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Impact of COVID-19-associated Mucormycosis in Kidney Transplant Recipients: A Multicenter Cohort Study.

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Background. COVID-19-associated mucormycosis (CAM) is a recently emerging entity. There is a lack of reports of CAM in organ transplant recipients. **Methods.** We conducted a multicenter (n = 18) retrospective research in India during November 2020 to July 2021. The purpose of this study was to explore the clinical spectrum, outcome and risk factors for mortality of CAM in kidney transplant recipients (KTRs). **Results.** The incidence of CAM was 4.4% (61/1382 COVID-19-positive KTRs) with 26.2% mortality. The median age of the cohort was 45 (38–54) y. Twenty (32%) were not hospitalized and 14 (22.9%) were on room air during COVID-19. The proportion of postdischarge CAM was 59.1%, while concurrent CAM was reported in 40.9%. The presentation of CAM was 91.8% rhino-orbital-cerebral mucormycosis and 8.2% pulmonary with 19.6% and 100% mortality, respectively. In the univariable analysis, older age, obesity, difficulty of breathing, high-flow oxygen requirement, and delay in starting therapy were significantly associated with mortality. In the multivariable logistic regression analysis, patients requiring high-flow oxygen therapy [odds ratio (95% confidence interval) = 9.3 (1.6-51); $P = 0.01$] and obesity [odds ratio (95% confidence interval) = 5.2 (1-28); $P = 0.05$] was associated with mortality. The median follow-up of the study was 60 (35–60) d. **Conclusions.** We describe the largest case series of CAM in KTRs. Morality in pulmonary CAM is extremely high. Severe COVID-19 pose extra risk for the development of CAM and associated mortality. Our report will help in better understanding the conundrum and management of CAM.

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INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) has grossly affected the transplantation communities across the world. As of June 2021, the developed world has mostly achieved a plateau of their coronavirus disease 2019 (COVID-19) numbers, but India is still battling to resume the transplantation activities in many centers amid the ferocious second wave.[1] Our understanding and knowledge of the clinical profile and outcome of COVID-19 in transplantation[2-5] has extensively evolved, but there is a scarcity of data about postdischarge complications of COVID-19. Mucormycosis is one such opportunistic infection that has recently gained a lot of focus in COVID-19 admitted and discharged patients. Mucormycosis is a group of fungal infection which is mostly exclusive to immunocompromised and diabetes patients. The culprit is ubiquitous and broadly has 5 modes of presentation: rhino-ocular-cerebral, pulmonary, cutaneous, gastrointestinal and disseminated. Organ transplantation is a classically described risk factor for mucormycosis and is associated with high morbidity and mortality.[6,7] And this fact makes it necessary for transplant physicians to be aware of the impact of COVID-19-associated mucormycosis (CAM) in transplantation. In the last few months, there have been reports of CAM around the world, and most of which came from the Indian subcontinent.[8-11] In India alone, there are a staggering 45 374 CAM cases with 4300 deaths.[12] However, there are only a few case reports pertaining to organ transplantation.[13-15] The purpose of this report was to explore the demography, clinical profile, outcome, and risk factors of mortality involved with CAM in kidney transplant recipients (KTRs). To the best of our attempts for literature search, our report is the largest cohort describing CAM in organ transplantation.

MATERIALS AND METHODS

Ethics

A retrospective cohort study was designed as per the Strengthening the Reporting of Observational Studies in Epidemiology statement,[16] and ethical permission for conducting the study was granted from the institute of Institute of Kidney Diseases and Research Centre, Dr HL Trivedi Institute of Transplantation Sciences, Ahmedabad (Registration number: ECRJ143/InstlGJ/2013/RR-19 with application number EC/App/20Jan21/07). The study also abided by the rules of the declaration of Helsinki, and the declaration of Istanbul. During the whole process of research, the confidentiality and privacy of participants were assured.

Design, Study Duration, and Settings

This study was designed as a retrospective analysis to measure the impact of CAM in KTRs. Through a nationwide collaboration, data from a total of 18 transplant centers (Figure S1, SDC, http://links.lww.com/TXD/A387) were accumulated.

Patient Selection

From November 2020 to July 2021 all KTRs (n = 1382) with diagnosis of confirmed COVID-19 by real-time polymerase chain reaction test from nasopharyngeal swab or rapid antigen test were screened for clinical symptoms of mucormycosis before discharge. KTRs on home treatment for COVID-19 were advised to report in case of any suspected symptoms. All COVID-19–positive KTRs who developed mucormycosis during their hospital stay in respective transplant centers or following clinical recovery from COVID-19 (in the case of home treatment) were identified and included in the study.

Definition and Assessment Tools in the Study

1. The severity of COVID-19 was described as per the modified WHO[17] ordinal scale: 1: Not hospitalized and no limitations of activities; 2: Not hospitalized with some limitations of activities; 3: hospitalized but without oxygen; 4: hospitalized with low-flow oxygen devices; 5: on high-flow oxygen therapy; 7: mechanical ventilation; and 8: death.
2. Recovery from COVID-19 in the study was defined as resolution of COVID-19 symptoms, irrespective of real-time polymerase chain reaction test COVID-19 status.
3. The mucormycosis cases were defined as per the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group[18] as proven, probable and possible. We included all the cases of proven CAM. The CAM identification and diagnosis of confirmed rhino-orbital-cerebral mucormycosis (ROCM) was made in the presence of at least one of the following criteria: (a) histopathological evidence of tissue invasion on tissue biopsy; (b) direct visualization of broad and aseptate hyphae in microscopy; and (c) positive culture from sinus tissue specimen. In cases of pulmonary mucormycosis confirmation was done by bronchoalveolar lavage + biopsy.
4. Recovery from CAM: Complete resolution of signs and symptoms, with radiological improvement compared with previous lesions in imaging.
5. Concurrent CAM is defined as those who developed mucormycosis during the hospital stay of COVID-19.
6. Post–COVID-19 CAM was defined as those who developed mucormycosis after discharge from hospital or had clinical recovery.
7. Definition of inadequately controlled sugar was defined as glycated hemoglobin level of >7%.[19]
8. Charlson's comorbidity index is a validated tool, which was calculated for measuring the burden of comorbidity.[20]
9. Modified medical research council dyspnea scale (mMRC) scale[21] is a validated tool was used to assess recovery (any residual difficulty in breathing) in post–COVID-19 discharge.
10. Recent rejection was defined as biopsy proven rejection within 3 mo of before the diagnosis of COVID-19.

Data will be available from the corresponding author on reasonable request.

Supplemental digital content (SDC) is available for this article. Direct URL citations appear in the printed text, and links to the digital files are provided in the HTML text of this article on the journal's Web site (www.transplantationdirect.com).

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Management Protocol

The management of COVID-19 in KTRs was done in accordance with the national guidelines for managing COVID-19 in transplantation.[22] Intravenous steroid therapy was given only in those with oxygen requirement. The choice of steroids was 6 mg dexamethasone or equivalent for 7–10 d. Importantly, there was some variation in the admission criteria and therapeutic drugs depending upon the logistics and settings. The immunosuppression protocol for COVID-19 was stopping/reducing antimetabolite in all cases and stopping/ reducing calcineurin inhibitors (CNIs) in cases requiring oxygen.

In cases of a diagnosis of CAM, both antimetabolite and CNI were stopped immediately, with continuing of baseline maintenance steroids. CNI was first reintroduced in minimum doses if mucormycosis symptoms and signs were improving. CNI was restored gradually during the course of illness. The decision to restart antimetabolite was made only in the case of resolution of radiological and clinical signs and symptoms. The reintroduction and up titration of drugs was at the physician discretion and individualized.

The dose of liposomal amphotericin B was 5 mg/kg, and conventional amphotericin B 1 mg/kg was given when liposomal preparation was unavailable. The dose was adjusted as per the availability and clinical improvement. The other agents like Posaconazole (800 mg/24 h in 2 divided doses) was added as a step-down therapy after the initial response from Amphotericin B as per the drug availability. Only a few cases Isavuconazole was used. The duration for antifungal therapy was 4 to ≥6 wks depending on the clinical response. The decision of shifting to oral therapy was based on initial response. The data for drug monitoring level of antifungal was not retrieved, but in general it was rarely done during admission.

Study Procedure

We reviewed the clinical profile, laboratory parameters, treatment, and outcome of 61 cases of CAM. All the demographic and clinical records were retrieved from the case files, and blood reports were electronically retrieved from all the centers. The proforma for the study was designed by 2 of the authors (V.K. and H.S.M.). One of the authors (V.K.) took responsibility for arranging all the data from the individual centers through emails, in a systematic manner. Data were integrated into a master excel sheet and prepared for analysis.

Statistical Analysis

Data were described as frequencies and percentages for categorical variables, and median and SD for scales. For skewed continuous variables median and interquartile range (IQR) were reported. The comparison between survived and the nonsurvived groups was done with Fisher's test and Chi-square test with Yates's correction. Mann–Whitney test or t-test was performed for comparing continuous data. A univariable analysis was performed for risk factors of mortality, and the variables with *P* value less than 0.1 were fit in the multivariable analysis which was done by logistic regression analysis. The variables with small size were not included for fitting in the model. Risk factors were reported as Odds ratio (upper limit and lower limit of 95% CI with *P* value). As the sample size and events were small, so the upper limit of the confidence interval for odds ratio should be cautiously interpreted. Log-rank (mantel-cox) test with Kaplan–Meir plot was done for pulmonary mucormycosis. A two-tailed *P* value of less than 0.05 was considered statistically significant. SPSS 21 software was used for the statistical analysis of the study.

RESULTS

Incidence of CAM in KTRs

During the study period from November 2020 to July 2021, there were 1382 COVID-19 cases reported across 18 centers of India, of which 61 had CAM estimating the incidence of 4.4% in COVID-19 positive KTR cases. In the centers, the cumulative data for number of mucormycosis in this 6-mo time period (n = 61) was almost 5.5 times higher than reported in the calendar year 2019 (n =11). The center which reported the highest CAM cases was located in Gujarat, and was the only center where both general and transplant patients were admitted in COVID-19 surge, and as it had a dedicated mucormycosis ward. A total of 949 general and 105 KTR COVID-19 patients were admitted in that single center. There was a total of 32 CAM cases (22 general and 10 KTRs) that corresponded to an incidence of 2.3% for the general and 10% for KTRs, which is significantly high.

Baseline Characteristics of the Cohort

Table 1 demonstrates the demographic characteristics of the cohort. The most common age group affected was 18–45 y (n = 31, 50.8%). The sex distribution of the cohort favored male (n = 54, 88.5%). The mean body mass index of the cohort was 25 (22.3–30) kg/m^2. A high proportion of the cases had living-related transplantation (n = 55, 90.2%) with thymoglobulin (n = 38, 62.3%) as induction. The duration from transplantation to COVID-19 was 4 (2–6) y. Graft function at baseline was fair with a serum creatinine of 1.2 (0.9–1.5) mg/dl. All cases were on steroid before COVID-19. The majority of the cohort were on triple immunosuppression of steroids, antimetabolite and CNI (n = 58, 95%). The immunosuppression regimen before the diagnosis of CAM consisted of only steroids (n = 9, 14.8%); steroids with half dose CNI (n = 6, 9.8%); steroids with full dose of CNI (n = 3, 5%); steroids, CNI and half dose of antimetabolite (n = 10, 16.4%), and restored baseline regimen (n = 33, 54%). Tacrolimus levels (n =2, 3.2%) were high only in a few cases. The mean (SD) Charlson's comorbidity index of the cohort was 3 (1). There was no occupational hazard in the cohort. Also, no history of recent trauma was elicited. No diabetic ketoacidosis history was reported.

The Course of COVID-19 in the Cohort

Table 2 summarizes the COVID-19 course of the study. WHO COVID-19 severity of the cohort was as follows: (1) not hospitalized = 32%; (2) hospitalized without oxygen = 22.9%; (3) needed low-flow oxygen = 21.4%; and (4) high-flow oxygen devices = 22.9%. Fever (96.7%) was the prominent symptom of the COVID-19. The neutrophil percentage and lymphocyte percentage was 10.5 (7–18.75) and 84 (77.2–88), respectively. The treatment regimen of majority of the cases was composed of systemic steroids (44%), anticoagulation (55.7%), and remdesivir (77%). The mMRC scale showed that most cases had no complaints after discharge (34.5%), while only a few cases had difficulty enough to leave home (4.9%). No statistical difference was found in mMRC scale between survivors and nonsurvivors.

TABLE 1.

Demographic characteristics of the KTRs with CAM

	Overall (n = 61)	Alive (n = 45)	Dead (n = 16)	*P*
Age, y	45 (38–54)	43 (37–53)	48.5 (57.75–44)	
Age group, y				
18–45	31 (50.8)	27 (60)	4 (25)	**0.02**
45–55	18 (29.5)	11 (24.4)	7 (43.7)	0.2
55–65	8 (13.1)	6 (13.3)	2 (12.6)	1
>65	4 (6.6)	1 (2.3)	3 (18.7)	**0.05**
Male sex	54 (88.5)	39 (86.6)	15 (93.7)	**0.002**
BMI, kg/m^2	25 (22.3–30)	24 (22–27.6)	30.2 (25.15–31.25)	
BMI > 30 kg/m^2	16 (26.2)	7 (15.5)	9 (56.3)	**0.002**
Blood group distribution				
A	23 (37.7)	18 (40)	5 (31.3)	0.76
B	23 (37.7)	18 (40)	5 (31.3)	0.76
0	13 (21.3)	8 (17.7)	5 (31.3)	0.29
AB	2 (3.3)	1 (2.3)	1 (6.1)	0.45
Native kidney disease				
Chronic kidney disease of unknown etiology	5 (8.2)	3 (6.7)	2 (12.6)	0.59
Diabetes	15 (24.6)	10 (22.2)	5 (31.3)	0.5
Hypertension	19 (31.1)	14 (31.1)	5 (31.3)	1
IgA nephropathy	2 (3.3)	2 (4.4)	0 (0)	1
Renal stone disease	5 (8.2)	4 (8.9)	1 (6.1)	1
Chronic glomerulonephritis	11 (18)	9 (20)	2 (12.6)	0.71
Autosomal dominant polycystic kidney	2 (3.3)	1 (2.3)	1 (6.1)	0.45
Retransplant	2 (3.3)	2 (4.4)	0 (0)	1
Type of transplantation				
Living-related	55 (90.2)	42 (93.3)	13 (81.3)	0.17
Deceased donation	6 (9.8)	3 (6.7)	3 (18.7)	0.17
Induction agent				
Thymoglobulin	40 (65.6)	31 (68.6)	9 (56.1)	0.36
Basiliximab	7 (11.5)	5 (11.1)	2 (12.6)	1
No induction	14 (22.9)	9 (20)	5 (31.3)	0.48
History of recent antirejection therapy given	3 (4.9)	0 (0)	3 (18.7)	**0.01**
Y from transplant to diagnosis of COVID-19	4 (2–6)	3 (2–6)	5.5 (2.75–10.25)	
<1	10 (16.4)	7 (15.6)	3 (18.7)	0.71
1–5	25 (41)	20 (44.4)	5 (31.3)	0.39
5–10	19 (31.1)	15 (33.3)	4 (25)	0.75
>10	7 (11.5)	3 (6.7)	4 (25)	0.07
Status of diabetes				
Nondiabetic	31 (50.8)	24 (53.3)	7 (43.7)	0.57
Diabetes	30 (49.2)	21 (46.7)	9 (56.3)	0.57
Diabetes on OHA	15 (24.6)	11 (24.4)	4 (25)	1
Diabetes on Insulin	15 (24.6)	10 (22.2)	5 (31.3)	0.5
Diabetes with inadequate glycemic control	4 (6.6)	2 (4.4)	2 (12.6)	0.27
Charlson's comorbidity index	3.06 (1)	2.9 (0.9)	3.5 (1.26)	

Qualitative data expressed as numbers and percentages, and continuous data are expressed as median (interquartile range) or mean (SD).

BMI, body mass index; CAM, COVID-19-associated mucormycosis; COVID-19, coronavirus disease 2019; IgA, immunoglobulin A; KTR, kidney transplant recipient; OHA, oral hypoglycemic agents.

Clinical Features of CAM and Diagnostic Evaluation of the Cohort

The majority of the cohort was ROCM (91.8%) with a few cases of pulmonary (8.2%) (Table 3). No disseminated, cutaneous, gastrointestinal tract, or renal mucormycosis were reported. The comprehensive details of the radiological involvement in ROCM are described in Table S1, SDC, http://links.lww.com/TXD/A387. The frequency of signs and symptoms in decreasing order of frequency included headache (81.9%), facial swelling (80.3%), proptosis (73.8%), conjunctival injection (60.6%), vision impairment (52.4%), orbital cellulitis (49.1%), paresthesia (34.4%), black discharge from the nose (29.5%), and fever (27.9%). The confirmatory diagnosis was mostly done by histopathological examination of the sinus tissues (62.3%). The data of isolated species at the time of analysis were available for 22 patients, of which 18 were rhizopus species and 4 were rhizomucor.

Outcome

The overall mortality of the cohort was 26.2% at a median follow-up of 60 (35–60) d. Fifty-five (91.8%) were successfully discharged and 5 cases (8.2%) are still admitted or had ongoing treatment. Antifungal regimen consisted of liposomal amphotericin B (63.9%), conventional amphotericin (6.5%), posaconazole (26.2%), and isavuconzole (3.2%). In 67.8% of cases of ROCM, functional endoscopic surgery

TABLE 2.

Summary of COVID-19 course of KTRs with CAM

	Overall (n = 61)	Alive (n = 45)	Dead (n = 16)	*P*
WHO ordinal scale for COVID-19 severity				
Not hospitalized	20 (32.8)	16 (35.5)	4 (25)	0.54
Hospitalized, no oxygen need	14 (22.9)	12 (26.7)	2 (12.6)	0.31
Low-flow oxygen required	13 (21.4)	10 (22.2)	3 (18.7)	1
High-flow oxygen or Bi-PAP	14 (22.9)	7 (15.6)	7 (43.7)	0.03
Mechanical ventilation	0 (0)	0 (0)	0 (0)	N/A
Cumulative symptoms during COVID-19 course				
Subjective fever	59 (96.7)	43 (95.5)	16 (100)	1
Difficulty in breathing	36 (59)	23 (51.1)	13 (81.2)	0.04
Appetite loss	39 (63.9)	28 (62.2)	11 (68.7)	0.76
Anosmia	20 (32.8)	15 (33.3)	5 (31.3)	1
Ageusia	20 (32.8)	14 (31.1)	6 (37.5)	0.75
Chest tightness	26 (42.6)	17 (37.8)	9 (56.2)	0.24
Cough	54 (88.5)	40 (88.9)	14 (87.5)	1
Diarrhea	4 (6.5)	2 (4.4)	2 (12.6)	0.27
Disturbed sleep	19 (31.1)	15 (33.3)	4 (25)	0.75
Anxiety	28 (45.9)	21 (46.7)	7 (43.7)	1
Depression	21 (34.4)	15 (33.3)	6 (37.5)	0.76
Fatigue	35 (57.3)	26 (57.8)	9 (56.2)	1
Laboratory findings during COVID-19				
Hb, 13–16 g/dl	12 (11–12.9)	12.4 (11.15–13.2)	11.9 (11.05–12.3)	0.64
TLC, 4000–11 000/mm^3	6400 (3075–9650)	5900 (2850–8400)	9800 (7875–12 500)	0.003
N, 60%–70%	84 (77.2–88)	80 (77–87.2)	89 (84.5–90)	0.12
L, 25%–33%	10.5 (7–18.75)	12 (7–19.5)	7 (4.2–12.5)	0.55
Platelet count, 150–400 × $10^3/mm^3$	208 (154–293)	185 (156–240)	208.5 (98–244)	0.22
IL-6, < 10 pg/ml (n = 15)	74.85 (38.6–112.6)	76.7 (47–160.7)	48.45 (17.36–85.17)	0.52
hsCRP, < 10 mg/L (n = 40)	36.8 (22.4–63.2)	33.8 (12–56.25)	74.5 (32.5–163.75)	0.0008
D dimer, 200–500 ng/ml (n = 37)	735 (437–1271)	695 (431–1193)	1196 (822–1949.7)	0.42
Ferritin, 13–400 ng/ml (n = 22)	698 (265–1240)	706 (311–1200)	560 (244–3162)	0.006
PCT, < 0.5 ng/ml	0.36 (0.18–1.7)	0.26 (0.14–0.8)	0.47 (0.24–4)	0.77
SGPT, 0-40 IU/L	31 (17–40)	30 (17–41)	32.5 (22–37.25)	0.75
LDH IU/L	326 (222–499)	307 (213–396)	549 (450–569)	0.03
Treatment received				
I V Dexamethasone/methyl prednisolone	27 (44)	17 (37.8)	10 (62)	0.14
IV remdesivir	47 (77)	35 (77)	12 (75)	0.73
Anticoagulation	34 (55.7)	25 (55.5)	9 (56.2)	1
Antibiotics	25 (40.9)	19 (42.2)	6 (37.5)	0.77
Postdischarge mMRC scoring for breathlessness				
Too breathless to leave house	3 (4.9)	1 (2.3)	2 (12.5)	0.16
Has to stop to breath after waking even few steps	5 (8.2)	3 (6.6)	2 (12.5)	0.59
Difficulty in breathing while walking for longer time	4 (6.6)	4 (8.9)	0 (0)	0.56
Difficulty in breathing when running or upstairs	3 (4.9)	1 (2.3)	2 (12.6)	0.16
No complaint of breathlessness	21 (34.5)	16 (35.5)	5 (31.2)	1
Concurrent COVID-19	25 (40.9)	20 (44.4)	5 (31.2)	0.39

Qualitative data expressed as numbers and percentages, and continuous data are expressed as median (inter quartile range).

Bi-PAP, bilevel positive airway pressure; CAM, COVID-19-associated mucormycosis; COVID-19, coronavirus disease 2019; Hb, hemoglobin; hsCRP, high-sensitive C reactive protein; IL-6, interleukin-6; KTR, kidney transplant recipient; L, lymphocyte; LDH, lactate dehydrogenase; mMRC, modified medical research council grading for dyspnea; N, neutrophil; PCT, Procalcitonin; SGPT, serum aspartate transferase; TLC, total leukocyte count; WHO, World Health Organization.

was done along with medical therapy. In 3 (5%) cases of extensive eye involvement with blindness, orbital exenteration was performed, 2 of whom survived. The right middle lobe lung excision of the nodule was done in one case of pulmonary mucormycosis, while no surgery was performed in the other 4. There were no reports of acute kidney injury requiring hemodialysis with amphotericin B therapy in the study, other than the 3 graft losses. All graft losses had chronic graft dysfunction before COVID-19. There were 3 graft losses during the period. The serum creatinine before COVID-19, peak creatinine during COVID-19, creatinine just before diagnosis of mucormycosis and on the last follow-up was 1.2 (0.9–1.5), 1.49 (1–2.39), 1.3 (1–2.1), and 1.2 (1–2.2) mg/dl, respectively. The serum creatinine trends of the cases are shown in Figure S2, SDC, http://links.lww.com/TXD/A387.

Risk Factors for Mortality in the Cohort

Sixteen cases (26.2%) died in the study. Postdischarge CAM was 59.1% while concurrent CAM was 40.9% with no statistical difference in mortality rates. Patients who died were relatively older [48.5 (44–57.5) versus 43 (37–53) y; $P = 0.02$]. Males had higher mortality (96.7% versus 86.6%; $P = 0.02$).

TABLE 3.

Clinical signs and symptoms, diagnosis, treatment modalities of the cohort

	Overall (n = 61)	Alive (n = 45)	Dead (n = 16)	*P*
Clinical signs/symptoms				
Facial swelling	49 (80.3)	38 (84.4)	11 (68.7)	0.27
Skin necrosis	6 (9.8)	3 (6.6)	3 (18.7)	0.17
Paraesthesia	21 (34.4)	12 (26.7)	9 (56.2)	0.06
Foul smelling nasal discharge	13 (21.4)	8 (17.8)	5 (31.3)	0.29
Black discharge from nose	18 (29.5)	10 (22.2)	8 (50)	0.05
Black discharge from mouth	8 (13.1)	3 (6.6)	5 (31.3)	0.02
Epistaxis	14 (22.9)	6 (13.3)	8 (50)	0.005
Orbital cellulitis	30 (49.1)	22 (48.9)	8 (50)	1
Conjunctival redness	37 (60.6)	29 (64.4)	8 (50)	0.37
Proptosis	45 (73.8)	35 (77.8)	10 (62.5)	0.32
Vision impairment	32 (52.4)	23 (51.1)	9 (56.2)	0.77
Headache	50 (81.9)	39 (86.7)	11 (68.7)	0.13
Fever	17 (27.9)	11 (24.4)	6 (37.5)	0.34
Diagnosis confirmation				
HPE + biopsy	38 (62.3)	29 (64.4)	9 (56.2)	0.56
KOH	30 (49.1)	21 (46.7)	9 (56.2)	0.57
Culture	22 (36)	14 (31)	7 (43)	N/A
Classification				0.0007
ROCM	56 (91.8)	45 (100)	11 (68.7)	
Pulmonary	5 (8.2)	0 (0)	5 (31.3)	
Treatment modalities				
Liposomal amphotericin B	39 (63.9)	28 (62.2)	11 (68.7)	0.76
Conventional amphotericin	4 (6.5)	3 (6.6)	1 (6.2)	1
Amphotericin + posaconazole	13 (21.4)	10 (22.2)	3 (18.7)	1
Isavuconazole alone	1 (1.6)	0 (0)	1 (6.2)	0.26
Amphotericin B + isavuconazole	1 (1.6)	1 (2.2)	0 (0)	1
Posaconazole alone	3 (4.9)	3 (6.6)	0 (0)	0.55
Antifungal + surgery for ROCM (n = 56)	38 (67.8)	32 (57.1)	6 (54.5)	0.30
Surgery for pulmonary mucormycosis (n = 5)	1 (20)	0 (0)	1 (20)	N/A
D from hospital admission to antifungal therapy	3 (2–5)	3 (2–5)	5 (2.7–7.7)	0.024

HPE, histopathological examination; KOH, potassium hydroxide microscopy test; N/A, not available; ROCM, rhino-orbital-cerebral mucormycosis.

Obese patients (56.3% versus 15.5%; $P = 0.02$) suffered higher mortality rates. History of recent antirejection (18.7% versus 0%; $P = 0.01$) had higher mortality. Among the symptoms reported during COVID-19, only dyspnea was common in patients who died from mucormycosis (81.2% versus 51.1%; $P = 0.04$). Patients requiring high-flow oxygen during COVID-19 (15.6% versus 43.7%; $P = 0.03$) had higher mortality. Among the laboratory parameters which are reported as peaks, total leukocyte count, high-sensitive C reactive protein, ferritin, lactate dehydrogenase, and discharge creatinine had statistically significant difference in terms of mortality with CAM. Among the mucormycosis symptoms, only black discharge from nose (50% versus 22.2%; $P = 0.05$), mouth (6.6% versus 31.3%; $P = 0.02$), and epistaxis (50% versus 13.3%; $P = 0.005$) were more frequently reported in nonsurvivors. Among the nonsurvivors, 5 (45.5%) of the 11 ROCM underwent surgery. The cases with pulmonary involvement faced higher mortality (19.6% versus 100%; $P = 0.001$) compared to ROCM. Delay in initiation of antifungal therapy from the onset of symptoms was more common in nonsurvivors [5 (2.7–7.7) versus 3 (2–5) d; $P = 0.024$].

Figure S3, SDC, http://links.lww.com/TXD/A387, shows Kaplan–Meir analysis done for pulmonary mucormycosis showing the statistically significant difference in mortality with ROCM (Log-rank test; $P = 0.001$). In the univariable analysis, older age, obesity, difficulty of breathing, high-flow oxygen requirement, and delay in starting therapy were associated with mortality. In the multivariable logistic regression analysis, only patients requiring high-flow oxygen therapy [OR = 9.3 (1.6–51); $P = 0.01$] and obesity [OR = 5.2 (1–28); $P = 0.05$] were associated with morality (Table 4).

DISCUSSION

We describe the presentation and outcome of an unusual pathogen detected during the SARS-CoV2 infection course in KTRs in India. Solid organ transplantation is classically described as a risk factor of this infection.[23] CAM has emerged as novel sequelae of SARS-CoV2 infection in recent times especially in India, which constitute bulk of the cases.[24,25] The authors have described no case of CAM in KTRs in the first wave.[26] This explosion of cases in the second wave, made us to organize a nationwide call among the transplant centers to study the profile and outcome of CAM in KTRs. One needs a thorough evaluation and teamwork of primary physician, transplant physicians, infectious disease specialist, intensivist, ophthalmologist, otolaryngologist, and pulmonologist to manage a case of CAM in KTRs. In our report, only patients having symptoms who reported back to the respective transplant centers were included. So, this may represent

TABLE 4.

Risk factors for mortality analysis

	Univariable analysis				Multivariable analysis			
		95% CI				95% CI		
	Odds ratio	Lower limit	Upper limit	*P*	Odds ratio	Lower limit	Upper limit	*P*
Age > 65 y	10.1	1	106	0.05	6.599	0.5	85.2	0.14
Male sex	2.3	0.2	20	0.45				
Obese	6.9	1.9	24	<0.01	5.261	1	28	0.05
DOB	4.1	1	16	0.04	2.539	0.4	13	0.26
HFO	4.2	1.1	15	0.02	9.337	1.6	51	0.01
Delay in starting therapy	1.1	1	1.3	0.03	1.178	0.9	1.4	0.129

CI, confidence interval; DOB, difficulty of breathing; HFO, high-flow oxygen.

an underreporting of the cases. In the COVID-19 pandemic where health resources are already overwhelmed, multidisciplinary management is a daunting task.

Impact of Mucormycosis in Solid Organ Transplantation

This opportunistic infection with staggering mortality is considered to be a rare infection and has shown wide geographic variation in incidence.[27] Previously, a study from the United States reported, the incidence in the first year after organ transplant as 0.07%.[28] A single-center study retrospectively reviewed 1330 kidney transplants > 4 y and found the overall incidence of mucormycosis as 1.02% (16 cases) with a 38% mortality rate.[29] Compared to previous year, the same center in this multicenter study has reported 12 cases in less than a year period. Clearly, there is almost 3-fold increase in mucormycosis cases in the COVID-19 era. In a recent meta-analysis of lung transplants (n = 121), the reported mortality was 41%, and the combination of surgical intervention along with antifungal resulted in lesser deaths.[30] In KTR acquiring mucormycosis, a meta-analysis (n = 174) reported a survival rate of 70.02% with antifungal and surgery combination compared to 30% survival in medical therapy alone.[18] Delay in starting antifungal agent has been shown to increase the mortality in mucormycosis.[31] The most common type described is ROCM in KTR.

Comparison of CAM in KTR With Mucormycosis of Prepandemic Times

As data from centers retrieved for non-COVID-19 mucormycosis was incomplete. We did a comparison (Table 5) with a meta-analysis of mucormycosis in KTR, which was chosen because it is one of the most comprehensive studies in the literature on this topic. We found the male sex to be affected more (88.5% versus 76%; $P = 0.04$). The mortality reported in male is lower with CAM compared to pre-COVID-19 era (27.7% versus 43%; $P = 0.04$). However, the comparison of sex would be inconclusive, as there is gross gender disparity in transplantation favoring males in India.[20] History of antirejection although was less reported (4.9% versus 18.9%; $P = 0.007$) in CAM. Nevertheless, it was associated with mortality in our study. This shows that even patients with normal graft functioning or who are not overimmunosuppressed can be affected with CAM. ROCM constituted higher number of cases in CAM (91.8% versus 33%; $P = 0.001$) compared to prepandemic era. The reason for this skewed deviation in the type of mucormycosis is unclear. Pulmonary mucormycosis had higher mortality in CAM compared to the pre-COVID-19 era (100% versus 42%; $P = 0.02$). The add-on damage by CAM from the already weakened lung by SARS-CoV2 is possibly responsible for the higher mortality along with the late diagnosis and inability to perform surgery. The overall mortality was lower (26% versus 33%) which reflects the better prognosis of ROCM cases with timely antifungal and surgery done in the cohort. The antifungal of choice switched to liposomal amphotericin B and patients receiving Posaconazole have also increased.

Comparison of CAM in KTR with CAM in the General Population

A recently, published analysis of CAM (86% ROCM and 4.5% pulmonary) in the general population[11] reported the incidence of CAM in the general population as 0.27% among hospitalized COVID-19 cases which is convincingly lower than our report of 4.4%. Their study also shows a 2.1-fold increase in the incidence of CAM compared to the previous year and found inappropriate use of steroids to be a risk factor for occurrence of CAM. In our report, 44% cases received systemic steroids, but steroids were not associated with mortality. Only cases requiring oxygen support were given steroids as per the protocol. This shows that organ transplant recipients are more prone to CAM. Interestingly, our report had comparatively lesser mortality (26.7% versus 44%) than the general patients.[30] This can be explained by a high number of ROCM cases in our study, which were detected early by dedicated transplant teams. Furthermore, we had no disseminated disease or cunninghamella species which have previously shown to be associated with higher fatality.[7] To note, all of our pulmonary mucormycosis died. We also report hypoxemic COVID-19 in multivariate analysis as a risk factor for mortality which is similar to the previous study.[10] But diabetes was not exclusive to our cohort and also was not associated with mortality unlike previously reported.[9,10] Thus, emphasizing the need for high suspicion even in nondiabetes KTRs.

Comparing Clinical Profile of CAM in KTR With COVID-19 in KTR Without CAM

The data of CAM in KTR was compared to the author's previous multicenter study of 250 COVID-19 KTR cases from India, where no mucormycosis was reported.[26] The mortality in CAM (26% versus 11.6%; $P < 0.01$) was understandably higher compared to previous report. In CAM diabetes (49.2% versus 32%; $P < 0.01$) was higher compared to the previous report. Among the COVID-19 symptom presentation,

TABLE 5.

Comparison of present study with a pre-COVID-19 meta-analysis of mucormycosis in KTR

	Song et al (overall = 174)	CAM in KTR (overall = 61)	*P*	Song et al (died = 74)	CAM in KTR (died = 16)	*P*
Characteristics						
Age, y	45.9 (11–70)	45 (38–54)				
Sex						
Male	133 (76)	54 (88.5)	0.04	58/133 (43.6)	15/54 (27.7)	0.04
Female	41 (24)	7 (11.5)	0.04	16/41 (39)	1/7 (14.2)	0.39
No-comorbidity	30 (25)	6 (9.8)	0.21	15/30 (50)	2/6 (33.3)	0.66
Diabetes	75 (43)	30 (49.2)	0.45	25/75 (33.3)	9/30 (30)	0.82
Antirejection therapy						
Yes	33/174 (18.9)	3 (4.9)	0.007	12/33 (36.4)	3/3 (100)	0.06
Induction therapy			N/A[a]			N/A[a]
Yes	33/174 (19)	47 (77.1)		12/33 (36.4)	11/47 (23.4)	
No induction	16/174 (9.2)	14 (22.9)		7/16 (43.8)	5/14 (35.7)	
Not reported	125/174 (71.8)	N/A		55/125 (71.8)	N/A	
Type of mucormycosis						
ROCM	58 (33)	56 (91.8)	0.0001	18/58 (31)	11/56 (20)	0.19
Pulmonary	45 (25.9)	5 (8.2)	0.003	19/45 (42.2)	5/5 (100)	0.02
Culture organism						
Rhizopus	52/88 (59.1)	18/22 (81)	0.051	19/52 (36.5)	5/18 (27.7)	0.57
Therapeutic regimen[b]						
Liposomal amphotericin B	64/174 (36.8)	39 (63.9)	0.0003	47/64 (73.4)	28/39 (71)	1
Combined surgery and antifungal	121/174 (69.5)	38/56 (67.8)	0.86	85/121 (70.2)	33/38 (86.8)	0.054
Posaconazole	13/174 (7.5)	13 (21.4)	0.007	12/13 (92.3)	10/13 (76.9)	0.59

Data reported as mean (range) or numbers (percentage).

[a]Comparison not appropriate as in most cases information for induction agent was not available in the meta-analysis.

[b]In therapeutic regimen, the number of patients who survived are reported.

CAM, COVID-19-associated mucormycosis; COVID-19, coronavirus disease 2019; KTR, kidney transplant recipient; N/A, not available; ROCM, rhino-orbital-cerebral mucormycosis.

CAM cases presented with more fever (96.7% versus 88%; $P = 0.05$) and difficulty in breathing (59% versus 22%; $P < 0.01$). Also, diarrhea phenotype (6.5% versus 24%; $P < 0.01$) was quite low in CAM. Moderate-to-severe COVID-19 cases (44.3% versus 34%; $P = 0.13$) were higher in CAM, although with statistically insignificant difference. We also found that lymphopenia was more frequent in CAM [10.5 (7–18.75) percentage versus 18 (12–24); $P < 0.01$]. Other potential risk factors for acquiring CAM like age, obesity, and baseline immunosuppression were not found to different between the 2 reports. These data highlight that presence of diabetes and lymphopenia in COVID-19 may add to the increased risk of acquiring CAM in KTR.

Need for Surveillance for Mucormycosis in Transplant Patients With COVID-19

Blood investigations like beta D-glucan and serum galactomannan used in the suspicion of fungal infection are not useful for mucormycosis and currently, there is no blood marker for diagnosing this invasive infection, so clinical acuity and self-examination is of prime importance during hospitalization and postdischarge, respectively. The symptoms to look for in follow-up include sinus pain, headache, nose obstruction, headache, face numbness, eye swelling, abdominal pain, lethargy, nausea, slurred speech, and double vision.[32] For transplant patients with high risks like severe COVID-19, we suggest having preliminary eye, nose, and oral examination for any signs like eschar, black nasal or oral discharge, and eye swelling. Sometimes it can present alone with cranial nerve palsy, so cranial nerve examination should be a part of clinical examination. After discharge, these patients should be informed about the risk and instructed to look for any signs at home. The use of steroids and other immunomodulatory drugs should be rationalized along with avoidable lengthy hospital stays as these basically cause overimmunosuppression, and have been found to important risk factors for mucormycosis in previous studies.[30] In a review of outbreak-associated mucormycosis,[33] only a low proportion of cases had ROCM. The study reported a possible source of air contamination through ventilation devices and air conditioning systems. Our report is less likely to be related to a nosocomial source, as 54.9% of the patients were not on oxygen. Still, we suggest strict measures to maintain the hygiene and standards of hospital infrastructure to minimize the chances of such transmission.

Limitations

The limitation of the study was the reports are exclusive to KTR and hence data for other organs may vary. We were also unable to investigate and isolate the species of the mucormycosis in most of the cases, which would have further provided granularity to the observations. In our study, there were no reports of mucormycosis with the disseminated, gastrointestinal tract, and cutaneous type, so their profile is unknown. The extremely high mortality in pulmonary mucormycosis might have been reduced as the quality of care was relatively compromised due to the lack of resources in the pandemic. The exact details and timing of the surgery performed were not retrieved in sufficient numbers to be analyzed. The 8 participating centers which contributed the bulk of CAM cases

(n = 48), reported no non-COVID-19 mucormycosis in KTR during the study period. And hence, our data of CAM was compared with a previously published meta-analysis. This comparison may be skewed to some extent as reports will be limited to case series due to rarity of this infection

Future Implications

The future implications of this study emphasize the need for continued research in follow-up sequelae of COVID-19. The data from various other nations in this context will further enrich our understanding of this rare disease, which has recently been recognized commonly worldwide. The study also asks questions about the ideal immunosuppression restoration regimen to be used in transplant patients who survived COVID-19.

Conclusion

The management of mucormycosis in the COVID-19 era proved extremely onerous and is associated with high morbidity and mortality. Our report of a comprehensive description of CAM in transplant patients can serve as a learning tool for the transplant physicians and help in early diagnosis and enhance the outcomes. Early detection and combined therapy with surgery and antifungal agents are the keys to improve the chances of survival.

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