Case report

**Clostridium and Bacteroides** bacteremia as initial presentation of uterine carcinosarcoma

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1. Introduction

*Clostridium*, a Gram-positive, anaerobic bacteria are generally associated with gastrointestinal and soft tissue infections. Less frequently, *Clostridium* is identified as the source of gynecologic or genitourinary infections. Although gynecologic *Clostridium* infections are more commonly peripartum, few case reports have described *Clostridium* infections in the setting of an underlying gynecologic malignancy, likely due to a hypoxic microenvironment.

Uterine carcinosarcoma, previously known as malignant mixed Mullerian tumor (MMMT), is a rare, aggressive solid tumor that makes up less than 5% of uterine cancers. The cancer consists of both epithelial and mesenchymal components. Presenting symptoms often include abnormal uterine bleeding, abdominal pain, or a rapidly enlarging uterus (Pezzicoli et al., 2021). We present where *Clostridium* and *Bacteroides* bacteremia was the initial presentation of an undiagnosed uterine carcinosarcoma.

2. Case

A 55 year old perimenopausal female with a history of non-insulin dependent diabetes presented to the emergency room with midline lower abdominal pain that had worsened over the past 4 days, associated with dysuria, lower back pain, nausea, and vomiting. She reported vaginal bleeding for four days, previously with 3 months of amenorrhea. The cancer presents both of epithelial and mesenchymal components. Presenting symptoms often include abnormal uterine bleeding, abdominal pain, or a rapidly enlarging uterus (Pezzicoli et al., 2021). We present where *Clostridium* and *Bacteroides* bacteremia was the initial presentation of an undiagnosed uterine carcinosarcoma.

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piperacillin-tazobactam) were begun and she was admitted to the Medical Intensive Care Unit (MICU). Initially her leukocytosis and lactate improved from 17 kg/mm$^3$ to 9.5 kg/mm$^3$ and from 4.0 mmol/L to 3.6 mmol/L, respectively. She remained persistently hypotensive and mildly tachycardic, but afebrile. In the MICU, the patient underwent serial physical and laboratory exams and antibiotics were continued. Despite broad spectrum antibiotics and aggressive fluid resuscitation, her clinical condition progressively deteriorated; she had worsening leukocytosis (66.3 k/mm$^3$) and lactic acidosis (4.9 mmol) and required increasing pressor support (vasopressin was added to the aforementioned norepinephrine). Antibiotics were broadened to vancomycin and meropenem. During her 9 h in the MICU, she had only 220 ml of urine output.

Sequential physical examinations revealed distinct lower abdominal guarding and the decision was made to proceed emergently to the operating room for exploratory laparotomy and source control given increasing suspicion for an intrauterine source without improvement on broad spectrum antibiotics. She was consented for exploratory laparotomy, total abdominal hysterectomy, and bilateral salpingooophorectomy. At start of surgery, patient still required pressor support with 2 pharmacologic agents. Intraoperative findings were notable for an enlarged 20 cm uterus with an 8 cm, necrotic, foul-smelling intrauterine mass (Fig. 2A-B). Frozen section and cultures from the specimen were not performed secondary to the emergent nature of the surgery and the patient’s critical status, however gross inspection did not show obvious myometrial invasion. She underwent an otherwise uncomplicated total abdominal hysterectomy and bilateral salpingooophorectomy with an estimated blood loss of 150 ml. Prior to closing, the abdomen and pelvis were irrigated with several liters of saline and a Blake drain was placed in the left lower quadrant. The fascia was closed and the subcutaneous tissue was irrigated and packed with sterile gauze. By the conclusion of case, the pressor support required was...
large range of antibiotic regimens, often making these infections difficult to treat (Wexler, 2007). Clostridium is a Gram-positive, spore-forming anaerobe that has previously been reported to colonize the vaginal microbiome in 1–10 % of women (Chong et al., 2016). Bacteroides is a Gram-negative, non-spore-forming, obligate anaerobe. It is thought to be an important pathogen in most anaerobic infections and has an associated mortality rate of up to 19 % (Wexler, 2007). The bacteroides group are involved in a beneficial relationship with the gut, but are highly pathogenic in other areas, often causing abscesses and bacteremia with high mortality (up to 19 %). The pathogenicity of the bacteroides group involves fimbriae- and agglutinin-mediated tissue adhesion, enzymatic evasion of host immunity, capsular induction of abscess formation, and tissue destruction with histolytic enzymes. This group of bacteria also holds high resistance patterns to a broad range of antibiotic regimens, often making these infections difficult to treat (Wexler, 2007).

It has been previously observed that clostridium infection in the obstetric or gynecologic patient is associated with high morbidity and mortality. Uterine infection with clostridium has been encountered after surgical, medical, or spontaneous abortion (Cohen et al., 2007; Barrett et al., 2002). There are also reports of Clostridium bacteremia and sepsis in the puerperal period as a result of endometritis. Pyometra in the gynecologic setting, which is rarely seen before menopause, is concerning for an underlying uterine malignancy. Although uncommon, uterine infections specifically caused by Clostridium have been identified in the setting of various gynecologic malignancies (Table 1) (Lacey et al., 1976; Symonds and Robertson, 1978; Braverman et al., 1987; Kurashina et al., 2010; Shetty et al., 2010; Kremer et al., 2017). Interestingly, claudin-3 and claudin-4 receptors, transmembrane proteins that mediate clostridium perfringens enterotoxin (CPE) binding and cytolysis, were found to be overexpressed in carcinosarcoma (Santin et al., 2007). Even less commonly encountered is Bacteroides bacteremia secondary to necrotic fibroids, however this has also been observed (Arnold et al., 2020).

Although a rare occurrence, Haplin and colleagues have offered management guidelines for Clostridium infection (Haplin and Molinari, 2002). They emphasize that quick recognition of infection, initiation of broad spectrum antibiotics, and surgical management are paramount to preventing poor outcomes. Shetty and associates also recommend early initiation of antibiotics and appropriate surgical debridement as the optimal management for this type of infection (Shetty et al., 2010). A similar approach was also employed for a patient with Bacteroides bacteremia whose MRI was consistent with a degenerating submucosal fibroid with hemorrhage or necrosis. The patient completed a complete course of antibiotics then proceeded to undergo surgical management with an open myomectomy (Arnold et al., 2020).

Our case was rare in that this patient had polymicrobial sepsis from both Clostridium and Bacteroides. Although more conservative treatment has been reported, including antibiotics only (Lichtenberg and Henning, 2004) or antibiotics followed by a myomectomy (Arnold et al., 2020), often times it is not adequate for management. In addition, we caution that imaging alone may be insufficient to rule out underlying malignancy. Given the increasing uterine tenderness over serial exams, with worsening leukocytosis and hypotension despite broad spectrum antibiotics, fluid resuscitation, and vasopressors, an exploratory laparotomy and hysterectomy were deemed necessary for evaluation and source control.

4. Conclusions

Anaerobic bacteremia in the setting of uterine pathology can lead to rapid deterioration and high mortality rates if not recognized quickly and treated appropriately. Management and treatment should start with a broad differential diagnosis. It is important to have a high clinical suspicion for intrauterine infections. Imaging and laboratory tests are important, however as demonstrated in our case, they do not always
Table 1
Cases of clostridium associated with underlying gynecologic malignancy.

| Year | Author          | Number of cases | Bacteria                        | Underlying malignancy                                      | Treatment of infection                                      | Outcome                                      |
|------|-----------------|-----------------|---------------------------------|------------------------------------------------------------|------------------------------------------------------------|----------------------------------------------|
| 1976 | Lacey           | 1               | Clostridium perfringens         | Metastatic Choriocarcinoma                                 | Antibiotics (penicillin G/gentamycin), TAH-BSO, hyperbaric oxygen | Recovered, received subsequent chemotherapy   |
| 1978 | Symonds         | 2               | Clostridium welchii             | Adenocarcinoma of the uterus                               | Antibiotics (benzylpenicillin & gentamicin)                  | Death within 52 h (1st); survived (2nd)      |
| 1987 | Braverman       | 1               | Clostridium welchii             | Stage IB adenocarcinoma of the uterus with spontaneous uterine perforation | Antibiotics (ampicillin, gentamicin, clindamycin; penicillin G), TAH-BSO, blood transfusion                    | Recovered and subsequent radiation therapy |
| 2010 | Kurashina       | 1               | Clostridium perfringens         | Stage IIIA, Grade 3 adenocarcinoma of the endometrium with spontaneous uterine perforation | Antibiotics (meropenem), TAH-BSO, positive pressure ventilation, pressor support, hemodialysis × 3 months | Recovered but required hemodialysis × 3 months, received subsequent chemo |
| 2010 | Shetty          | 1               | Clostridium perfringens         | Stage IVB undifferentiated uterine sarcoma                 | Antibiotics, resection (TAH-BSO, ‘pelvic clearance’) with extension of disease into left pelvic sidewall         | Recovered, received subsequent chemo        |
| 2017 | Kremer          | 1               | Clostridium perfringens         | Stage IVB poorly differentiated uterine adenocarcinoma     | Antibiotics (piperacillin, tazobactam), TAH/BSO, small bowel resection with anastomosis for a utero-ileo fistula | Recovered, received subsequent chemotherapy |
| 2022 | Imo             | 1               | Clostridium, bacteroides vulgatus | pT1a carcinosarcoma of the uterus                          | Antibiotics (vancomycin, piperacillin-tazobactam; meropenem; outpatient amoxicillin-clavulane and metronidazole), TAH/BSO | Recovered, received subsequent chemotherapy |

* 2nd patient without confirmed bacteremia.

Convey the complete clinical picture. Frequent bedside clinical assessment and physical examination of the patient are critical in management. Oftentimes, emergent surgical intervention is necessary in the management Clostridium and Bacteroides infection. All of these were employed in our case before blood culture results were available. This ultimately led to the rapid recognition and treatment of this infection and the positive outcome we observed.

CRediT authorship contribution statement

Chinonye S. Imo: Investigation, Writing – original draft, Writing – review & editing. Alexandra Spiritos: Conceptualization, Investigation, Writing – review & editing. Yevgenia Fomina: Investigation, Writing – review & editing. Jared Eaves: Investigation, Writing – review & editing. Kevin Kremer: Conceptualization, Writing – review & editing. Jayanthi S. Lea: Supervision, Conceptualization, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.gore.2022.101043.

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