

Covid-associated pulmonary mucormycosis

The COVID-19 pandemic caused a massive surge in the number of cases of a rare opportunistic fungal infection, mucormycosis.^[1,2] In India, during the first wave of COVID-19, the prevalence of mucormycosis was reported to be 2.1 times higher than normal.^[3] However, during the second wave, these numbers exploded, with over 28,000 cases reported.^[4] The causal relationship between COVID-19 and mucormycosis is largely unknown. Various proposed theories included 1. prolonged uncontrolled hyper-glycaemic state 2. glucocorticoid-induced immunosuppression, hyperglycaemia and lymphopenia, 3. viral-induced lymphopenia and endothelitis, 4. increased serum levels of free iron (hyper-ferritinemic state), 5. ketonemia and ketoacidosis, even in the absence of diabetes mellitus.^[5-9]

Pulmonary mucormycosis is the third most common variant of COVID-associated Mucormycosis.^[10] COVID-associated pulmonary mucormycosis (CAPM) is characterised by its angio-invasive and thrombotic nature, which causes tissue necrosis.^[11] Due to this nature, this disease most commonly presents as large cavitation in lung parenchyma or in some cases as diffuse lung infiltrates. Due to the invasive nature, mucor can spread rapidly to the surrounding structures such as the pulmonary artery causing pseudoaneurysms, hilar lymph nodes, mediastinum, heart, and sometimes can disseminate haematogenously to other organs.^[12] A high degree of suspicion is needed, and active search for the fungus should be made in sputum (low yield) or preferably, a bronchoscopically obtained sample from the involved lobe or in trans-thoracic tru-cut lung biopsy material. Initiation of antifungal therapy at the earliest suspicion, even before the definitive diagnosis, should be practiced for better therapeutic outcomes. There is enough evidence in the literature, which quantified and confirmed the benefits of early initiation of liposomal amphotericin-B in pulmonary mucormycosis.^[13,14]

The essential components of management of pulmonary mucormycosis include 1. reversal of underlying risk factors such as hyperglycaemia and/or tapering of steroids, 2. optimal anti-fungal therapy and 3. aggressive surgical resection.^[15,16] However, the clinical situation in COVID-19 is so unique and challenging that all three components of the management are compromised. First, due to the requirement of the cortico-steroids, uncontrolled hyperglycaemia is a rule rather than an exception in moderate and severe COVID-19. The underlying multi-organ dysfunction, diffuse lung infiltrates and baseline oxygen requirement complicates the matter further and add to the current problem.^[17] Second, at the time of the pandemic, all health care facilities were

overwhelmed by COVID-19 patients, which significantly curtailed the supply of essential services, including anti-fungal medications.^[18] Third, due to the rarity of this condition, there were no clear-cut guidelines regarding the extent and timing of the surgery. The majority of reported studies in CAPM were anecdotal case reports.^[17,19,20] Therefore, the facts/details about the true incidence and the factors affecting post-surgical complications, including mortality, were sparse in the literature.

Surgery is complementary to anti-fungal therapy rather than an alternative. However, clear-cut guidelines regarding the extent and timing of surgical resection have never been defined. However, a successful attempt at methodological management of pulmonary mucormycosis was made by the authors in the previously reported surgical series in non-COVID pulmonary mucormycosis.^[21] The salient observations from the previous study were as follows: 1. Earliest possible aggressive surgical resection should be performed with the aim of achieving clear margins; 2. Peri-operative anti-fungal therapy is mandatory. Similar recommendations were reported by other authors as well.^[22]

Surgery for CAPM is challenging due to dense pleural adhesions and difficult anatomical planes with the major blood vessels^[22] Pseudo-aneurysm of the pulmonary artery/branches (mycotic aneurysm) is not uncommon in pulmonary mucormycosis due to the angio-invasive nature of the infection. Due to all these factors, completion of surgery by the video-assisted thoracoscopic (VATS) method is challenging and open surgery is usually required.

Due to all these factors, mortality in COVID-associated mucormycosis was considered to be higher than in non-COVID patients.^[1] In the current issue of Lung India, a case series of CAPM in critical care settings is presented wherein all patients were initiated on Liposomal Amp B but could not be operated due to instability, extensive disease, and fibrosis— a feature seems to be unique to CAPM.^[23] However, findings from an unpublished personal experience of the author over 36 patients of CAPM were quite contradictory. In this series, out of total of 36 patients, 25 patients were offered comprehensive management with intravenous liposomal amphotericin-B followed by aggressive surgical resection, and the rest 11 patients received intravenous liposomal amphotericin alone due to extensive bilateral multi-lobe involvement or extensive mediastinal involvement. All these 11 patients died within 2 weeks of initiation of anti-fungal therapy, that is, mortality was 100%. However, in the surgical cohort, the peri-operative mortality was 20%. In addition,

the post-operative complications and mortality were no different in CAPM compared to the non-COVID PM. This can be explained by 1. previous surgical experience of managing a significant number of pulmonary mucormycosis patients; 2. following time-proven and successful institutional guidelines^[22] for the management of this complex situation and 3. proper patient selection and robust anaesthesia and critical care support.

In conclusion, pulmonary mucormycosis is an opportunistic, fatal fungal infection, which posed a great therapeutic challenge for clinicians, in COVID-19 patients. A high degree of suspicion is essential for the early diagnosis and anti-fungals should be started at the earliest suspicion, even before confirmation of the diagnosis. Aggressive surgical resection with clear margins should be offered whenever feasible as anti-fungal therapy alone will have sub-optimal outcomes. Surgical resection should be synergised with peri-operative anti-fungal therapy to improve long-term survival.

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Conflicts of interest

There are no conflicts of interest.

Arvind Kumar, Mohan V. Pulle, Belal B. Asaf, Harsh V. Puri

Institute of Chest Surgery, Chest Onco Surgery and Lung Transplantation, Medanta The Medicity, Gurugram, Haryana, India
E-mail: arvindreena@gmail.com

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