References

1. Kauffman CA, Malani AN. Zygomycosis: an emerging fungal infection with new options for management. *Curr Infect Dis Rep*. 2007;9:435-440.
2. Spellberg B, Edwards J Jr, Ibrahim A. Novel perspectives on mucormycosis: pathophysiology, presentation, and management. *Clin Microbiol Rev*. 2005;18:556-569.
3. Roden MM, Zaoutis TE, Buchanan WL, et al. Epidemiology and outcome of zygomycosis: a review of 929 reported cases. *Clin Infect Dis*. 2005;41:634-653.
4. Agha FP, Lee HH, Boland CR, Bradley SF. Mucormycoma of the colon: early diagnosis and successful management. *Am J Roentgenol*. 1985;145:739-741.
5. Lawrence IC, Radford-Smith GL, Bampton PA, et al. Serious infections in patients with inflammatory bowel disease receiving anti-tumor-necrosis-factor-alpha therapy: an Australian and New Zealand experience. *J Gastroenterol Hepatol*. 2010;25:1732-1738.
6. D'Haens G, Colombel JF, Hommes DW, et al. Corticosteroids pose an increased risk for serious infection: an interim safety analysis of the ENCORE registry. *Gastroenterology*. 2008;34(suppl):A-140.
7. Korzenik JR. Is Crohn's disease due to defective immunity? *Gut*. 2007;56:2-5.
8. Vavricka SR, Rogler G. New insights into the pathogenesis of Crohn's disease: are they relevant for therapeutic options? *Swiss Med Wkly*. 2009;139:527-534.
9. Wall GC, Leman BI. Mucormycosis in a Crohn's disease patient treated with infliximab. *Digestion*. 2009;80:182-184.
10. Devlin SM, Hu B, Ippoliti A. Mucormycosis presenting as recurrent gastric perforation in a patient with Crohn's disease on glucocorticoid, 6-mercaptopurine, and infliximab therapy. *Dig Dis Sci*. 2007;52:2078-2081.
11. Hunter AJ, Bryant RE. Abdominal wall mucormycosis successfully treated with amphotericin and intraconazole. *J Infect*. 2002;44:203-204.
12. Hyvernat H, Dunais B, Burel-Vandenbos F, Guidicelli S, Bernardin G, Gari-Toussaint M. Fatal peritonitis caused by *Rhizopus microsporus*. *Med Mycol*. 2010;48:1096-1098.
13. Gubarev N, Separovic J, Gasparovic V, Jelic I. Successful treatment of mucormycosis endocarditis complicated by pulmonary involvement. *Thorac Cardiovasc Surg*. 2007;55:257-258.
14. Ibañez R, Serrano-Heranz R, Sánchez-Zaballos I, Carbonero P, López G. Disseminated mucormycosis due to *Absidia corymbifera* in a patient with inflammatory bowel disease. *Clin Microbiol Infect*. 1997;3:268-270.
15. Boelaert JR, Van Cutsem J, de Locht M, Schneider YJ, Crichton RR. Deferoxamine augments growth and pathogenicity of *Rhizopus*, while hydroxypyridinone chelators have no effect. *Kidney Int*. 1994;45:667-671.

Review

Gastrointestinal Mucormycosis: An Evolving Disease

Brad Spellberg, MD

Division of General Internal Medicine, Los Angeles Biomedical Institute at Harbor-UCLA Medical Center, Torrance, California; David Geffen School of Medicine at UCLA, Los Angeles, California

Mucormycosis is a life-threatening infection caused by fungi of the subphylum Mucoromycotina, order Mucorales.[1] Traditional risk factors for the development of invasive mucormycosis include diabetes, defects in host phagocytes, corticosteroid use, organ or stem cell transplantation, and increased levels of available serum iron as a result of acidosis or administration of deferoxamine.[2-4] In recent years, the disease has also increasingly been described in patients without traditional risk factors.[2]

Mucormycosis can affect any organ system, but the most common presentations involve either the nasal sinuses, orbit, and brain (rhino-orbital-cerebral) or the lung. For many years, gastrointestinal mucormycosis was quite rare, especially in industrialized nations. However, there has been a substantial increase in the number of cases of gastric and gastrointestinal mucormycosis indexed on PubMed over the past 2 decades, particularly over the past decade. For example, a PubMed search for the title words "gastric" or "gastrointestinal" and "mucormycosis" or "zygomycosis" revealed 8 publications from 1959–1989 (31 years), 23 publications from 1990–1999 (10 years), and 50 publications from 2000–2011 (12 years).

The stomach is the most common site of gastrointestinal mucormycosis, followed by the colon and ileum. In the past, gastrointestinal mucormycosis was seen primarily in premature neonates, often in association with widespread disseminated disease.[5-12] For example, necrotizing enterocolitis has been described largely in premature neonates and, more rarely, in neutropenic adults.[8,9,13-20] Other rare cases of gastrointestinal mucormycosis were previously described in association with other immunocompromising conditions, including AIDS, systemic lupus erythematosus, and organ transplantation.[21-26] Cases of hepatic mucormycosis have also been associated with ingestion of herbal medications.[27] Because this infection is acute and rapidly fatal, it is often diagnosed postmortem.

The symptoms of gastrointestinal mucormycosis are varied and depend on the affected site. Nonspecific abdominal pain and distention associated with nausea and vomiting are the most common symptoms. Fever and

Address correspondence to:
Dr. Brad Spellberg, 1124 W. Carson St. RB3, Torrance, CA 90502;
Tel: 310-781-3680; E-mail: bspellberg@labiomed.org

hematochezia may also occur. The patient is often thought to have an intra-abdominal abscess. The diagnosis may be made by biopsy of the suspected area during surgery or endoscopy. Recently, an iatrogenic outbreak of gastric mucormycosis occurred due to contamination of wooden applicators that were used to mix drugs for patients with nasogastric feeding tubes.[28] These patients presented with massive gastric bleeds. The diagnosis was made by culturing gastric aspirates and the wooden tongue depressors. This experience further underscores the alarming trend of increasing iatrogenic/nosocomial onset of mucormycosis.

As mentioned previously, older clinical literature (prior to 1990) primarily describes cases of mucormycosis in neonates and premature infants.[15-18] During the 1990s, cases were predominantly described in patients receiving immunosuppressant medications due to solid organ transplantation.[23,24,29,30] While such cases continue to be described in the 21st century, a substantial proportion of the cases described since 2000 have occurred in more widely disparate patient populations; these patients may have risk factors such as diabetes mellitus or corticosteroid use, a gastric or peptic ulcer that apparently became infected with the fungi, or no predisposing risk factors.[4,31-37]

The case reported by Morton and colleagues is typical of the increasing experience with this illness in the 21st century.[38] This patient had preexisting gastrointestinal mucosal ulcerations due to her underlying Crohn's disease, and she was immunosuppressed due to her corticosteroid therapy. When she presented with her perforation, there was no specific reason to suspect mucormycosis; indeed, the disease was much less likely than more typical causes of colonic perforations in such patients. Only the appearance of the fungi on histopathology caused the diagnosis to be made and appropriate therapy to be initiated. Thus, this case highlights the need to maintain a high index of suspicion for invasive fungal infections, including mucormycosis, in patients who are being treated with corticosteroids and who present with disease that crosses tissue planes.

The need to make a rapid diagnosis is underscored by recent data from the oncology setting, in which initiation of polyene antifungal therapy within 6 days of presentation was strongly associated with improved survival.[39] There have been no prospective randomized trials to define the optimal antifungal therapy for mucormycosis. Nevertheless, primary antifungal therapy for mucormycosis should be based on a polyene antifungal agent, as this drug class is by far the most active against the relevant pathogens. Most experts prefer to use lipid formulations of amphotericin B, which can be administered at higher doses and with less toxicity than amphotericin B deoxycholate.[3] The role of combination therapy in mucormycosis remains unclear, although data from mouse studies and concordant retrospective data in humans suggest that combining lipid polyenes with echinocandins may improve outcomes.[3] Additional research is needed to confirm this hypothesis in prospective trials.

Antifungal therapy alone is typically inadequate to control mucormycosis, and surgery to debulk the fungal infection and/or resect all infected tissue is often required to effect cure. Aside from the resistance of some fungal strains to amphotericin B, several hallmark features of mucormycosis—including angioinvasion, thrombosis, and tissue necrosis—result in poor penetration of antiinfective agents to the site of infection. Therefore, even if the causative organism is susceptible to the antifungal agent in vitro, the antifungal agent may be ineffective in vivo. In a logistic regression model, surgery was found to be an independent variable for favorable outcomes in patients with mucormycosis.[2] Furthermore, in multiple case series, patients who did not undergo surgical debridement of mucormycosis had a far higher mortality rate than patients who underwent surgery.[40-48] While there is potential selection bias in these case series—patients who did not undergo surgery likely differed in disease severity and/or comorbidities from those who did undergo surgery—these data support the concept that surgical debridement is necessary to optimize cure rates. Finally, immunosuppressive medications, particularly corticosteroids, should be dose-reduced or stopped if at all possible.

Given the increasing incidence of cancer in the aging US population, an ongoing epidemic of obesity and diabetes, and the increasing population of patients receiving corticosteroid therapy for inflammatory diseases and/or solid organ or stem cell transplantation, it is not surprising that recent studies have reported alarming increases in the incidence of mucormycosis.[49-51] Clinicians will likely continue to encounter this disease more frequently in the coming years, especially in the nosocomial setting. Further research is needed regarding new diagnostic and therapeutic modalities for these devastating infections. In the meantime, improvement in patient outcomes will require a high index of suspicion and emergent diagnostic evaluation to allow early initiation of antifungal and surgical therapy.

References

1. Hibbett DS, Binder M, Bischoff JF, et al. A higher-level phylogenetic classification of the Fungi. *Mycol Res*. 2007;111:509-547.
2. Roden MM, Zaoutis TE, Buchanan WL, et al. Epidemiology and outcome of zygomycosis: a review of 929 reported cases. *Clin Infect Dis*. 2005;41:634-653.
3. Spellberg B, Walsh TJ, Kontoyiannis DP, Edwards J Jr, Ibrahim AS. Recent advances in the management of mucormycosis: from bench to bedside. *Clin Infect Dis*. 2009;48:1743-1751.
4. Spellberg B, Edwards J Jr, Ibrahim A. Novel perspectives on mucormycosis: pathophysiology, presentation, and management. *Clin Microbiol Rev*. 2005;18:556-569.
5. Gatling RR. Gastric mucormycosis in a newborn infant; a case report. *AMA Arch Pathol*. 1959;67:249-255.

6. Kahn LB. Gastric mucormycosis: report of a case with a review of the literature. *S Afr Med J*. 1963;37:1265-1269.
7. Sharma MC, Gill SS, Kashyap S, et al. Gastrointestinal mucormycosis—an uncommon isolated mucormycosis. *Indian J Gastroenterol*. 1998;17:131-133.
8. Reimund E, Ramos A. Disseminated neonatal gastrointestinal mucormycosis: a case report and review of the literature. *Pediatr Pathol*. 1994;14:385-389.
9. Kecskes S, Reynolds G, Bennett G. Survival after gastrointestinal mucormycosis in a neonate. *J Paediatr Child Health*. 1997;33:356-359.
10. Kline MW. Mucormycosis in children: review of the literature and report of cases. *Pediatr Infect Dis*. 1985;4:672-676.
11. Craig NM, Lueder FL, Pensler JM, et al. Disseminated *Rhizopus* infection in a premature infant. *Pediatr Dermatol*. 1994;11:346-350.
12. Amin SB, Ryan RM, Metlay LA, Watson WJ. *Absidia corymbifera* infections in neonates. *Clin Infect Dis*. 1998;26:990-992.
13. Vadeboncoeur C, Walton JM, Raisen J, Soucy P, Lau H, Rubin S. Gastrointestinal mucormycosis causing an acute abdomen in the immunocompromised pediatric patient—three cases. *J Pediatr Surg*. 1994;29:1248-1249.
14. White CB, Barcia PJ, Bass JW. Neonatal zygomycotic necrotizing cellulitis. *Pediatrics*. 1986;78:100-102.
15. Woodward A, McTigue C, Hogg G, Watkins A, Tan H. Mucormycosis of the neonatal gut: a "new" disease or a variant of necrotizing enterocolitis? *J Pediatr Surg*. 1992;27:737-740.
16. Diven SC, Angel CA, Hawkins HK, Rowen JL, Shattuck KE. Intestinal zygomycosis due to *Absidia corymbifera* mimicking necrotizing enterocolitis in a preterm neonate. *J Perinatol*. 2004;24:794-796.
17. Siu KL, Lee WH. A rare cause of intestinal perforation in an extreme low birth weight infant—gastrointestinal mucormycosis: a case report. *J Perinatol*. 2004;24:319-321.
18. Nissen MD, Jana AK, Cole MJ, Grierson JM, Gilbert GL. Neonatal gastrointestinal mucormycosis mimicking necrotizing enterocolitis. *Acta Paediatr*. 1999;88:1290-1293.
19. Suh IW, Park CS, Lee MS, et al. Hepatic and small bowel mucormycosis after chemotherapy in a patient with acute lymphocytic leukemia. *J Korean Med Sci*. 2000;15:351-354.
20. 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.
21. Brullet E, Andreu X, Elias J, Roig J, Cervantes M. Gastric mucormycosis in a patient with acquired immunodeficiency syndrome [letter]. *Gastrointest Endosc*. 1993;39:106-107.
22. Hosseini M, Lee J. Gastrointestinal mucormycosis mimicking ischemic colitis in a patient with systemic lupus erythematosus. *Am J Gastroenterol*. 1998;93:1360-1362.
23. Singh N, Gayowski T, Singh J, Yu VL. Invasive gastrointestinal zygomycosis in a liver transplant recipient: case report and review of zygomycosis in solid-organ transplant recipients. *Clin Infect Dis*. 1995;20:617-620.
24. Martinez EJ, Cancio MR, Sinnott JT 4th, Vincent AL, Brantley SG. Nonfatal gastric mucormycosis in a renal transplant recipient. *South Med J*. 1997;90:341-344.
25. Mazza D, Gugenheim J, Baldini E, Mouiel J. Gastrointestinal mucormycosis and liver transplantation; a case report and review of the literature [letter]. *Transpl Int*. 1999;12:297-298.
26. Knoop C, Antoine M, Vachiéry JL, et al. Gastric perforation due to mucormycosis after heart-lung and heart transplantation. *Transplantation*. 1998;66:932-935.
27. 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.
28. Maravi-Poma E, Rodriguez-Tudela JL, de Jalon JG, et al. Outbreak of gastric mucormycosis associated with the use of wooden tongue depressors in critically ill patients. *Intensive Care Med*. 2004;30:724-728.
29. Winkler S, Susani S, Willinger B, et al. Gastric mucormycosis due to *Rhizopus oryzae* in a renal transplant recipient. *J Clin Microbiol*. 1996;34:2585-2587.
30. Corley DA, Lindeman N, Ostroff JW. Survival with early diagnosis of invasive gastric mucormycosis in a heart transplant patient. *Gastrointest Endosc*. 1997;46:452-454.
31. Garg PK, Gupta N, Gautam V, Hadke NS. Gastric zygomycosis: unusual cause of gastric perforation in an immunocompetent patient. *South Med J*. 2008;101:449-450.
32. Goswami R, Cabrera-Kapetanos Y, Gupta MP, Thakkar S, Bhanot N. Necrotic gastric ulcer in an elderly patient: a rare case of gastric zygomycosis. *South Med J*. 2010;103:387-388.
33. Benjamin S. Primary gastric mucormycosis: role of preexisting ulcerative and erosive lesions. *J Postgrad Med*. 2009;55:73-74.
34. Chhaya V, Gupta S, Arnaout A. Mucormycosis causing giant gastric ulcers. *Endoscopy*. 2011;43 Suppl 2 UCTN:E289-E290.
35. Shiva Prasad BN, Shenoy A, Nataraj KS. Primary gastrointestinal mucormycosis in an immunocompetent person. *J Postgrad Med*. 2008;54:211-213.
36. Al-Rikabi AC, Al-Dohayan AD, Al-Boukai AA. Invasive mucormycosis in benign gastric ulcer. *Saudi Med J*. 2000;21:287-290.
37. Johnson CB, Ahmeti M, Tyroch AH, Zuckerman MJ, Hakim MN. Gastric mucormycosis as a cause of life-threatening upper gastrointestinal bleeding in a trauma patient. *Am Surg*. 2010;76:E76-E77.
38. Morton J, Nguyen V, Ali T. Mucormycosis of the intestine: a rare complication in Crohn's disease. *Gastroenterol Hepatol (N Y)*. 2012;8:137-140.
39. Chamilos G, Lewis RE, Kontoyiannis DP. Delaying amphotericin B-based frontline therapy significantly increases mortality among patients with hematologic malignancy who have zygomycosis. *Clin Infect Dis*. 2008;47:503-509.
40. Nithyanandam S, Jacob MS, Battu RR, Thomas RK, Correa MA, D'Souza O. Rhino-orbito-cerebral mucormycosis. A retrospective analysis of clinical features and treatment outcomes. *Indian J Ophthalmol*. 2003;51:231-236.
41. Peterson KL, Wang M, Canalis RF, Abemayor E. Rhinocerebral mucormycosis: evolution of the disease and treatment options. *Laryngoscope*. 1997;107:855-862.
42. Khor BS, Lee MH, Leu HS, Liu JW. Rhinocerebral mucormycosis in Taiwan. *J Microbiol Immunol Infect*. 2003;36:266-269.
43. Petrikkos G, Skiada A, Sambatakou H, et al. Mucormycosis: ten-year experience at a tertiary-care center in Greece. *Eur J Clin Microbiol Infect Dis*. 2003;22:753-756.
44. Tedder M, Spratt JA, Anstadt MP, Hegde SS, Tedder SD, Lowe JE. Pulmonary mucormycosis: results of medical and surgical therapy. *Ann Thorac Surg*. 1994;57:1044-1050.
45. Pavie J, Lafaurie M, Lacroix C, et al. Successful treatment of pulmonary mucormycosis in an allogenic bone-marrow transplant recipient with combined medical and surgical therapy. *Scand J Infect Dis*. 2004;36:767-769.
46. Reid VJ, Solnik DL, Daskalakis T, Sheka KP. Management of bronchovascular mucormycosis in a diabetic: a surgical success. *Ann Thorac Surg*. 2004;78:1449-1451.
47. Asai K, Suzuki K, Takahashi T, Ito Y, Kazui T, Kita Y. Pulmonary resection with chest wall removal and reconstruction for invasive pulmonary mucormycosis during antileukemia chemotherapy. *Jpn J Thorac Cardiovasc Surg*. 2003;51:163-166.
48. Kontoyiannis DP, Wessel VC, Bodey GP, Rolston KV. Zygomycosis in the 1990s in a tertiary-care cancer center. *Clin Infect Dis*. 2000;30:851-856.
49. Kontoyiannis DP, Lionakis MS, Lewis RE, et al. Zygomycosis in a tertiary-care cancer center in the era of *Aspergillus*-active antifungal therapy: a case-control observational study of 27 recent cases. *J Infect Dis*. 2005;191:1350-1360.
50. Marr KA, Carter RA, Crippa F, Wald A, Corey L. Epidemiology and outcome of mould infections in hematopoietic stem cell transplant recipients. *Clin Infect Dis*. 2002;34:909-917.
51. Gleissner B, Schilling A, Anagnostopolous I, Siehl I, Thiel E. Improved outcome of zygomycosis in patients with hematological diseases? *Leuk Lymphoma*. 2004;45:1351-1360.