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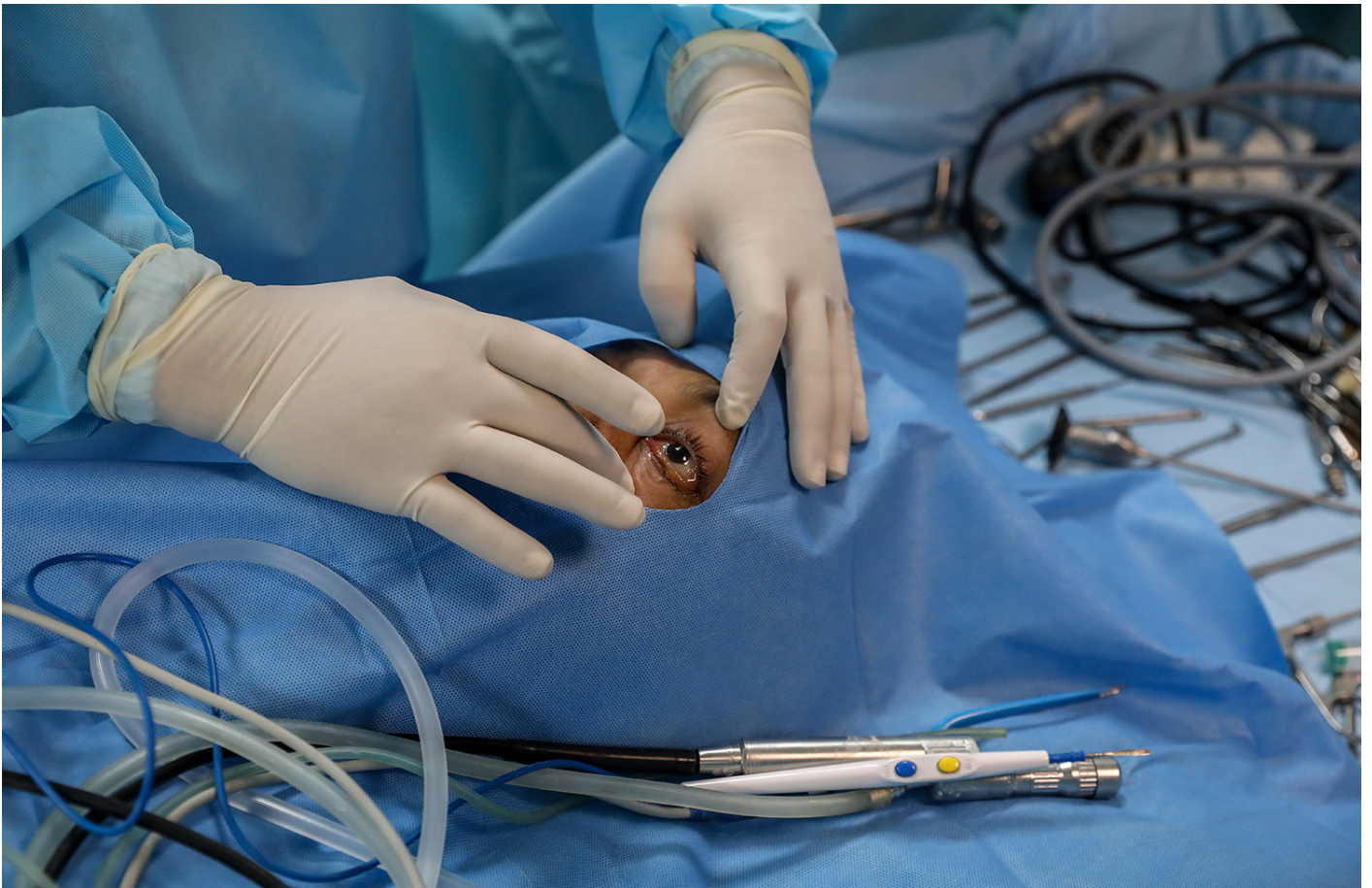
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NEWS / HEALTH

COVID-19, steroids and diabetes—why mucormycosis is now a deadly epidemic in India

CHAHAT RANA

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Doctors perform endoscopic surgery on a mucormycosis patient at Harsh ENT hospital in Ghaziabad, Uttar Pradesh on 3 June 2021. RAJAT GUPTA / EPA

COVID-19



[\(/covid-19\)](#)

In mid April, 59-year-old Dilip Menon, his wife and son were just about recovering from COVID-19, when he started developing new symptoms. “His eye was swollen and he complained of pain in his face,” Dilind, his son, told me. “We thought it was just an insect bite.” However, it turned out that Menon had mucormycosis, a fungal infection that quickly spread across his facial tissues, causing him to lose vision in his right eye and have it removed. “We have brought him back to the house now, but still worried about infection, he is still on medication,” Dilind said. “This was a horrifying experience. Everything has gone downhill.”

Dilip Menon was one of thousands of people who have developed mucormycosis along with COVID-19 during the second nationwide wave. It is an opportunistic infection, in which spores of the fungus take hold of tissues in immunocompromised patients, such as those who have contracted COVID-19 or are on immunosuppressants such as steroids. The fungus damages cells and nerves and cuts off blood supply as it spreads. The lack of blood supply turns tissue black, earning the disease the misnomer “black fungus.” “But there is nothing black about the fungus,” Jagdish Chander, the former head of the department of microbiology at Chandigarh’s Government Medical College and Hospital, said. Mucormycosis is often deadly and pre-pandemic reviews of literature on mucormycosis suggested that mortality (<https://www.cdc.gov/fungal/diseases/mucormycosis/statistics.html#:~:text=Mucor>) be as much as 54 percent.

The union health ministry recently declared mucormycosis an epidemic in India. On 7 June, Harsh Vardhan, the health minister, said (<https://www.livemint.com/news/india/black-fungus-28-states-see-28-252-mucormycosis-cases-maharashtra-gujarat-among-worst-hit-states-11623069135171.html>) that 28,252 cases of mucormycosis had been identified in the country since the disease was notified in early May 2021. Eighty-six percent of these cases had a history of COVID-19 infection and 62.3 percent had a history of diabetes. At least 900 of these patients had died as of 28 May, according to an affidavit filed by the union government in the Delhi High Court.

Doctors corroborated this data with cases they had seen in emergency rooms. “Before the pandemic, our hospital received five to ten such cases per year, and now at least five patients are referred to our hospital daily,” Abdul Ghafur, an infectious-disease physician at Apollo Hospital in Chennai, said.

Mucormycosis was considered rare in India until this year. Atul Patel, an infectious-disease expert in Ahmedabad, estimated that around 300 cases

were diagnosed annually before the pandemic. Patel was the lead author of a multi-centre study conducted between January 2016 and September 2017, according to which 465 mucormycosis patients were diagnosed in India's foremost tertiary care hospitals. However, the disease was endemic in India, and there was a 70-percent prevalence of the disease globally.

This rose dramatically in 2020 after the spread of COVID-19. Doctors across 16 hospitals that were part of a research network called the MucoCovi Network, which looked into mucormycosis and COVID-19, conducted a study (https://wwwnc.cdc.gov/eid/article/27/9/21-0934_article) in November and December. They found that mucormycosis cases had doubled compared to the same period in 2019. The retrospective study further examined 287 mucormycosis patients and found that 187 had COVID-19-associated mucormycosis or CAM. In their paper, the authors attribute the doubling of cases to coronavirus infections. An early print of the paper appeared in *Emerging Infectious Diseases*, a journal published by the United States Centres for Disease Control. "The main takeaway from the study was that COVID was indeed driving cases of mucormycosis up, even before the second wave of the pandemic struck India," Patel, who was one of the authors of the MucoCovi study, said.

The threat of mucormycosis stems from the ease with which it can take hold of an immunocompromised body. Spores of mucormycetes, the group of fungi that cause the disease, exist suspended in the air almost everywhere. "It's the same group which causes bread mould, it grows on rotten fruit, it's everywhere and all of us inhale some of it," Chander said. "It is when these spores find a host which is immunocompromised or has high levels of blood sugar or both, that the disease manifests."

Chander is one of the leading experts on mucormycosis in India. He diagnosed his first mucormycosis patient in July of 1995 and has studied the disease extensively over the past decade. "I was on the hunt for the

disease,” he said. “My students and I actively looked out for it, and asked doctors from other departments to look out for the telltale signs and inform us so we can test for fungal infection.” The more Chander and his students looked, the more mucormycosis they found. “I remember thinking this disease is so frightening. *Bhoot bana deti hai aadmi ka*—It makes ghosts out of men,” he said.

Chander observed how quickly the disease consumed patients. He created more awareness about the disease and its symptoms amongst his hospital staff and ensured that his students studied the disease closely. “Ten years ago, one of my students went to the government college in Bathinda as a resident doctor, and in her first month diagnosed two patients with the disease,” he said. “It is not like there weren’t any patients in Bhatinda with the disease earlier. How could that be, when we found so many patients in Chandigarh itself? It is just that people were not aware of the disease and were not diagnosing patients on time.”



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“If you catch the disease, patients will most likely survive, but due to our ignorance, many rotted away in their beds without any adequate treatment,” he said. “If we didn’t have a high index of suspicion while diagnosing the disease, mortality would be high, because the infection progresses so quickly.” He said the Government Medical College and Hospital diagnosed twenty to thirty patients with the disease every year

even before the pandemic. “Most of the patients diagnosed in India were from Chandigarh, only because we had experts who were specifically researching on such fungal diseases,” he said. He was referring to himself as well as researchers from the Post Graduate Institute of Medical Education and Research in Chandigarh, such as Arunaloke Chakrabarti, a global expert in medical mycology and a co-author of the MucoCovi study.

Chander published studies in 2013, 2015 and 2018 on the growing burden of the disease in India. These warned that early diagnosis (<https://pubmed.ncbi.nlm.nih.gov/29642408/>), knowledge of risk factors, a high suspicion index and aggressive interventions such as surgery and antifungal treatment were needed to save patients’ lives. The 2015 case study was on a diabetic patient who had a pulmonary tuberculosis and mucormycosis co-infection. It warned that with mucormycosis cases on the rise, incidences of such co-infections were likely to increase.

In the *Textbook on Medical Mycology*, which Chander wrote in 2018, he made the ominous prediction that “mucormycosis is going to destroy India shortly, in a couple of years.” Chander told me he made this prediction based on his decades-long experience in treating these patients. “People ask me now if this is an offhand remark,” he said. “It is not. It comes from a real place of fear. I have seen so many people lose their lives to this, so many young people even. And every year it seems to get worse.” He made this prediction without anticipating a pandemic of the kind that is ongoing. “No one could have seen this pandemic coming. And diseases like COVID will come and go, but mucor is something else. It is here to stay and it will only get worse in times of an epidemic.”

Chander’s research had already shown that diabetes mellitus was the main risk factor for mucormycosis infections. He wrote in the textbook that the rising number of diabetics was causing mucormycosis to emerge more or less as an epidemic in south-east Asia.

A body afflicted with diabetes mellitus does not produce enough insulin to regulate glucose levels. High glucose serves as fertile ground for microbes such as bacteria and fungi to quickly multiply. “The sugar is basically what the fungus then feeds off, it becomes breeding ground for the fungal spores that cause mucormycosis,” Yudhyavir Singh, critical-care specialist at the All India Institute of Medical Sciences, explained. Singh manages AIIMS’ COVID-19 intensive-care unit.



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Singh and other medical experts told me that negligence in monitoring blood sugar levels, both at hospitals and home care settings, contributed significantly to the 2021 mucormycosis epidemic. “There are many patients who have underlying diabetes that they don’t know about, and then still others who have temporary hyperglycemia due to excessive steroid use,” Singh said.

Mucormycosis researchers also believe that an increasing dependence on steroids has left COVID-19 patients vulnerable to the fungal infection. Steroids such as dexamethasone are one of very few therapies proven to decrease mortality among COVID-19 patients. The immune systems of severely-ill COVID-19 patients can be overactive and cause dangerous levels of inflammation. Steroids provide an anti-inflammatory effect but this life-saving intervention has its drawbacks. “First, it disturbs glucose metabolism in our body which leads to rise in glucose levels,”

Chakrabarti said. “Secondly it also disturbs macrophage production, leading to a reduced immune response.”

Macrophages are white blood cells that engulf invading microbes as part of a body’s immune response. They can defend the body from fungal spores. A hampered macrophage response disrupts the body’s innate defence mechanism, leaving it more susceptible to infections like mucormycosis.

Singh said many patients under his care had been self-medicating with high doses of steroids before they were referred to AIIMS for treatment. “Many doctors themselves started using steroids when they didn’t need it,” he added. “There are many inflammatory markers that we monitor before administering the right dose of steroids, but people were just popping steroids like it was candy, sometimes even before they were diagnosed with COVID.”

Over the course of the last few months, Chakrabarti has also observed that patients were prescribed high doses of steroids for prolonged periods of time, even when they had only mild symptoms. He said that patients should not be given more than six milligrams of dexamethasone per day, but many were prescribed up to 30 milligrams. “Five times the upper limit! Of course it caused problems for patients,” he said.

Singh does not believe that doctors or patients can be faulted for steroid overuse during the COVID-19 crisis. “There was just so much confusion and chaos, we needed very specific and clear guidelines on rational steroid use from the start, which we didn’t have,” he said. “Our healthcare workers need information on what inflammatory markers to look at, what tests need to be conducted.”

The mucormycosis epidemic is also a failure of public-health interventions. “It is also about prevention, and that happens if we monitor sugar levels in the population, and propagate rational use of

medicines such as steroids or other strong antibacterial drugs,” Singh said.

Ghafur, the infectious-disease expert in Chennai, said that hospitals (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6787571/>) needed to take preventive measures to regulate and control air-quality levels to reduce secondary mucormycosis infections in patients with COVID-19 or other health conditions. “Hospital settings are often the source of infections like mucormycosis, or even other bacterial and fungal infections,” he said. At most large corporate-run hospitals, like the one Ghafur works at, the air quality is continuously monitored, especially in wards with immunocompromised patients. “But we can’t really expect such a level of awareness and monitoring in our public hospitals. They are overburdened and resource starved. How can we ensure infection control in a hospital where patients are lying on the floor?” Ghafur asked.

Doctors told me that many COVID-19 patients develop mucormycosis in hospital wards or a few days after they are discharged. The MucoCovi study (https://wwwnc.cdc.gov/eid/article/27/9/21-0934_article#fn2) found a 0.27-percent prevalence of COVID-19-associated mucormycosis among all patients with COVID-19 across seven hospitals, and a 1.6-percent prevalence in patients admitted in ICUs of these hospitals. The study also observed that most patients were diagnosed with the fungal infection at least eight days after they were diagnosed with COVID-19. “And that is why it's important that patients be counselled about the early symptoms of mucor, even while they are getting treatment for COVID, or when they are being discharged,” SP Kalantri, a professor of medicine at the Mahatma Gandhi Institute of Medical Sciences in Wardha, said. Kalantri was not associated with the study.

Kalantri thinks that there must be something beyond the “steroids and sugar” theory to explain the sudden surge in mucormycosis cases in India. He reasoned that the cases during the first COVID-19 wave were

far fewer compared to the second. “Till 15 February we had admitted 2,800 COVID-19 patients in our hospital but none with mucor,” he said. “In this current wave, we have had more than 5,000 COVID patients and at least thirty six of them developed mucor. Even in the first wave, we had many patients who were taking steroids and frighteningly high blood sugar levels. So what has changed now?”

Kalantri and Chakrabarti suspect that changing properties of the SARS-CoV2 virus made patients more susceptible to mucormycosis. For instance, there is evidence ([https://www.cghjournal.org/article/S1542-3565\(20\)30537-1/pdf](https://www.cghjournal.org/article/S1542-3565(20)30537-1/pdf)) that the virus causes damage to the pancreas, which in turn affects the production of insulin, the hormones released by the pancreas that helps to regulate blood-sugar levels. “There were autopsies conducted even in the first wave of the virus, early last year, that showed significant damage to the pancreas of deceased COVID-19 patients,” Chakrabarti said.

The virus often causes a spike in blood-ferritin levels as well. Ferritin is a protein that contains iron. Singh said that mucormycetes spores feed off and thrive in blood serum containing high levels of ferritin.

Both Kalantri and Chakrabarti said they worried that the highly infectious Delta variant (<https://www.washingtonpost.com/world/2021/06/07/delta-variant-britain-reopening/>) of the virus might be causing more damage to pancreatic functioning as compared to earlier strains of the virus. “This is a more aggressive, possibly more virulent strain,” Kalantri said. “There is a chance it is directly affecting glucose metabolism in the body, spiking blood sugar levels.”

Though there is no conclusive research yet on whether this particular variant is more virulent and life-threatening than other variants, public-health authorities in the United Kingdom have observed that the Delta strain led to increased hospitalisation (<https://www.bmj.com/content/373/bmj.n1445>) among COVID-19

patients. “There is nothing we know for sure about how this new strain is directly increasing mucor infections in COVID patients, but I have a very strong hunch that the Delta strain is also directly affecting our immune system in a way that it allows for mucor to invade our body easily,” Chakrabarti said. “There is no evidence of COVID decreasing the number of these white blood cells in our body, but I believe the new strain could be hampering the function of macrophages, preventing them from effectively killing these spores. Of course, this is just a hypothesis for now, yet to be tested.” He is working on a study to examine the link between mucormycosis and COVID-19-caused immune dysregulation in the body.

Chander told me he was truly frightened. “I am hearing now from students who are identifying mucor cases along with other fungal infections, or two types of strains of mucormycosis affecting the same individual,” he said. “These are deadly cocktails of infection, and I am afraid we are going to lose many more lives if we don’t take this seriously.”

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CHAHAT RANA (/AUTHOR/37386) is a reporting fellow at *The Caravan*.

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