Diagnosis and Treatment of Appendiceal Mucormycosis

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Background	We present a case of appendiceal mucormycosis treated with prompt surgical and medical intervention, in a 21-year-old female who was immunosuppressed due to chemotherapy for recent relapse of acute myelogenous leukemia (AML). Appendiceal mucormycosis is a rare fungal infection typically diagnosed in patients who are neutropenic secondary to chemotherapy for a hematological malignancy. Patients may present with symptoms indicative of bacterial appendicitis. A non-surgical approach is sometimes taken due to severe neutropenic state and low counts of other blood lines. A surgical approach is often needed to eradicate the infection.
Summary	The patient underwent a laparoscopic appendectomy for presumed acute appendicitis secondary to bacterial infection. The pathology of the specimen was consistent with mucormycosis of the appendix with positive margins. She was placed on IV antifungals. A postoperative Computed Tomography (CT) scan showed findings concerning for spread of the mucormycosis and she underwent a more extensive surgical debridement. She continued to decompensate and died approximately four weeks after the initial presentation.
Conclusion	Mucormycosis is a rare and aggressive infection most commonly diagnosed in immunosuppressed patients. A high mortality rate is associated with this infection, and mortality increases in the setting of disseminated infection. Antifungals and an early surgical approach are required to prevent dissemination of the infection.
Keywords	Appendiceal mucormycosis, acute myelogenous leukemia

DISCLOSURE:
The authors have no conflicts of interest to disclose.

To Cite: Krupa KM, Tomsic JP. Diagnosis and Treatment of Appendiceal Mucormycosis. *ACS Case Reviews in Surgery.* 2018;2(2):54-58.

Case Description

Mucormycosis is a severe fungal infection caused by subphylum Mucoromycotina, order Mucorales. Common genera include *Rhizopus*, *Mucor*, *Rhizomucor*, and *Lichtheimia,*[1] which rarely cause infection of the appendix; however, with dissemination these carry a high mortality rate. Infection commonly presents in patients who are immunosuppressed and neutropenic.[2] There are only a few cases of appendiceal mucormycosis reported in the medical literature. Here we present a case of appendiceal mucormycosis in a 21-year-old female who was diagnosed with relapsing acute myelogenous leukemia (AML) and underwent chemotherapy.

The patient was initially diagnosed with AML at 19 years old and at high risk with complex cytogenetics and PHF6 molecular mutation. She underwent induction with cytarabine and anthracycline (7+3 regimen) followed by two cycles of high-dose cytarabine and anthracycline (HidAC) and proteolysis inducing factor. At 21 years old, she relapsed and had reinduction with cladribine and cytarabine. She underwent a mismatched, unrelated donor, peripheral blood stem cell transplant with fludarabine, busulfan, and total body irradiation (FLUBUTBI) and posttransplant cyclophosphamide. Over the course of her treatment, she developed infectious complications. She was placed on voriconazole and acyclovir prophylaxis. Voriconazole was discontinued due to bone pain with periosteal reaction. The patient had a subsequent relapse and was placed on induction with mitoxantrone, etoposide, and an intermediate dose cytarabine (MEC) for six cycles. She presented three days post-induction to our hospital with a one-day history of bilateral lower quadrant abdominal pain, nausea, and loss of appetite. Vitals were stable and she was afebrile. Laboratory findings were significant for leukopenia with neutropenia, with a white blood cell count (WBC) of 0.11 and thrombocytopenia with platelets 26. Computed tomography (CT) scan of abdomen/pelvis revealed focal cecal wall thickening along the lateral wall of the cecum extending to the appendiceal origin, dilated proximal appendix with mucosal hyperenhancement in the mid and distal appendix, and mild stranding present in the periappendiceal fat, consistent with acute appendicitis with reactive cecal wall thickening (Figure 1 and Figure 2).

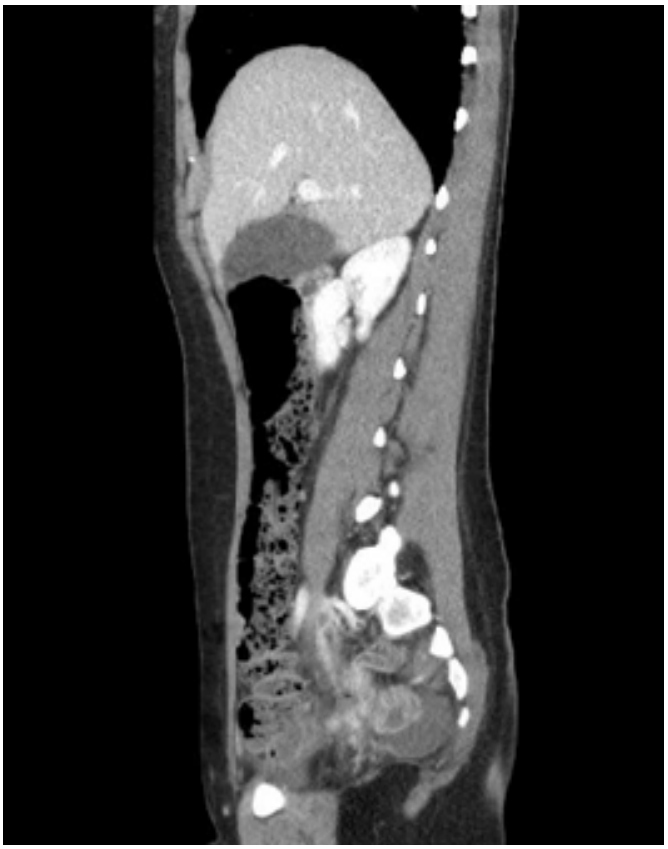

Figure 1. CT abdomen/pelvis consistent with appendicitis. Sagittal scan showing inflamed appendix with reactive cecal wall thickening.

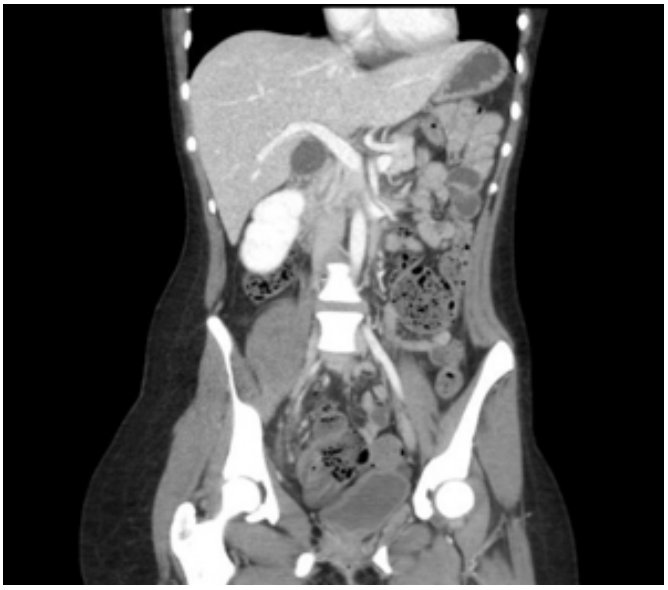

Figure 2. CT abdomen/pelvis consistent with appendicitis. Coronal scan showing inflamed appendix with reactive cecal wall thickening.

A multidisciplinary discussion about surgical and non-surgical options was conducted. The conclusion was to pursue a more aggressive surgical approach with laparoscopic appendectomy, due to impending rupture of the appendix. The patient received one unit of platelets before and one more unit during surgery. Intraoperative findings included necrosis at the midportion of the appendix with inflammation distally. The abdominal wall that the appendix was in contact with appeared inflamed. The proximal portion of the appendix and cecum appeared healthy. The patient tolerated the surgery well. Pathology of the specimen was consistent with mucormycosis of the appendix with positive margins (Figure 3).

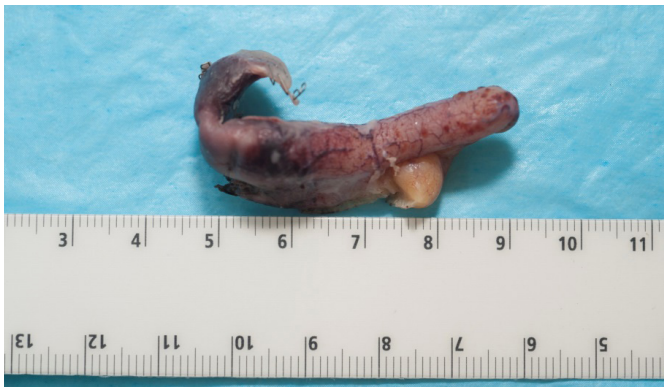

Figure 3. Gross appendix. Necrosis at midportion of appendix.

Per the infectious diseases service recommendations, the patient was placed on liposomal Amphotericin B, IV micafungin and oral posaconazole. Further imaging was obtained to assess dissemination of mucormycosis. CT head and sinus did not show dissemination. CT abdomen/ pelvis showed inflammation of the right lower quadrant and the bladder, concerning for mucormycosis (Figure 4 and Figure 5).

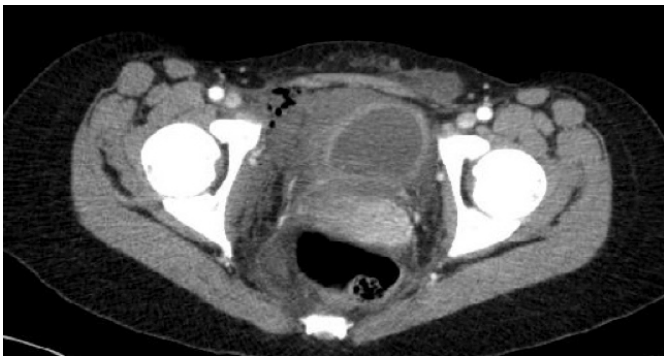

Figure 4. CT abdomen/ pelvis concerning for disseminated mucormycosis. Inflamed and thickened bladder.

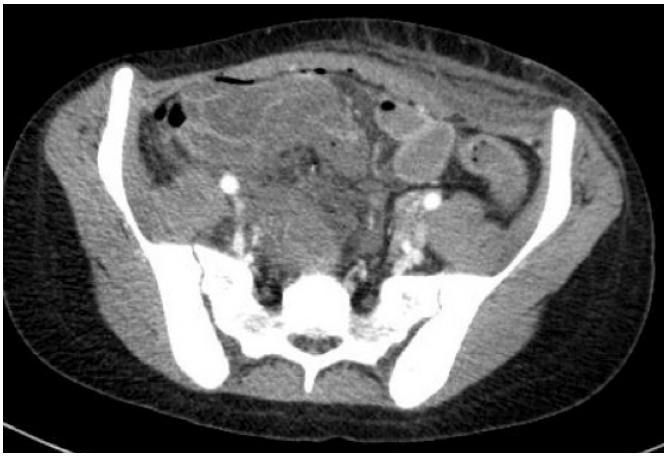

Figure 5. CT abdomen/ pelvis concerning for disseminated mucormycosis. Inflammation of the right lower quadrant and cecum.

On postoperative day four, she underwent an exploratory laparotomy for aggressive surgical debridement to give the best chance of halting spread of the disease. Intraoperative findings included: fungal infection of the skin, subcutaneous tissue and muscle fascia of the abdominal wall around the umbilicus; fungal infection involving the terminal ileum and cecum; 4 cm involvement of fungal infection of the descending colon; 4–5 cm area of fungal infection at the rectosigmoid junction; fungal infection involving the right ovary and the right half of the uterus; fungal infection involving the right portion of the bladder wall. At this time, a total abdominal colectomy with end ileostomy was performed. Gynecology was consulted intra-operatively and it was decided to not perform a total abdominal hysterectomy and cystectomy at this juncture, so as to allow a discussion with the patient and family about risks, benefits, and quality of life. The patient decided to not pursue more surgical debridement due to high likelihood of not surviving the surgery, in her acute neutropenic state. Zosyn was added to her antibiotic regimen and she was placed on

a granulocyte infusion of sargramostim. She underwent two of seven hyperbaric oxygen (HBO) treatments to try to limit fungal proliferation and decompensated. She was discharged with home hospice. She died four weeks after initial laparoscopic appendectomy surgery.

Discussion

Mucormycosis is a rare, but life threatening, angioinvasive fungal infection that affects immunocompromised patients. This includes patients undergoing chemotherapy for hematological malignancies and transplant recipients on chronic immunosuppression. It also affects patients who are malnourished and most commonly affects the pulmonary and rhinocerebral systems. Rarely, the gastrointestinal system is involved, with the stomach being the most common, followed by colon and small bowel; the rate of GI involvement is 3 to 7 percent.[2, 4] Notably, infection of the appendix is extremely rare. GI mucormycosis infections develop through the breakdown of the gastrointestinal mucosa, allowing cells or spores to infiltrate. Fungus then grows in the vasculature and thus can spread to other organs, including the liver and lungs. Dissemination via the vasculature additionally causes thrombosis, infarction, and hemorrhage.[4] In its disseminated form, the mortality rate of Mucormycosis approaches 95 percent.[3]

Symptoms of appendiceal mucormycosis are similar to bacterial appendicitis which includes fever, diarrhea, nausea and abdominal pain. The presentation may also be confused with typhlitis, which is managed conservatively with antibiotics. CT imaging shows thickening of the bowel wall that over time develops into bowel wall thinning and necrosis.[2] Among patients with hematological malignancies undergoing treatment, those diagnosed with AML are at the highest risk of developing mucormycosis (1 to 1.9 percent in AML compared to 0.1 percent, respectively).[1] Treatment of mucormycosis involves early surgical and medical treatment. Guidelines from the Third European Conference on Infections in Leukemia (ECIL 3) recommend liposomal amphotericin B as the initial treatment, as the liposomal formulation has less nephrotoxicity. Liposomal amphotericin B can be used in combination with posaconazole for patients who are refractory or intolerant to liposomal amphotericin B. A systematic review performed by ECIL 3, examined 929 published cases between 1885 and 2005 (200 years), and found that patients treated with surgery and antifungal therapy had significantly improved mortality rates compared to those treated with surgery only or liposomal amphotericin B only (70 percent vs 61 percent vs 57 percent, respectively).[1, 5] In neutropenic patients, ECIL 3 recommends the use of granulocyte colony-stimulating factor (G-CSF), granulocyte macrophage colony-stimulating factor (GM-CSF), and interferon-gamma (IFN-gamma) to increase the amount of polymorphonuclear leukocytes and macrophages, improving the immune defense against mucormycosis.[1] The diagnosis of mucormycosis is established by pathology, which shows aseptate, wide hyphae branching at right angles.[2] Mucormycosis is rarely diagnosed preoperatively, which results in delay in proper treatment.

There are very few case reports of Mucormycosis involving the appendix. Akhilesh et al described a case of a 14-year-old boy diagnosed with AML on induction therapy who developed acute appendicitis. Due to severe neutropenia and thrombocytopenia the patient was managed non-operatively with antibiotics. Subsequently the patient deteriorated, and he underwent a laparoscopic appendectomy. The infection spread throughout his body and the patient died on postoperative day six.

Guymer et al[3] reported a case of an 11-year-old female diagnosed with T-cell acute lymphoblastic leukemia. She was receiving delayed intensification chemotherapy and developed disseminated Mucormycosis of the kidney, brain, pancreas, lung, kidney and appendix. She underwent aggressive medical treatment with antifungals and surgical debridement. She survived due to early treatment and quick recovery of her immune system after her chemotherapy was held.

Larbcharoensub et al[6] performed a case series and found that in 262 appendices resected for acute appendicitis, three of them (1.15 percent) were infected with fungal organisms. All three patients presented with signs of acute appendicitis and were immunocompromised; two of the three patients died due to fungal dissemination.

Borg et al[7] presented a patient who underwent chemotherapy for acute T-lymphoblastic leukemia and developed a fatal case of mucormycosis of the appendix with dissemination to the liver.

In the appropriate clinical setting, early surgical intervention and medical management are mandatory to provide the highest likelihood of survival The patient in our case report recently received chemotherapy, which likely caused a breakdown in her gastrointestinal mucosal allowing fungi to penetrate and proliferate.

Conclusion

Mucormycosis of the appendix is a rare illness that can present similar to bacterial appendicitis. Most commonly affected patients are those who are immunosuppressed. It is imperative to have a high index of suspicion in the appropriate patient population and promptly perform surgical debridement and medical treatment to prevent dissemination of disease which carries a high mortality rate.

Lessons Learned

Mucormycosis is a rare disease but carries a high mortality. It should be kept in the differential of intraabdominal pathology in an immunosuppressed patient. Early aggressive treatment including antifungals and surgery provide the best chance of survival.

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