COVID-19-Associated Mucormycosis: What Neurologists Should Know?

During the ongoing coronavirus disease 2019 (COVID-19) pandemic, there has been an unprecedented rise in the number of cases of mucormycosis especially in India during the second wave.[1-4] COVID-19-associated mucormycosis (CAM) most commonly involves nasal cavity, para-nasal sinuses, orbits, and at times the central nervous system (CNS); collectively, the disease is known as rhino-orbito-cerebral mucormycosis (ROCM). Otorhinolaryngologists, ophthalmologists, maxillofacial surgeons, and neurologists usually tend to manage these patients along with physicians and infectious disease experts. There have been many reports of neurological manifestations of CAM[1,2] including one in this issue of Annals of Indian Academy of Neurology.[5]

Various hypotheses have been suggested for the increased incidence of CAM during the pandemic, especially during the second wave.[6-9] Excess steroid use, a cumulative dose of 97 milligrams of dexamethasone or equivalent,[8] pre-existing or new onset diabetes mellitus, diabetic keto-acidosis, prolonged use of masks, immune dysregulation because of COVID-19, and high ferritin levels are some of the important factors. Other known factors such as immunosuppressive therapy, underlying malignancy, chemotherapy, organ transplant, and chronic kidney disease were also seen in the studies.[5,10] Two different case-control studies have shown that use of aspirin and anti-coagulation and zinc therapy were associated with a decrease in the risk of CAM.[8,9]

The most common neurological complication of ROCM is cranial neve involvement, and they get involved by spread from adjacent para-nasal sinuses and orbits. Trigeminal nerve involvement in the form of facial pain; infiltrative, compressive, or ischemic optic neuropathy; facial nerve involvement; and oculomotor nerve involvement at the orbital apex or at the cavernous sinus are the most common cranial neuropathies. Local extension of the disease from para-nasal sinuses and orbits leads to cerebritis, cavernous sinus involvement, and skull base osteomyelitis. The internal carotid artery can get involved in the cavernous sinus, and less commonly, the basilar artery gets engulfed by clival osteomyelitis, leading to vascular complications in the form of acute ischemic stroke, intra-cranial hemorrhage, mycotic aneurysm formation causing subarachnoid hemorrhage, and rarely carotico-cavernous fistula. Uncommon complications are meningitis and intra-cranial abscess formation. These complications have also been reported with CAM.[1,2,4,5,11] Because the patient who has presented with facial pain, nasal discharge, proptosis, and vision loss can develop additional neurological complications any time during the course of illness, a high level of vigilance is needed to detect them early. Whether CAM has more neurological involvement compared to non-CAM cases has not been looked at in detail. In their article, Garg *et al*.[5] have described neurological manifestations more than twice in CAM versus non-CAM patients. Strokes were seen in >10% of CAM in our studies.[1,11] The clinical features of CAM may begin during the course of COVID-19 and can also appear up to 2 months after recovery from COVID-19.[1]

There are several implications of CNS involvement. The mortality is higher with CNS involvement. Early diagnosis and treatment may reduce the mortality; hence, a neurological examination is necessary as a part of initial evaluation so as to pick up involvement early. Neurological involvement occurs any time during the course of illness. Therefore, the imaging of a CAM patient should include the brain and its vessels along with the nose, para-nasal sinuses and orbits to pick up early intra-cranial extension. Protocols have been formulated to serve this purpose.[12] In terms of treatment, the dose of liposomal amphotericin B needs to be increased to 10 mg/kg/day in patients with cerebral involvement.[13] Liposomal preparation is expensive in resource-limited circumstances and in such epidemic times when COVID-19 management has already taken a toll on finances. Therefore, in our country, we may have to use conventional amphotericin B with stringent renal monitoring.[14] Although amphotericin B is the gold standard of treatment, two oral triazoles, posaconazole and isavuconazole, can be used in treatment of mucormycosis. Posaconazole has poor CNS penetration compared to isavuconazole.[15,16] Therefore, isavuconazole can be preferred over posaconazole in CNS involvement. The treatment duration is much longer with CNS involvement and skull base osteomyelitis and cerebral abscess and may need to be extended maybe for months.

Because the COVID-19 pandemic is waning, we are already observe a drop in the number of cases of CAM. Because India has the highest prevalence of mucormycosis,[17] we may encounter such cases more frequently than neurologists outside India. The neurology fraternity must be aware of the devastating disease, the process of its diagnosis, monitoring, its treatment protocol, and adjustments that need to be undertaken in resource-limited situations.

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