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CLOSTRIDIUM SEPTICUM FASCIITIS IN A PATIENT WITH OCCULT COLON MALIGNANCY: A CASE REPORT AND LITERATURE REVIEW

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Summary

Introduction and aim. Gas gangrene is usually related to a trauma and can involve different districts of the body. It is a life-threatening condition, and its consequences lead to functional and aesthetical deficit. Atraumatic gas gangrene is a rare event, sometimes related to a *Clostridium septicum* (*C. septicum*) bacteremia. Aim of this article is to discuss existing literature about relation between colon adenocarcinoma and *Clostridia* infections, integrating with a case-report.

Patients and methods. A 54-year-old obese female patient developed an atraumatic gas gangrene of the posterior trunk, started from a *C. septicum* bacteremia. Gas gangrene involved skin, soft tissues and muscles of the back. A multidisciplinary clinical and surgical management involved anesthesiologists, general and plastic surgeons. During hospitalization, an occult colon adenocarcinoma was diagnosed and recognized as the bacteremia trigger, and it was successfully addressed. The gangrene was properly treated with seriate surgical debridement and final soft tissue coverage. After a long hospital stay, the patient was discharged in stable clinical conditions.

Results and conclusions. *C. septicum* gas gangrene remains one of the most fearful infections. An early diagnosis and a prompt antibiotic and surgical treatment, with life supportive care, are mandatory to avoid the necrotizing fasciitis spreading and the death of the patient. However, due to the rarity and variability of this condition, there is no standardized protocol for its treatment. Since a strong relation between *C. septicum* infection and colon malignancy is reported in literature, in cases of C. *septicum* bacteremia it should be mandatory to investigate gastrointestinal tract to exclude colon malignancy.

Key words: atraumatic gas gangrene, clostridium septicum, colon adenocarcinoma, necrotizing fasciitis, occult cancer

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INTRODUCTION AND AIM

The Clostridia species are opportunistic pathogens responsible for life-threatening conditions including tetanus, botulism, and gas gangrene with the necrosis of the skin, soft tissues and muscles.

Clostridium septicum (*C. septicum*) is a Gram positive bacterium responsible of the 80% of infections associated with underlying malignancies [1]. Sepsis by *C. septicum* has often a fulminant course and it is associated with a high mortality rate, with the majority of deaths occurring within the first 24 hours [2].
Consistent reports in literature have established a relationship between *C. septicum* infection and gastrointestinal tract neoplasms [3-7].
We present an uncommon case of a female patient who developed a necrotizing fasciitis of the posterior trunk without any external wounds and an unclear etiology. The systemic infection and the necrotizing fasciitis were successfully treated with antibiotics and multiple surgical debridement. During hospitalization, an occult colon adenocarcinoma was discovered and treated.
Finally, we discuss, through a non-systematic review of literature, the relationship about *C. septicum* bacteremia and occult colorectal cancer, and the implications for physicians in approaching patients presenting gas gangrene of unknow trigger in which a colorectal cancer is the hidden cause of the disease.

CASE REPORT

A 54-year-old woman affected by type II diabetes mellitus and related retinopathy, arterial hypertension, depressive syndrome and obesity (120 kg, 1.60 m, 46.87 kg/m^2), was admitted to the emergency service of a countryside hospital, due to a syncopal episode occurred while she was working in her own chicken coop. Laboratory tests reported high white blood cells count (> *16 103/microL*) and high level of C-reactive protein (210.67 mg/dL). Physical examination revealed a subcutaneous emphysema of the back involving the right and left scapular regions and the right side of the back extending to the right hip, suggesting a necrotizing fasciitis (Fig. 1). A further partial loss of left foot dorsiflection and sensation was noticed due to closed trauma of common peroneal nerve. The calculated Laboratory Risk Indicator for necrotizing fasciitis (LRINEC) score was 10. Computerized tomography (CT) of the chest revealed a pneumomediastinum extending to the upper thoracic outlet, related to a suspected fracture of the tracheal ring at D4 level. Empiric broad spectrum antibiotic therapy was promptly started, together with venous thromboembolism prophylaxis. After 24 hours, hemoculture tested positive for *C. septicum*. A lower airways endoscopy investigation was performed to evaluate tracheal integrity, but a sudden desaturation and worsening of general clinical condition led to emergent orotracheal intubation and Intensive Care Unit (ICU) admission of a Tertiary Referral Hospital.
At first a broad-spectrum empiric antibiotic therapy was started, including intravenous piperacillin/tazobactam 4.0/0.5 g every 6 hours and intravenous metronidazole 500 mg every 8 hours. Once antibiogram confirmed sensitivity to these antibiotics, targeted therapy was continued.
A second bronchoscopy and an oesophagogastric-duodenoscopy were performed thus confirming tracheal integrity and evaluating upper gastrointestinal tract.

Figure 1. The 54-year-old obese female admitted at the emergency room. Physics revealed blistering and a subcutaneous emphysema of the back involving the right and left scapular regions and the right side of the back extending to the right hip, suggesting a necrotizing fasciitis.

Figure 2. The patient once transferred in Intensive Care Unit for life-supportive care treatment. The necrotic process has demarcated, and the non-viable areas are evident in correspondence with the black eschars.

Figure 3. The patient after the first debridement surgery to remove the eschars and most of all non-viable tissues. Deep muscles involvement is noticeable. Further non-viable tissues persist at the wound bed.

Figure 4. The patient after the second debridement surgery. The defect has been reduced by approximating edge of healthy soft tissue. Major loss of substance deserved the use of negative pressure wound therapy, while waiting for definitive soft tissue coverage.

During ICU stay an area of skin necrosis developed over the subcutaneous emphysema (about 30x30 cm^2 wide), involving bilateral scapular regions and the right side of the back. Few days later, hemoculture tested negative for *C. septicum* and the pneumomediastinum improved spontaneously. Hence the patient was extubated and transferred to our Plastic and Reconstructive Surgery Unit, to manage soft tissues coverage.
The necrotic skin and subcutaneous area of the back (Fig. 2) was treated with seriate surgical debridements (Figs. 3-4). During excision of devitalized tissue, entire muscular groups were removed, as it was noticed that latissimus dorsi, trapezius, rhomboid, and teres major muscles were involved by the necrotic process. A negative pressure wound therapy (NPWT) was applied with a continuous working pressure of -120 mmHg (Fig. 5). NPWT was carried on up to three weeks after soft tissue debridement. Hence, NPWT was removed and seriate dressings (paraffin gauzes and iodine-soaked gauzes) were applied to prepare the wound bed for final coverage (Fig. 6). Definitive coverage was obtained by performing meshed skin grafts, due to lack of wide surface microsurgical options and poor vascular condition after necrotizing fasciitis. Despite local improvement of the back, a progressive and subacute anemia was noticed. The anemization process was not related to NPWT treatment or blood loss from the open wounds.
Due to the previous finding of *C. septicum* bacteremia and considering the possible relationship with gastrointestinal occult neoplasm, fecal occult blood test and tumor markers were investigated and then tested positive. A total body CT and a colonoscopy confirmed a stenotizing mass of the ascending colon with no distant metastases. Hence, a laparoscopic right hemicolectomy was performed, revealing a moderately differentiated adenocarcinoma of the large bowel (pT3 N0 M0, G2) [8]. Two weeks after, the patient was discharged in stable clinical conditions. Intestinal transit was preserved and the tissue coverage of posterior trunk was completely healed. Concurrent loss of left foot dorsiflection and sensation spontaneously resolved during hospitalization.
Prolonged stay associated with gas gangrene and intestinal cancer treatment caused a weight loss of 25 kg (final BMI of 37.11 kg/m^2). After discharging (Fig. 7), the patient started a rehabilitation program to support the motorial deficit concerning shoulders and the excessive prominence of the back bones (spinous process of C7 and spina scapulae) due to muscle loss and skin graft coverage. One-year follow-up the patients presented with a complete healed posterior trunk despite persisting the anatomy distortion (Fig. 8). No colon cancer recurrence was evidenced and physical improvement was achieved with rehabiltation therapy.

DISCUSSION

C. septicum is a gram positive, anaerobic, spore-forming rod which grows normally in the soil, and usually is not a part of the normal bowel flora. It is a rare cause of infection, accounting for as less than 1.3% of all blood cultures positive for *Clostridia* [9].
The case we presented is aligned with scientific literature, despite, to date, few works are reported as

Figure 5. The patient after the second debridement surgery and application of negative pressure wound therapy.

Figure 6. After cycle of negative pressure wound therapy and a further third debridement surgery and approximating the edges of healthy skin, wound bed appears substantially reduced, despite distortion of the posterior trunk. Residual wounds received a further application of negative pressure wound therapy before being covered with meshed skin grafts.

regards *C. septicum* infections and their association with gastrointestinal malignancies.

In a review by Hermsen and colleagues, among 320 patients with *C. septicum* infection, dating back to 1969, the 39% of these cases had a gastrointestinal malignancy [9]. Clostridial infections at a single institution were reviewed to determine impact on mortality. Between 1966 and 1993 Larson and colleagues reported 281 patients with confirmed cultural *Clostridium spp.* infection and *C. septicum* was found to be the responsible species in 11.4% (n = 32) of cases. There was a 56% mortality rate in *C. septicum* patients compared to a 26% mortality rate in all other clostridial infections. An associated malignancy was found in 50% of *C. septicum* cases, and the remaining 50% of patients had evidence of immunosuppression [10]. Previously a 25% mortality rate for all clostridial infections was reported by Bretzke, with the 80% mortality rate to be charged to *C. septicum* species alone [11].

Kornbluth and colleagues presented two cases of. *C. septicum* infection and performed a literature review, considering 163 patients. They evidenced that 81% of patients had an associated malignancy. More specifically 34% of 163 patients had an underlying colon carcinoma and 40% had an associated hematologic malignancy [12].

Clostridium spp. virulence may be related to production of multiple toxins, aggressive tissue invasion, and infection in compromised hosts [13]. The mortality rate of *C. septicum* sepsis is particularly high, ranging from 45% up to 70% [2,4,5].

In a most recent work by Stevens et al. 241 clostridial infections were identified, of which 7.8% were *C. septicum related.*

The postulated mechanism of infection in colon cancer involves disruption of the normal mucosal barrier due to tumor-induced ulceration, followed by bloodstream invasion. Anaerobic glycolysis in the tumor may provide an acidic and hypoxic environment facilitating spore germination [2]. Then, *C. septicum* and other pathogens may pass gastrointestinal mucosal barrier, accessing the bloodstream and being able to spread a systemic infection [2,3,6,7]. A contribution to bacterial growth is provided by pH, osmotic, and electrolytic environment variation in a colon carcinoma [14]. Finally, impaired host immunity from alcohol abuse, steroidal therapy, atherosclerosis, diabetes, or neutropenia is also believed to facilitate bacterial translocation [15] from bowel lumen to bloodstream.

The clinical spectrum of *C. septicum* infections is particularly diversified, presenting as cellulitis, fasciitis, myonecrosis, gas gangrene, visceral or soft tissue abscess. A potentially catastrophic soft tissue involvement is the nontraumatic spontaneous gas gangrene [15] as the one described in our clinical case.

The diagnosis of *C. septicum*-associated large bowel malignancy may be delayed or missed, as clinical manifestations are commonly nonspecific, mimicking more common disorders [15].

In fact, the pathogen can be cause of common symptoms including abdominal pain, fever, and malaise [15], which could be ascribed to any gastrointestinal disease, from gastroenteritis to acute appendicitis, diverticulitis or even non-gastroenteric issues.

Figure 7. Patient after successfully coverage with meshed skin grafts at the time of discharge. Notice the important weight loss of the patient that dramatically change the posterior trunk shape, together with the reconstructive process which allowed a complete coverage of tissue loss. The patient followed a rehabilitation program to support the shoulder deficits and the prominence of back bones (spinous process of C7 and spina scapulae).

Figure 8. One-year follow-up. Muscles loss, negative pressure wound therapy and reapproximating the healthy tissue edges caused a distortion of the normal anatomy of the back, together with the important weight loss during hospitalization.

At times, no clinical clue of a colon malignancy is present, hence the condition is treated such as an infective non-neoplastic disease. Some clinicians may be unaware of the association. However, bacterial sepsis may be the initial feature of previously undiagnosed and unsuspected large bowel carcinoma. Hence, when associated with necrotizing skin or soft tissue infections, *C. septicum* should promptly be considered related to an underlying malignancy [15]. Patients surviving bacteremia and gangrene should have diagnostic studies to rule out pathology of the gastrointestinal tract. Metastatic spread may occur if the primary focus is not removed [16].
The treatment of *C. septicum* bacteremia related to underlying single or multiple sites of infections consists of early surgical debridement and antibiotic therapy. At first a broad-spectrum empiric antibiotic therapy is started, including intravenous piperacillin/tazobactam 4.0/0.5 g every 6 hours and intravenous metronidazole 500mg every 8 hours. Once antibiogram confirms sensitivity to antibiotics, targeted therapy is continued. Other *Clostridium spp.* infection are adequately treated with several drugs including penicillin, clindamycin, cefoxitin, ampicillin/sulbactam, and imipenem/cilastatin. The optimal duration of intravenous antibiotic treatment has not been defined, although treatment should continue until no further surgical debridement is needed and the patient's hemodynamic status has been stabilized [17].
As previously stated, *C. septicum* infection is a rare but lethal diagnosis. Therefore, early identification and initiation of treatment are crucial to decrease mortality. There should be a high suspicion of *C. septicum* infection in patients who present with an underlying colonic malignancy with signs of sepsis. Indeed, *C. septicum* infection should be considered an epiphenomenon of gastrointestinal cancer, especially when a clear underlying cause of infection is not detected [18]. Hemocultures should be obtained early in order to achieve a timely diagnosis [2].
The connection between *C. septicum* infection and haematological or large bowel malignancies has been withdrawn in multiple literature reviews, as aforementioned discussed [4,9,10,12-14]. Therefore, if a hematological malignancy is excluded, a colonoscopy is warranted to investigate possible underlying colon carcinoma or other gastrointestinal tumors. Finally, *C. septicum* and its association with malignancy should be further considered in any patient suffering from myonecrosis without a history of trauma [19].

If the condition is not promptly diagnosed and an appropriate therapy is not started as soon as possible [20], the clostridial infection may have devastating consequences [18,21].

Fundamentals of gas gangrene surgical treatment, after *Clostridium spp.* Infection, consist in exposition of involved sites following debridement. Definitive soft tissue coverage is often represented by a delayed primary closure or skin graft/local flaps after the infection is completely resolved, depending on patient's general conditions.

Further reconstructive options for soft tissue coverage, including local or free flaps were considered in our case [22,23]. However, a more complex reconstruction a part of skin grafts was not feasible due to patient's general conditions and the underlying paraneoplastic anemia, which dictated the surgical management of the gangrene. The main purpose of the surgical treatment was to achieve a prompt wound closure and the infection solving.

Finally, as regards the postraumatic deficit of left foot dorsiflection and sensation, no treatment was started, since the closed nature of trauma, which was responsible of the possible underlying neurapraxya and the spontaneous improvement occurred within 3-4 month [24].

which spontaneously resolved during hospitalization.

CONCLUSIONS

C. septicum gas gangrene remains one of the most fearful infections. An early diagnosis and a prompt treatment are mandatory to avoid the necrotizing fasciitis spreading and the death of the patient. An aggressive antibiotic treatment and life-supportive care, together with multi-steps surgeries represents the most useful measures for a life-saving approach and a damage-control strategy. However, due to the rarity and variability of this condition, there is no standardized protocol for its treatment.

Since a strong relation between *C. septicum* infection and colon malignancy exists documented in literature, in cases of *C. septicum* bacteremia it should be mandatory to investigate gastrointestinal tract to exclude colon malignancy and exclude hematological cancer. The final aesthetic and functional reconstruction are postponed once the patient life is not threatened anymore, since the infection is solved, and the underlying malignancy has been detected and treated.

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Conflict of interest statement

The Authors declare no conflict of interest.

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Author contributions

The Authors contributed equally to the work.

Ethical consideration

The research was conducted ethically, with all study procedures being performed in accordance with the requirements of the World Medical Association's Declaration of Helsinki.

Written informed consent was obtained from each participant/patient for study participation and data publication.

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