COVID-19 associated mucormycosis: the urgent need to reconsider the indiscriminate use of immunosuppressive drugs

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Invasive mycoses represent opportunistic infections occurring predominantly among highly immunosuppressed individuals, including those with advanced human immunodeficiency virus-associated immunosuppression, uncontrolled diabetes mellitus, drug-induced immunosuppression during transplantation, autoimmune disorders, or hematological malignancies. The overuse of high-dose glucocorticoids and the administration of highly immunosuppressive drugs such as inhibitors of the Janus kinase inhibitors or IL-6 receptor inhibitors to treat patients with the coronavirus disease 2019 (COVID-19) are responsible in part for the increasing number of life-threatening opportunistic infections identified in this patient population.[1,2] In addition to the iatrogenic immunosuppression induced by these medications, there has been clear evidence from the onset of the COVID-19 pandemic that lymphopenia is a common laboratory finding, indicating some degree of immunological dysfunction in individuals with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.[3,4]

Indeed, lymphopenia is a predictor of poor clinical outcome in the elderly with COVID-19.[3] Furthermore, autopsy-based data demonstrate the paucity of inflammation identified during COVID-19 infection.[5] When one compares the occurrence of viral pneumonia in patients with SARS (SARS-CoV-1), Middle-Eastern respiratory syndrome (MERS), and influenza, there are numerous data to suggest that the main pathologic process is disruption of the alveolar-capillary unit by viral-induced necrosis and apoptosis of the respiratory epithelium.[6] The overuse of high-dose glucocorticoids in these viral infections is not only of questionable benefit, but has been associated with increased mortality in the case of influenza.[7–9] Based on the currently available literature, the pathogenesis of viral pneumonia seen in patients with COVID-19 is not significantly different compared with that seen in SARS, MERS, and influenza, except for the increasing number of micro thrombosis or large embolism identified in autopsy studies in patients with COVID-19.[5]

The increasing number of recent case series of mucormycosis complicating COVID-19 patients in the United States,[10–16] Austria,[17] Brazil,[18] Mexico,[19] Italy,[20] France,[21] Iran,[22–24] and India,[25–34] raises concerns regarding the misuse of immunosuppressive drugs in patients with COVID-19. Mucormycosis is a neglected mycosis that should be considered in the context of patients with COVID-19, in the same way as COVID-19 associated pulmonary aspergillosis, and it is possibly underreported. High doses of corticosteroids or their prolonged use should be balanced between the risk and benefit of *primum non nocere*. It is crucial to know the interaction between host, environment, SARS-CoV-2, and Mucorales to establish individual risk stratification and prevention measures, carry out rapid diagnosis, and offer timely treatment that may impact the morbidity and mortality of this deadly fungus.[35]

As observed in the pandemic, the indiscriminate use of high-dose glucocorticoids or early corticosteroids use in patients with COVID-19 stems from some studies that evidenced benefits in certain specific clinical scenarios, such as those with severe disease needing oxygen or intubation, where its correct use may decrease fatal outcomes.[36] However, for those of us in the trenches

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caring for patients with COVID-19, the empiric overuse of corticosteroids has been associated with negative outcomes. Classically, uncontrolled diabetes mellitus, neutropenia, and corticosteroid therapy are known risk factors for mucormycosis.[22,37] There is an urgent need to reconsider the careful use of these drugs in patients with severe COVID-19 due to the high prevalence of underlying comorbidities in these patients,[11–13,25,28–30] including diabetes mellitus,[13,16,19,26,28–30] hematological malignancies (i.e. acute myeloid leukemia),[17] end-stage kidney disease,[27] and organ transplant recipients.[15] A recent review of published cases found eight reports[27] where diabetes mellitus was the most common risk factor for the development of mucormycosis. Three subjects had no risk factor other than glucocorticoid administration for severe COVID-19.[22] Authors found that mucormycosis usually developed 10–14 days after hospitalization.[27] The combination of steroid therapy and diabetes mellitus increases the risk of mucormycosis mediated by hyperglycemia-induced immunosuppression.[22] Immunosuppression in mucormycosis is majorly related to dysfunction in mononuclear and polymorphonuclear phagocytes in addition to increased oxidative and non-oxidative mechanisms. These changes are increased in severe COVID-19.[38–40] Most of the published cases identified *Rhizopus* as the most frequent species.[11,12,15,17,21,27,33,41] The occurrence of COVID-19-associated mucormycosis (CAM) in this group of patients may present with rhino-orbital involvement, but often involves other organs (i.e. pulmonary, gastrointestinal, intracranial), leading to fatal outcomes.[12,13,18–20,23,28,30,42] Diagnosis of invasive aspergillosis, mucormycosis, and other opportunistic fungal infections occurs frequently during post-mortem examinations.[17,22,39,43,44]

A recent case series of 18 patients with COVID-19 in India found that 16 developed mucormycosis, six of them with a fatal outcome (>37%).[28] Another series of 10 patients in India identified 10 patients with CAM, suggesting that this condition is more common than expected.[29] Treating physicians should have a high suspicion for CAM in patients with uncontrolled diabetes mellitus and severe COVID-19 presenting with rhino-orbital or rhino-cerebral syndromes.[16] Regardless of the reported regional differences in the underlying causes, manifestations, and treatment of mucormycosis is noted in studies throughout Europe, Asia, and Latin America,[45] and, given the wide global distribution of the order Mucorales,[41,46,47] CAM should be considered among the differential diagnosis of co-infections in patients with COVID-19. A prompt diagnosis and treatment should be established because of the angioinvasive character and rapid disease progression leading to a high mortality.[48,49] This is especially true in India; with an increased incidence of COVID-19 cases, apparently thousands of CAM cases are reported. However, Nepal, Brazil, Colombia, the USA, and other severely affected nations should consider this fungal threat amid the pandemic. Also, it is essential to limit the dose and duration of high-dose dexamethasone as a treatment for COVID-19 in patients with a low likelihood of benefit or with an increased risk of complications (delayed presentation, or presence of uncontrolled diabetes mellitus).

The therapeutic approach during the COVID-19 pandemic should consider existing guidelines for mucormycosis management, such as those proposed by the European Confederation of Medical Mycology in cooperation with the Mycoses Study Group Education and Research Consortium.[50] Specific guidelines in the context of COVID-19 are needed,[51] and new and updated COVID-19 guidelines should also include CAM as a diagnostic consideration.[52] Upon suspicion of mucormycosis, appropriate imaging is strongly recommended to document the extent of the disease followed by a surgical assessment for debridement.[50] First-line treatment is high-dose liposomal amphotericin B. Intravenous isavuconazole and intravenous or delayed-release tablet posaconazole are recommended for de-escalation or maintenance therapy.[53–57] Amphotericin B deoxycholate is advised against, given substantial toxicity, but maybe the only option in resource-limited settings. Management of mucormycosis depends on recognizing disease patterns and on early diagnosis. Despite treatment, case-fatality rates due to mucormycosis during the pre-COVID-19 pandemic era were already high, ranging from 32% to 70%, according to organ involvement. However, in SARS-CoV-2 infection, the mortality maybe even higher.[58]

The prescription of immunosuppressing drugs can lead to life-threatening opportunistic infections in patients with COVID-19, and the lack of

substantial evidence for many of these therapies calls for an urgent reassessment of the current treatment guidelines for COVID-19, including monitoring for opportunistic fungal infections. The rationale and benefit of administering steroids in patients with COVID-19 need continuous reappraisal to avoid the increasing number of iatrogenic deaths linked to steroid overuse in those with SARS-CoV-2 infection.

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We dedicate this Editorial to the memory of Dr. Francisco Miguel Marty, who died tragically in 2021. Dr. Marty is remembered as a gentle, well-rounded individual with extensive expertise in mucormycosis and other opportunistic infections, including mucormycosis in organ transplant recipients and patients with malignancies.

Author contributions

AJRM conceived the idea of the Editorial and drafted the first version. The rest of the authors contributed to subsequent versions. All authors read and approved the final submitted version.

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References

1. Hanley B, Naresh KN, Roufosse C, *et al.* Histopathological findings and viral tropism in UK patients with severe fatal COVID-19: a post-mortem study. *Lancet Microbe* 2020; 1: e245–e253.
2. Song G, Liang G and Liu W. Fungal co-infections associated with global COVID-19 pandemic: a clinical and diagnostic perspective from China. *Mycopathologia* 2020; 185: 599–606.
3. Tavakolpour S, Rakhshandehroo T, Wei EX, *et al.* Lymphopenia during the COVID-19 infection: what it shows and what can be learned. *Immunol Lett* 2020; 225: 31–32.
4. Rodriguez-Morales AJ, Cardona-Ospina JA, Gutierrez-Ocampo E, *et al.* Clinical, laboratory and imaging features of COVID-19: a systematic review and meta-analysis. *Travel Med Infect Dis* 2020; 34: 101623.
5. Vasquez-Bonilla WO, Orozco R, Argueta V, *et al.* A review of the main histopathological findings in coronavirus disease 2019. *Hum Pathol* 2020; 105: 74–83.
6. Short KR, Kroeze E, Fouchier RAM, *et al.* Pathogenesis of influenza-induced acute respiratory distress syndrome. *Lancet Infect Dis* 2014; 14: 57–69.
7. Arabi YM, Mandourah Y, Al-Hameed F, *et al.* Corticosteroid therapy for critically ill patients with Middle East respiratory syndrome. *Am J Respir Crit Care Med* 2018; 197: 757–767.
8. Stockman LJ, Bellamy R and Garner P. SARS: systematic review of treatment effects. *PLoS Med* 2006; 3: e343.
9. Rodrigo C, Leonardi-Bee J, Nguyen-Van-Tam J, *et al.* Corticosteroids as adjunctive therapy in the treatment of influenza. *Cochrane Database Syst Rev* 2016; 3: CD010406.
10. Werthman-Ehrenreich A. Mucormycosis with orbital compartment syndrome in a patient with COVID-19. *Am J Emerg Med* 2021; 42: 264.e5–264.e8.
11. Placik DA, Taylor WL and Wnuk NM. Bronchopleural fistula development in the setting of novel therapies for acute respiratory distress syndrome in SARS-CoV-2 pneumonia. *Radiol Case Rep* 2020; 15: 2378–2381.
12. Kanwar A, Jordan A, Olewiler S, *et al.* A fatal case of *Rhizopus azygosporus* pneumonia following COVID-19. *J Fungi (Basel)* 2021; 7: 174.
13. Dallalzadeh LO, Ozzello DJ, Liu CY, *et al.* Secondary infection with rhino-orbital cerebral mucormycosis associated with COVID-19. *Orbit*. Epub ahead of print 23 March 2021. DOI: 10.1080/01676830.2021.1903044.
14. Johnson AK, Ghazarian Z, Cendrowski KD, *et al.* Pulmonary aspergillosis and mucormycosis in a patient with COVID-19. *Med Mycol Case Rep* 2021; 32: 64–67.

15. Khatri A, Chang KM, Berlinrut I, *et al*. Mucormycosis after coronavirus disease 2019 infection in a heart transplant recipient – case report and review of literature. *J Mycol Med* 2021; 31: 101125.

16. John TM, Jacob CN and Kontoyiannis DP. When uncontrolled diabetes mellitus and severe COVID-19 converge: the perfect storm for mucormycosis. *J Fungi (Basel)* 2021; 7: 298.

17. Zurl C, Hoenigl M, Schulz E, *et al*. Autopsy proven pulmonary mucormycosis due to *Rhizopus microsporus* in a critically ill COVID-19 patient with underlying hematological malignancy. *J Fungi (Basel)* 2021; 7: 88.

18. Monte Junior ESD, Santos M, Ribeiro IB, *et al*. Rare and fatal gastrointestinal mucormycosis (Zygomycosis) in a COVID-19 patient: a case report. *Clin Endosc* 2020; 53: 746–749.

19. Waizel-Haiat S, Guerrero-Paz JA, Sanchez-Hurtado L, *et al*. A case of fatal rhino-orbital mucormycosis associated with new onset diabetic ketoacidosis and COVID-19. *Cureus* 2021; 13: e13163.

20. Pasero D, Sanna S, Liperi C, *et al*. A challenging complication following SARS-CoV-2 infection: a case of pulmonary mucormycosis. *Infection*. Epub ahead of print 17 December 2020. DOI: 10.1007/s15010-020-01561-x.

21. Bellanger AP, Navellou JC, Lepiller Q, *et al*. Mixed mold infection with *Aspergillus fumigatus* and *Rhizopus microsporus* in a severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2) patient. *Infect Dis Now*. Epub ahead of print 27 January 2021. DOI: 10.1016/j.idnow.2021.01.010.

22. Ahmadikia K, Hashemi SJ, Khodavaisy S, *et al*. The double-edged sword of systemic corticosteroid therapy in viral pneumonia: a case report and comparative review of influenza-associated mucormycosis versus COVID-19 associated mucormycosis. *Mycoses*. Epub ahead of print 16 February 2021. DOI: 10.1111/myc.13256.

23. Karimi-Galougahi M, Arastou S and Haseli S. Fulminant mucormycosis complicating coronavirus disease 2019 (COVID-19). *Int Forum Allergy Rhinol*. Epub ahead of print 13 March 2021. DOI: 10.1002/alr.22785.

24. Veisi A, Bagheri A, Eshaghi M, *et al*. Rhino-orbital mucormycosis during steroid therapy in COVID-19 patients: a case report. *Eur J Ophthalmol*. Epub ahead of print 10 April 2021. DOI: 10.1177/11206721211009450.

25. Mehta S and Pandey A. Rhino-orbital mucormycosis associated with COVID-19. *Cureus* 2020; 12: e10726.

26. Sen M, Lahane S, Lahane TP, *et al*. Mucor in a viral land: a tale of two pathogens. *Indian J Ophthalmol* 2021; 69: 244–252.

27. Garg D, Muthu V, Sehgal IS, *et al*. Coronavirus disease (Covid-19) associated mucormycosis (CAM): case report and systematic review of literature. *Mycopathologia* 2021; 186: 289–298.

28. Moorthy A, Gaikwad R, Krishna S, *et al*. SARS-CoV-2, Uncontrolled diabetes and corticosteroids-an unholy trinity in invasive fungal infections of the maxillofacial region? A retrospective, multi-centric analysis. *J Maxillofac Oral Surg*. Epub ahead of print 6 March 2021. DOI: 10.1007/s12663-021-01532-1.

29. Sarkar S, Gokhale T, Choudhury SS, *et al*. COVID-19 and orbital mucormycosis. *Indian J Ophthalmol* 2021; 69: 1002–1004.

30. Sharma S, Grover M, Bhargava S, *et al*. Post coronavirus disease mucormycosis: a deadly addition to the pandemic spectrum. *J Laryngol Otol*. Epub ahead of print 8 April 2021. DOI: 10.1017/S0022215121000992.

31. Saldanha M, Reddy R and Vincent MJ. Paranasal mucormycosis in COVID-19 patient. *Indian J Otolaryngol Head Neck Surg*. Epub ahead of print 22 April 2021. DOI: 10.1007/s12070-021-02574-0.

32. Revannavar SM, Supriya PS, Samaga L, *et al*. COVID-19 triggering mucormycosis in a susceptible patient: a new phenomenon in the developing world? *BMJ Case Rep* 2021; 14: e241663.

33. Maini A, Tomar G, Khanna D, *et al*. Sino-orbital mucormycosis in a COVID-19 patient: a case report. *Int J Surg Case Rep* 2021; 82: 105957.

34. Ravani SA, Agrawal GA, Leuva PA, *et al*. Rise of the phoenix: mucormycosis in COVID-19 times. *Indian J Ophthalmol* 2021; 69: 1563–1568.

35. Lamoth F, Lewis RE, Walsh TJ, *et al*. Navigating the uncertainties of COVID-19 associated aspergillosis (CAPA): a comparison with influenza associated aspergillosis (IAPA). *J Infect Dis*. Epub ahead of print 26 March 2021. DOI: 10.1093/infdis/jiab163.

36. Group RC, Horby P, Lim WS, *et al*. Dexamethasone in hospitalized patients with Covid-19. *N Engl J Med* 2021; 384: 693–704.

37. Kwak EJ, Kim DJ, Nam W, *et al*. Mucormycosis in the jaw: a report of 2 cases and literature

review. *Oral Health Prev Dent* 2020; 18: 1011–1016.

38. Spellberg B, Edwards J Jr and Ibrahim A. Novel perspectives on mucormycosis: pathophysiology, presentation, and management. *Clin Microbiol Rev* 2005; 18: 556–569.
39. Rajendra Santosh AB, Muddana K and Bakki SR. Fungal infections of oral cavity: diagnosis, management, and association with COVID-19. *SN Compr Clin Med*. Epub ahead of print 27 March 2021. DOI: 10.1007/s42399-021-00873-9.
40. Verma DK and Bali RK. COVID-19 and mucormycosis of the craniofacial skeleton: causal, contributory or coincidental? *J Maxillofac Oral Surg*. Epub ahead of print 27 March 2021. DOI: 10.1007/s12663-021-01547-8.
41. Mejia Buritica L and Karduss Urueta AJ. Pulmonary mucormycosis. *N Engl J Med* 2021; 384: e69.
42. Mekonnen ZK, Ashraf DC, Jankowski T, *et al*. Acute invasive rhino-orbital mucormycosis in a patient with COVID-19-associated acute respiratory distress syndrome. *Ophthalmic Plast Reconstr Surg* 2021; 37: e40–e80.
43. Szarpak L. Mucormycosis – a serious threat in the COVID-19 pandemic? *J Infect*. Epub ahead of print 21 May 2021. DOI: 10.1016/j.jinf.2021.05.015.
44. Gangneux JP, Bougnoux ME, Dannaoui E, *et al*. Invasive fungal diseases during COVID-19: we should be prepared. *J Mycol Med* 2020; 30: 100971.
45. Stemler J, Hamed K, Salmanton-Garcia J, *et al*. Mucormycosis in the Middle East and North Africa: analysis of the FungiScope® registry and cases from the literature. *Mycoses* 2020; 63: 1060–1068.
46. Nucci M, Engelhardt M and Hamed K. Mucormycosis in South America: a review of 143 reported cases. *Mycoses* 2019; 62: 730–738.
47. Pena CE. Deep mycotic infections in Colombia. A clinicopathologic study of 162 cases. *Am J Clin Pathol* 1967; 47: 505–520.
48. Alekseyev K, Didenko L and Chaudhry B. Rhinocerebral mucormycosis and COVID-19 pneumonia. *J Med Cases* 2021; 12: 85–89.
49. Miller MA, Molina KC, Gutman JA, *et al*. Mucormycosis in hematopoietic cell transplant recipients and in patients with hematological malignancies in the era of new antifungal agents. *Open Forum Infect Dis* 2021; 8: ofaa646.
50. Cornely OA, Alastruey-Izquierdo A, Arenz D, *et al*. 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; 19: e405–e421.
51. Honavar SG. Code mucor: guidelines for the diagnosis, staging and management of rhino-orbito-cerebral mucormycosis in the setting of COVID-19. *Indian J Ophthalmol* 2021; 69: 1361–1365.
52. Saaavedra-Trujillo CH. Consenso colombiano de atención, diagnóstico y manejo de la infección por SARS-COV-2/COVID-19 en establecimientos de atención de la salud – recomendaciones basadas en consenso de expertos e informadas en la evidencia. *Infectio* 2020; 24: 1–102.
53. Steinbrink JM and Miceli MH. Mucormycosis. *Infect Dis Clin North Am* 2021; 35: 435–452.
54. Peixoto D, Gagne LS, Hammond SP, *et al*. Isavuconazole treatment of a patient with disseminated mucormycosis. *J Clin Microbiol* 2014; 52: 1016–1019.
55. Marty FM, Ostrosky-Zeichner L, Cornely OA, *et al*. Isavuconazole treatment for mucormycosis: a single-arm open-label trial and case-control analysis. *Lancet Infect Dis* 2016; 16: 828–837.
56. Marques GN, Silva NU, Leal MO, *et al*. The use of posaconazole delayed-release tablets in the successful treatment of suspected mucormycosis in a bottlenose dolphin (*Tursiops truncatus*) calf. *Med Mycol Case Rep* 2021; 32: 77–80.
57. Perfect JR, Cornely OA, Heep M, *et al*. Isavuconazole treatment for rare fungal diseases and for invasive aspergillosis in patients with renal impairment: challenges and lessons of the VITAL trial. *Mycoses* 2018; 61: 420–429.
58. Brunet K and Rammaert B. Mucormycosis treatment: recommendations, latest advances, and perspectives. *J Mycol Med* 2020; 30: 101007.

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