



## Case report

Uterine *Clostridium perfringens* infection related to gynecologic malignancyKevin M. Kremer<sup>a</sup>, Megan E. McDonald<sup>b</sup>, Michael J. Goodheart<sup>b,\*</sup><sup>a</sup> Department of Obstetrics and Gynecology, University of Missouri, Columbia, MO 65202, United States<sup>b</sup> Department of Obstetrics and Gynecology, Division of Gynecologic Oncology, University of Iowa Hospitals and Clinics, 200 Hawkins Dr, Iowa City, IA 52242, United States

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## ABSTRACT

Uterine gas gangrene caused by *Clostridium perfringens* is a serious, often life-threatening infection that is rarely encountered in the practice of gynecologic oncology. However, the hypoxic nature of gynecologic cancers due to necrosis and/or prior radiation therapy creates a microenvironment optimal for proliferation of anaerobic bacteria such as the *Clostridium* species. Early recognition and aggressive treatment with IV antibiotics and surgical debridement remain the cornerstones of management in order to decrease morbidity and mortality. Here we present the case of a 52 year-old woman with a remote history of cervical cancer who was previously treated at our institution with primary chemotherapy and radiation and was then admitted decades later with *Clostridium perfringens* bacteremia and CT evidence of intrauterine abscess. The patient received a prolonged course of IV antibiotic therapy and subsequently underwent definitive surgical management with a total abdominal hysterectomy, bilateral salpingo-oophorectomy, small bowel resection with anastomosis for a utero-ileal fistula identified intraoperatively. Pathology from the uterine specimen demonstrated a primary poorly differentiated uterine adenocarcinoma. The patient recovered fully from her *Clostridium perfringens* infection and was discharged from the hospital shortly after surgical intervention.

## 1. Case report

A 52 year-old female presented to the emergency department with acute worsening of chronic lower abdominal pain present for the past 3 months. Her past medical history was significant for a remote history of cervical cancer treated 30 years prior with Cisplatin, 5-fluorouracil, and external beam and vaginal brachytherapy. Upon presentation to the emergency department, she met SIRS criteria, as she was febrile (39.2 °C), tachypneic (20 rpm), tachycardic (121 bpm), and had accompanying leukocytosis (36.5 k/mm<sup>3</sup>). Her other laboratory findings were significant for evidence of hemolysis with anemia, hyperbilirubinemia, hemoglobinuria, and subsequent acute kidney injury. Her abdomen was non-acute but was notable for mild tenderness to palpation in the bilateral lower quadrants. Pelvic exam revealed no abnormal vaginal discharge; however, the patient was noted to have complete coaptation of the vaginal apex related to prior radiation therapy. CT of the abdomen and pelvis revealed a large uterine mass with internal fluid and gas extending into the myometrium. The scan was also notable for large inguinal lymphadenopathy and omental nodularity concerning for recurrent disease versus secondary malignancy of the uterine corpus. Given coaptation of the vaginal apex, endometrial biopsy could not be performed. Fine needle aspirate of the

enlarged inguinal lymphadenopathy was performed which returned as adenocarcinoma of uncertain origin, favor GI or uterine. The patient was started on broad spectrum antibiotic therapy with piperacillin-tazobactam 3.375 g q8 h for presumed polymicrobial pelvic abscess. On hospital day (HD) #2 the patient underwent CT-guided transabdominal intrauterine drain placement. Final speciation on HD#4 of blood cultures drawn at the time of admission grew *Clostridium perfringens*.

The patient experienced only modest improvement with intravenous antibiotics and drain placement with persistent leukocytosis and intermittent fevers. The infectious disease specialists were consulted who recommended changing antibiotics to continuous piperacillin-tazobactam 13.5 g q24 h. Hysterectomy was discussed as a means to remove nidus of infection but was initially deferred until patient was deemed stable for surgery. While on continuous piperacillin-tazobactam, the patient's WBC count began to decrease to a preoperative nadir of 9.6 on HD#13. On HD#19 she was taken to the OR for a total abdominal hysterectomy and bilateral salpingo-oophorectomy. She was found to have fistulization of her small bowel to the uterine mass requiring a small bowel resection with side to side anastomosis. There was no evidence of intraabdominal metastatic disease at the time of surgical exploration. Debulking of the inguinal lymphadenopathy was deferred at this time given uncertain primary and concurrent infectious

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comorbidity. Final pathology showed a poorly differentiated adenocarcinoma of suspected uterine primary with involvement of the cervix, uterus, and ileum. Antibiotics were discontinued on POD#2. The patient remained afebrile and her white blood count normalized to 6.9. She was discharged without antibiotics on POD#4.

Following discharge from the hospital, the patient underwent a separate bilateral inguinal lymph node debulking with pathology confirming metastatic high grade endometrial adenocarcinoma with extranodal extension in bilateral nodes. The patient subsequently received six cycles of carboplatin and paclitaxel. Six weeks following completion of chemotherapy, the patient was found to have increasing tumor burden in the pelvis and upper abdomen on CT imaging. After discussion of treatment options, the patient elected for palliation and passed away shortly thereafter.

## 2. Discussion

Uterine gas gangrene caused by *Clostridium perfringens* is a serious, often life-threatening infection that is most commonly seen in the peripartum period, with a dramatic decrease in incidence seen following the legalization of therapeutic abortions. In a non-pregnancy setting, most documented cases of uterine gas gangrene have been associated with underlying gynecologic malignancies (Braverman et al., 1987; Kurashina et al., 2010; Symonds and Robertson, 1978; Lacey et al., 1976). There has been one documented case of uterine *Clostridium perfringens* infection associated with benign degenerating leiomyoma (Kaufmann et al., 1974).

*Clostridium perfringens* (previously known as *Clostridium welchii*) is a Gram-positive, obligate anaerobe that is the most common cause of gas gangrene. *Clostridium perfringens* is part of the normal vaginal flora in 1% to 10% of healthy women and is also a saprophytic bacterium of the bowel. It is thought most uterine *Clostridium perfringens* infections are secondary to ascension of bacteria from the vagina or from the transfer of bacteria with uterine instrumentation. Given our patients exam finding of complete vaginal coaptation, we favor seeding of the uterus with *Clostridium perfringens* in this case to be from the bowel via utero-ileal fistulization rather than ascension from the vagina. As anaerobic bacteria, *Clostridium perfringens* colonize damaged tissues that have a compromised vascular supply leading to low oxygen tension. In this hypoxic environment, anaerobic bacteria proliferate and by doing so, release exotoxins. If left untreated, the effects of these exotoxins can be fatal in as little as 12 h (Halpin and Molinari, 2002). The mortality rate of gas gangrene with sepsis is reportedly as high as 30% (Leal et al., 2008).

As with our patient, the clinical picture of gas gangrene is characterized by sepsis and clinical exam or CT findings consistent with myonecrosis. Patients often present with signs of hemolytic anemia, such as jaundice and hemoglobinuria, secondary to intravascular hemolysis caused by release of the alpha exotoxin. Eventually, renal failure ensues due to acute tubular necrosis. Coagulopathy is also often seen. If left untreated, the above preterminal events and negative ionotropic effects of the alpha endotoxin may lead to cardiovascular collapse and death (Lichtenberg and Henning, 2004).

The cornerstones of treatment remain early recognition and aggressive treatment with broad-spectrum antibiotics and surgical debridement (Halpin and Molinari, 2002). Upon presentation, patients should be started on broad spectrum antibiotics for polymicrobial coverage. Once *Clostridium* species is isolated, antibiotic coverage can be tailored to penicillin 3–4 million units intravenously every 4 h. Patients with a penicillin allergy can be treated with Clindamycin 900 mg every 8 h. The combination of penicillin and clindamycin has been used in experimental animal models, and although not statistically significant, mice treated with the combination therapy demonstrated greater survival (Stevens et al., 1987). Antibiotic therapy should at least be continued until surgical debridement has been performed; although, Lichtenberg and Henning have reported the successful use of

conservative management with antibiotic therapy alone in 5 cases of women who presented with either uterine gas gangrene or *Clostridial* bacteremia without presenting signs of sepsis (Leal et al., 2008). In severe cases, the use of hyperbaric oxygen can be considered in conjunction with, but not in place of, antibiotics and surgical debridement. As described by Henry's Law, through hyperoxygenation of plasma, there is a transient increase in the percentage of dissolved oxygen in blood, thereby increasing delivery of oxygen to hypoxic tissues. The creation of oxygen free radicals in these tissues is incompatible with anaerobic bacterial growth (Kaide and Khandelwa, 2008). The efficacy of hyperbaric oxygen treatments is best documented in retrospective reviews of necrotizing soft tissue skin infections but randomized trials regarding its use are lacking (Escobar, 2005).

Our patient was started on broad spectrum penicillin based antibiotics upon presentation with appropriate treatment response. Conservative management without surgical intervention was initially favored in our patient given potential surgical morbidity due to prior radiation therapy and the inflammatory response due to active infection. After a prolonged course of antibiotic therapy, surgical intervention was warranted to optimize source control, as well as for treatment of secondary malignancy. The antibiotics were stopped after surgical intervention and the patient did well with no further infectious sequelae.

As noted, our patient was found to have a secondary endometrial cancer after previous radiation treatment of cervical cancer. A large retrospective study performed by Boice et al. of women previously treated with pelvic radiation for cervical cancer found a statistically significant increase in risk of secondary endometrial when compared to the general population (RR 1.3, 95% CI = 0.5–0.7) (John et al., 1985). Diagnosis of uterine malignancies can be difficult in previously radiated patients, as the most common presenting symptom of vaginal bleeding can be absent due to radiation induced cervical stenosis or vaginal coaptation. Furthermore, this cervical stenosis and/or vaginal coaptation can prohibit endometrial sampling. As in our patient, radiographic findings of an enlarged, fluid-filled uterus in the previously radiated patient should alert the clinician to the possibility of an underlying secondary malignancy of the uterine corpus.

## 3. Conclusion

Uterine gas gangrene is a serious, often life-threatening infection. In the gynecologic cancer patient, the necrotic and hypoxic micro-environment within tumors creates an optimal incubation site for anaerobic bacteria such as the *Clostridium* species. In this particular case, we initially used a conservative approach in treating this patient taking into account her past history of pelvic radiation and history of unstable clinical status. Ultimately, the patient underwent therapeutic hysterectomy to obtain source control. At the time of our surgery, the patient was found to have a second advanced uterine malignancy with fistulization to the small bowel. To our knowledge this is the first case of uterine gas gangrene potentially arising from utero-ileal fistulization. Practicing clinicians should keep uterine gangrene high on their differential in patients with known pelvic malignancy or prior radiation therapy who present with sepsis and CT findings consistent with myonecrosis, as early recognition and aggressive treatment is key to survival.

## Disclosures

The authors have no conflicts to disclose.

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