American Journal of Clinical Cancer Research

American Journals of Clinical Cancer Research
http://ivyunion.org/index.php/ajcre
Vol. 1, Article ID 20130200151, 6 page

Case Report

Toxic Megacolon and Perforated Fungal Diverticulitis due to *Mucor indicus* Infection in a Patient with Chronic Myelogenous Leukemia

Qing Zhao[1], Xiang-Yang Han[2], Aparna Balachandran[3] Huamin Wang[1]

[1]Department of Pathology, The University of Texas MD Anderson Cancer Center, United States

[2]Department of Laboratory Medicine, The University of Texas MD Anderson Cancer Center, United States

[3]Department of Diagnostic Radiology, The University of Texas MD Anderson Cancer Center, United States

Abstract

Introduction: Intestinal zygomycosis is a rare infection by the fungi zygomycetes that have little intrinsic pathogenicity in normal hosts and mainly affects immune compromised patients. *Mucor indicus* is a rare, emerging cause of intestinal zygomycosis with only 8 reported cases in English literature since 1986.

Presentation of Case: We reported an unusual case of toxic megacolon, fungal diverticulitis with perforation and liver abscesses caused by *Mucor indicus* in a patient with chronic myelogenous leukemia (CML), B-lymphoid blast crisis and pancytopenia. The patient was treated with total colectomy and aggressive systemic anti-fungal regimens consisting of amphotericin, caspofungin and posaconazole. However, his fungal abscess in the liver persisted after colectomy, which was confirmed by liver biopsy at four months after total colectomy. His CML and B-lymphoid blast crisis was successfully treated with hyper-CVAD plus dasatinib and had been in complete remission. The patient was alive and continued to have stable fungal infection in the liver based on CT scan at 32 months after total colectomy, for which he has been on posaconazole monotherapy.

Conclusions: Mucor indicus may cause a rare invasive zygomycosis that tends to involve gastrointestinal tract and to disseminate to the liver.

Keywords: Zygomycosis; Mucor indicus; Chronic myelogenous leukemia; Acute fungal diverticulitis; Toxic megacolon

Peer Reviewers: Carlos E. Paiva, PhD,Medical Oncology Department, Barretos Cancer Hospital, Brazil

Academic Editor: Xiaoning Peng, PhD, Department of Internal Medicine, School of Medicine, Hunan Normal University, China

Received: May 9, 2013; **Accepted**: September 30, 2013; **Published:** October 19, 2013

Competing Interests: The authors have declared that no competing interests exist.

Consent: Informed consent obtained and was approved by the institutional review board.

*Correspondence to: Huamin Wang, Department of Pathology, The University of Texas MD Anderson Cancer Center. Email: hmwang@mdanderson.org

Introduction

Zygomycosis is a fungal infection that can occur either in patients with no predisposing conditions immune compromised patients with hematologic malignancies, transplantation receiving immunosuppressive therapy, children with malnutrition, and patients with ketoacidotic diabetes, renal or heart failure. Based on the common isolates, zygomycosis represents infections by the class *zygomycetes*, which the genera of *Absidia*, *Mucor*, *Rhizomucor*, *Rhizopus*, *Cunninghamella*, *and others* [1]. *Mucor indicus* is a rare, emerging cause of zygomycosis with only 8 cases previously reported in the literature. Interestingly, five such patients with *Mucor indicus* presented with pain or acute gastric bleeding, and the primary site of infection was found to be in the stomach, cecum, appendix or liver. To our knowledge, toxic megacolon and acute diverticulitis caused by *Mucor indicus* has not been reported. Here we reported a case of toxic megacolon and acute diverticulitis with perforation caused by *Mucor indicus* in a 60 year-old male, who had chronic myelogenous leukemia (CML), B-lymphoid blast crisis and severe pancytopenia.

Presentation of the Case

A 60-year-old male rancher, who initially with fatigue, weight loss and splenomegaly, was diagnosed with chronic myelogenous leukemia (CML) with philadelphia chromosome (Ph+) and BCR-ABL translocation [t(9:22)] in January of 2008. He received induction chemotherapy with good response to nilotinib (400 mg daily) and remained asymptomatic. He had persistent grade 2 thrombocytopenia (platelet count: 62,000/μl) and was slightly neutropenic one year after chemotherapy. His CML progressed to an accelerated blast phase (12% blast in bone marrow) and further into B-lymphoid blast crisis (62% in bone marrow), for which he was treated with hyper-CVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone) and nilotinib treatment for nine months.

During the blast crisis, the patient had one episode of fever and chills with accompanying abdominal pain. He was treated with unknown antimicrobials for presumed diverticulitis and his symptom resolved subsequently. Two weeks after initial antibiotics treatment, he had a repeated episode of fever and chill with an elevated liver functional test (ALT 218 IU/L, AST 163 IU/L, total bilirubin 10.7 mg/dL, alkaline phosphatase 294 IU/L), neutropenia (white blood cell count: 4900/μl with 142/μl neutrophils), anemia, and thrombocytopenia (platelet count 49,000/μl) that required a platelets transfusion. He was admitted to our hospital and was found to have *E. coli* bacteremia. His symptoms resolved after being treated with linezolid, tigecycline, tobramycin, voriconazole, and valacyclovir. He was discharged afebrile and asymptomatic and continued on antibiotics. Within one week after discharge, the patient was readmitted to the hospital with worsening abdominal pain, recurrent fever, diarrhea, and dysuria. Computed tomography (CT) of the abdomen and pelvis showed diffuse bowel thickening of sigmoid colon with pelvic abscess, suggestive of acute diverticulitis with perforation of the sigmoid colon. The perforation was confined within the pelvis and there was no free air in the peritoneal cavity. The abscess was located between the sigmoid colon and urinary bladder, which accounts for the bladder spasms and dysuria. The CT scan also showed possible microabscesses in the liver and spleen. Cultures were obtained by percutaneous fine needle aspiration from abdomen, which revealed polymicrobial infection with fungal hyphae identified. The patient was persistently febrile and became more distended with diffuse tenderness of abdomen. An emergency exploratory laparotomy was performed. Segmental sigmoid colon resection and subsequent total colectomy with surgical debridement were performed.

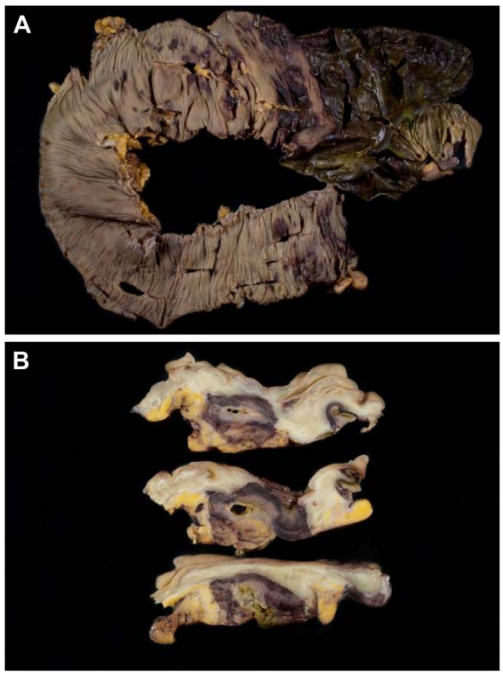

Figure 1 A. Gross photo of formalin fixed extended right hemicolectomy shows the toxic megacolon and transmural necrosis involving the cecum and proximal ascending colon with many hemorrhagic ulcers. B. Representative cross sections of the perforated fungal diverticulitis in the sigmoid colon.

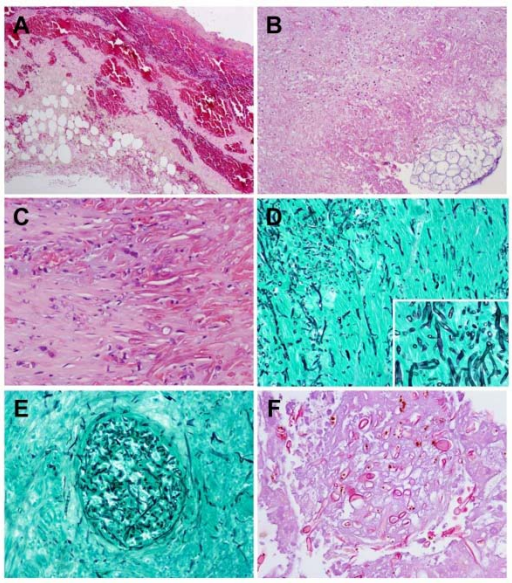

Figure 2 Representative micrographs show transmural necrosis with hemorrhage (A & B). Numerous fungal hyphae present in the wall of colon involved by toxic megacolon (C). D and E, representative micrographs show numerous irregularly shaped, broad non-septate hyphae with the right angle branching (D, insert) in the colonic wall and invading the blood vessels. Fungal culture and identification confirmed infection by *Mucor incidus*. F. Periodic acid-Schiff (PAS) stain for fungus show the fungal hyphae in the needle core biopsy of liver abscess 4 months after the total colectomy. Original magnifications: 40x for A and B; 100x for D and E; 400x for C, D insert and F.

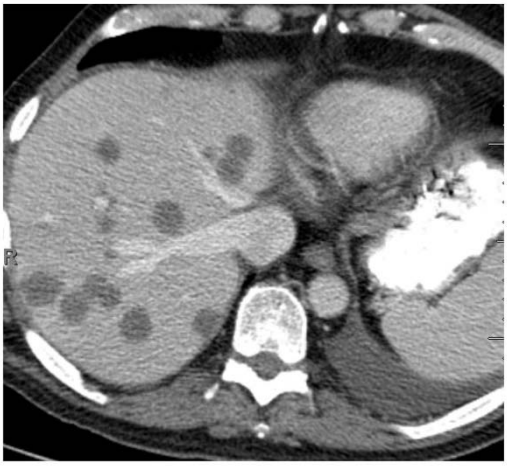

Figure 3 Representative Computed tomography (CT) scan image shows multiple liver abscesses at four months after surgery.

Gross examination showed toxic megacolon involving the cecum and proximal ascending colon with many shallow, hemorrhagic ulcers in the distal ascending and transverse colon (Figure 1A) and severe acute diverticulitis with perforation in the sigmoid colon (Figure 1B). Microscopic examination reveals numerous fungal hyphae invading the colonic wall and blood vessels with hemorrhage in the segment of toxic megacolon, hemorrhagic ulcer beds, and the area of acute diverticulitis. Invasive fungal hyphae involved the full thickness of colonic wall and pericolonic adipose tissue at the perforation site of the sigmoid colon and the segment of toxic megacolon. The fungal hyphae were broad, non-septated with a typical right-angle branching (Figure 2). Fungal culture from the debridement tissue and identification studies at the University of Texas San Antonio Health Science Center confirmed mucor species, *Mucor indicus*. Tissue culture also identified *candida albicans* mixed with multiple

gram-negative and gram positive bacteria, which is consistent with perforation. Postoperatively, the patient was doing well with anti-fungal therapy and hyper-CVAD therapy for the lymphoid blast phase of CML. Four months after surgery, CT scan revealed multiple liver lesions which increase in size during the follow-up (Figure 3). Needle core biopsies of the liver lesion showed liver abscess with fungal hyphae morphologically consistent with *Mucor indicus* as seen in the toxic megacolon. The patient received extended combination antifungal therapy of amphotericin, caspofungin and posaconazole for 21 months after total colectomy. He has now been on monotherapy with posaconazole for the last 11 months. The patient continued to have stable disease in the liver based the CT scan. His CML and B-lymphoid blast crisis was successfully treated with hyper-CVAD plus dasatinib and is now in complete remission. At the last follow-up, the patient's blood count was the following: hemoglobin 10.5 grams/dL; white blood cell count of 4100/μL with 53.4% of neutrophils, 27.3% of lymphocytes and 0.2% of immature ganulocytes; platelet of 58000/uL. BCR-ABL quantitative PCR show a BCR-ABL to ABL transcript ratio of <0.01. The bone marrow biopsy showed normocellular bone marrow with 30% cellularity, mild dyserythropoiesis and megakaryocytic hypoplasia and no morphologic evidence of CML. The patient is alive at 32 months after the total colectomy.

Discussion

Intestinal zygomycosis is an extremely rare invasive fungal infection mainly seen in patients with hematological malignancies, particularly in patients with therapy-induced neutropenia. It is the third most common cause of fungal infection after candidiasis and aspergillosis [2, 3]. The diagnosis of zygomycosis is rarely suspected and antemortem diagnosis is made in only 23–50% of cases [4]. Early medical and surgical intervention is critical to prevent fatality. Our patient had CML with lymphoid blast phase and pancytopenia. He presented with acute abdomen due to perforated diverticulitis and toxic megacolon secondary to invasive M*ucor indicus* infection.

It is believed that severe neutropenia poses the major risk for fungal infection when the absolute white blood cells counts of less than 1000/μl for one week or longer in immunocompromised patients [5]. Once infection is established, neutrophils play a pivotal role in fighting fungal infections in the normal host. In patients with neutropenia, the mortality rate from all reported cases of gastrointestinal zygomycosis is 85% [6]. In 40% of the reported cases of gastrointestinal zygomycosis, the infection was disseminated to involve other organ systems and has a mortality rate close to 90% [7]. However, some patients may be cured by prompt surgical excision and effective anti-fungal treatment [1, 8]. Our patient was successful treated with total colectomy and antifungal treatment. Interestingly, he was found to have persistent disseminated infection of *mucor indicus* in the liver and spleen even after four months of anti-fungal therapy. To our knowledge, this is a first case of successfully treated intestinal mucomycosis in an immunosuppressed patient infected with *mucor indicus*, who had a complication of megacolon and disseminated fungal abscesses in both the liver and spleen. He is alive 32 months after colectomy with stable disease in the liver at the last follow-up. The remission of his CML, adequate WBC and antifugal treatment seems to contribute to the long-term suppression of the hepatic zygomycosis in our patient.

Among the reported patients with gastrointestinal zygomycosis, stomach is the most frequent site of involvement (60% of the cases), followed by colon (30% of the cases) and small intestine (30% of the cases) [4] [9] [10]. Unlike rhinocerebral zygomycosis, the sign and symptoms of gastrointestinal zygomycosis are obscured in many cases by the underlying disease. Gastrointestinal zygomycosis, especially in colorectum, also tends to disseminate to liver

through portal system with abscess formation [11] [12]. A high clinical suspicion is required for timely diagnosis. Our patient has a previous diagnosis of diverticulitis, which was initially successfully treated with broad-spectrum antibacterials. His granulocytopenia and the prolonged treatment with broad-spectrum antibiotics may contribute to the infection of *Mucor indicus*, which has been thought to be acquired through direct ingestion of the pathogen [13]. The ubiquitous air or food-borne fungal spores may germinate in previous enterocolonic ulcers.

Eight cases of human infection of *Mucor indicus* have been previous reported [6, 11, 13, 14], giving a total of nine cases including the present case. Five of these patients had predisposing conditions, including two patients with T-lymphoblastic leukemia or CML in B-lymphoblastic crisis and neutropenia, one with bone marrow transplant receiving prednisone for graft versus host disease, one with acute head injury and one patient with left ventricular assist device (LVAD). The remaining four patients had no known predisposing conditions. There were five male and four female patients with age ranging from 6 months to 82 years. Interestingly only two of these nine patients died of the infection, including one patient with both appendiceal and liver involvement and one patient with LVAD and involvement of heart and aorta. However, gastrointestinal zygomysosis caused by other species carries a fatality rate of 85% [6].

The diagnosis of gastrointestinal zygomycosis needs invasive procedure, biopsy and fungal culture. Endoscopy examination may show a black ulcer with deep red edges [14]. Biopsies from the edge of the ulcer are most likely to reveal fungi. The hyphae of zygomycosis are visible by routine hematoxylin-and-eosin (H & E) stain, Special stains such as periodic-acid-schiff (PAS) stain and the Gomori-methenamine silver (GMS) stain and fungal culture help to confirm the diagnosis. Amphotericin B remains the drug of choice, in conjunction with surgical resection.

Conclusions

Mucor indicus may cause a rare invasive zygomycosis that tends to involve gastrointestinal tract and to disseminate to liver through portal vein. High suspicion in patients with neutropenia, proper tissue or blood culture in conjunction with radiographic studies, prompt surgical resection and systemic antifungal therapy are essential in cure and management. The mortality of this fungal infection may be better than those caused by other species in general. The remission of CML, adequate WBC and antifugal treatment seems to contribute to the long-term survival and suppression of hepatic zygomycosis in our patient.

References

1. Ribes JA, Vanover-Sams CL, Baker DJ. Zygomycetes in human disease. ***Clin Microbiol Rev***. 2000, 13:236-301
2. Roden MM, Zaoutis TE, Buchanan WL, Knudsen TA, Sarkisova TA, Schaufele RL, Sein M, Sein T, Chiou CC, Chu JH, Kontoyiannis DP, Walsh TJ. Epidemiology and outcome of zygomycosis: A review of 929 reported cases. ***Clin Infect Dis***. 2005, 41:634-653
3. Pagano L, Caira M, Candoni A, Offidani M, Fianchi L, Martino B, Pastore D, Picardi M, Bonini A, Chierichini A, Fanci R, Caramatti C, Invernizzi R, Mattei D, Mitra ME, Melillo L, Aversa F, Van Lint MT, Falcucci P, Valentini CG, Girmenia C, Nosari A. The epidemiology of fungal infections in patients with hematologic malignancies: The seifem-2004 study. ***Haematologica***. 2006, 91:1068-1075
4. Pagano L, Ricci P, Tonso A, Nosari A, Cudillo L, Montillo M, Cenacchi A, Pacilli L, Fabbiano F, Del Favero A. Mucormycosis in patients with haematological malignancies: A retrospective clinical study of 37 cases.

Gimema infection program (gruppo italiano malattie ematologiche maligne dell'adulto). ***Br J Haematol***. 1997, 99:331-336

5. Brown AE. Overview of fungal infections in cancer patients. ***Semin Oncol***. 1990, 17:2-5
6. Karanth M, Taniere P, Barraclough J, Murray JA. A rare presentation of zygomycosis (mucormycosis) and review of the literature. ***J Clin Pathol***. 2005, 58:879-881
7. Suh IW, Park CS, Lee MS, Lee JH, Chang MS, Woo JH, Lee IC, Ryu JS. Hepatic and small bowel mucormycosis after chemotherapy in a patient with acute lymphocytic leukemia. ***J Korean Med Sci***. 2000, 15:351-354
8. Martinez EJ, Cancio MR, Sinnott JTt, Vincent AL, Brantley SG. Nonfatal gastric mucormycosis in a renal transplant recipient. ***South Med J***. 1997, 90:341-344
9. Michalak DM, Cooney DR, Rhodes KH, Telander RL, Kleinberg F. Gastrointestinal mucormycoses in infants and children: A cause of gangrenous intestinal cellulitis and perforation. ***J Pediatr Surg***. 1980, 15:320-324
10. Parfrey NA. Improved diagnosis and prognosis of mucormycosis. A clinicopathologic study of 33 cases. ***Medicine (Baltimore)***. 1986, 65:113-123
11. ter Borg F, Kuijper EJ, van der Lelie H. Fatal mucormycosis presenting as an appendiceal mass with metastatic spread to the liver during chemotherapy-induced granulocytopenia. ***Scand J Infect Dis***. 1990, 22:499-501
12. Meyer RD, Rosen P, Armstrong D. Phycomycosis complicating leukemia and lymphoma. ***Ann Intern Med***. 1972, 77:871-879
13. Oliver MR, Van Voorhis WC, Boeckh M, Mattson D, Bowden RA. Hepatic mucormycosis in a bone marrow transplant recipient who ingested naturopathic medicine. ***Clin Infect Dis***. 1996, 22:521-524
14. Parra R, Arnau E, Julia A, Lopez A, Nadal A, Allende E. Survival after intestinal mucormycosis in acute myelogenous leukemia. ***Cancer***. 1986, 58:2717-2719