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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. She was afebrile, normotensive, and non-tachycardic on evaluation, with a normal cardiovascular exam. She appeared uncomfortable, with general lower abdominal tenderness and her uterus was palpable at the level of the umbilicus. On pelvic exam, she had normal external female genitalia. The uterus was enlarged, filling the pelvis and displacing the cervix anteriorly. There was no cervical motion tenderness. The cervix itself could not be directly visualized. A wet prep was negative and an endometrial biopsy was performed in the emergency room. Her workup was notable for leukocytosis (19 k/mm^3) and urinalysis with nitrites, leukocytes, and blood and leukocytosis. A transvaginal ultrasound showed uterine masses consistent with leiomyomata. The largest fibroid was fundal and measured 6 cm. The fibroids affected the contour of the endometrium and the serosa. The endometrium was also noted to be thickened (46.9 mm) and echogenic, with lobulated areas of tissue noted within the cavity. The ovaries were not visualized. (Supplemental Fig. 1A-B). Differential diagnosis included acute cystitis, leiomyomata, degenerating fibroids, or an underlying malignancy. While in the emergency room, her pain improved with acetaminophen and ibuprofen. She was treated for acute cystitis and discharged home with close follow up for her symptoms, cultures, and endometrial biopsy result.

Four days later, the patient re-presented to the emergency room with worsening suprapubic pain, fevers, chills, nausea, and vomiting. She reported ongoing vaginal bleeding but had not noticed any malodorous discharge. Her exam was notable for lower abdominal and suprapubic tenderness; her pelvic exam was otherwise unchanged from her prior presentation. She was initially afebrile with a normal heart rate, but was hypotensive (systolic range 60–90, diastolic range 30–50), with leukocytosis (17 k/mm^3) and elevated lactate (4.0 mmol/L). CT of the abdomen and pelvis revealed a fibroid uterus, a small amount of pelvic free fluid, and an expanded endometrial cavity to 8 cm; there was a discrete 4 cm hyperdensity within the mass diagnosed on imaging as an organized hematoma or a hyperdense component of this endometrial mass (Fig. 1A-D). While sepsis due to a urinary source seemed possible, evaluation continued for a gynecologic source such as endometritis, or a gastrointestinal source.

She received crystalloid for fluid resuscitation with minimal improvement in blood pressures and was started on norepinephrine for blood pressure support. Broad spectrum antibiotics (vancomycin and

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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/mm3 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 salpingo-oophorectomy. 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 salpingo-oophorectomy 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

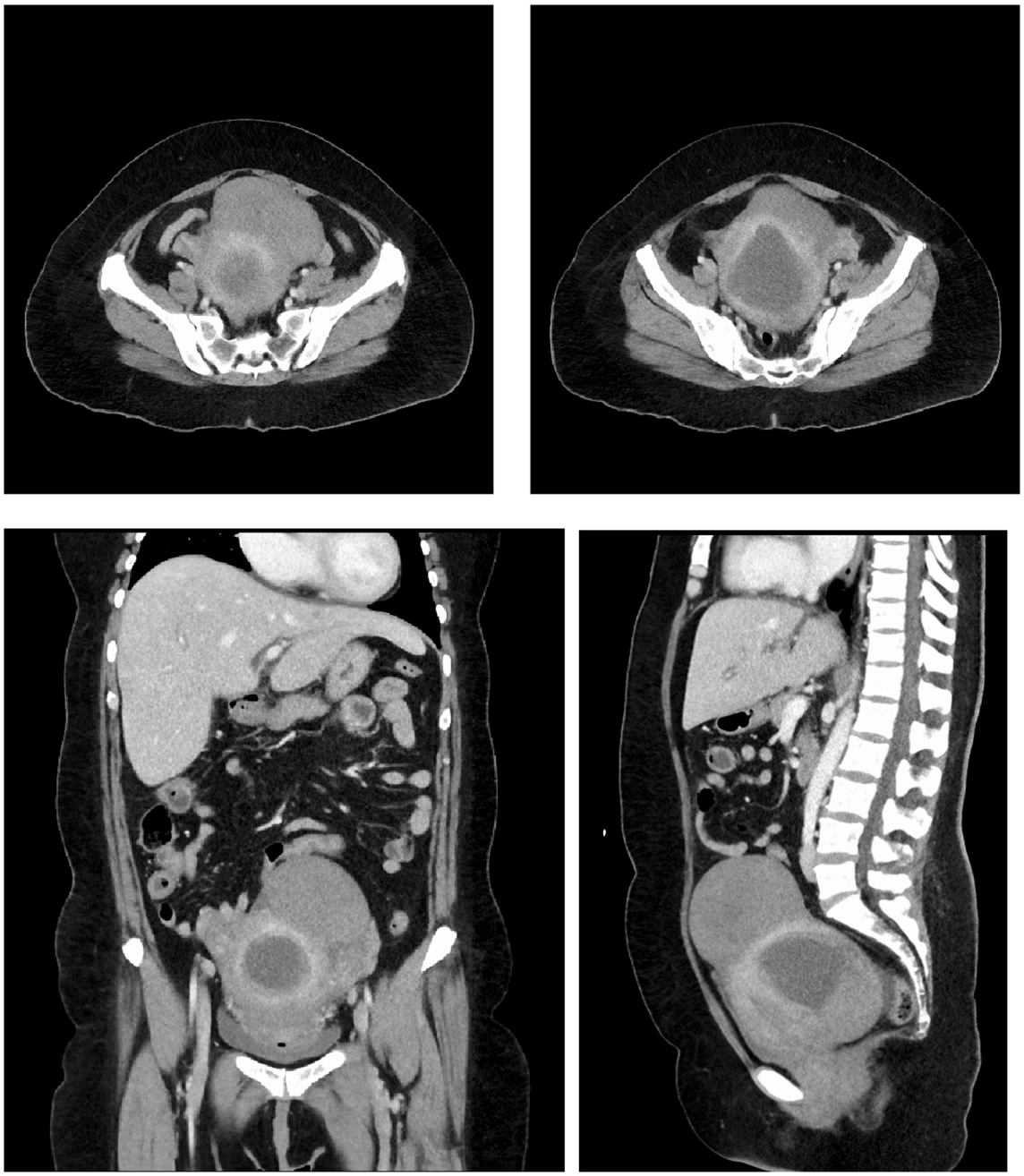

Fig. 1. A-D. CT of the abdomen and pelvis demonstrating fibroid uterus with expanded endometrial cavity and 4 cm hyperdensity.

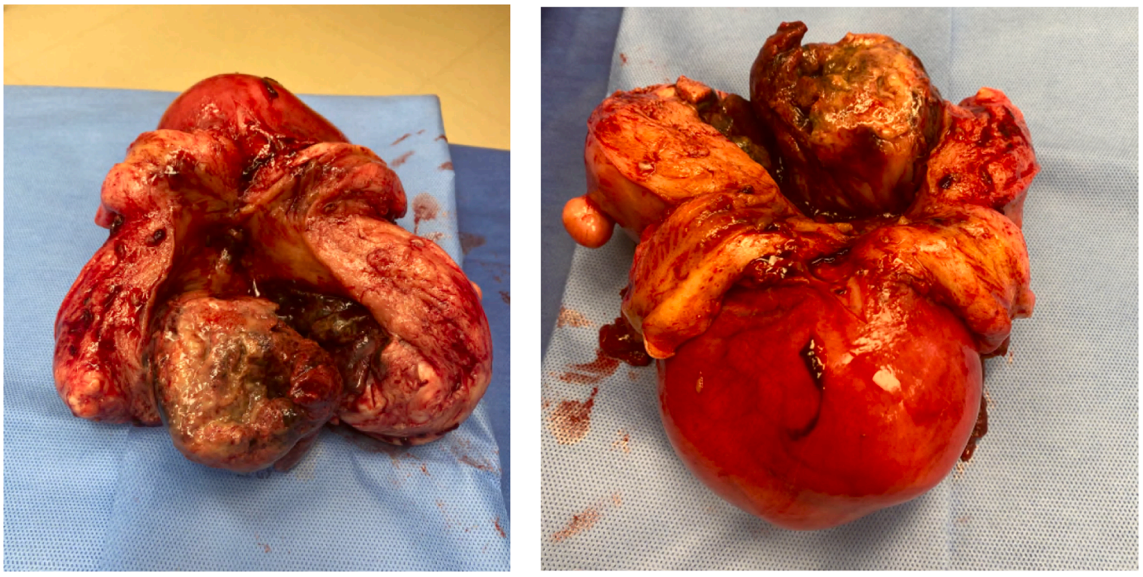

Fig. 2. A-B. Surgical specimen – uterus and necrotic uterine mass.

decreasing and the patient's urine output had increased significantly. She was extubated in the operating room.

She was transferred to Surgical Intensive Care Unit (SICU) for post-operative care. She was able to be completely weaned off vasopressors within 15 h post-operatively. Initial blood cultures drawn upon presentation resulted as *Clostridium* species and *Bacteroides vulgatus*. Antibiotics were narrowed to ampicillin-sulbactam and clindamycin. Patient did well post-operatively. She was transferred out of SICU on post-operative day number 3. She was meeting all post-operative milestones by post-operative day number 7. She was maintained on IV antibiotics until post-operative day 12, when her white blood cell count eventually normalized. She was discharged home in stable condition with a wound-vac and plan for 7 day course of amoxicillin-clavulanate and metronidazole. Surgical pathology resulted as a pT1a carcinosarcoma with 9 % myometrial invasion. She was presented at a multidisciplinary tumor board and the decision was made to proceed with adjuvant carboplatin, paclitaxel and vaginal brachytherapy.

3. Discussion

Clostridium is a Gram-positive, spore-forming anaerobe that has previously be 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 large 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 (Halpin 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-ileal fistula	Recovered, received subsequent chemotherapy
2022	Imo	1	Clostridium, bacteroides vulgatus	pT1a carcinosarcoma of the uterus	Antibiotics (vancomycin, piperacillin-tazobactam; meropenem; outpatient amoxicillin-clavulanate 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 Spirtos:** 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.

References

Arnold, Z., Wiggins, A., Santos, R.L., Breighner, C., 2020. *Bacteroides* bundle of joy: sepsis from a degenerating/necrotic fibroid. BMJ Case Rep. 13 (8), e237811.

Barrett, J.P., Whiteside, J.L., Boardman, L.A., 2002. Fatal clostridial sepsis after spontaneous abortion. Obstet. Gynecol. 99 (5 Pt 2), 899–901.

Braverman, J., Adachi, A., Lev-Gur, M., Fallen, S., Rosenzweig, M., Greston, W.M., Kleiner, G.J., 1987. Spontaneous clostridia gas gangrene of uterus associated with endometrial malignancy. Am. J. Obstet. Gynecol. 156 (5), 1205–1207.

Chong, E., Winikoff, B., Charles, D., Agnew, K., Prentice, J.L., Limbago, B.M., Platais, I., Louie, K., Jones, H.E., Shannon, C., NCT01283828 Study Team, 2016. Vaginal and rectal clostridium sordellii and clostridium perfringens presence among women in the United States. Obstet. Gynecol. 127(2), 360–368.

Cohen, A.L., Bhatnagar, J., Reagan, S., Zane, S.B., D'Angeli, M.A., Fischer, M., Killgore, G., Kwan-Gett, T.S., Blossom, D.B., Shieh, W.J., Guarner, J., Jernigan, J., Duchin, J.S., Zaki, S.R., McDonald, L.C., 2007. Toxic shock associated with Clostridium sordellii and Clostridium perfringens after medical and spontaneous abortion. Obstet. Gynecol. 110 (5), 1027–1033.

Halpin, T.F., Molinari, J.A., 2002. Diagnosis and management of clostridium perfringens sepsis and uterine gas gangrene. Obstet. Gynecol. Surv. 57 (1), 53–57.

Kremer, K.M., McDonald, M.E., Goodheart, M.J., 2017. Uterine *Clostridium perfringens* infection related to gynecologic malignancy. Gynecol. Oncol. Rep. 21 (22), 55–57.

Kurashina, R., Shimada, H., Matsushima, T., Doi, D., Asakura, H., Takeshita, T., 2010. Spontaneous uterine perforation due to clostridial gas gangrene associated with endometrial carcinoma. J. Nippon Med. Sch. 77(3), 166–169.

Lacey, C.G., Futoran, R., Morrow, C.P., 1976. Clostridium perfringens infection complicating chemotherapy for choriocarcinoma. Obstet. Gynecol. 47 (3), 337–341.

Lichtenberg, E.S., Henning, C., 2004. Conservative management of clostridial endometritis. Am. J. Obstet. Gynecol. 191 (1), 266–270.

Pezzicoli, G., Moscaritolo, F., Silvestris, E., Silvestris, F., Cormio, G., Porta, C., D'Oronzo, S., 2021. Uterine carcinosarcoma: An overview. Crit. Rev. Oncol. Hematol. 163, 103369.

Santin, A.D., Bellone, S., Siegel, E.R., McKenney, J.K., Thomas, M., Roman, J.J., Burnett, A., Tognon, G., Bandiera, E., Pecorelli, S., 2007. Overexpression of Clostridium perfringens enterotoxin receptors claudin-3 and claudin-4 in uterine carcinosarcomas. Clin. Cancer Res. 13 (11), 3339–3346.

Shetty, P., Deans, R., Abbott, J., 2010. A case of Clostridium perfringens infection in uterine sarcoma. Aust. N. Z. J. Obstet. Gynaecol. 50 (5), 495–496.

Symonds, R.P., Robertson, A.G., 1978. Clostridium welchii septicaemia after intrauterine caesium insertion. Br. Med. J. 1 (6115), 754–755.

Wexler, H.M., 2007. Bacteroides: the good, the bad, and the nitty-gritty. Clin. Microbiol. Rev. 20 (4), 593–621.