

Mucor Appendicitis Resolution Following Surgical Excision Without Antifungal Therapy

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KEY WORDS: appendicitis, mucormycosis, neutropenic fever

IMAJ 2018; 20: 592–593

Mucormycosis is an invasive fungal disease usually found in immunocompromised patients. Predisposing factors include neutropenia, defects in phagocytic activity, diabetes mellitus, corticosteroids use, malignant hematologic disorders, organ or stem cell transplants, acidosis, increased available serum iron, trauma, and burns. *Rhizopus* species (with *R. oryzae* the most common) are the most common causes of mucormycosis [1]. Gastrointestinal mucormycosis is a rare presentation of the disease [1] and might be caused by ingestion of contaminated food or even pharmaceutical products [2]. The main therapy includes surgical debridement and antifungal drugs. The mortality rate is high, especially in patients with disseminated disease or with persistent neutropenia [1].

PATIENT DESCRIPTION

A 19 year old male with extraskeletal Ewing's sarcoma was admitted to the hospital 11 days after completing his last course of chemotherapy due to fever of 1 day duration, neutropenia, and abdominal pain. Eighteen months earlier, he underwent

surgical removal of a 1 cm subcutaneous chest wall mass that had been present for 2 years. Pathologic examination showed a small round blue cell tumor, immunohistochemically positive for CD99. Reverse transcription polymerase chain reaction (RT-PCR) for t(11;22)(q24,q12)(EWS-FLI1) was positive. A diagnosis of extraskeletal Ewing's/PNET sarcoma was made.

The bone marrow was uninvolved. Magnetic resonance imaging did not reveal any residual disease at the surgical site, and whole body positron emission tomography-computed tomography (PET-CT) was within normal limits. Following surgery, he started chemotherapy with VAC/IE protocol (vincristine, doxorubicin, cyclophosphamide, ifosfamide, and etoposide) with support of neutostim with no complications.

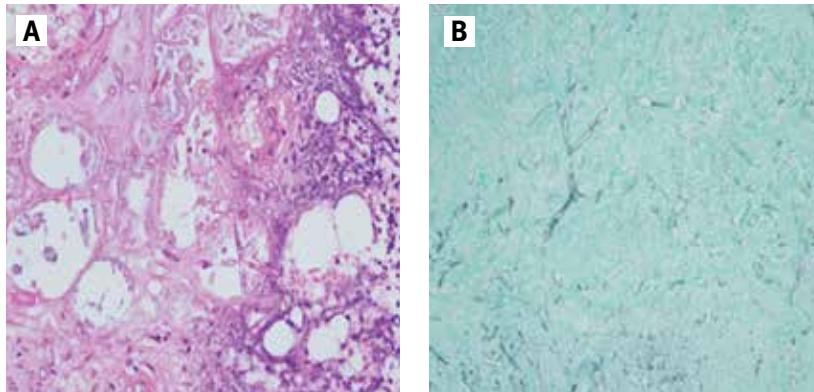
After six cycles, a surgical re-wide excision was performed on the scar and no tumor was found. He completed three more cycles of chemotherapy with no complications. He had no other past medical history. He was taking vitamin D and prophylaxis therapy with sulfamethoxazole/trimethoprim.

On admission, physical exam was unremarkable. The white-cell count was 600/ μ l, with neutropenia of 300/ μ l. His hemoglobin level was 10.5 gr/dl and the platelet count 118/ μ l. Peripheral and central blood cultures, as well as urine culture, were negative. He was admitted to the pediatric hemato-oncology department. Antibiotic therapy

with piperacillin/tazobactam and amikacin was started. On day 3, right lower quadrant abdominal pain was reported. Findings on abdominal sonography were compatible with acute appendicitis and an appendectomy was performed. At the time of surgery, his hemoglobin was 9.8 gr/dl, absolute neutrophil count 400/ μ l, and platelet count 99/ μ l. The appendix was sent for pathologic exam, with samples sent for culture.

After surgery, he was treated with piperacillin/tazobactam for 7 days and was discharged to home uneventfully. His absolute neutrophil count 9 days after surgery was 9000/ μ l. In pathology, on gross examination, the appendix was mildly hyperemic, measuring 4.6 cm in length and 1 cm in its maximal diameter. The submucosa of the appendix was infiltrated by fungi with broad non-septate hyphae, consistent with invasive *Mucor* infection. Hyphae were also seen infiltrating the submucosal blood vessels walls. PAS and GMS (silver) stains for fungal hyphae were positive [Figure 1]. A diagnosis of *Mucor* appendicitis was made. The oncologists were alerted to this diagnosis only a month after the patient's discharge from the hospital. A PET-CT that was conducted 2 weeks after discharge showed no evidence of residual tumor and he was considered cured with no need for further chemotherapy. The cultures from the appendix were negative. A CT-angiogram of the abdomen was within normal limits. A PCR test for fungal DNA was performed on the paraffin embedded sections and the

Figure 1. [A] The photomicrograph demonstrates *Mucor* hyphae within the submucosa of the appendix on H&E stain [B] On silver stain, hyphae stains are dark and well demarcated



DNA sequence had > 99% identity with *R. microsporus*. After a discussion of the case among the infectious diseases, oncology, and pathology physicians, taking into consideration that the patient was doing well and the imaging studies were unremarkable, it was decided to continue follow-up with no further treatment. Eighteen months after surgery, the patient was doing well and continued follow-up visits.

COMMENT

Antifungal treatments, as well as surgical debridement, have been shown to increase survival in patients with mucormycosis infection [1]. Interestingly, in two studies, 57% and 56% of the patients who received surgery alone survived [1]. In a recent report, only one out of six patients with symptomatic appendix infection survived [2], even after receiving both surgical and antifungal treatment. None of the previously reported cases of *Mucor* appendicitis resolved following surgical treatment alone [2-5]. Surprisingly, our patient had complete and rapid recovery following surgical removal of the appendix, without any antifungal treatment.

Several factors might have contributed to our case's unique feature. The patient was a young adult with no other co-morbidities. His main predisposing factor for *Mucor* infection was the chemotherapy-related neutropenia, which was transient,

as expected. Neutrophils have a critical role in controlling *Mucor* infection and neutropenia is a known major risk factor for the disease. After the neutrophil count is restored, the natural host's defense mechanism can effectively control the infection.

This case demonstrates that reversal of the predisposing condition, if possible, is the most important aspect of treatment. Also, in this case, the infection was localized to the appendix without perforation or local peritonitis. No spreading beyond the appendix occurred and thus surgery alone, in addition to the transient nature of the neutropenia, was adequate with no need for further systemic therapy. Previous reports of patients with *Mucor* appendicitis, which had a perforation or extension to other organs, either died or survived after combined surgical and antifungal therapy [2-5].

Another factor with potential effect on the clinical course was the pathogen's virulence. In their epidemiological study, Roden and colleagues [1] showed that there are differences in virulence between different species, with *Cunninghamella bertholletiae* causing the highest mortality rate (76% vs. 64% for *R. microsporus*). *R. microsporus* is a rare cause of *Mucor* infection in humans [1]. It has virulence factors, including the *FTR1* (high affinity iron permease) gene and rhizoferrin that are similar to those present in the more common pathogen *R. oryzae* and therefore, *R. microsporus* is

not expected to be less virulent. Moreover, a previous case series [2] reported several cases of death from gastrointestinal *R. microsporus* infection highlighting its association with significant risk of death. Thus, it appears that the host characteristics of our case (age, lack of co-morbidities, transient immunosuppression, and a disease that is localized to an organ that can be easily excised), and not the specific subspecies of the pathogen, were responsible for his favorable clinical course.

CONCLUSIONS

To the best of our knowledge, this case report is the first one of *Mucor* appendicitis that was treated by surgery and antibiotics alone, without antifungal therapy, that resolved uneventfully. It also points to the importance of considering uncommon pathogens as a cause of a common disease presentation like appendicitis, especially in immunocompromised patients with neutropenia. Further investigation of the epidemiology of *Mucor* appendicitis, specifically the incidence, risk factors, survival rates comparing different species, different patient characteristics, and different therapy approaches, is needed.

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