Mycopathologia (2022) 187:31–37
https://doi.org/10.1007/s11046-021-00610-9

SHORT COMMUNICATION

Pulmonary Artery Pseudoaneurysm in COVID-19-Associated Pulmonary Mucormycosis: Case Series and Systematic Review of the Literature

Himanshu Pruthi · Valliappan Muthu · Harish Bhujade · Arun Sharma · Abhiman Baloji · Rao G Ratnakara · Amanjit Bal · Harkant Singh · Manavjit Singh Sandhu · Sunder Negi · Arunaloke Chakrabarti · Manphool Singhal

Received: 11 October 2021 / Accepted: 6 December 2021 / Published online: 22 December 2021

Abstract Literature on COVID-19-associated pulmonary mucormycosis (CAPM) is sparse. Pulmonary artery pseudoaneurysm (PAP) is an uncommon complication of pulmonary mucormycosis (PM), and rarely reported in CAPM. Herein, we report five cases of CAPM with PAP managed at our center and perform a systematic review of the literature. We diagnosed PM in those with clinico-radiological suspicion and confirmed it by microbiology or histopathology. We encountered five cases of CAPM with PAP (size ranged from 1 × 0.8 cm to ~ 4.9 × 4.8 cm). All subjects had diabetes and were aged 55–62 years (75% men). In two cases, COVID-19 and mucormycosis were diagnosed simultaneously, while in three others, COVID-19 preceded PM. One subject who underwent surgery survived, while all others died (80% mortality). From our systematic review, we identified one additional case of CAPM with PAP in a transplant recipient. CAPM with PAP is rare with high mortality. Early diagnosis and multimodality management are imperative to improve outcomes.

Keywords Mycotic aneurysm · Angiography · Mucorales · *Rhizopus* · Fungal pneumonia · Pulmonary aspergillosis

Himanshu Pruthi and Valliappan Muthu have contributed equally as first authors.

Handling Editor: Sanjay Haresh Chotirmall.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s11046-021-00610-9.

H. Pruthi · H. Bhujade · A. Sharma · A. Baloji · M. S. Sandhu · M. Singhal (✉)
Department of Radiodiagnosis and Imaging, Postgraduate Institute of Medical Education and Research, Sector-12, Chandigarh 160012, India
e-mail: drmsinghal@yahoo.com

V. Muthu · R. G. Ratnakara
Department of Pulmonary Medicine, Postgraduate Institute of Medical Education and Research, Chandigarh, India

A. Bal
Department of Pathology, Postgraduate Institute of Medical Education and Research, Chandigarh, India

H. Singh
Department of Cardiothoracic Vascular Surgery, Postgraduate Institute of Medical Education and Research, Chandigarh, India

S. Negi
Department of Cardiac Anesthesia, Postgraduate Institute of Medical Education and Research, Chandigarh, India

A. Chakrabarti
Department of Medical Microbiology, Postgraduate Institute of Medical Education and Research, Chandigarh, India

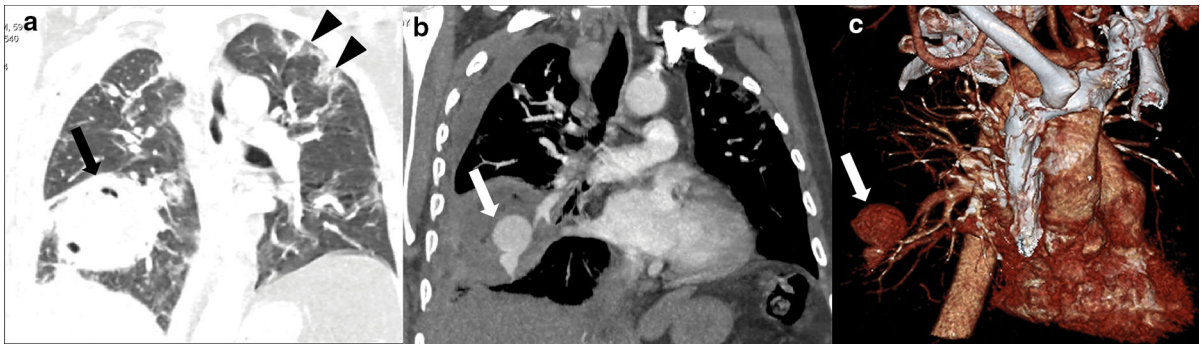

Fig. 1 Reconstructed coronal image **a** in the lung window shows a patch of consolidation in the right lower lobe (arrow). Note multiple subpleural ground-glass opacities in the left upper lobe (arrowheads). Coronal maximum intensity projection (MIP) & Volume rendered (VR) images **b, c** show pseudoaneurysm ($\sim$ 2.2 $\times$ 3.5 cm) arising from a branch of the right descending pulmonary artery within the cavity (arrows)

Introduction

Mucormycosis following coronavirus disease (COVID-19) has emerged as a serious problem worldwide.[1, 2] Lungs from COVID-19 patients have been shown to have widespread thrombosis and vascular endothelialitis.[3] COVID-19 may thus potentiate the vascular complications associated with pulmonary mucormycosis (PM), an aggressive angioinvasive infection. While COVID-19-associated pulmonary mucormycosis (CAPM) has been described,[4–6] pulmonary artery pseudoaneurysm (PAP) in CAPM is rare.[7] Herein, we report on five cases of CAPM with PAP. We also systematically review the literature for additional cases and discuss the challenges in the management of CAPM with PAP.

Case series

Case 1

A 59-year-old male was diagnosed with mild COVID-19 when he developed fever, dry cough, and sore throat. His oxygen saturation in room air was 95% and was managed on home isolation and systemic glucocorticoids (methylprednisolone) for two weeks. Three weeks after the COVID-19 illness, he developed a productive cough and mild hemoptysis. He was referred to us when symptoms did not resolve with broad-spectrum antibiotics. At our hospital, chest radiograph and high-resolution computed tomography (HRCT) showed right hydropneumothorax with a thick-walled cavity in the right lower lobe. His sputum did not grow bacteria, and smear for acid-fast bacilli was negative. KOH smear from sputum showed aseptate hyphae (subsequently identified as *Mucor spp.* by molecular diagnostics), and he was started on liposomal amphotericin B (3 mg/kg). Ten days after hospitalization and treatment with intravenous amphotericin, he developed an episode of massive hemoptysis (200 mL). Computed tomography bronchial angiography (CTBA) (Fig. 1) revealed a pseudoaneurysm ($\sim$ 2.2 $\times$ 3.5 cm) from a branch of the right descending pulmonary artery (RDPA). He underwent digital subtraction angiography (DSA) and coil embolization (Fig. 2) of the offending branch of RDPA. The hemoptysis was controlled, and he underwent right lower lobectomy (Fig. 3). He was discharged after 45 days and is currently doing well after two months of follow-up.

Summary of the index cases (Table 1)

The summary of the other index cases is provided in Table 1, and the additional case details are described in the supplemental file. We diagnosed PM in all five subjects based on a clinico-radiologic suspicion and confirmed it by the presence of aseptate hyphae on a fungal smear (KOH mount) or growth of Mucorales in the culture of sputum or bronchoalveolar lavage, or histopathology of the surgical specimen. PM was diagnosed simultaneously or within eight weeks of confirmed SARS-CoV-2 infection in all the included cases. The organism causing CAPM was identified to

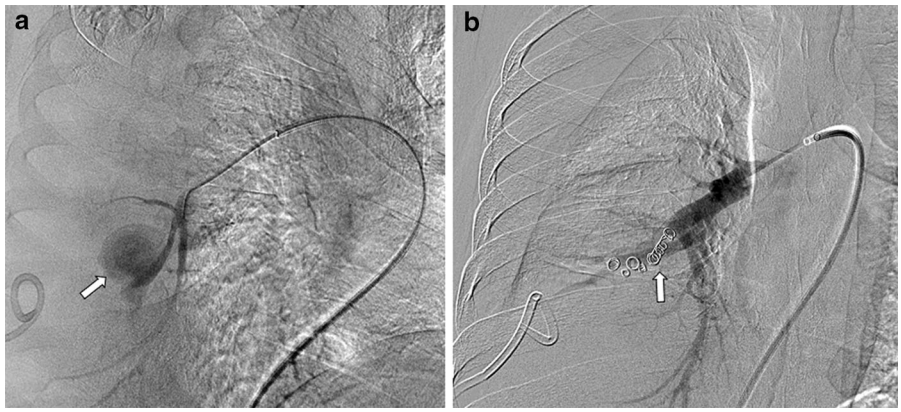

Fig. 2 Selective angiogram of right descending pulmonary artery (RDPA) **a** shows (arrow) pseudoaneurysm arising from one of the branches of RDPA (arrow). Post-coil embolization angiogram **b** shows coils in the offending branch (arrow) with complete non-opacification of the aneurysmal sac

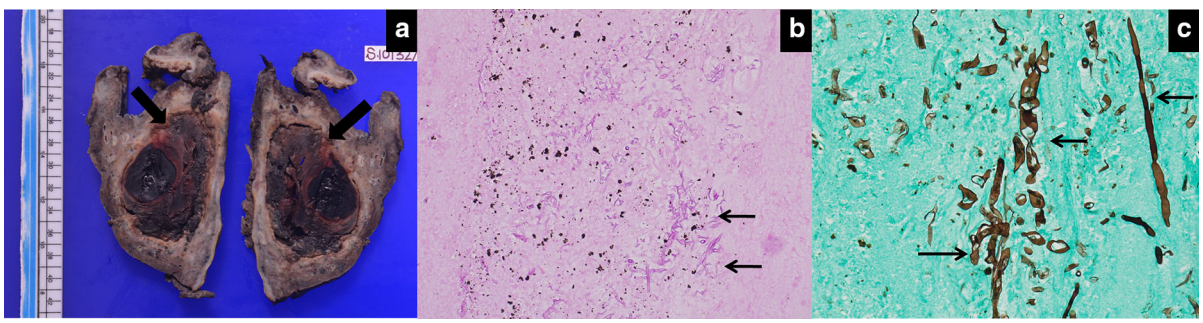

Fig. 3 Gross photograph **a** shows a large hemorrhagic lesion in the lung parenchyma (arrows). Photomicrograph **b** shows areas of bland necrosis with numerous fungal hyphae (arrows), which are thin-walled, broad, and aseptate conforming to the morphology of mucormycosis (H&E, × 100). Photomicrograph **c** of fungal hyphae (arrows) highlighted on Grocott's stain (Grocott's stain, × 200)

be *Rhizopus arrhizus* in two subjects (case 2 and 5) by molecular methods (sequencing of the internal transcribed spacer [ITS] region of rDNA). Culture showed growth of *Rhizopus homothallicus* and *Rhizopus microsporus* in case 4. The index patients were aged 55–62 years, and four of the five cases were men. CAPM and COVID-19 were simultaneously diagnosed in two cases (cases 2 and 3). In cases 1, 4, and 5, CAPM was diagnosed three and four weeks after COVID-19, respectively. None of the five cases had hypoxemia during COVID-19 illness (yet three were treated inappropriately with glucocorticoids [cases 1, 4, and 5]). All five subjects had diabetes mellitus (diagnosed during this presentation in case 1). One of the patients also had alcohol-related chronic liver disease (case 2). Case 3 also had rhino-orbital mucormycosis, which was surgically treated.

We managed patients as per the existing guidelines.[2] Briefly, liposomal amphotericin-B (beginning with 3 mg/kg) was used for the medical management of pulmonary mucormycosis. After initial medical therapy (preferably 10–14 days) and glycemic control, patients with resectable disease were offered surgery. Early surgery or digital subtraction angiography and embolization were performed in cases of massive hemoptysis after a multidisciplinary discussion involving pulmonary physicians, radiologists, and thoracic surgeons.

Systematic review of the literature

We searched the PubMed and Embase databases using the following terms: ("COVID" OR "SARS-CoV"

Table 1 Summary of the five index cases of pulmonary mucormycosis (PM) and pulmonary artery pseudoaneurysm (PAP) and one additional case identified from our review of literature(7)

Case number	Age/ Sex	Co-morbid illness	Hemoptysis at presentation	Massive hemoptysis[a]	Duration between COVID-19 and PM	HRCT findings	Location and size of PAP	Vessel of origin of PAP	Confirmation of mucormycosis	Treatment	Outcome
1	59/M	Diabetes mellitus (HbA1c 12.4%)	Mild	Yes	21 days	Right hydropneumothorax, right LL consolidation and cavity	Right LL (~ 2.2 × 3.5 cm)	Right LL segmental branch of RDPA	Aseptate hyphae in sputum fungal smear (*Mucor spp.*) Surgical specimen showing PM	L-AMB, DSA embolization, and right lower lobectomy	Improved
2	60/M	Diabetes mellitus (HbA1c 11.3%) Hypothyroidism CLD	Streaky	No	Simultaneously diagnosed	Right LL cavity and right sided pleural effusion	Right LL (~ 1.2 × 0.9 cm)	Right LL segmental branch of RDPA	Aseptate hyphae in sputum fungal smear (*Rhizopus arrhizus*)	L-AMB, DSA embolization	Died 7 days after discharge
3	55/F	Diabetes mellitus (HbA1c 14.5%)	Streaky	No	Simultaneously diagnosed	Right UL cavity with central GGO (RHS) Mosaic pattern	Right UL (~ 4.9 × 4.8 cm)	Anterior segmental branch of right UL pulmonary artery	Aseptate hyphae in fungal smear. No growth in culture Maxillectomy specimen showing invasive mucormycosis	L-AMB	Died
4	57/M	Diabetes mellitus (HbA1c 10.9%) Hypertension	No	Yes	30 days	Left UL and left LL consolidation, and cavity	Left LL (~ 1 × 0.8 cm)	Left LL segmental branch of LPA	BAL smear aseptate hyphae Culture showed *Rhizopus homothallicus* and *Rhizopus microsporus*	C-AMB	Died
5	62/M	Diabetes mellitus, hypertension, coronary artery disease	Streaky	Yes	20 days	Left UL nodule, and left LL thick-walled cavity	Left LL	Superior segmental branch of LL pulmonary artery	Surgical specimen showing PM (Identified as *Rhizopus arrhizus* by sequencing)	L-AMB Pneumonectomy	Died in the post-operative period

Table 1 continued

Case number	Age/ Sex	Co-morbid illness	Hemoptysis at presentation	Massive hemoptysis[a]	Duration between COVID-19 and PM	HRCT findings	Location and size of PAP	Vessel of origin of PAP	Confirmation of mucormycosis	Treatment	Outcome
Dantis et al. [7]	46/M	Post renal transplant on prednisolone, tacrolimus	Yes	NA	7 weeks	Right LL cavity with air-fluid level	Right LL	Basal segmental branch of RPA	Transthoracic biopsy and surgical specimen	L-AMB Right lower lobectomy	Improved

[a]Massive hemoptysis (respiratory failure, life-threatening, or > 200 mL in 24 h) any time during the disease course

BAL – bronchoalveolar lavage; C-AMB – amphotericin B deoxycholate; CLD—chronic liver disease; COVID-19—coronavirus disease; DSA–digital subtraction angiography; GGO-ground-glass opacity; HbA1C - glycated hemoglobin; HRCT—high resolution computed tomography; L-AMB – liposomal amphotericin B; LL-lower lobe; LPA-left pulmonary artery; PA – Pulmonary artery; PAP-Pulmonary pseudoaneurysm; RDPA—right descending pulmonary artery; RHS-reverse halo sign; UL-upper lobe

OR "coronavirus") AND (mucor* OR "zygomycosis" OR "mucormycosis") to identify cases of CAPM. We obtained 277 unique citations (after discarding duplicates) from inception till 25-Sep-21. Of these, we could identify one additional case of CAPM with PAP (Table 1). [7] Dantis et al. reported the case of a 46-year old renal transplant recipient on immunosuppressive therapy developed CAPM seven weeks following COVID-19 illness. The patient was successfully managed with liposomal amphotericin-B and surgery.

Discussion

In our case series of five patients with COVID-19-associated pulmonary mucormycosis and pulmonary artery pseudoaneurysm, we noted a high case fatality rate (80%). One patient who received multimodality management (DSA embolization followed by surgery) survived. We identified only one additional case of CAPM with PAP.

Infection with SARS-CoV-2 can result in a myriad of pulmonary complications. Hemoptysis is unusual in coronavirus disease (COVID-19), [8] and has been observed with pulmonary embolism or invasive pulmonary aspergillosis. [9–11] Bronchial circulation (contributes to 2% of the blood supply to the lungs) accounts for most cases of hemoptysis. Pulmonary artery as a source of bleeding is uncommon, easily missed, and challenging to manage. [12–16] We observed that only four of the five cases had presented with hemoptysis (either mild or streaky), and two of them developed severe hemoptysis later. Notably, one of the patients who died due to CAPM (case 4) had no hemoptysis at presentation and later developed massive hemoptysis (despite improving on appropriate treatment). Hence, a high index of suspicion needs to be maintained, and CT angiography should be considered at the earliest.

PM accounts for only about 10–20% of the total mucormycosis (and < 10% among COVID-19-associated mucormycosis) but carries a high mortality. [17–20] PM is difficult to diagnose, primarily due to the non-specific imaging findings [21] and lack of awareness. [22, 23] Massive hemoptysis can be seen in as high as one-third of PM [24] and is an independent predictor of survival. [25] However, the proportion of PM with PAP is unknown. Undiagnosed and

unsuspected PAP may underlie several of these cases of massive hemoptysis. Further, diagnostic modalities such as bronchoscopy may also result in severe bleeding in patients with PM. [26] Additionally, COVID-19 poses difficulties in diagnosing PM. [5] Early initiation of appropriate antifungal therapy (amphotericin B) and timely surgery are key factors determining the outcome. [2, 17] Endovascular therapy can act as a bridge before more definite surgical therapy is undertaken (case 1). While surgery can improve outcome, several patients with PM may be inoperable due to bilateral disease, hypoxemia, and systemic illness such as chronic liver disease (case 2). In such instances, medical management and interventional endovascular treatment (including direct coil embolization of the feeding vessel) may help.

Our study is limited by its retrospective design. Also, the current series is from a single referral center with the required expertise to diagnose and manage mucormycosis, and the results may not be generalizable.

Pulmonary artery pseudoaneurysm is a severe complication of CAPM and can be fatal. Early diagnosis and multimodality management are imperative to improve outcomes. Further research and a systematic evaluation are required to ascertain the various findings of CAPM.

Funding None.

Declarations

Conflict of interest None of the study authors have any conflicts of interest to declare.

References

1. Muthu V, Rudramurthy SM, Chakrabarti A, Agarwal R. Epidemiology and pathophysiology of COVID-19-associated Mucormycosis: India versus the rest of the world. Mycopathologia. 2021. https://doi.org/10.1007/s11046-021-00584-8.
2. Rudramurthy SM, Hoenigl M, Meis JF, Cornely OA, Muthu V, Gangneux JP, et al. ECMM/ISHAM recommendations for clinical management of COVID-19 associated mucormycosis in low- and middle-income countries. Mycoses. 2021;64(9):1028–37. https://doi.org/10.1111/myc.13335.
3. Ackermann M, Verleden SE, Kuehnel M, Haverich A, Welte T, Laenger F, et al. Pulmonary vascular Endothelialitis, Thrombosis, and Angiogenesis in Covid-19. N Engl J Med. 2020;383(2):120–8. https://doi.org/10.1056/NEJMoa2015432.
4. 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(9):2349–59. https://doi.org/10.3201/eid2709.210934.
5. Garg D, Muthu V, Sehgal IS, Ramachandran R, Kaur H, Bhalla A, et al. Coronavirus disease (Covid-19) associated mucormycosis (CAM): case report and systematic review of literature. Mycopathologia. 2021;186(2):289–98. https://doi.org/10.1007/s11046-021-00528-2.
6. Garg M, Prabhakar N, Muthu V, Farookh S, Kaur H, Suri V, et al. CT Findings of COVID-19-associated Pulmonary Mucormycosis: a case series and literature review. Radiology. 2021. https://doi.org/10.1148/radiol.2021211583.
7. Dantis K, Rathore V, Kashyap NK, Gupta N, De S, Singha SK. SARS-CoV-2 sequel: Pulmonary mucormycosis with a mycotic aneurysm in a transplant recipient. Tuberc Respir Dis (Seoul). 2021. https://doi.org/10.4046/trd.2021.0098.
8. Argun Barış S, Coşkun İS, Selvi G, Boyacı H, Başyiğit İ. Case Series of COVID-19 presenting with massive hemoptysis. Turk Thorac J. 2020;21(6):454–6. https://doi.org/10.5152/TurkThoracJ.2020.20150.
9. Khurram R, Karia P, Naidu V, Quddus A, Woo WL, Davies N. Pulmonary artery pseudoaneurysm secondary to COVID-19 treated with endovascular embolisation. Eur J Radiol Open. 2021;8: 100346. https://doi.org/10.1016/j.ejro.2021.100346.
10. Baeza I, Romera I, Fortuño JR. Massive hemoptysis due to Aspergillus-related pulmonary artery pseudoaneurysm in a patient with COVID-19 pneumonia. Med Intensiva (Engl Ed). 2021. https://doi.org/10.1016/j.medin.2021.01.006.
11. Jajodia S, Goenka U, Jas D, Tiwary I, Goenka MK. Endovascular management of massive haemoptysis due to covid-19 related pulmonary artery pseudoaneurysm: a rare entity. Radiol Case Rep. 2021. https://doi.org/10.1016/j.radcr.2021.08.048.
12. Singhal M, Lal A, Prabhakar N, Yadav MK, Vijayvergiya R, Behra D, et al. Non-bronchial causes of haemoptysis: imaging and interventions. Pol J Radiol. 2020;85:e328–39. https://doi.org/10.5114/pjr.2020.97014.
13. Souza LVS, Souza AS, Marchiori E. Mucormycotic pulmonary pseudoaneurysm causing fatal hemoptysis. Arch Bronconeumol (Engl Ed). 2019;55(11):597–8. https://doi.org/10.1016/j.arbres.2019.03.019.
14. Muthu V, Singh H, Gorsi U, Agarwal R. Large pulmonary artery pseudoaneurysm in mucormycosis: successfully managed with surgery and amphotericin. BMJ Case Rep. 2021. https://doi.org/10.1136/bcr-2020-240813.
15. Agarwal R, Kumar V, Gupta D. Pulmonary mucormycosis: two of a kind. Eur J Intern Med. 2006;17(1):63–5. https://doi.org/10.1016/j.ejim.2005.08.009.
16. Chhabria B, Sharma A, Agarwal R, Muthu V. An unusual cause of massive hemoptysis: the demise of clinical history and a teachable moment from a fatal case. Lung India. 2019;36(4):365–6. https://doi.org/10.4103/lungindia.lungindia_510_18.
17. Muthu V, Agarwal R, Dhooria S, Sehgal IS, Prasad KT, Aggarwal AN, et al. Has the mortality from pulmonary mucormycosis changed over time? A systematic review and

meta-analysis. Clin Microbiol Infect. 2021;27(4):538–49. https://doi.org/10.1016/j.cmi.2020.12.035.
18. Muthu V, Kumar M, Paul RA, Zohmangaihi D, Choudhary H, Rudramurthy SM, et al. Is there an association between zinc and COVID-19-associated mucormycosis? Results of an experimental and clinical study. Mycoses. 2021. https://doi.org/10.1111/myc.13365.
19. Patel A, Kaur H, Xess I, Michael JS, Savio J, Rudramurthy S, et al. A multicentre observational study on the epidemiology, risk factors, management and outcomes of mucormycosis in India. Clin Microbiol Infect. 2020;26(7):944.e9-e15. https://doi.org/10.1016/j.cmi.2019.11.021.
20. Kumar HM, Sharma P, Rudramurthy SM, Sehgal IS, Prasad KT, Pannu AK, et al. Serum iron indices in COVID-19-associated mucormycosis: a case-control study. Mycoses. 2021. https://doi.org/10.1111/myc.13391.
21. Maturu VN, Agarwal R. Reversed halo sign: a systematic review. Respir Care. 2014;59(9):1440–9. https://doi.org/10.4187/respcare.03020.
22. Muthu V, Dhooria S, Singh Sehgal I, Thurai Prasad K, Agarwal R. The reversed Halo sign and the Bronchus sign: the eyes see only what the mind knows. Ann Am Thorac Soc. 2019;16(9):1203. https://doi.org/10.1513/AnnalsATS.201905-360LE.
23. Muthu V, Agarwal R. Cavity in pulmonary mucormycosis: Is it rare? Trop Doct. 2021. https://doi.org/10.1177/00494755211010007.
24. Klimko N, Khostelidi S, Shadrivova O, Volkova A, Popova M, Uspenskaya O, et al. Contrasts between mucormycosis and aspergillosis in oncohematological patients. Med Mycol. 2019;57(2):S138–44. https://doi.org/10.1093/mmy/myy116.
25. Feng J, Sun X. Characteristics of pulmonary mucormycosis and predictive risk factors for the outcome. Infection. 2018;46(4):503–12. https://doi.org/10.1007/s15010-018-1149-x.
26. Muthu V, Gandra RR, Dhooria S, Sehgal IS, Prasad KT, Kaur H, et al. Role of flexible bronchoscopy in the diagnosis of invasive fungal infections. Mycoses. 2021;64(6):668–77. https://doi.org/10.1111/myc.13263.