Rhino-Orbital-Cerebral Mucormycosis— Another Deadly Complication of COVID-19 Infection

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SARS-CoV-2, which causes the clinical disease COVID-19, has now affected more than 200 million patients worldwide with close to 5 million deaths. Ophthalmic manifestations of COVID-19 are wide-ranging and present in up to 10% of patients, most commonly as conjunctivitis. The enormous number and high acuity of infected patients have placed significant burdens on health care systems worldwide. The resulting deferral of medical care for other life-threatening conditions such as cancer and heart disease may lead to additional morbidity and mortality.

In this issue of JAMA Ophthalmology, Choksi et al1 join other authors in focusing our attention on another potentially lethal complication of SARS-CoV-2 infection, rhino-orbital-cerebral mucormycosis (ROCM) associated with COVID-19, that is, COVID-19-associated mucormycosis (CAM). Prior to the pandemic, mucormycosis was considered a rare disease, with an incidence of 0.005 to 1.7/million. Fewer than 10 cases are encountered annually at Mayo Clinic Rochester (N. Wengenack, PhD, oral communication, October 15, 2021). The current series, by contrast, includes 73 cases of CAM treated over a 3-month period. The authors’ experience confirms the massive increase in ROCM cases in India associated with COVID-19, with more than 15 000 cases as of May 2021.5

Hematological malignancy, diabetes, pharmacological immunosuppression, high-dose steroid therapy, and HIV infection are well-established risk factors for ROCM. In this study, the main risk factors for CAM were diabetes and steroid use. Three-quarters of patients had diabetes, with more than half with disease characterized as uncontrolled. More than 80% received steroids, either intravenous (IV) or oral, to offset the massive cytokine response driving COVID-19-related pneumonitis and acute respiratory distress syndrome. Supplemental oxygen or ventilatory support was required in 82% of patients. Vaccine information was available for 47 patients, of whom 89% were unvaccinated and none were fully vaccinated.

Care for patients with ROCM often involves a multidisciplinary and resource-intensive approach combining surgical debridement by otolaryngologists, neurosurgeons, and orbital surgeons, as well as treatment by specialists in infectious disease, endocrinology, nephrology, laboratory medicine, pharmacology, and pathology. Medical management includes glucose control and administration of IV liposomal amphotericin B, possibly combined with azole-class agents. The daily cost of the latter antifungal medications alone may approach $10000, not including hospital admission costs. Such costs, as well as limited availability of drugs due to pandemic-related supply chain disruptions, may complicate the delivery of care. The authors and other caregivers in India have confirmed, in fact, shortages of amphotericin B for CAM treatment. Azole agents were not administered in the current study.

It is likely that outcomes are less favorable for patients facing COVID-19 as well as ROCM. All-cause mortality from mucormycosis alone ranges from 40% to 80% depending on underlying conditions. The mortality rate from CAM in this study was 53% at 21 days. At the 30-day time point, more than 50% of patients had either stable or progressive disease and only 7 had regressed disease. The long-term mortality may therefore be higher than 53%. Because of medication shortages, only 67% of patients received IV amphotericin B. On multivariate analysis, there was a trend toward improved survival in this group, although this did not reach statistical significance (hazard ratio, 0.31; 95% CI, 0.06-1.43; P = .13). Additionally, no patients receiving amphotericin B required exenteration. Importantly, in this retrospective, nonrandomized study, it is difficult to exclude the possibility that the limited supply of amphotericin B was administered preferentially to more severely ill patients, potentially making it more difficult to detect a beneficial effect of amphotericin B on survival. Eighteen patients underwent retrobulbar amphotericin B injection without reduction in mortality, although nearly 40% of patients received only 1 dose. Multivariate analysis also disclosed a 9-fold increased risk of death associated with the need for ventilatory support as well as increased mortality with NLP vision at presentation.

In caring for more than 70 patients with CAM, Choksi and colleagues have amassed unique clinical expertise as well as a valuable database of patient outcomes. Like any case series database, however, it has limitations, including incomplete data, lack of randomization of treatment, and loss to follow-up. Although the authors understandably sought to derive maximal insights from their data, the testing of 28 clinical covariates for significance in this study also raises the possibility of finding a spurious association between the clinical variable and the outcome. With a type I error rate of 5%, they could expect to find at least 1 positive association by chance alone. Similarly, the inclusion of 9 covariates in the Cox proportional hazard model runs the risk of rejecting the null hypothesis incorrectly. With 22 deaths, a conservative approach that follows the statistical “rule of thumb” of having 5 to 10 events per predictor variable would have limited the multivariate model to 2 to 4 covariates.

Despite these limitations, this case series helps raise important questions to generate hypotheses and guide data collection for future research. For example, what risk factors might clinicians monitor and mitigate to reduce the risk of CAM? In this study and others, diabetes and corticosteroid use were the most common risk factors for the development of CAM. Corticosteroid use to treat COVID-19 pneumonitis may
be unavoidable, but is there a threshold of steroid therapy (in terms of either duration or cumulative dose) that increases CAM risk? Obesity has been established as a risk factor for COVID-19 severity. Is elevated body mass index also a risk factor for CAM? Other questions include the association between systemic hypoxemia and CAM progression. This study demonstrated increased mortality in patients requiring mechanical ventilation. Hypoxic conditions can affect gene expression and promote virulence in pathogenic fungi, thereby creating a favorable environment for mucormycosis growth. Separately, SARS-CoV-2 infection may induce T-cell immunodepletion and impair immune system activity and immune regulation. Future studies focusing on the association between SARS-CoV-2 infection, hypoxemia, T-lymphocyte and NK-cell dysfunction, and CAM progression and response to therapy may be valuable.

In terms of therapy, no patients in this study received azole agents, and it would be helpful to study the effect of combined amphotericin B-azole treatment on CAM mortality. In this regard, the authors have indicated that prophylactic posaconazole will be administered to high-risk patients with COVID-19 in their institution, the premier referral center for COVID-19 care in the state of Maharashtra, India, in the future (A. Insole, MBBS, MS, written communication, October 18, 2021). Finally, no patients in the current study were fully vaccinated, and further studies investigating the relationship between vaccination and CAM incidence will be welcome. Indeed, hopefully more effective prevention and treatment of severe COVID-19 infection through increased vaccination and more efficacious antiviral therapy, respectively, will ultimately decrease the incidence of CAM.

The current study adds survival data to our understanding of CAM and identifies patients at greatest risk for mortality from this condition. We congratulate the authors and their medical and surgical colleagues on their tremendous efforts in caring for an unprecedentedly large number of patients with ROCM. We appreciate the authors’ efforts as well in sharing their experience with caregivers worldwide, and in paving the way with this report for future studies of this devastating disorder.

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Published Online: December 9, 2021. doi:10.1001/jamaophthalmol.2021.5202

Conflict of Disclosures: None reported.

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