

***Clostridium septicum* Can Cause Distant Myonecrosis in Patients with Ovarian Cancer**

SARAH ZURMEYER, CHRISTINA FOTOPOULOU,
JALID SEHOULI, ELENA BRAICU and UWE SCHLICHTING

Department Gynecological Oncology Charite, Campus Virchow Hospital, Berlin, Germany

Abstract. *A case report of lethal distant myonecrosis with gas gangrene is presented. Blood cultures and tissue biopsies revealed Clostridium septicum. The 55-year-old female patient presented with recurrent ovarian cancer of transitional cell type, initially diagnosed as FIGO IIb in January 2011, with hepatic metastasis and invasion of the ceecal wall. She underwent several operations, including partial bowel and liver resection in September 2011. Second-line therapy with topotecan three weekly was started in October 2011 while the patient was still in the hospital. During this chemotherapy, the patient revealed symptoms of severe pain and erythema of the skin. Within hours she died of septic shock after a debridement. The diagnosis was gas gangrene due to Clostridium septicum. Because it is a rare and severe disease and the time slot in which therapeutic measures can be taken is narrow, we discuss clinical symptoms and therapeutic options.*

Ovarian cancer is a rare disease and even after optimal surgical therapy and subsequent chemotherapy, 70-90% of the patients will experience a relapse within five years, dependent on the initial FIGO stage (Dembo *et al.* 1990, Pecorelli *et al.* 2001, Mink *et al.* 2002, Sehouli *et al.* 2004-2). These patients usually undergo cytoreductive surgery and chemotherapy for several times.

Gas gangrene is known to occur mostly in patients with large, contaminated wounds occurring for example in injury during war, and is mainly caused by *Clostridium perfringens* (2). The tissue must be deprived of oxygen in order to give rise to this bacteria. The Distant myonecrosis itself is a rare event and usually occurs in patients with underlying

immunodeficiency, malignancy (mostly colorectal cancer or leukaemia) or some other predisposing factors, such as diabetes mellitus or peripheral arteriosclerosis.

Of all clostridial infections, *Clostridium perfringens* is most commonly isolated (2). *Clostridium septicum* appears to make up only 1.3% of all infections (3).

This report describes a case of distant myonecrosis with gas gangrene due to *Clostridium septicum*, associated with an underlying malignancy, namely recurrent ovarian cancer in a progressive state.

Case Report

A 55-year-old woman with relapse of platinum resistant ovarian cancer presented to our clinic with nausea, dyspnea and a reduced performance status. She had undergone secondary surgical cytoreduction due to peritoneal and lymphogenic ovarian cancer relapse ten weeks earlier. The initial diagnosis has been made nine months earlier at an initial FIGO stage IIb, and was primarily optimally debulked, followed by six cycles of systemic carboplatin and paclitaxel. The patient was now planned to receive second-line postoperative chemotherapy with topotecan; however, the treatment had to be delayed due to recurrent pleural effusions and persistent cystitis, with elevated infection markers. The comorbidities of the patient included hypertension and multiple sclerosis, well-controlled under oral medication.

Pleural effusion was treated by pleural drainage, and the cystitis was treated successfully with intravenous antimycotics and antibiotics until complete clinical remission.

The patient then started systemic chemotherapy with topotecan d1-d5 three weekly one week after admission, while having low levels of inflammatory markers and no signs of an active infection. On day three of the first cycle, the patient complained of diarrhoea, and during the night at one a.m. of pain in her left leg and lower back without adequate response to *i.v.* analgesics. Laboratory results were

Correspondence to: Sarah Zurmeyer, Department für Gynecological Oncology Charite, Campus Virchow Hospital, Augustenburger Platz 1, 13353 Berlin, Germany. E-mail: sarah.zurmeyer@charite.de

Key Words: Clostridium septicum, distant myonecrosis, gas gangrene, ovarian cancer, distant myonecrosis in ovarian cancer.



Figure 1. Erythema and bullae of the skin of the upper left leg and the abdomen.

normal, with a white blood cell count of 10/nl (ULN 10/nl), creatinine 0.61 mg/dl (ULN 1.09 mg/dl), but an elevated alkaline phosphatase-level of 845 U/l (ULN 120U/l) due to hepatic impairment. The elevation of liver enzymes due to the rapid progression of liver metastasis had been known for weeks.

In the morning of day four, the patient was in moderate distress from her pain. Her temperature was 36.5°C, pulse rate 78/min and blood pressure 110/70 mmHg. Examination of her lungs showed no abnormalities; abdominal examination revealed a well-healed scar and, normal bowel sounds and no ascites. There were no skin lesions, but there was a nodular erythema on both arms, the abdominal skin and both legs. No crepitation was palpable, the pain in the leg and lower back did not change on pressure, nor during active or passive movement, both feet were warm, and peripheral pulses were strong and regular. There was no sign of deep vein thrombosis, and the patient received low molecular weight heparin as thrombosis prophylaxis during her entire hospital stay.

During the day the pain in the patients leg grew stronger and persisted, despite parenteral analgesics. Within four hours the patient was evaluated again because the pain rapidly increased in intensity. Temperature was 36.5°C, blood pressure 80/60 mmHg, and pulse rate 110/min. On physical examination at 4 p.m., the left upper leg exhibited a livid coloured swelling with small bullae (Figure 1).

The patient was immediately examined by surgeons and infectiologists and was admitted to the operating theatre with a suspected diagnosis of necrotizing fasciitis. High-dose clindamycin and penicillin therapy was initiated intravenously after taking blood cultures.

A debridement and resection of muscle, fascia and skin was performed on the same day at 7 p.m. on the patients left leg. The patient very quickly developed a fulminant renal failure, and was put on haemodialysis. The patient had to be supported with *i.v.* catecholamines, but her condition deteriorated rapidly, despite the surgical removal of the source of infection and antibiotic treatment with clindamycin and penicillin. The patient died of septic shock and organ failure early in the morning within twenty-four hours from the onset of the first symptoms. The pathological examination of the samples taken during surgery showed muscles with phlegmonous inflammation and acantholysis of the dermis, no granulocytous reaction and massive invasion of gram-positive fusiform bacteria (Figures 2, 3).

Microbiological investigation revealed *C. septicum* in all samples and blood culture, sensitive to penicillin. The white blood cell count from the day before and the day of the exitus letalis showed a remarkable downshift from 12.72/nl to 0.75/nl; the platelet count and clotting markers were normal at all times.

Discussion

Myonecrosis, or gas gangrene, is generally caused by *C. perfringens*, a commensal which is normally found in the lower intestine and the female genital tract. Gas gangrene due to *C. perfringens* occurs in settings with contaminated muscle injury such as compound fractures and penetrating war wounds, but also in surgical wounds, particularly after bowel or biliary tract surgery and in cases of arterial insufficiency in an extremity (4). Although clostridial contamination of major traumatic wounds is over 80%, the incidence of gas gangrene is only 1-2%, confirming the need for the presence of de-vitalized tissue in the pathogenesis (5). The lethal toxin of *C. septicum* is phospholipase C, which hydrolyzes the major phospholipid component of mammalian cell membranes, phosphatidylcholine (6).

Gas gangrene in the absence of trauma is an unusual and very rare clinical presentation. This so-called distant myonecrosis or non traumatic gas gangrene is mostly caused by *C. septicum* (7).

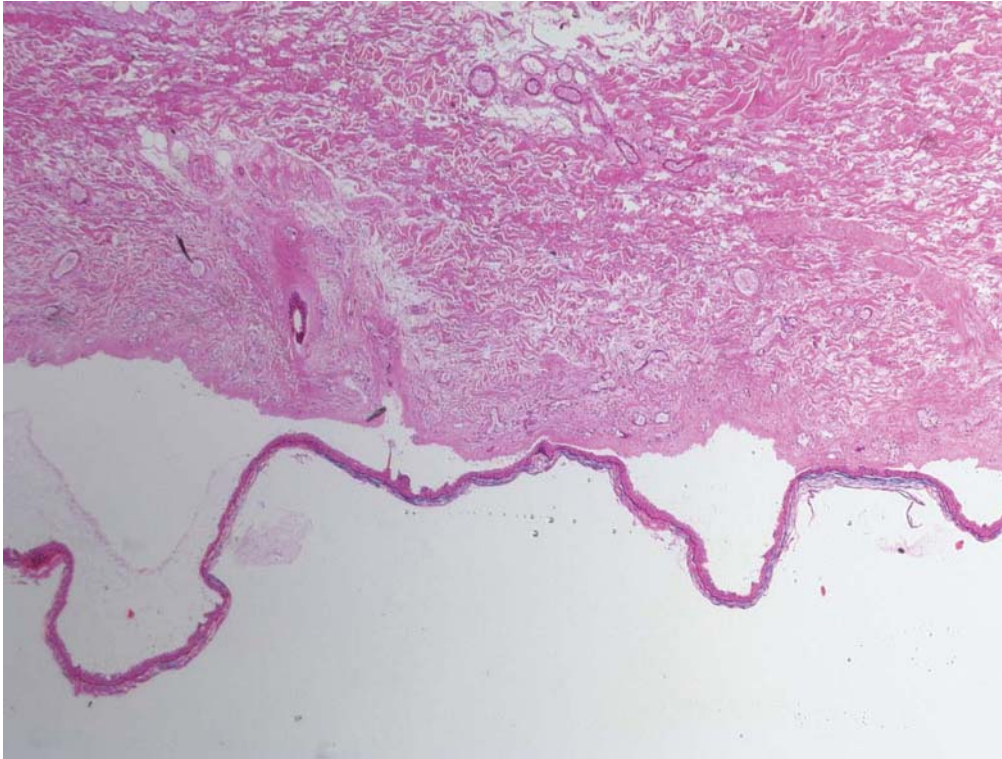


Figure 2. Acantholysis of the dermis, with subepidermal bulla and minimal inflammation in 100-fold magnification. (H&E stain)

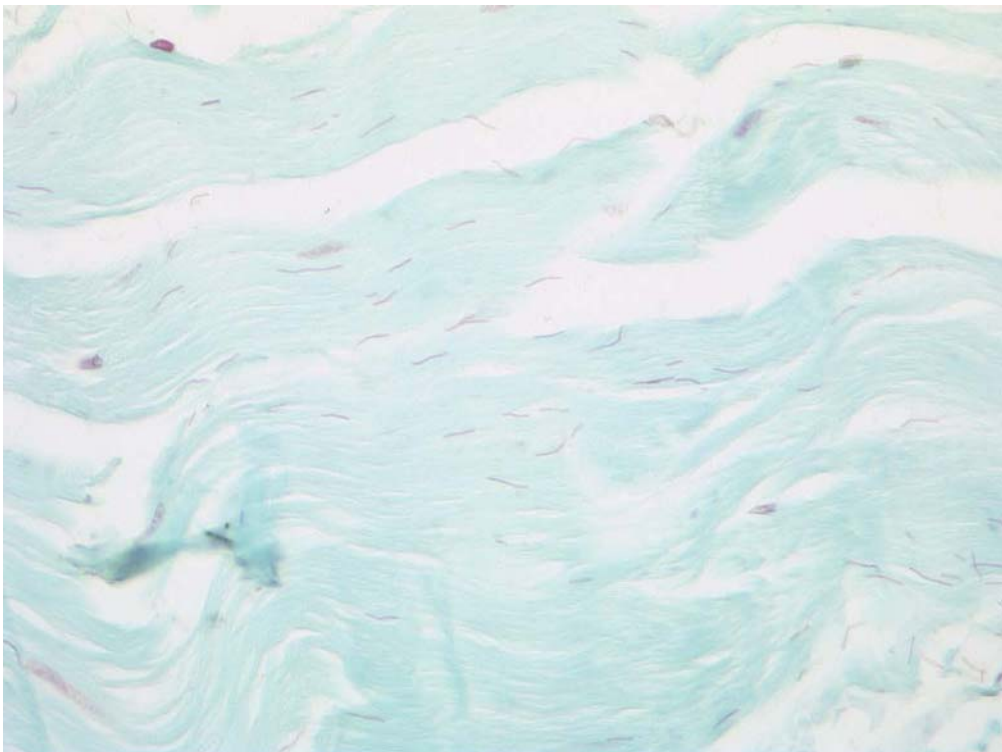


Figure 3. Rod-shaped gram-positive organisms without inflammatory cell infiltrates can be seen in this gram stained striated muscle 400-fold magnification.

The most probable port of entry is mucosal ulcerative site, or even perforation of the lower intestinal tract. However, unlike *C. perfringens*, *C. septicum* is not a normal inhabitant of the bowel (8).

Although tissue necrosis and ischaemia are usually involved, it is yet not fully-understood which mechanisms lead to the development of this syndrome. Distant myonecrosis has been described to be associated with underlying malignancies. A study of Koransky showed that of 59 patients with *C. septicum*-induced bacteraemia, 71% had a malignancy, 50% with haematological disease and the remainder with solid tumors. Of the 21 patients with a solid tumor, 14 (67%) had colonic carcinoma (7).

Wynne *et al.* stated the hypothesis that all bacteraemias have originated from the bowel and are induced by systemic chemotherapy, radiation therapy, and surgical procedures (9). The authors attributed the predisposition to bacteraemia to the advanced stage of the malignant disease, in combination with the chemotherapy-induced immune- and myelo-suppression, resulting in thrombocytopenia and internal bleeding from microtraumata of the intestinal tract. In another series of 136 patients with Clostridial bacteraemia, the most common species isolated was *C. perfringens*, responsible for 32% out of the 82 monomicrobial bacteraemias, followed by *C. septicum*, responsible for 20%. Smaller numbers of other species were also found, while polymicrobial bacteraemias accounted for 39% of all episodes.

Leukaemia and other hematological malignancies were the underlying disease in 44% of the cases, while solid tumors of various sites (genitourinary, gastrointestinal, head, neck, muscle and lung) accounted for the remaining cases (8). The comparison of *C. septicum* and *C. perfringens* is worthy of highlight. *C. perfringens* is the most common Clostridial species isolated from blood cultures. It can signal a wide spectrum of clinical contingencies, from benign to life-threatening situations; *C. septicum* is strikingly associated with underlying neoplasia (10). The survival rate of patients with distant myonecrosis compared to patients with local, trauma-related myonecrosis appears to be significantly worse at 21% compared to 50% (3). *C. septicum* was shown to be relatively aerotolerant and at least 300-fold more virulent than *C. perfringens*. It is therefore more likely to cause infections in viable tissues (11).

Clinical findings leading to the diagnosis of distant myonecrosis or gas gangrene are the acute onset of pain in the affected muscle, which seems to be out of proportion to any injury, considering the initial absence of macroscopic local alterations. The pain rises rapidly in intensity, while the first local symptoms may consist only of mild oedema. The patient soon exhibits hemorrhagic bullae and soft-tissue crepitation may arise. Finally, shock with diffuse intravascular coagulation and multiple organ failure often

leads to death within twenty-four hours. An x-ray film may reveal emphysema in subcutaneous tissue. A pathognomic characteristic in gram staining from involved tissue or fluids of the bullae is the absence of acute inflammatory cells, possibly as a result of very potent antigranulocytic activity of an as yet unidentified toxin produced by *C. septicum* (3).

The most important factors for a favourable outcome are early diagnosis and the immediate treatment of gas gangrene, which consists of antibiotic therapy and surgical treatment of necrosis, ranging from debridement to amputation. In addition, the primary focus of the infection should be removed (1). Patients treated with antibiotics alone have a very poor outcome (12).

Antimicrobials of first choice are penicillin, tetracycline, erythromycin, clindamycin, chloramphenicol and metronidazole.

To our knowledge, the presence of distant myonecrosis in a patient with ovarian cancer has been described only once so far (13). Patients with ovarian cancer generally present with peritoneal carcinomatosis without transmural invasion of the bowel. In the case report mentioned above, autopsy revealed a large necrotic metastasis of the caecal wall as the probable port of infection.

In our case, however, the hypothesis of necrotic metastasis of the bowel mucosa could not finally be proven as no autopsy was performed.

In conclusion, we believe that in the patient with sepsis with known malignancy, *C. septicum* should be considered. In the absence of external source of infection in a patient with Clostridial myonecrosis or sepsis, the caecum or distal ileum should be considered as a possible site of infection. Increased awareness of this association between *C. septicum* and malignancy, and aggressive surgical treatment, may result in improvement in the present 50-70% mortality rate.

References

- 1 de Virgilio C, Klein S, Chang L, Klassen M and Bongard F: Clostridial bacteraemia: Implications for the surgeon. *Am Surg* 57: 388-393, 1991.
- 2 Becker RC, Guilani M, Savage RA and Weick JK: Massive hemolysis in *Clostridium perfringens* infections. *J Surg Oncol* 35: 13-18, 1987.
- 3 Kornbluth AA, Danzig JB and Bernstein LH: *Clostridium septicum* infection and associated malignancy. *Medicine* 68: 30-37, 1989.
- 4 Mandell GL, Bennet JE and Dolin R: Mandell, Douglas and Bennet's Principles and Practice of Infectious Diseases. New York, Churchill Livingstone, 4th ed, ch. 73, pp. 929-936, 1995.
- 5 Altemeier WA and Furste WL: Gas gangrene. *Surg Gynecol Obstet* 84: 507-523, 1947.
- 6 Mac Lennan JD: The histotoxic clostridial infections of man. *Bacteriol Rev* 26: 177-276, 1962.

- 7 Koransky JR, Stargell MD and Dowell VR: *Clostridium septicum* bacteraemia: its clinical significance. *Am J Med* 66: 63-66, 1989.
- 8 Bodey GP, Rodriques S, Fainstein V and Elting LS: Clostridial bacteremia in cancer patients. A 12-year experience. *Cancer* 67: 1942-1982, 1991.
- 9 Wynne, JW and Armstrong D: Clostridial septicaemia. *Cancer* 29: 215-221, 1972.
- 10 Beebe JL and Elmar W: Recovery of uncommon bacteria from blood: Association with neoplastic disease *Clin Microbiol Re* 8: 336-356, 1995.
- 11 Stephens DL, Musher DM, Watson DA, Eddy H, Hamill RJ, Gyorkey F, Rosen H and Mader J: Spontaneous, nontraumatic gangrene due to *Clostridium septicum*. *Rev Infect Dis* 12: 286-296, 1990.
- 12 Brazier JS, Levett PN, Stanmard AJ, Phillips KD and Willis AT: Antibiotic susceptibility of clinical isolates of Clostridia. *J Antimicrob Chemother* 15: 181-185, 1985.
- 13 Prinssen HM, Hoekman K and Burger CW: *Clostridium septicum* myonecrosis and ovarian cancer: A case report and review of literature. *Gynecol Oncol* 72: 116-119, 1999.

Received January 28, 2013

Revised March 8, 2013

Accepted March 8, 2013