleural fluid collection and was negative. The patient's anemia became more pronounced with a hemoglobin and hematocrit of 7/21 respectively. One unit of packed red blood cells was administered.

On Post op day 12, *Clostridium subterminale* was identified as the final anaerobic isolate and ID recommended Meropenem along with Doripenem and Metronidazole 500 milligrams. ID decided to discontinue Meropenem and suggested the regimen of Doripenem and Metronidazole. Another CT of the head and neck was ordered on Post op day 13 to document resolution of the infection (Fig. 5). Interpretation of the CT indicated residual fluid in the left submasseteric and pterygomandibular spaces consistent with a seroma (arrow). On Post op day 14, the patient passed a spontaneous breathing trial, was weaned off the ventilator, and transferred to the stepdown unit. The patient's status continued to improve though bouts of delirium were still occurring. A psychiatric consultation was requested for further evaluation. It should be noted that the patient never admitted to any substance abuse. By Post op day 18, the patient's clinical status had significantly improved and she was able to open to 25 mm. The anaerobic/aerobic cultures from sputum grew out a second organism, *Clostridium baratii*, while the fungal culture isolated yeast. IV Doripenem and Metronidazole were continued with addition of IV fluconazole. The leukocytosis resolved with a white blood cell count of 9.6. The hypotension, pulmonary edema, acute kidney injury, hypokalemia, and

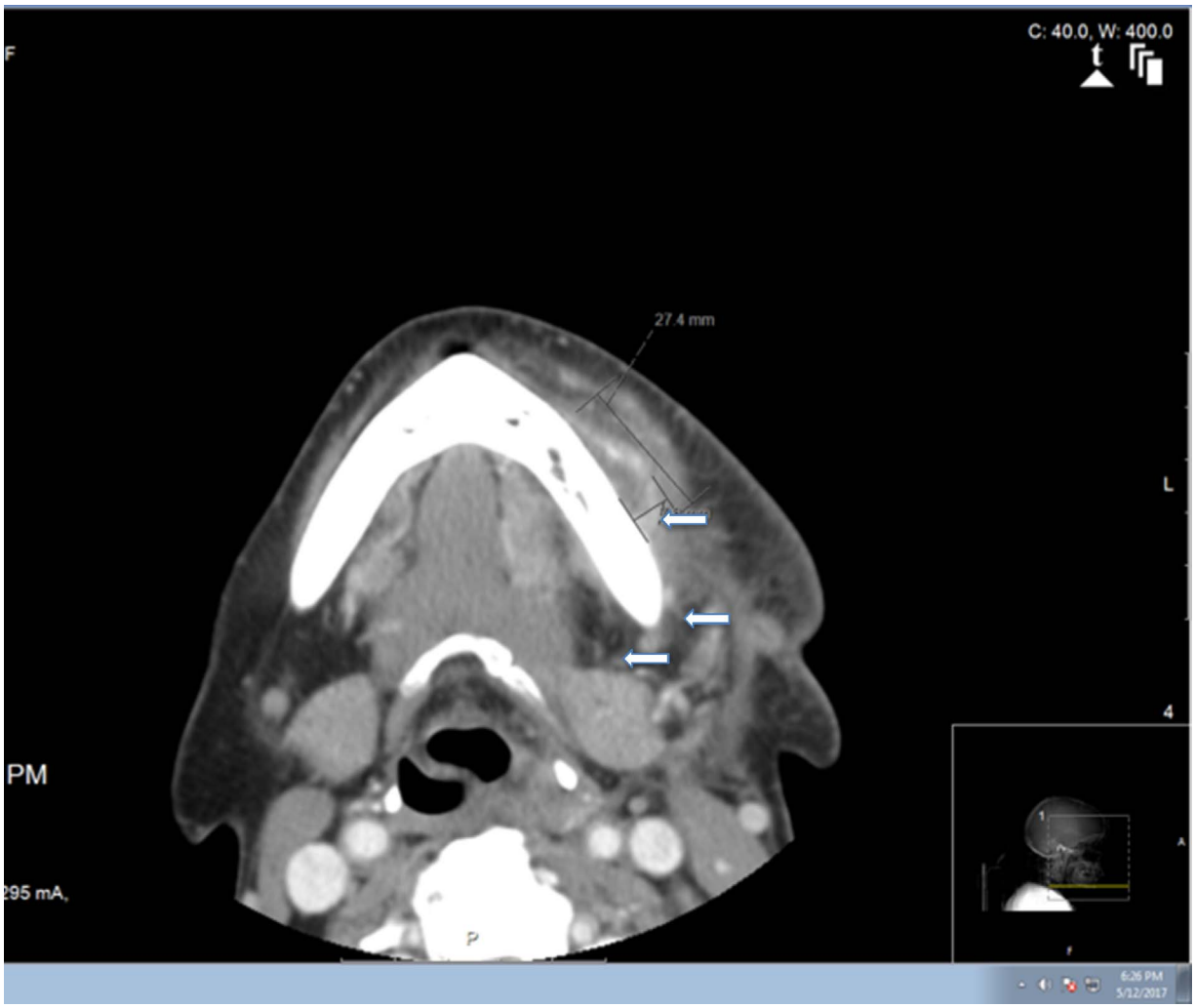

Fig. 5. Fig. 5 depicts a CT Soft Tissue Axial View. A focal fluid collection is present along the left mandibular body and in the left masseter muscle without significant wall enhancement. Edematous enlargement of the left masseter and pterygoid musculature are evident (white arrows).

delirium were all successfully treated. On Post op day 19, patient was transferred to the floor and social services assisted with obtaining a walker, home physical therapy, and home health. The patient was discharged to the home after a 21-day hospital stay and followed up at our clinic with complete resolution of her infections.

Discussion

This is the first case report to describe an unusual presentation of *Clostridium subterminale* as an isolate in a multifascial plane odontogenic infection involving an immunocompetent patient. It is rarely associated with human diseases and most inoculates of *Clostridium subterminale* are a result of traumatic exposure, as well as immunocompromised illnesses [6–9]. To date, only ten cases of *Clostridium subterminale* have been found in the medical literature: two cases in empyema, three cases of skin and soft tissue infections, one case of meningitis, two cases of bacteremia, one case presenting as an open fracture, and one case in an immunocompetent patient with sepsis (Table 1) [2–9].

Clostridia spores from the environment can inoculate human tissue by sharp-edge devices or by direct contamination of open wounds [5,9]. Abscess formation can occur up to 3–5 weeks after the initial insult, usually around bone and foreign body fragments and can initiate a cascade of disease progression from localized infection to invasive septicemia with devastating consequences [5,9]. Gorbach and Thadeplli have reported over 152 strains of Clostridium sp. with the majority isolated from abdominal sepsis associated with trauma [8]. Denny and Bonawitz have reported a case of clostridial infection in the temporalis fascia complicating a complex facial fracture and suggest that its origin was secondary to oral flora that gained access to traumatized and hemorrhagic soft tissue planes via mucosal lacerations in the fractured palate [5]. This species of Clostridium, however, was not identified but was present with coagulase negative Staphylococcus and Cornybacterium [5].

The patient's history of alcoholism is interesting in light of studies by Gorbach and Thadepalli, as well as others who suggest that patients with chronic alcoholism develop aspiration pneumonia with blood and sputum cultures yielding isolates of *Clostridium subterminale* in soft tissue infections [6,8]. The history of chronic alcoholism seen in the patient population studied by Gorbach and Thadepalli suggest this route of inoculation as a segway for clostridial septicemia [6]. Our patient was diagnosed with post-odontogenic sepsis and subsequent pulmonary pneumonitis as well as pulmonary edema. No isolates of Clostridium were seen in the lung sputum samples. A second clostridial isolate, *Clostridium baratii* was identified. Identification of *Clostridium baratii* is also an unusual finding. Lima et al. reported a rare case presenting as a severe pneumonia in a patient with Alzheimer's disease [10]. The isolation of this species may not be surprising since diseased teeth and periodontal tissue have been implicated in anaerobic pleuropulmonary infections [5]. Species of Clostridium have been identified as solitary pathogens in pulmonary infections [10,11]. Questions

Table 1
Clostridium Subterminale Literature Review.

	Date	Age	Gender	Diagnosis	Inoculation	Treatment	Reference
1	1975	–	–	Empyema	Pulmonary Embolism/Infarct	–	Grobach SL, Thadepalli H. Isolation of Clostridium in human infections. Evaluation of 114 cases. J Infect Dis 1975;131:S81–5.
2	1975	–	–	Skin, Soft Tissue	Frost Bite	–	Grobach SL, Thadepalli H. Isolation of Clostridium in human infections. Evaluation of 114 cases. J Infect Dis 1975;131:S81–5.
3	1989	63	Male	Pleuropulmonary Infection	Possible seeding of a pulmonary embolus and infarct during an occult anaerobic bacteremia	Day 1–8: Amoxicillin IV until day 8 Day 9–22: Amoxicillin plus clavulanic acid IV Penicillin G 3 million units Iv six times daily	Gubler JG, Wuest J, Hany A. Pleuropulmonary infection due to Clostridium subterminale. J Infect 19: 277–280, 1989.
4	1993	16	Male	Skin, Soft Tissue	MVA with PAN Facial fractures and soft tissue injuries	Initial: Ceftriaxone, 2gm q24HR IV Penicillin 2million units q6H Midpoint: Penicillin 4million units IV q4H s/p Surgery: Cefazolin, Clindamycin and Gentamicin	Denny, Arlen D., and Steven C. Bonawitz. "Clostridial infection following severe facial trauma." *Annals of plastic surgery* 33.3 (1994): 313–316.
5	1996	6	Female	Meningitis	Penetrating Injury to the brain	Penicillin and Cefotaxime	Neal G, Downing EF. Clostridial meningitis as a result of craniocerebral arrow injury. J Trauma. 1996;40:476–480
6	2003	41	Female	Bacteremia	Hx of CML s/p umbilical blood transplantation	Ceftazidime, Vancomycin	Miyazaki K, Mori T, Takayama N, et al. Clostridium subterminale septicemia in a recipient of allogeneic cord blood transplantation. Intern Med. 2003;42:374–375.
7	2009	18	Male	Skin, Soft Tissue	ORIF Right Forearm Fracture	Sultamicillin Clindamycin	Tappe, Dennis, et al. "Clostridium subterminale-Infection Secondary to an Open Fracture." *Infections in Medicine* 26.1 (2009).
8	2011	51	Male	Bacteremia	Hx of ALL, ulceration near anal verge	Initial: Cefepime, Vancomycin and Metronidazole Secondary: Imipenem Discharge: Augmentin	Haussen, Diogo C., et al. "Clostridium subterminale sepsis in adult acute lymphoblastic leukemia." *Leukemia & lymphoma* 52.6 (2011): 1137–1138.
9	2014	77	Male	Bacteremia	Hx of metastatic esophageal cancer/mucosal manipulation during stent placement or during repeat endoscopy	Cefepime, vancomycin and metronidazole	Thind, Sharanjeet K., and Jana I. Preis. "Clostridium subterminale septicemia in a patient with esophageal cancer." *IDCases* 1.3 (2014): 47–49.
10	2016	50	Male	Bacteremia	Spontaneous esophageal rupture	Imipenem, Vancomycin and Metronidazole	Daganou, Maria, et al. "Clostridium subterminale septicemia in an immunocompetent patient." *IDCases* 5 (2016): 43–45.

remain as to the likelihood of poor dental hygiene contributing to bacterial inoculation as a source of pulmonary infections [10,11].

Numerous classes of antibiotics are shown to be effective against Clostridial species including penicillins, cephalosporins, carbapenems, clindamycin, and metronidazole. Other studies have shown that Clostridium species are resistant to cephalosporins, quinolones, and aminoglycosides [3,7]. The resistance of this species to our original choices of antibiotics led the infectious disease service to choose a combination of carbapenems and metronidazole. Our successful antimicrobial regimen is supported by other studies that utilize combination therapy to treat *Clostridium* species that cause septicemia in patients infected with *Clostridium subterminale* [5–7,9,10].

In conclusion, this case presents a rare occurrence of a multifascial odontogenic infection associated with *Clostridium subterminale*. The difficulty in obtaining specimens for culture and sensitivity testing of *Clostridium subterminale* warrants careful decision making occasionally requiring multiple regimens of antimicrobial therapy. Severity of Infection may warrant several imaging strategies to fully identify the potential spread of the infection into fascial planes of the head and neck.

"Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request"

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