The "Black Fungus" in India: The Emerging Syndemic of COVID-19–Associated Mucormycosis

Sumanth Gandra, MD, MPH; Sanjay Ram, MBBS; and Stuart M. Levitz, MD

Mucormycosis is a rare disease caused by fungi of the order Mucorales (1). The agents of mucormycosis are ubiquitous environmental molds found in soil and decaying organic matter; exposure to airborne spores is commonplace, yet disease is very rare. In a susceptible person, spores germinate into hyphae, which then invade surrounding tissue, including blood vessels, resulting in hemorrhagic infarction. The name "black fungus" given to mucormycosis in news reports refers to the dark, necrotic tissue seen in people afflicted by this disease. Major risk factors for mucormycosis include poorly controlled diabetes mellitus and immunosuppression due to hematologic cancer or receipt of immunosuppressive chemotherapy including corticosteroids. The 2 most common clinical syndromes are rhino-orbito-cerebral and pulmonary mucormycosis. The rhino-orbito-cerebral form generally begins in the sinuses and progresses over several days to involve contiguous structures, which can result in facial disfigurement, cranial nerve palsies, blindness, and brain invasion. Treatment requires aggressive surgical debridement and antifungal agents. The drug of choice for initial treatment is amphotericin B, preferably as a lipid formulation. Fluconazole and voriconazole have no activity against the causative fungi. Mortality is high, especially if diagnosis and prompt initiation of medical and surgical therapy are delayed.

India has more than 65 million adults with diabetes (2). A survey of 13 055 blood samples in 4 states in India revealed a weighted prevalence of diabetes and prediabetes that ranged from 5.3% to 13.6% and from 8.1% to 14.6%, respectively (3). The prevalence of diabetes was higher in urban than in rural areas. In all 4 states surveyed, rates of diabetes were highest among urban men in the 55- to 64-year-old age group (range, 25% to 45%). Rapid urbanization and an increasingly sedentary lifestyle are believed to contribute to the high prevalence of diabetes in India.

India is experiencing a second wave of COVID-19, with 28.2 million cases reported as of this writing, although this is likely an underestimate; the true toll is estimated at more than 500 million cases (4). The unprecedented increase in COVID-19 cases during this second wave exposed the crippled health care system. Oxygen supplies have dwindled, hospitals have turned away patients because of a lack of beds, and shortages of critical medicines have occurred. In the midst of this crisis, a "syndemic" of rhino-orbito-cerebral mucormycosis infections has arisen, with nearly 9000 cases reported so far from several states in India (5). A syndemic recognizes the interactions between social and biological factors that result in more adverse disease outcomes (6). Compounding the crises are reported shortages of amphotericin B, the main drug used to treat mucormycosis. Although COVID-19–associated mucormycosis is not unique to India, emerging data indicate that the extraordinarily high prevalence is multifactorial, with contributions from poorly controlled diabetes, excessive use of corticosteroids and possibly antibiotics, and environmental exposure (7). The hot and humid environment in India likely promotes growth of Mucorales species.

Based on the RECOVERY trial, dexamethasone at a dosage of 6 mg once a day for up to 10 days is recommended for hospitalized patients with COVID-19 who are receiving supplemental oxygen or mechanical ventilation (8). However, glucocorticoids have no benefit in patients who do not require respiratory support. Despite this, many patients with mild COVID-19 not requiring supplemental oxygen have been treated with glucocorticoids, sometimes with higher doses and longer durations than recommended in the RECOVERY trial. Corticosteroids predispose to mucormycosis by suppressing the immune system and by increasing blood glucose levels in persons with prediabetes and diabetes. More than 80% of patients with COVID-19–associated mucormycosis are reported to have had elevated blood glucose levels at presentation with fungal infection (7). Indeed, misuse of glucocorticoids and failure to adequately control elevated glucose levels appear to be the major contributing factors.

Other possible contributing factors include shortages of oxygen and overuse of antibiotics. Although these effects are not proven, hypoxia may exacerbate damage of tissue partially infarcted by angioinvasion, and antibiotics may suppress normal bacterial flora, allowing fungi to become established in the sinuses. In India, antibiotics have been extensively used for mild and moderate COVID-19 cases despite their ineffectiveness. During the first wave of COVID-19, an estimated 216 million excess doses of all antibiotics and 6.2 million azithromycin treatment courses were attributed to COVID-19 (9).

What can be done to curtail the ongoing syndemic of COVID-19–associated mucormycosis in India? First, nonpharmacologic measures, such as masking policies and social distancing, should be taken to reduce risk for transmission of SARS-CoV-2. Several states in India have imposed lockdowns, which is helping to reduce the spread of COVID-19. These nonpharmacologic measures have short-term benefits; the long-term solution involves vaccination. International efforts are underway and are much needed to replenish critical health care supplies and materials needed for vaccine manufacturing. Second, implementation of mitigation strategies is urgently needed to decrease the risk for mucormycosis in persons infected with SARS-CoV-2. The Indian Health Ministry recently issued evidence-based guidelines for appropriate mucormycosis management (10). Corticosteroids should be used only in situations in which there is evidence of their effectiveness, and then only at recommended doses and durations (8). Blood glucose levels must be closely monitored and controlled, particularly in patients who are known to be diabetic or are receiving

This article was published at Annals.org on 8 June 2021.

corticosteroids. Antibiotics should be reserved for situations in which bacterial superinfections are suspected. People should avoid environments where exposure to Mucorales is likely to occur. Third, efforts must be undertaken to educate health care providers and the public about the signs and symptoms of mucormycosis because early aggressive surgical treatment and antifungal therapy improve outcomes. Regarding antifungal therapy, hospitals need to have adequate supplies of amphotericin B. The COVID-19 crisis has unmasked inequities and strained health care systems globally, particularly in low- and middle-income countries. The overuse of corticosteroids and antibiotics may have been an attempt to avoid hospitalizations because of the shortage of hospital beds and oxygen. Stronger restrictions on over-the-counter sales of systemic corticosteroids and antibiotics should be considered. Restrictions were issued for hydroxychloroquine in March 2020, which contributed to reduced hydroxychloroquine sales during the first wave of the pandemic (9). Finally, strengthening infrastructure and improving health care delivery systems are high priorities to forestall such crises.

From Washington University School of Medicine, Saint Louis, Missouri (S.G.); and University of Massachusetts Medical School, Worcester, Massachusetts (S.R., S.M.L.).

Disclosures: Authors have reported no disclosures of interest. Forms can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M21-2354.

Corresponding Author: Stuart M. Levitz, MD, Department of Medicine, University of Massachusetts Medical School, 364 Plantation Street, Room LRB317, Worcester, MA 01605; e-mail, stuart.levitz@umassmed.edu.

Current author addresses and author contributions are available at Annals.org.

Ann Intern Med. doi:10.7326/M21-2354

References

1. **Jeong W, Keighley C, Wolfe R, et al.** The epidemiology and clinical manifestations of mucormycosis: a systematic review and meta-analysis of case reports.Clin Microbiol Infect. 2019;25:26-34. [PMID: 30036666] doi:10.1016/j.cmi.2018.07.011

2. **Nanditha A, Ma RC, Ramachandran A, et al.** Diabetes in Asia and the Pacific: implications for the global epidemic. Diabetes Care. 2016;39:472-85. [PMID: 26908931] doi:10.2337/dc15-1536

3. **Anjana RM, Pradeepa R, Deepa M, et al; ICMR-INDIAB Collaborative Study Group.** Prevalence of diabetes and prediabetes (impaired fasting glucose and/or impaired glucose tolerance) in urban and rural India: phase I results of the Indian Council of Medical Research-INdia DIABetes (ICMR-INDIAB) study. Diabetologia. 2011;54:3022-7. [PMID: 21959957] doi:10.1007/s00125-011-2291-5

4. **Gamio L, Glanz J.** Just how big could India's true Covid toll be? New York Times. 25 May 2021. Accessed at www.nytimes.com/interactive/2021/05/25/world/asia/india-covid-death-estimates.html?smid=em-share on 25 May 2021.

5. **Biswas S.** Black fungus: India reports nearly 9,000 cases of rare infection. BBC News. 23 May 2021. Accessed at www.bbc.com/news/world-asia-india-57217246 on 25 May 2021.

6. **Singer M,Bulled N,Ostrach B,et al.**Syndemics and the biosocial conception of health. Lancet. 2017;389:941-950. [PMID: 28271845] doi:10.1016/S0140-6736(17)30003-X

7. **Singh AK, Singh R, Joshi SR, et al.** Mucormycosis in COVID-19: a systematic review of cases reported worldwide and in India. Diabetes Metab Syndr. 21 May 2021. [Epub ahead of print]. doi:10.1016/j.dsx.2021.05.019

8. **Horby P, Lim WS, Emberson JR, et al; RECOVERY Collaborative Group.**Dexamethasone in hospitalized patients with Covid-19. N Engl J Med. 2021;384:693-704. [PMID: 32678530] doi:10.1056/NEJMoa2021436

9. **Sulis G, Batomen B, Kotwani A, et al.** Sales of antibiotics and hydroxychloroquine in India during the COVID-19 epidemic: an interrupted time series analysis. PLoS Med. 2021. [Forthcoming].

10. **Ministry of Health and Family Welfare; Government of India.** Evidence based advisory in the time of COVID-19: screening, diagnosis & management of mucormycosis. Accessed at www.icmr.gov.in/pdf/covid/techdoc/Mucormycosis_ADVISORY_FROM_ICMR_In_COVID19_time.pdf on 25 May 2021.

Current Author Addresses: Dr. Gandra: 4523 Clayton Ave, Campus Box 8051, Saint Louis, MO 63110.
Dr. Ram: University of Massachusetts Medical School, Lazare Research Building, 3rd Floor, Room 322, 364 Plantation Street, Worcester, MA 01605.
Dr. Levitz: Department of Medicine, 364 Plantation Street, Room LRB317, Worcester, MA 01605.

Author Contributions: Administrative, technical, or logistic support: S.M. Levitz.
Analysis and interpretation of the data: S. Gandra, S.M. Levitz, S. Ram.
Collection and assembly of data: S. Gandra, S.M. Levitz, S. Ram.
Conception and design: S. Gandra, S.M. Levitz, S. Ram.
Critical revision for important intellectual content: S. Gandra, S.M. Levitz, S. Ram.
Drafting of the article: S. Gandra, S.M. Levitz, S. Ram.
Final approval of the article: S. Gandra, S.M. Levitz, S. Ram.