Initial and ongoing challenges with COVID-19-associated mucormycosis

Secondary bacterial and fungal infections complicating the course of viral epidemics have been previously noted. Be it pneumococcal pneumonia with Spanish flu a century ago, Aspergillosis associated with influenza, or fungal infections including mucormycosis associated with the previous SARS epidemic of 2003, one can find numerous such references throughout history.[1-4] On this occasion, COVID-19-associated mucormycosis (CAM) has captured the headlines as a disfiguring and potentially life-threatening disease complicating the course of COVID-19 infection. Though reported from many parts of the globe, India particularly has had an alarming epidemic of CAM from April to June 2021. It has been declared as a notifiable disease by various state governments. The overwhelming numbers reported from across the country at a time when the nation is yet struggling with the COVID-19 pandemic has presented unique challenges to patients, clinicians, policymakers, and administrators. The ophthalmologic community has been particularly proactive in taking on this challenge.

The setting in which CAM takes root is now well established.[4-6] Prospectively derived data from our institution has noted the triad of hyperglycemia, frequent use of steroids and immuno-compromising treatments, and perhaps COVID-19-associated immune compromise as the prime drivers of impaired immunity facilitating entry and growth of this opportunistic infection. It was found that 95% of patients at presentation had uncontrolled hyperglycemia, 57% had recent steroid use, and in many instances, this use was deemed as inappropriate.[7] Whether virus variants, use of supplements, and other factors have further contributed to this epidemic are questions to which answers should soon be available. The epidemic has now waned, and in some measure, it was the immediate understanding of the causative factors and the dissemination of information to professionals and the public on this aspect that has contributed to its easing.

An aspect not noted conclusively in the recent literature but very much part of our experience is regarding frequent COVID-19 positive status on nucleic acid amplification-based tests at presentation of CAM.[7] This could be ascribed to a false positive test caused by "dead virus," but in this setting of immune compromise, it is just as likely to reflect persisting disease activity and possible infectivity. Accordingly, our policy for inpatient admissions has been as per this categorization into separate COVID-19 positive and negative facilities. Additionally, concurrent manifestations of moderate and severe COVID-19 illness have been frequent in our experience, and this too may be at variance with the experience at standalone non-COVID-19 or ophthalmological facilities wherein the spectrum of patients would not include such patients with ongoing COVID-19 illness.

Among our earliest initiatives was to set up multispecialty teams inclusive of otolaryngology, endocrinology, ophthalmology, internal medicine, neurology, and anesthetic critical care for the care of patients with multiple comorbidities inclusive of hyperglycemia, immune compromise, and ongoing COVID-19. Spreading awareness of the disease setting (hyperglycemia and steroid use) and of the early and sentinel signs for early detection by healthcare workers was the next step. Information templates were promptly made and circulated. Wide and rapid information disseminated to the public via television and social media helped with public awareness and has likely contributed significantly to the rapid decline of the epidemic.

Diagnostic and Therapeutic Challenges

Initial challenges related to confirmation of diagnosis, radiological assessment, and ascertaining the timing of surgery. A large number of patients being COVID-19 positive at presentation necessitated the setting up of appropriate facilities with requisite precautions and personal protective equipment for nasal endoscopy, sampling, and radiology. The nasal cavity and nasal secretions are a nidus for the COVID-19 virus, and nasal endoscopy undertaken in potentially COVID-19 positive patients can be especially hazardous and infectious for healthcare personnel. A specific Mucor screening clinic was set up with appropriate protocols, personnel, and equipment for endoscopic evaluation and biopsy of all suspected patients. Fungal elements become nonviable after a few hours of refrigeration.[8] Thus, rapid tissue processing must be ensured to obtain a higher yield. A team of mycologists was designated to process samples ensuring 24/7 availability. Tissue fungal polymerase chain reaction, being a promising technique with sensitivity ranging from 54% to 100%, was additionally used to increase the yield.[9] The initial swab positivity rate with blind nasal swabbing was noted at only 15%, but the institution of the above-listed quality improvement measures led us to achieve a swab/biopsy positive confirmation rate of 85%.

Magnetic resonance imaging has traditionally been advocated as the radiological evaluation of choice, but for patients with COVID-19-positive status, uncontrolled comorbidities, and oxygen requirement, we have tended to prefer initial and emergent radiological evaluation by contrast-enhanced tomography rather than by MRI. CECT was preferred for the advantages of rapid scan time and for immediate feasibility with the availability of designated CT scanners for COVID-19-positive patients.[10] Innovations in CT techniques developed for this indication have proved to be appropriate for evaluation of the Paranasal sinuses and contiguous soft tissues including the orbit, as well as the venous and arterial anatomy [Fig. 1].

Treatment principles have centered on control of immune compromise (hyperglycemia control and reconsideration of immunosuppressive medication), anti-fungal treatment, and appropriate debridement. Navigating the shortage of liposomal amphotericin B (LAMB) has been problematic, and this has been minimized by triaging patient requirements as per disease status and stage. Mortality and disease progression is maximal in the first week of illness,[11,12] and our priority has been to ensure appropriate doses (3–5 mg/kg of LAMB) at the time of acute presentation, and in patients with manifest orbital, cerebral, or cavernous sinus disease. Patients with stable disease and full control of comorbidities in the post-surgical period have been managed with lower daily doses of LAMB or with oral posaconazole treatment.

Figure 1: CECT paranasal sinuses in a 47-year-old male with COVID-19-associated mucormycosis. Coronal soft tissue window (a), coronal bone window (b), axial soft tissue window (c), and volume-rendered image (d) showing mucosal disease in the right ethmoid sinuses (black arrow). There is orbital invasion with involvement of medial rectus (*), optic nerve (arrowhead), and orbital apex (dotted arrow), with inflammation in retro-orbital fat and axial proptosis. Further, there is erosion of cribriform plate with intracranial extension (white arrow). Right cavernous sinus is also involved with narrowing of the cavernous segment of right ICA (black arrow)

Surgical debridement is deemed as appropriate and complete when all necrotic and diseased tissue is cleared and the residual margin at the surgical site is noted as normal and freely bleeding. While endoscopic nasal debridement is currently the norm and minimizes morbidity, it provides limited access to the anterolateral maxillary wall and to the palate. We have, therefore, had a low threshold to transition to the sublabial approach and to open surgical approaches. The greater challenge, however, has been with regard to the timing of surgery in patients with continuing COVID-19-associated respiratory involvement and hypoxia. Surgical intervention in such patients is known to be associated with significantly greater morbidity and mortality.[13] Our previous unpublished experience has indicated the prognostic role of acute phase reactants, particularly serum ferritin, in such cases. Thus, along with clinical staging and disease progression, biochemical parameters were used as guiding tools for triage. While addressing COVID-19-positive patients, debridement was planned after initial patient stabilization with control of comorbidity and initiation of LAMB. A low threshold was kept for supporting the post-op course by a temporary tracheostomy in patients with poor pulmonary function or those likely to have a compromised airway.

The role of intraocular amphotericin B is yet to be based on a sound evidence base. Current practices are based on expert opinion and the expectation of efficacy by instilling antifungal medication around suspicion.[5,14] The indications in our practice included patients with minimal orbital invasion and preserved vision with an intent for orbital preservation,[15] and other situations wherein it is used as a temporizing measure for patients with obvious orbital invasion but orbital exenteration cannot be immediately undertaken for reasons of coexistent uncontrolled comorbidities or moderate-severe COVID-19 illness. Long-term outcomes from this practice are awaited. Never have we had the occasion to treat so many patients and the outcomes as noted from this experience shall serve as the evidence base to guide future practice.

Challenges Ahead

Post discharge, such patients need regular follow-up to ensure disease-free status and comorbidity control. In our series, approximately 30% of operated patients suffered a deforming loss of the orbit or palate. The higher incidence of deformity in our practice may relate to the referral patterns to our institution wherein higher stage illness tends to be referred. These patients require appropriate rehabilitation and reconstruction by way of either prosthetic rehabilitation (palatal prosthesis and orbital prosthesis) or surgical reconstruction by regional or free flap reconstruction. A comprehensive and separate multidisciplinary rehabilitation clinic has been activated with the involvement of prosthodontics and facial plastic reconstruction teams. Immediate rehabilitation has been primarily with spectacle anchored prosthesis for the orbit and dental anchored prosthesis for the palate, with subsequent planning for osteo-integrated implants and free flap reconstruction as appropriate.

One often neglected aspect of patient management includes addressing the psychological burden of the disease. Suffering from COVID-19 in itself is psychologically distressing; one can only imagine the wretchedness of a patient being infected with a morbid disease as mucor at the time of potential recovery from COVID-19. Surgery can be further disfiguring as it may involve orbital exenteration, maxillectomy with resulting nasogastric feeding, craniotomies with residual defects, and scars. Being rapidly progressive, these patients are often unable to resign themselves to the morbidity in such a short span of time. The admission in COVID-19 isolation wards distant from their relatives further adds to the agony. One can also not ignore the financial burden the disease brings with itself—prolonged hospital stay, long recovery period, maintenance therapy with posaconazole, and reconstructive surgeries among others. In such situations, it rests upon healthcare workers to provide patients with possible moral support and keep an open communication channel.

As the current COVID-19 wave recedes, resurgence and a possible third wave remain distinct possibilities. It does seem though that the lessons learned with regard to the factors that led to CAM will not be easily forgotten. The biochemical evaluation of COVID-19 now regularly includes testing of blood sugar levels even in patients not previously documented as diabetics. Caution is now exercised with the use of corticosteroids and immune-modulators and use is moderated as per guidelines. Proper use of well-fitted masks will protect not only against COVID-19 but also filter out fungal spores. It is also hoped that our population would continue to abide by COVID-19-appropriate social distancing and undertake vaccinations as recommended.

A comprehensive rehabilitation addressing psychological, social, and economical issues needs to be commenced.

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References

1. Brundage JF, Shanks GD. Deaths from bacterial pneumonia during 1918-19 influenza pandemic. Emerg Infect Dis 2008;14:1193-9.
2. Kwon OK, Lee MG, Kim HS, Park MS, Kwak KM, Park SY. Invasive pulmonary aspergillosis after influenza infection in an immunocompetent patient. Tuberc Respir Dis (Seoul) 2013;75:260-3.
3. Blaize M, Mayaux J, Nabet C, Lampros A, Marcelin AG, Thellier M, *et al*. Fatal invasive aspergillosis and coronavirus disease in an immunocompetent patient. Emerg Infect Dis 2020;26:1636.
4. Zhang Y, Li WX, Huang KW, Cao ZX, Hao JY. Hospital acquired pneumonia occurring after acute stage of the serious SARS and its treating strategies. Chin J Nosocomiol 2003;11:1081-7.
5. Sen M, Honavar SG, Bansal R, Sengupta SR, Raksha K, Usha K, *et al*. Epidemiology, clinical profile, management, and outcome of COVID-19-associated rhino-orbital-cerebral mucormycosis in 2826 patients in India – Collaborative OPAI-IJO study on mucormycosis in COVID-19 (COSMIC), report 1. Indian J Ophthalmol 2021;69:1670-92.
6. Patel A, Agarwal R, Rudramurthy SM, Shevkani M, Xess I, Sharma R, *et al*. Multicenter epidemiologic study of coronavirus disease–associated mucormycosis, India. Emerg Infect Dis 2021;27:2349-59.
7. Singh A, Sikka K, Goel G, Kanodia A, Chandran A, Konkimalla A, *et al*. COVID-19 asociated rhino orbito cerebral mucormycosis (CAROM) in Delhi demographics and risk factors in a single centre consecutive cohort of 200 patients. Natl Med J India. (in press)
8. Balows A, Hausler W, Herrmann K, Isenberg H, Shadomy HJ. Manual of Clinical Microbiology. 5th ed. American Society for Microbiology; New Delhi; 1991.
9. Baldin C, Soliman SSM, Jeon HH, Alkhazraji S, Gebremeriam T, Gu Y, *et al*. PCR-based approach targeting mucorales-specific gene family for diagnosis of mucormycosis. J Clin Microbiol 2018;56:e00746-18.
10. Manchanda S, Semalti K, Bhalla AS, Thakar A, Sikka K, Verma H. Revisiting rhino-orbito-cerebral acute invasive fungal sinusitis in the era of COVID-19: Pictorial review. Emerg Radiol 2021. doi: 10.1007/s10140-021-01980-9.
11. Talmi YP, Goldschmied-Reouven A, Bakon M, Barshak I, Wolf M, Horowitz Z, *et al*. Rhino-orbital and rhino-orbito-cerebral mucormycosis. Otolaryngol Head Neck Surg 2002;127:22-31.
12. Dhiwakar M, Thakar A, Bahadur S. Improving outcomes in rhinocerebralmucormycosis-early diagnostic pointers and prognostic factors. J Laryngol Otol 2003;117:861-5.
13. Nipogidiev D, Bhangu A, Glasbey JC, Elizabeth E, Omar OM, Simoes JF, *et al*. Mortality and pulmonary complications in patients undergoing surgery with perioperative SARS-CoV-2 infection: An international cohort study. Lancet 2020;396:27-38.
14. Davin C, Ashraf MD, Oluwatobi O, Idowu MD, Kristin E, Hirabayashi MD, *et al*. Outcomes of a modified treatment ladder algorithm using retrobulbar amphotericin B for invasive fungal rhino-orbital sinusitis. Am J Ophthalmol 2021. ISSN 0002-9394.
15. Honavar SG. Code mucor. Indian J Ophthalmol 2021;69:1361-65.

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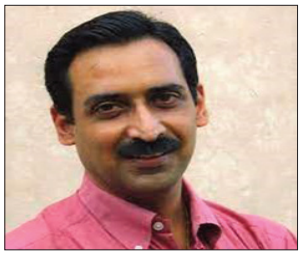

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