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Case report

Distant myonecrosis by atraumatic *Clostridium septicum* infection in a patient with metastatic breast cancerKelsey M. Gray^a, Pablo L. Padilla^b, Blake Sparks^b, Peter Dziewulski^{b,c,*}^a School of Medicine, University of Texas Medical Branch, Galveston, TX, USA^b Division of Plastic Surgery, Department of Surgery, University of Texas Medical Branch, Galveston, TX, USA^c Department of Surgery and Shriners Hospitals for Children, Galveston, TX, USA

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ABSTRACT

Clostridium septicum is an anaerobic, gram-positive bacillus known to cause myonecrosis, also known as gas gangrene, a life-threatening necrotizing soft tissue infection. Though it accounts for just 1 % of all infections attributable to *Clostridia* spp., *C. septicum* is a highly virulent and aggressive pathogen. Classic presentations of infection include bacteremia resulting in shock, myonecrosis, and vascular seeding. *C. septicum*-associated gas gangrene most commonly occurs in the setting of traumatic injury, but has also been reported in patients with colorectal malignancy, immunosuppression, neutropenia, and exceedingly rare in association with breast cancer. We report the case of a 56-year-old female patient with stage IV mixed lobar and ductal breast carcinoma with metastasis to the bone and liver, who presented with spontaneous *C. septicum* myonecrosis of the right hand. No prior traumatic injury was noted. Following amputation of the right forearm, antibiotic treatment, and multiorgan support, the patient passed following transition to palliative care. We hope to increase awareness of this relatively uncommon, though potentially deadly pathogen, as well as to discuss treatment options in patients infected with *C. septicum*.

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Introduction

Clostridia spp. Are anaerobic, gram-positive bacilli known to cause gas gangrene (myonecrosis), a necrotizing soft tissue infection characteristically associated with crepitus. Though *C. perfringens* is the most well-known member of this family of pathogens, being responsible for 80–95 % of traumatic myonecrosis, *C. septicum* is more often responsible for atraumatic, or spontaneous, myonecrosis occurring by hematogenous spread without antecedent external injury [1–5].

Amongst *Clostridia* spp., atraumatic *C. septicum* infection is uniquely associated with colorectal carcinoma. Additional associations have been made with hematologic malignancies, immunosuppression, neutropenia, diabetes, necrotizing enterocolitis, cecitis, or distal ileitis, among others [5–7]. A number of key adaptations are thought to account for the organism's propensity

and potential to cause atraumatic myonecrosis.¹ As a facultative anaerobe, *C. septicum* is 300 times more aerotolerant than *C. perfringens*, and thus able to colonize healthy, well-perfused tissues [2,6,8,9].

C. septicum also produces four main toxins, alpha (cytotoxic, hemolytic, causing tissue necrosis), beta (DNase), gamma (hyaluronidase), and delta (oxygen-labile hemolysin), as well as a protease and neuraminidase [8]. Secondary tissue breakdown releases creatine phosphokinase, myoglobin, and potassium, which contribute to the organism's local cytotoxic effects, while an overblown immune response to the *C. septicum* toxins results in shock and consequent multiorgan failure [1,8]. Treatment of this obscure pathogen is further complicated by an often subtle initial presentation limited to tachycardia. Severe pain, hypotension, and fever as typically seen in clostridial infections are late findings [2].

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¹ *In vitro* studies have shown that the presence of mucin induces swarm cell formation during times of nutrient depletion, while the production of mucin degrading enzymes provides a nourishment source. *C. septicum* therefore is afforded both an advantage over other species and a mechanism of compromising the mucosal barrier [5].

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Case

A 56-year-old Caucasian female presented to the Emergency Department at an academic tertiary care center with a two-day history of increasing pain, discoloration, and swelling of her right hand. Of note, pertinent past medical history included stage IV mixed lobar and ductal breast cancer with metastasis to the bone and liver. She was originally treated with palbociclib and letrozole, which were discontinued after progression of the cancer. She remained on docetaxel chemotherapy, with her most recent treatment received ten days prior to admission. In light of her malignancy and diminished radial pulses, acute limb ischemia and sepsis were initially suspected. The patient was started on intravenous heparin and fluids, as well as, empiric vancomycin, piperacillin-tazobactam, and levofloxacin. She was transferred to the Intensive Care Unit where computed tomography (CT) angiography of the right upper extremity demonstrated blood flow at the level of the palmar arch, making ischemia unlikely. Extensive subcutaneous and intramuscular emphysema was seen throughout the hand and wrist, extending proximally into the forearm, suggesting a necrotizing process (Fig. 1A, B).

The patient progressed into septic shock at the end of day 1 into day 2 of admission, becoming severely hypotensive and requiring hemodynamic support. She was emergently transported to the operating room and underwent a below elbow amputation for source control (Fig. 1D). Blood cultures returned positive for anaerobic gram-positive bacilli on day 3 of admission growth, at which time the patient's antibiotic regimen was narrowed to penicillin and clindamycin to reflect organism sensitivities, while remaining on vancomycin until methicillin

sensitive or resistant *Staphylococcus aureus* (MSSA, MRSA) was definitely ruled out. Unfortunately, the patient's condition continued to decline, developing progressive multiorgan failure involving the cardiovascular, respiratory, gastrointestinal, and renal systems. Physical exam on day 4 revealed the appearance of a grey, dusky discoloration of her left hand and of her toes bilaterally, with associated mottling (Fig. 1C). *C. septicum* was identified as the responsible pathogen from admission blood cultures.

Following an extensive discussion with the patient's family in light of her continued decline despite treatment, worsening mental status due to multiorgan failure, and pre-existing metastatic breast cancer, a decision to transition toward palliative care was made for the next day. The patient passed within hours of withdrawal of treatment on day 8.

Discussion

Extant literature suggests a strong association between *C. septicum* and gastrointestinal malignancy. Of all microbial species studied by Kwong et al. in 13,096 patients with bacteremia, *C. septicum* was most strongly associated with underlying colorectal carcinoma [10]. Another study by Corredoira et al. in 44 cases of *C. septicum* bacteremia found 43.1 % to have concomitant colorectal neoplasm, with 73.7 % of those cases being occult malignancies and 94.7 % of them being invasive carcinomas [11]. Available data is far less clear in regards to infection associated with other malignancies. However, it is clear that acquiring *C. septicum* bacteremia can be rapidly fatal with an estimated survival rate of 50 % in external trauma associated

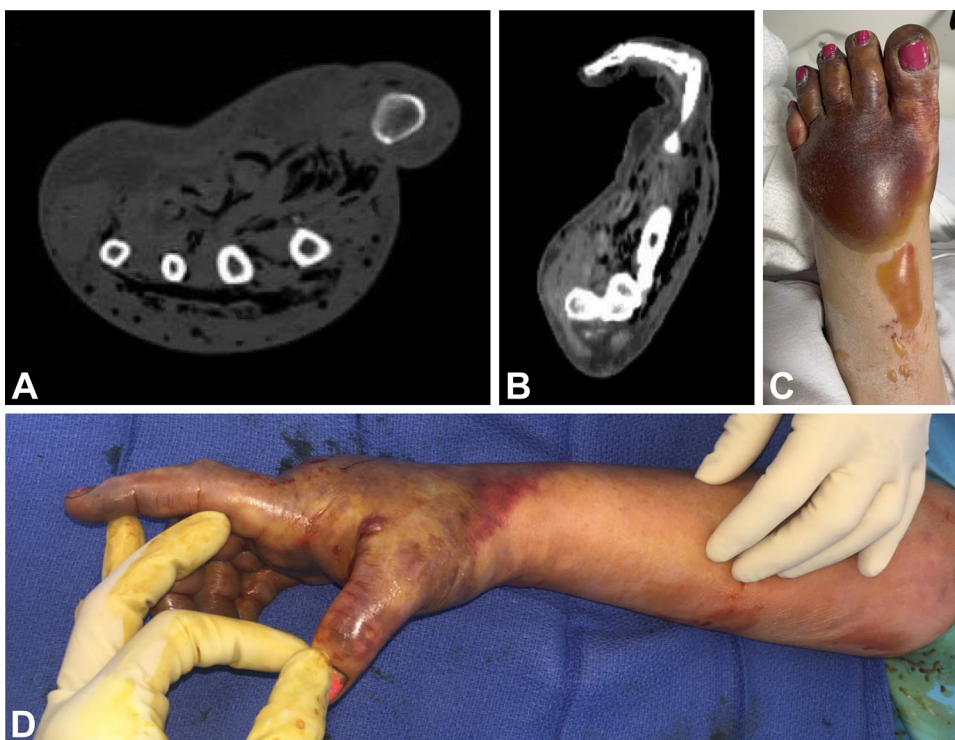


Fig. 1. A–B. Computed Tomography Angiogram of Right Upper Extremity upon ED arrival. Imaging showed patent radial, palmar arch, and ulnar artery without stenosis. Extensive subcutaneous, intramuscular, and vascular emphysema along with soft tissue edema was found throughout the hand, suggestive of myonecrosis. Gas was most prominently visualized along the dorsal and ventral aspects of the metacarpals of the (A) wrist and (B) hand. **C. Physical exam finding on Day 6.** Extensive ecchymosis, bullae, and dusky mottling on extremities. **D. Preoperative Photos.** Visual characteristics along with imaging were suggestive that below elbow amputation would sufficiently provide margins clear of infection for source control.

infection and further falling to only 21 % survival in spontaneously acquired myonecrosis [3].

Multiple theories exist as to how *C. septicum*, a constituent of the gut flora, gains access to the bloodstream to cause spontaneous myonecrosis at distant sites. In the setting of gastrointestinal malignancy, the increased permeability of blood vessels in the inflamed gut microenvironment in early disease, as well as damage to the mucosa via ulceration and necrosis from more advanced tumors are thought to facilitate entry of the gut microbe into systemic circulation [10,12]. The pathogen is found to be most strongly associated with stage III and IV gastrointestinal malignancy [10]. Moreover, chemotherapy-associated neutropenia and enterocolitis may cause damage to the intestinal wall, increasing susceptibility to *C. septicum* [5]. By extension, any condition causing a defect in the gut's epithelial barrier, such as ischemia or diverticulitis, may be expected to increase risk of *C. septicum* bacteremia, which means infection does not necessitate gastrointestinal malignancy.

The patient we present in this case, however, developed *C. septicum* infection likely by hematogenous seeding, in the setting of advanced breast cancer and not gastrointestinal malignancy. Sparingly few previous studies to date have demonstrated an association between disseminated *C. septicum* and breast cancers [13,14].

Other cases of atraumatic *C. septicum* gas gangrene in the setting of non-gastrointestinal malignancies include those of individuals with metastatic prostate and ovarian cancers [2,3,9]. These patients' disease processes ostensibly involved abdominal inflammation that may have compromised the integrity of the gut mucosal barrier and therefore permitted hematogenous dissemination of gut-borne *C. septicum*. However, cases of *C. septicum* dissemination have also been seen amongst immunocompromised patients without malignancy, which could suggest that immune compromise itself may permit dissemination of *C. septicum* [5,15]. In our patient's case, an autopsy was deferred by the family. It was therefore unclear if *C. septicum* bacteremia, presenting in this case with distant myonecrosis of the upper extremity, was attributable to a frank breach of the protective gut mucosa due to malignant process, or due to her state of immunocompromise from chemotherapy.

C. septicum bacteremia is severe and rapidly progressive, with limited treatment options to address its associated morbidity and mortality. Overwhelming infection and sepsis quickly leads to adult respiratory distress syndrome (ARDS), renal failure, myocardial irritability, and disseminated intravascular coagulation, as ultimately occurred in our patient [16].

As with any disseminated bloodborne infection, systemic antibiotics represent the mainstay of treatment. The three clinically relevant strains of *C. septicum* have shown strong sensitivity to penicillin, clindamycin, and tetracycline in vitro [6]. However, studies on *C. septicum* susceptibility have suggested that there could be an intrinsic resistance to vancomycin within the species [6,17]. This can be confusing for clinicians, and therefore contribute to delays in appropriate antibiotic therapy, since vancomycin is often employed as an empiric treatment in the bacteremic patient when the pathogen is unknown. To complicate matters, studies have indicated subinhibitory concentrations of some antimicrobial agents may lead to the release of potent *C. septicum* exotoxins [6]. Caution should therefore be exercised when prescribing vancomycin if a *C. septicum* infection is suspected. Supplementing antibiotic treatment with the use of hyperbaric oxygen has shown mixed evidence of benefit. However, one study reported a decrease in mortality from 70 % to 25 %, warranting its consideration for therapeutic use despite *C. septicum*'s established aerotolerance [4,5,16].

In addition to medical management, immediate surgical consultation and debridement of necrotic tissue as a means to control the spread of infection is a mainstay of treatment [16]. As *C. septicum* is a component of the gut flora, colectomy could theoretically provide source control as well. This has been attempted with promising results when combined with antibiotic therapy [4,5,7,18,19]. A systematic study has demonstrated that elimination of the bacterial nidus is crucial in controlling the infection, suggesting resection of the lesion undermining the protective gastric mucosa would eliminate the systemic access point [20].

CRedit authorship contribution statement

Kelsey M. Gray: Writing - original draft, Writing - review & editing. **Pablo L. Padilla:** Writing - review & editing, Data curation. **Blake Sparks:** Writing - review & editing, Data curation. **Peter Dziejewski:** Conceptualization, Writing - review & editing, Data curation, Supervision.

Declaration of Competing Interest

None.

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