

Spontaneous Uterine Perforation Due to Clostridial Gas Gangrene Associated with Endometrial Carcinoma

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Abstract

Few cases of clostridial gas gangrene associated with uterine malignancy have been reported. We report on a 46-year-old woman with clostridial sepsis. On the day of admission due to severe abdominal pain, peritonitis was diagnosed, and computed tomography showed free air in the abdomen. At emergency laparotomy, perforation of the necrotic uterine wall was observed. During hysterectomy, septic shock developed, and life-saving therapy was performed in the intensive care unit after surgery. Pathological examination of the necrotic uterine wall showed grade III endometrial adenocarcinoma of the uterine endometrium (International Federation of Gynecology and Obstetrics stage IIIa) with gas gangrene due to *Clostridium perfringens*. This report aims to alert gynecologists to the possibility that clostridial gas gangrene of the uterus can occur in patients with peritonitis and intra-abdominal free air. Early recognition and aggressive therapy can save patients' lives.

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Key words: clostridium perfringens, gas gangrene, clostridial sepsis, uterine endometrial adenocarcinoma, uterine perforation

Introduction

Clostridium perfringens is an anaerobic Gram-positive rod. It is part of the normal human intestinal flora and is also part of the normal vaginal flora of 1% to 27% of healthy women^{1–4}. It is also found in 10% to 27% of patients undergoing elective abortion².

Clinical infection develops in only a small fraction of patients carrying *C. perfringens*. In particular, progression to gas gangrene is a rare but greatly feared complication resulting in potentially fatal

sepsis. Fulminant sepsis caused by *C. perfringens* is typically complicated by hemolytic anemia, renal failure, jaundice, hemoglobinuria, and gas gangrene. The mortality rate of fulminant sepsis is as high as 70%⁵. A PubMed literature search using the key words “*C. perfringens*”, “clostridium gas gangrene”, “uterus”, and “uterine tumor” from 1966 through 2008 identified only 18 case reports of clostridial sepsis^{1–18}. Of these cases, 14 were associated with pregnancy and 4 were not^{1,4,14,18}. We describe a nonpregnant woman in whom uterine perforation developed owing to uterine gas gangrene and sepsis due to *C. perfringens*.

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Case Report

A 46-year-old Japanese woman, nullipara and nulligravida, visited the emergency outpatient clinic of our hospital with a chief complaint of severe abdominal pain and high fever (39°C). She was agitated and appeared anemic and icteric, although the blood pressure and pulse rate were normal. The lower abdominal pain had developed a few days earlier, 14 days from her last menstrual period, and the pain had gradually become severe. She had not had atypical vaginal bleeding. On examination, the abdomen was diffusely distended, firm, and tender, indicating acute peritonitis. Transvaginal examination and ultrasonography were relatively difficult to perform because of the severe abdominal pain. However, a slightly enlarged uterus which corresponds to approximately 8 × 6 cm in sagittal section was found by the ultrasonography. Blood tests showed evidence of inflammation, with a white blood cell count of 26,680/μL and a C-reactive protein level of 10.0 mg/dL. The presence of hemolysis was indicated by the levels of hemoglobin (5.9 g/dL), hematocrit (17.9%), and indirect bilirubin (4.67 mg/dL), as well as by dark brown urine containing hemoglobin. Laboratory studies also indicated liver dysfunction (aspartate aminotransferase, 512 IU/L; lactate dehydrogenase, 8,775 IU/L) and renal dysfunction (blood urea nitrogen, 38.7 mg/dL; creatinine 1.87 mg/dL). Emergency computed tomography of the abdomen showed free air around the uterus (**Fig. 1**), although no free air was seen on plain chest X-ray films. Because upper gastrointestinal endoscopy revealed no abnormalities, perforation of the lower abdominal tract was suspected, and exploratory laparotomy was performed.

At laparotomy, a small amount of bloody ascites fluid was found. A foul-smelling, yellowish-brown area of necrosis (4 × 5 cm) was found in the uterine fundus, but no perforation of the gastrointestinal tract was found. In the central part of the necrotic area a small pore was noted which reached the uterine cavity. Spontaneous perforation of the uterus was diagnosed. Because the necrotic part of the



Fig. 1 Arrows indicate small bubbles of air in the abdominal cavity.

uterus suggested malignant change, total abdominal hysterectomy and bilateral salpingo-oophorectomy were performed. The para-aortic lymph nodes were not palpable. There were no adhesions between the uterus and other organs, including the intestines, omentum, and peritoneum. The surgical time was 3 hours, and the volume of blood loss was 1,100 mL. A drainage tube was placed in the cul-de-sac. During surgery, the systolic blood pressure fell to 60 mmHg, and it was difficult to maintain an appropriate blood pressure despite administration of intravenous fluid, ephedrine, and phenylephrine. Oliguria, which was present at the beginning of surgery, progressed to anuria, and was accompanied by a high fever, indicating septic shock.

After surgery, the patient was transferred to the intensive care unit. Intermittent positive-pressure ventilation was needed to treat pulmonary edema until 25 days after surgery. Antibiotics (2.0 g of meropenem), gamma globulin (5 g), packed red blood cells, and fresh frozen plasma were transfused daily. Antithrombin III (1,500 U) was added. No steroids were used. The patient improved gradually without symptoms of disseminated intravascular coagulation; the hemolysis stopped, and the fever resolved after 5 days, but hemodialysis was necessary for 3 months because of renal failure.

C. perfringens was cultured from the necrotic part of the uterus and from vaginal secretions. Histopathologic examination showed grade III

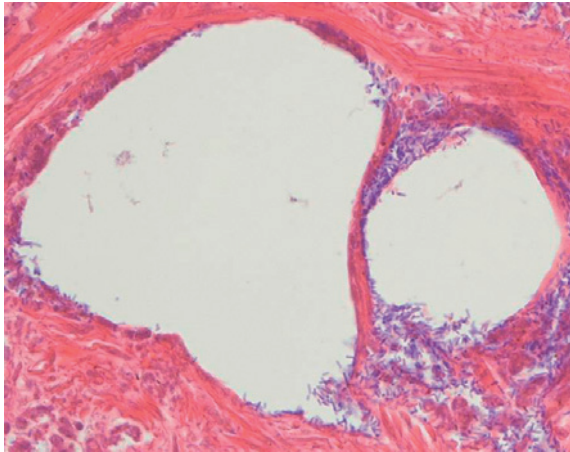


Fig. 2 Bacilli, presumably *C. perfringens*, within vascular spaces and gas bubbles in the uterine myometrium.

adenocarcinoma of the uterine endometrium with multiple areas of necrosis due to gas gangrene (**Fig. 2**), although cytological examination of the ascites fluid and peritoneum showed no malignant cells. The carcinoma was International Federation of Gynecology and Obstetrics stage IIIa. Cyclic chemotherapy with carboplatin and paclitaxel was begun 3 months after surgery while the patient was undergoing hemodialysis.

Comment

C. perfringens is part of the normal vaginal flora of 1% to 27% of healthy women¹⁻⁴. Therefore, ascending infection from the vagina to the uterus may occur. However, more than 95% of *C. perfringens* strains are benign⁴. Most cases of infection are cured with antibiotics alone. A more serious type of infection is sepsis with gas gangrene at the infection site, as in the present case. In cases of gas gangrene, the mortality rate ranges from 50% to 85%¹.

C. perfringens, formerly called *Clostridium welchii*, is a Gram-positive, anaerobic, nonmotile, spore-forming organism that is often encapsulated and is capable of producing exotoxins. Of these, an alpha toxin, lecithinase C, which acts on the surfaces of red and white blood cells, is responsible for intravascular hemolysis, which causes anemia and jaundice, and it may also produce hemorrhage as a result of its necrotizing action on capillaries and arteriolar walls.

The onset of symptoms from the time of infection is rapid, 12 to 24 hours⁷.

Bryan et al.¹⁹ have reported the following course of development of gas gangrene by clostridial toxin in rat experiments. When infection occurs, absorption of the toxin saturates the postcapillary venous system and then the arterioles. Aggregates of activated platelets and platelet/polymorphonuclear leukocyte complexes sequentially occlude small, medium, and large vessels, which reduces local perfusion and contributes to endothelial cell damage. The decreases in tissue pH and oxygen tension provide optimal conditions for the growth of anaerobic bacteria. As infection progresses, major blood vessels become affected, leading to anoxia and necrosis of large muscle groups. Bryan et al. also found that the decrease in perfusion induced by the toxin was time- and dose-dependent. Accordingly, growth of clostridia that can produce the toxin is key in the development of fatal sepsis with gas gangrene. However, it must be emphasized that only 5% of 640 different strains of *C. perfringens* are pathologically virulent². The determination of virulence is a major concern when treating patients in whom cultures are positive for *C. perfringens*.

When the organism is introduced into the uterus and sepsis develops, injured or necrotic tissue must remain in the uterus, which permits bacterial incubation and the growth of bacterial colonies. This is why clostridial infection occurs frequently after abortion and delivery. Pathological conditions develop in the uterus and predispose to infection, unlike normal conditions that resist such bacteria.

From 1966 through 2008, there have been only 4 case reports of clostridial septicemia in nonpregnant patients, whereas the majority of cases were related to pregnancy. Of the nonpregnant patients, 2 had uterine endometrial adenocarcinoma. The symptoms of sepsis appeared after the insertion of radiocesium (¹³⁷Cs) for treatment¹⁴. The other patients included a patient undergoing chemotherapy for choriocarcinoma¹⁸ and a patient with endometrial adenocarcinoma and spontaneous septicemia⁴. The fourth report included only 1 case that was associated with a nonmalignant tumor: a degenerating uterine myoma¹. The present case is

the second case of adenocarcinoma with spontaneous uterine gangrene and sepsis. Previous reports suggest that pathological conditions inside the uterus leading to gas gangrene are rare in cases of uterine malignancy. In such cases the host defensive system is likely impaired and allows the clostridium to grow. However, details of the conditions remain poorly understood.

The typical clinical manifestations of clostridial sepsis include hemolysis, hemoglobinuria, renal failure, and gas in the pelvic soft tissue. When these are present or the patient's condition worsens owing to sepsis, surgery should be performed immediately to remove the affected site. In the present case, all of the signs were already present at the first visit. Early aggressive therapy, including antibiotics and surgery, has reduced the mortality rate in clostridial sepsis from 50 to 80 percent to 10 to 20 percent¹⁸. In the present case, early hysterectomy could be performed because intra-abdominal free air was identified, and the intensive care, including life-saving therapy, was effective after surgery.

This report aims to alert gynecologist to the possibility that clostridial gas gangrene of the uterus may be present when intra-abdominal free air is found in patients with peritonitis. Early recognition and aggressive therapy can save patients' lives.

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