CASE REPORT

Rare Mixed Infections; Mucormycosis with Concomitant Actinomycosis in the Post-Covid Period: A Case Series

Latha Mary Cherian[1], Indu M[2], Aishwarya Menon P[1], Bhagya J[1]

Abstract

Introduction: COVID-19 is a viral infection caused by SARSCoV2. This pandemic can have pulmonary and extrapulmonary symptoms. The immunosuppression caused by co-morbidities of patients or COVID-19 may lead to secondary microbial infections which can be bacterial, fungal, or viral. Sometimes, the co-existence of multiple infections may worsen the scenario.

Case Presentation: Here, we present two known cases of diabetes mellitus of Indian ethnicity having chief complaints of mobility of upper teeth and exposed alveolar bone in the post-COVID period. Both patients were diagnosed with co-existence of two opportunistic infections; Covid-associated mucormycosis and actinomycosis (CAMA).

Management: Patients were treated with surgical debridement, and antimicrobial medication and were recovered.

Conclusion: We conclude that occurrence of COVID-19 infection, mucormycosis, and actinomycosis are interrelated and early diagnosis of multiple opportunistic infections is most important for better prognosis of patients. We also suggest strict monitoring of patients with co-morbidities in the post-COVID period.

Keywords: Actinomycosis, Coinfection, COVID-19, Diabetes mellitus, Immunosuppression, Mucormycosis

Introduction

Coronavirus disease – 2019 (COVID-19) is an infectious respiratory and vascular disease caused by SARS – CoV 2 virus (severe acute respiratory syndrome coronavirus 2) and was declared as a global health emergency by WHO on January 30, 2020.[1,2] The disease presented as mild to life-threatening pneumonia and extrapulmonary symptoms.[3] COVID-19 puts patients with other co-morbidities more prone to secondary/ opportunistic infections.[4]

Mucormycosis and actinomycosis are debilitating opportunistic infections encountered in COVID-19 patients. Mucormycosis, commonly known as "black fungus" is caused by a group of fungi called Mucormycetes.[3,5] Actinomycosis is also a rare infection caused by the genus Actinomyces – a heterogenous group of filamentous gram-positive bacilli.[6,7] Like mucormycosis, actinomycosis is also seen in patients with immunodeficiencies however treatment options for both differ.[6] Here, we present a case series of COVID-associated mucormycosis co-existing with actinomycosis (CAMA) in patients of Indian ethnicity.

Case Presentation

The present case was a 60-year-old male patient with mobile left upper front teeth for 3 weeks. One and half years after the COVID infection he had a fever, nasal obstruction with black-colored discharge, and blurring of vision on his left side. He was a chronic smoker and had uncontrolled type II diabetes mellitus which was detected 2 weeks back, after which the patient started taking medications. The patient tested positive for COVID-19 1 year back. On examination, black crusts on the left inferior meatus, exposed bone at the left maxillary alveolar region, and midline of the palate were noted. The patient had poor oral hygiene with generalized periodontitis. The radiograph showed generalized interdental bone loss and thinning of the floor of maxillary sinus. (Figure 1) Routine blood investigations showed increased blood glucose levels (Fasting blood glucose level 222 mg/dl, Postprandial blood glucose level 313 mg/dl). Erythrocyte Sedimentation Rate (ESR) was elevated (82mm/hr.). Comput-

Department and Institution Affiliation: [1]Department of Oral Pathology and Microbiology. Government Dental College, Kottayam, Kerala, India; [2]Department of Oral Pathology and Microbiology. Government Dental College, Thrissur, Kerala, India.

Corresponding author: Indu M, Department of Oral Pathology and Microbiology. Government Dental College, Thrissur, Kerala, India. Email Id: indumohan2011@gmail.com

How to cite the article: Cherian LM, Indu M, Menon P A, Bhagya J. Oral Maxillofac Pathol J 2025; 16(1); 118-122.

Source of Support: Nil

Conflict of Interest: None

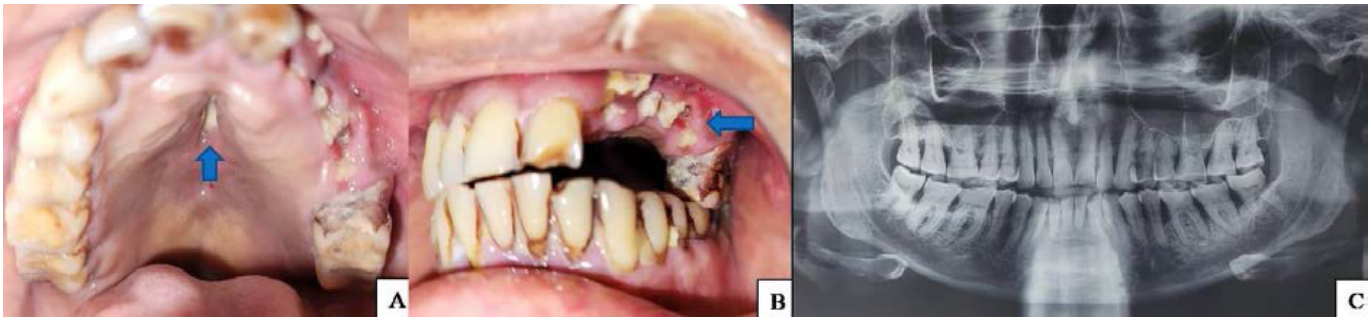
ed tomography (CT) and Magnetic resonance imaging (MRI) scans revealed mucosal thickening of paranasal sinuses and bony erosion of the medial wall of the maxillary sinus.

KOH mount of samples from the palate revealed branching hyphae. Histopathological examination revealed bony trabeculae interspersed with broad aseptate fungal hyphae branching at a right angle. Gomori Methenamine Silver staining (GMS) revealed numerous black-colored branching aseptate fungal hyphae. Later, the patient underwent functional endoscopic sinus surgery (FESS). Microscopic examination of the FESS specimen revealed fungal hyphae with radiating colonies of actinomyces. This was further confirmed by staining with GMS. The final diagnosis of mucormycosis coexisting with actinomycosis was given. (Figure 2 and 3)

Injection Liposomal Amphotericin and Crystalline penicillin were administered and the patient survived.

The second case reported was a 42-year-old male patient with pain and mobility of left upper back teeth for 1 year. He was a chronic smoker, betel quid chewer, and had uncontrolled type II diabetes mellitus for which insulin therapy was started 2 months back. He had a history of COVID-19 infection 1 year back. Intraoral examination revealed denuded mucosa

Case1



Case 1. Fig. 1A: Palatal erosion exposing bone at the midline, **Fig.1B:** exposed bone at left maxillary region, **Fig.1C:** Panoramic radiograph showing generalized interdental bone loss and thinning of the floor of maxillary sinus.)

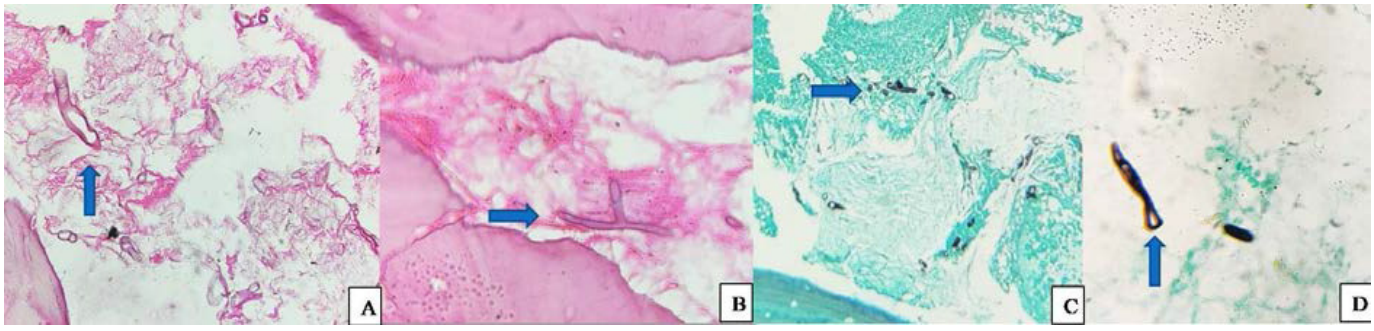


Fig.2A and B: broad aseptate hyphae (H& E, X 40), **2Cand D:** broad aseptate hyphae in GMS staining (GMS, X 40)]

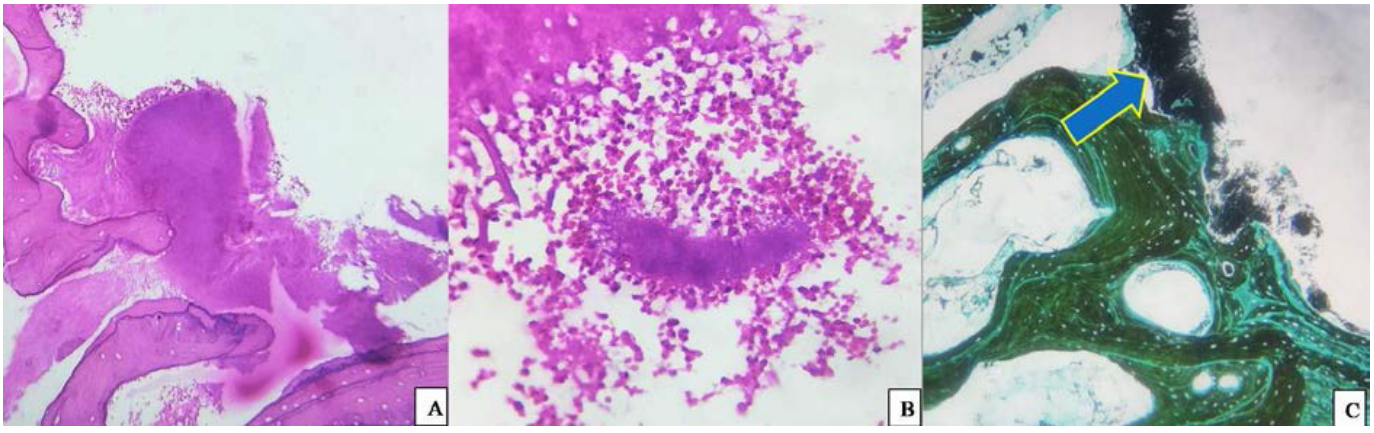


Fig. 3A: Actinomycotic colonies, **Fig. 3B:** Splendor Hoeppli phenomena (H& E, X 40), **Fig. 3C:** Actinomycotic colonies in GMS staining (GMS, X 40)]

with exposed necrotic bone in the left maxillary posterior region and mobility of the associated dentoalveolar segment. The patient had poor oral hygiene with generalized periodontitis along with segmental mobility of the dentoalveolar segment of the maxilla from 24 to 28 region. Routine blood investigations showed an increased fasting blood glucose level 158 mg/dl and postprandial blood glucose level 264 mg/dl). CT showed erosion of the floor and posterolateral wall of the left maxillary sinus. (Figure 4)

Histopathological examination of partial sequestrectomy samples revealed necrotic bony trabeculae interspersed with broad aseptate fungal hyphae branching at right angles. Tissue sections also showed numerous bacterial colonies exhibiting club-shaped filaments arranged in a radiating pattern. Both fungal hyphae and bacterial colonies were stained positively by GMS staining. A final diagnosis of mucormycosis coexisting with actinomycosis was given. (Figure 5 and 6) Amphotericin B 10 mg/Kg for 28 days was administered followed by inferior maxillectomy and FESS. The patient recovered well.

Discussion

The causative agent of COVID-19 is single-stranded RNA (ssRNA) viruses. These viruses have a crown-like appearance due to the spike glycoproteins on its envelope.

It affects respiratory and extrapulmonary systems.[3] According to the WHO COVID-19 epidemiological update, as of 23 June 2024, over 775 million confirmed cases and over 7 million deaths have been reported globally.[8] Among the extrapulmonary sites, more cases of oral involvement are reported. According to Lin W et al., two-thirds of the patients have at least one oral symptom. Dysgeusia, xerostomia, and oral mucosal lesions are the most frequently observed. Among the oral mucosal lesions, aphthous-like lesions, herpes-like lesions, geographic tongue, plaque-like lesions, fungal infections (candidiasis and mucormycosis), mucosal petechiae, herpes simplex virus (HSV) reactivation-related ulcers, oral herpes zoster, gingivitis, and bleeding gums are frequently seen.[9]

Certain factors associated with COVID-19 promote oppor-

Case 2.

Fig. 4A: Denuded mucosa with exposed necrotic bone in the left maxillary posterior region

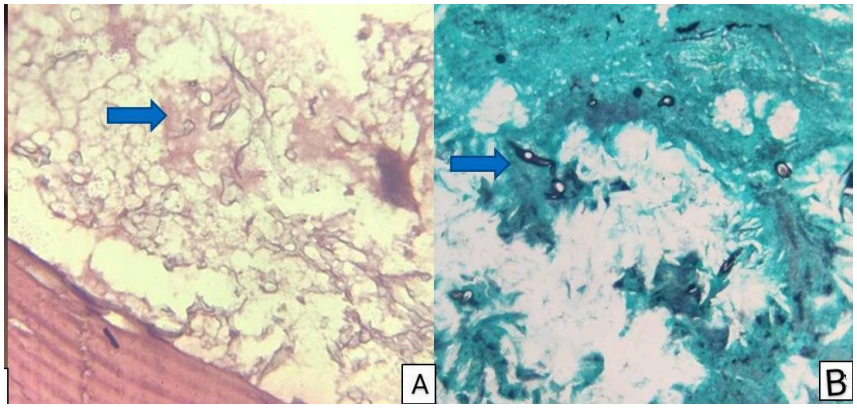


Fig. 5A: Photomicrograph shows broad aseptate hyphae (H and E, X 40), **Fig. 5B:** broad aseptate hyphae in GMS staining (GMS, X 40)]

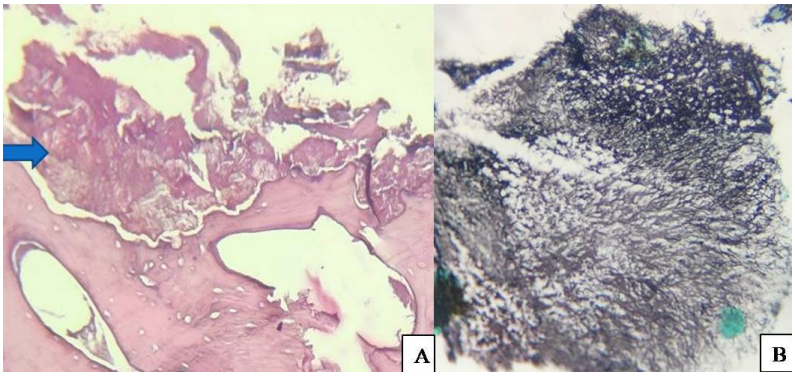


Fig. 6A: Actinomycotic colonies (H and E, X 40), **Fig. 6B:** Actinomycotic colonies in GMS staining (GMS, X 40)]

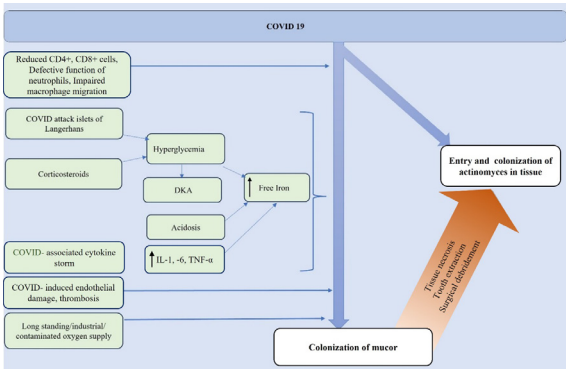


Fig. 7: Causal relationship of Covid 19, mucormycosis and actinomycosis

tunistic infections. One of such main factors is COVID-associated lymphopenia. SARS CoV 2 causes a decrease in CD4+ T, CD8+ T & B cells, NK cells, and eosinophils. Other factors include elevated blood glucose levels and Diabetic Ketoacidosis (DKA). This situation can arise due to the destruction of Islets of Langerhans and steroid treatment. DKA lowers pH of tissues. Low pH due to DKA provides a favorite medium for fungal spore germination.[1,4] In COVID-19 infection, there will be an increase in pro-inflammatory markers (IL 1, IL 6, TNFα) which causes cytokine storm in some cases.[1,4] Acidosis and increased levels of cytokines (IL 1, IL 6, TNF α) increase free iron by increasing ferritin levels. Hyperglycemia increases free iron levels by reducing the ironbinding capacity of transferrin. Free iron is a good resource for the growth of mucor. High glucose, low pH, free iron, and ketones in the presence of decreased phagocytic activity enhance the progress of mucor. COVID-19 causes endothelial damage and thrombosis which are favorable for secondary infections. The monoclonal antibodies and broad-spectrum antibiotics used for Covid treatment also indirectly enhance microbial growth.[1,4] The possible co-infections in a COVID-19 patient include bacterial, viral, and fungal infections. (Figure 7)

During the second wave of COVID-19 in India, B.1.1.7 and B.6.117 variants of SARSCoV2 accelerated fungal invasion

Table 1: Summary of reported CAMA cases of Indian ethnicity. [1,2,4,6]

Source (Author, Year)	Jawanda et al 2021 (1 case) [1]	Jagtap et al 2021(1 case) [2]	Mishra N et al 2021(1 case) [6]	Menia R et al 2022 (1 case) [4]
Country	India	India	India	India
Age/ Gender	70/M	46/M	37/M	53/F
Comorbidities	type II DM	type II DM	No known co-morbidities	type II DM and hypertension
Time of diagnosis of Covid	4 months before secondary infection	1 month before secondary infection	2 months before secondary infection	1 month before secondary infection
Covid severity/hospitalized/ ICU	Hospitalized	Not mentioned	Hospitalized for 19 days and in ICU for 7 days	No hospitalization
Treatment for COVID	Steroids, Ivermectin, Remdesvir, Tocilizumab	Not mentioned	Inj. remdesivir, inj. tocilizumab and total aggregate of 240 mg of dexamethasone	Methyl-prednisolone 16 mg orally for 15 days
Microbiology of CAMA				
KOH mount	Not mentioned	Not mentioned	aseptate hyphae	Not mentioned
Histopathology	Necrotic bone interspersed with broad, aseptate hyphae, branching at right angles and club shaped filamentous colonies arranged in a radiating pattern	Necrotic areas showed numerous colonies of mucormycosis consisting of broad, aseptate hyphae along with actinomycotic colonies	Necrotic tissue with broad aseptate fungal hyphae consistent with mucormycosis along with actinomycosis	Necrotic debris admixed with broadbased, aseptate fungal hyphae of Mucorales and colonies of filamentous bacteria suggestive of Actinomyces.
Culture	Not mentioned	Not mentioned	Not mentioned	Not mentioned
Treatment for CAMA	Sequestrectomy Posaconazole (400 mg BD × 3 months), oral Clindamycin (300 mg TID × 6 weeks)	Hemi maxillectomy, debridement and curettage, Amphotericin-B –antifungal therapy	Inj. liposomal amphotericin B 250 mg daily for 6 weeks duration followed by T. Posaconazole 300 mg once a day regimen and palatal defect closure. inj. ampicillin 2 gm IV every 6th hourly for 2 weeks.	Symptomatic treatment
Outcome (alive/deceased/lost follow up	Survived	Survived	Survived	Survived

(M: Male, F: Female, DM: Diabetes Mellitus, CAMA: Covid associated mucormycosis and actinomycosis)

through changing immunomodulation and gene expression and there was an increase in the incidence of fungal infections.[10] According to Pasquier et al, the incidence of COVID-associated mucormycosis in India ranged from 0.27% to 1.8% in hospitalized patients during the pandemic.[5]

Mucormycosis (zygomycosis/ Phycomycosis) is caused by saprophytic fungi of the order Mucorales. Mucorales enter the body through contaminated food, inhalation, and skin abrasions however in healthy individuals these spores are phagocytosed easily. The predisposing factors of CAM include DM, corticosteroid treatment, immunosuppressive therapy, malignancy, organ transplantation, long-standing/industrial oxygen therapy, poor mask hygiene, steam inhalation, contaminated oxygen/humidifiers, and increased zinc intake.[3] Fungal spores become more pervasive during construction work.[11] Common diagnostic methods include KOH **(**Potassium hydroxide**)** method and histopathologic examination under H&E, PAS (Periodic Acid-Schiff), and GMS. Culture methods can be done using SDA and PDA (SDA: Sabouraud's dextrose agar, PDA: potato dextrose agar), and molecular identification with the help of PCR can also be done.[12] The management includes antifungal therapy, surgical debridement of the necrotic tissue, and reversal of underlying risk factors. According to Muthu et al, the mortality rate of CAM in India was reported to be 36.5% which was significantly less than the globally reported mortality rate (61.9%).[13]

Actinomycosis is an anaerobic infection caused by gram-positive filamentous bacteria Actinomyces israelii. It is the normal commensal in human body.[4,6] The most common variant; cervicofacial type is characterized by the presence of multiple sinus tracts with Sulphur granules. Mucormycosis-associated tissue necrosis, tooth extraction, and surgical debridement help the entry of actinomyces into body systems. Histopathologic examinations under H&E, GMS, and culture are usual diagnostic methods.[1,6] Gram stain shows non-spore forming gram-positive rods in tissue sections. The mainstay of treatment includes drainage of pus, sinus tract excision, and long-term antibiotics administration. The mortality rate can rise to 28%.[7]

Few CAMA cases were reported in patients of Indian ethnicity and a majority of such patients had DM and a history of steroid medication.[1,2,4,6] (Table 1) Many authors have shown that the co-existence of Mucormycosis and actinomycosis is not a coincidence but interrelated.

Conclusion

Occurrence of COVID-19 infection, mucormycosis, and actinomycosis are interrelated. Health professionals should be aware of the co-existence of infections as this could help in early diagnosis and treatment planning. Since multiple secondary infections are noted during the post-COVID period, we suggest strict monitoring of patients especially those with co-morbidities.

References

1. Jawanda MK, Narula R, Gupta S, Sharma V, Sidhu SK, Kaur N. Mixed Infections (Mucormycosis, Actinomycosis and Candidiasis) Leading to Maxillary Osteomyelitis in a Diabetic Mellitus Patient in Post COVID Phase: First Case Report. Acta Medica 2021;64(4):218-223.
2. Jagtap SV, Hulwan A, Vartak S et.al. Co-infection of mucormycosis and actinomycosis in COVID-19 infection. Int J Health Sci Res. 2021; 11(8): 127-130.
3. Swain SK, Jena PP. Coronavirus disease 2019associated mucormycosis of the headandneck area: A new rise of dreaded black fungus in the current pandemic. J Sci Soc 2022; 49:223-8.
4. Menia R, Raychaudhuri S, Agarwal C, Taneja J. COVID19 associated Mucormycosis – "The Black fungus" with associated Invasive Aspergillosis and Actinomycosis infection: Series of 5 cases in the Indian scenario. Indian J Pathol Microbiol 2022.
5. Pasquier G. COVID-19-associated mucormycosis in India: Why such an outbreak? J Mycol Med. 2023;33(3):101393.
6. Mishra N, Mutya VSS, Ibrahim KI, Rai G. Post COVID-19 invasive mucormycosis and actinomycosis co-infection: a case report. Int J Otorhinolaryngol Head Neck Surg 2021; 7:1537-9.
7. Acevedo F, Baudrand R, Letelier LM, Gaete P. Actinomycosis: a great pretender. Case reports of unusual presentations and a review of the literature. Int J Infect Dis. 2008 Jul;12(4):358-62.
8. https://www.who.int/publications/m/item/covid-19-epidemiological-update-edition-169. Last accessed on 3rd October 2024. 7 pm.
9. Lin W, Gao F, Wang X, Qin N, Chen X, Tam KY, Zhang C, Zhang M, Sha O. The oral manifestations and related mechanisms of COVID-19 caused by SARS-CoV-2 infection. Front Cell Neurosci. 2023 Jan 4;16:1006977.
10. Goddanti, N., Reddy, Y.M., Kumar, M.K. et al. Role of COVID 19 Inflammatory Markers in Rhino-Orbito-Cerebral Mucormycosis: A Case Study in Predisposed Patients at a Designated Nodal Centre. Indian J Otolaryngol Head Neck Surg 2022; 74 (2): 3498–3504.
11. Srinivasan A, Beck C, Buckley T, Geyh A, Bova G, Merz W, Perl TM. The ability of hospital ventilation systems to filter Aspergillus and other fungi following a building implosion. Infect Control Hosp Epidemiol 2002; 23: 5204
12. Cornely OA, Alastruey-Izquierdo A, Arenz D, Chen SCA, Dannaoui E, Hochhegger B et al; Mucormycosis ECMM MSG Global Guideline Writing Group. Global guideline for the diagnosis and management of mucormycosis: an initiative of the European Confederation of Medical Mycology in cooperation with the Mycoses Study Group Education and Research Consortium. Lancet Infect Dis. 2019 Dec;19(12): e405-e421.
13. Muthu V, Rudramurthy SM, Chakrabarti A. et al. Epidemiology and Pathophysiology of COVID-19-Associated Mucormycosis: India Versus the Rest of the World. Mycopathologia 2021;186 :739–754.