Case series

Case Series on Post renal transplant fungal infections of the lung.

Abstract: Invasive fungal infections are a significant concern for solid organ transplant (SOT) patients, especially those who have undergone small bowel or lung transplants. Renal transplant recipients commonly develop fungal infections like candidiasis, aspergillosis, and cryptococcosis, contributing to post-transplant infections. This case series presents three cases of pulmonary fungal infections after renal transplantation: cryptococcosis, mucormycosis, and invasive pulmonary aspergillosis. The objective is to highlight challenges in diagnosing and managing invasive fungal infections in SOT recipients, emphasizing early diagnosis, timely treatment initiation, and optimized antifungal drug pharmacokinetics for successful outcomes.

Aims & Objectives include emphasizing the importance of prompt diagnosis and treatment, optimizing antifungal drug pharmacokinetics, and highlighting the need for intensive antifungal therapy in SOT patients with fungal infections.

Methods: The cases involve comprehensive clinical information, diagnostic procedures (imaging, endoscopy, biopsies, microscopy, culture, and serologic testing), and treatment approaches. Antifungal therapy was promptly initiated, even without laboratory confirmation, to ensure timely treatment. Antifungal drug pharmacokinetics were optimized to minimize nephrotoxicity in SOT patients.

Results: Case 1 describes a middle-aged obese woman with respiratory symptoms diagnosed with cryptococcosis. Case 2 presents a young male kidney transplant recipient with mucormycosis. Case 3 involves a male patient with cough and hemoptysis diagnosed with invasive pulmonary aspergillosis. All cases received appropriate antifungal therapy, leading to symptom resolution and radiological improvement, although some patients had persistent radiological opacities.

Discussion: Diagnosing invasive fungal infections in transplant patients remains challenging, relying on clinical presentation and supportive diagnostic procedures. Management requires a multidisciplinary approach involving antifungal therapy, surgical intervention (if applicable), and control of predisposing factors. Primary treatments included liposomal amphotericin B and voriconazole, considering combination therapy and newer antifungal agents. Early detection and prompt treatment initiation are crucial to reduce mortality rates, especially in disseminated disease.

Conclusion: Invasive fungal infections present significant challenges in solid organ transplant recipients. Despite advancements in diagnostics and antifungal therapies, mortality and graft loss rates remain high, particularly in disseminated disease cases. Future research should integrate data from various sources to enhance understanding of fungal pathogenesis, host immune responses, and pharmacological aspects, aiming to develop more effective prevention and treatment strategies for fungal infections in transplant recipients.

Introduction

Invasive fungal infections are a major problem in solid organ transplant (SOT) recipients. Host and environmental factors are critically important determinants in the epidemiology of fungal infections in transplantation. The highest risk is in small bowel (11.6%) and lung (8.6%) transplants, followed by liver (4.7%), heart (4.0%), pancreas (3.4%) and kidney (1.3%) [1]. Factors that impact the risk of developing an invasive fungal infection include the patient's environmental exposure and/or colonization with pathogenic fungi, use of antifungal prophylaxis, as well as the net state of immunosuppression. Fungal infections represent 5% of infections in renal transplant recipients. Candidiasis is the most frequent, followed by aspergillosis and cryptococcosis. Invasive aspergillosis is severe and has a poor prognosis, but recent series focused on outcomes are scarce in the literature. whereas aspergillosis is most common in lung transplant recipients. The net state of immunosuppression varies widely depending on the type of transplant received. The interplay between host and environmental factors and the impact of antifungal prophylaxis strategies is more relevant to the development of specific fungal infections than several days after transplantation. For example, the median time to onset of invasive candidiasis ranges from several weeks to months in lung and liver transplant recipients, to over 2 years in kidney recipients [2]. Similarly, the median time to invasive aspergillosis is <6 months in liver transplant recipients, but occurs much later in kidney, heart and lung transplant recipients. The latter onset of invasive aspergillosis in lung transplant recipients is likely influenced by the widespread use of mould-active prophylaxis in that population. Finally, cryptococcosis tends to occur between 2 and 5 years post-transplant but can be observed much earlier in cases of donor transmission or heavy environmental exposure [2].

Improvements in therapeutic and diagnostic options are providing clinicians with unprecedented tools to evaluate, manage and prevent invasive fungal infection in solid organ transplant (SOT) recipients. Despite these advances, invasive fungal infections continue to be a major cause of morbidity and mortality in this population. Recent studies have shed new light on the epidemiology of invasive fungal infections in SOT recipients [1–3]. The overall cumulative incidence during the first year after transplantation is approximately 3%, although this varies depending on the type of organ transplanted [1]. However, the risk of infection, particularly due to inhaled fungi, persists for many years after transplant. Current epidemiological trends indicate a shift towards later infections. The consequences of fungal infection can be dire and include long hospitalizations, allograft damage and high mortality rates. Data from 15 centres involved in a prospective cohort study of invasive fungal infections in SOT recipients indicate that mortality at 12 months is approximately 40% for aspergillosis, 34% for candidiasis and 27% for cryptococcosis [1].

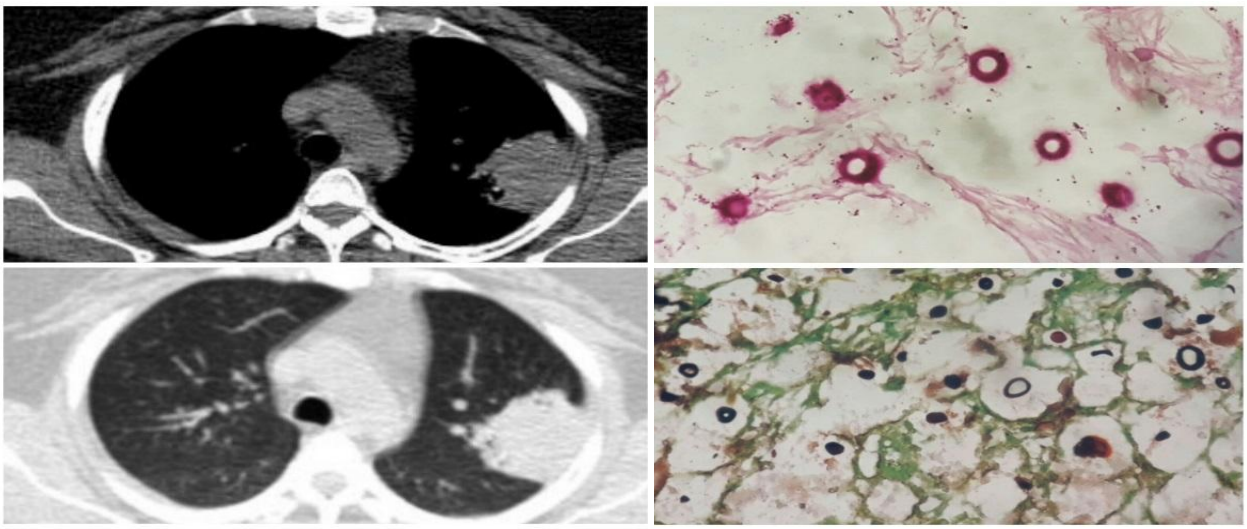
The study conducted on 2020 by Krishan L Gupta, Sahil Bagai, Raja Ramachandran, and Vivek Kumar examined fungal infections in post-renal transplant patients. Amongst 550 renal transplant recipients, The most common invasive fungal infection isolated in their single-center experience was Mucormycosis (26.7%). This was followed by Aspergillosis (23.2%), Pneumocystis jiroveci (21.4%), Cryptococcus (10.7%), Candida (7.1%), Histoplasmosis (5.3%), and Phaeohypomycosis (3.5%). Additionally, the fungal etiology remained undetermined in (8.9%) of the patients.

Infections caused by geographically limited endemic fungi are infrequent, and Aspergillus species, Mucorales species, Candida species, mucormycosis and Cryptococcus neoformans are the opportunistic fungi responsible for most such infections. The symptoms of systemic fungal infections are nonspecific, particularly in their early stages. The high rates of mortality and graft loss owing to fungal infections render early diagnosis and treatment imperative in immunosuppressed patients. Current methods for the diagnosis of systemic fungal infections include imaging procedures, endoscopic methods, biopsies, microscopic and culture techniques, antibody and antigen-based serologic testing, and the detection (via polymerase chain reaction) of fungal deoxyribonucleic acid in blood or bronchoalveolar lavage fluid, as well as the careful analysis of signs and symptoms. Antifungal therapy should be initiated early in patients with suspected fungal infection (even before laboratory findings have confirmed that diagnosis) and should be administered with appropriate adjustment of immunosuppressive regimens. It is challenging to manage fungal infections in post-renal transplant patients, optimizing the pharmacokinetics of antifungal drugs to reduce the risk of nephrotoxicity is crucial. In this article, we describe the 3 cases of post-transplant pulmonary fungal infections.

Case presentation

CRYPTOCOCCOSIS

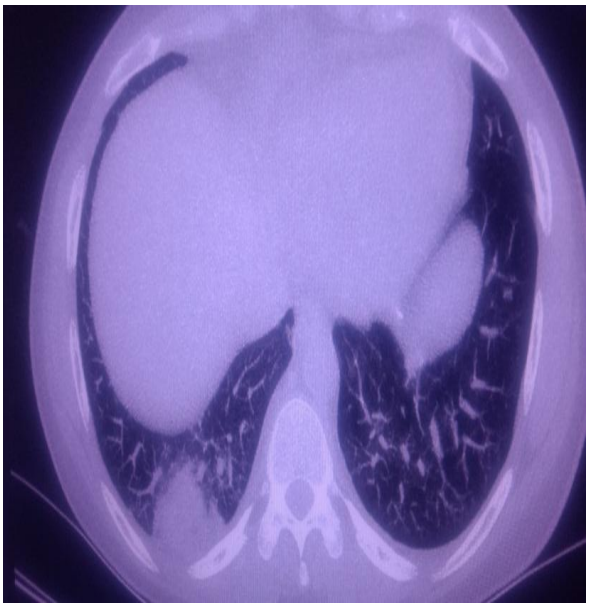
Case 1-A Middle-aged obese lady 6 months post-renal transplant presented to our institute with complaints of dry cough, chest pain and on-off low-grade fever since 1 month. She also had one episode of hemoptysis and complained of reduced appetite. Her general examination was unremarkable. Vitals were also within normal limits. Her respiratory system examination revealed a dull percussion note on the left side with reduced breadth sounds in the axillary region. Oxygen saturation was 97% at room air and normal body temperature was recorded. Her routine blood chemistry was within normal limits. She was negative for HIV and any chronic infections. Renal function, liver function, and coagulation studies were within normal limits. She underwent a chest x-ray which showed left upper lobe opacity with blunting of cardio phrenic angle. Her contrast CT scan was also done which showed a peripheral well-defined solid mass lesion in the left upper lobe apical posterior segment with a thin rim of pleural effusion **(Figure 1. a).** Pleural fluid was exudative but negative for malignant cells. Her bronchoscopic findings were unremarkable and BAL was negative for any malignant cells and the culture was also sterile. Subsequently, she underwent a CT-guided trans-thoracic biopsy of a solid lesion and the tissue was sent for histopathological examination. Distinctively, it was negative for malignancy but revealed abundant fungal yeast. Gomori's silver Methenamine staining and Mucicarmine staining were carried out which confirmed the presence of cryptococcal infection **(Figure 1. b).** She was also found positive for serum cryptococcal antigen. Her blood, urine and CSF culture were negative for cryptococcal. She denied any travel history or any immunosuppressant drug exposure. Her detailed immunological screening was carried out. Her IgG, IgM and IgA levels were within normal limits with normal absolute CD4 counts. She was diagnosed with Cryptococcal pneumonia and treatment was started with Inj. Amphotericin B for 2 weeks followed by oral Fluconazole 400mg BD for 10 weeks. The patient was followed up after completion of treatment with resolution of symptoms but had persistent radiological opacity.

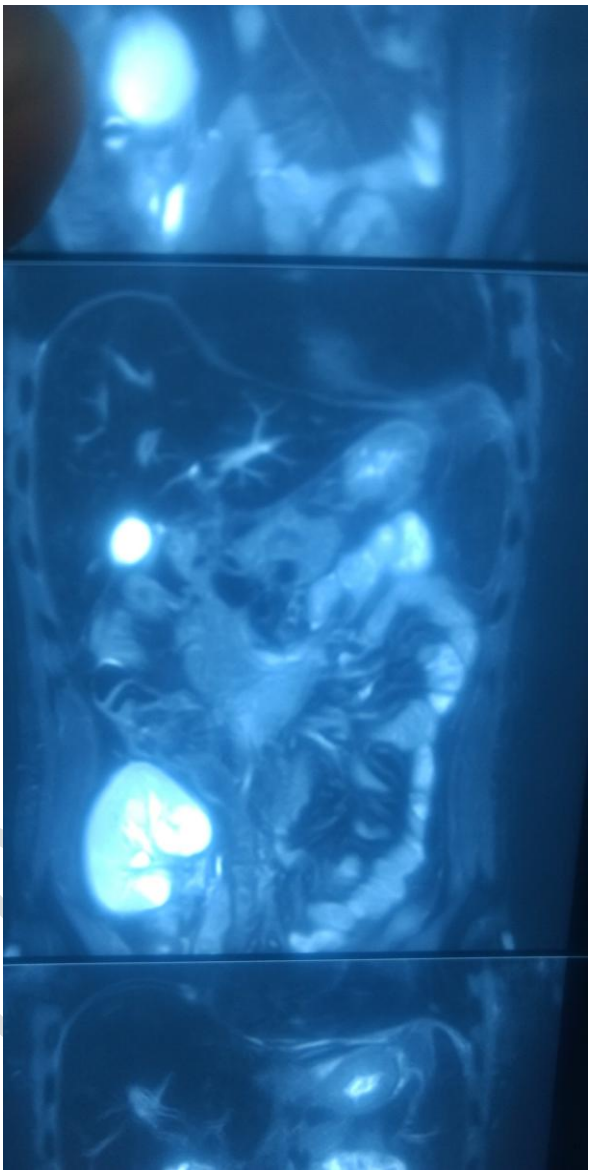


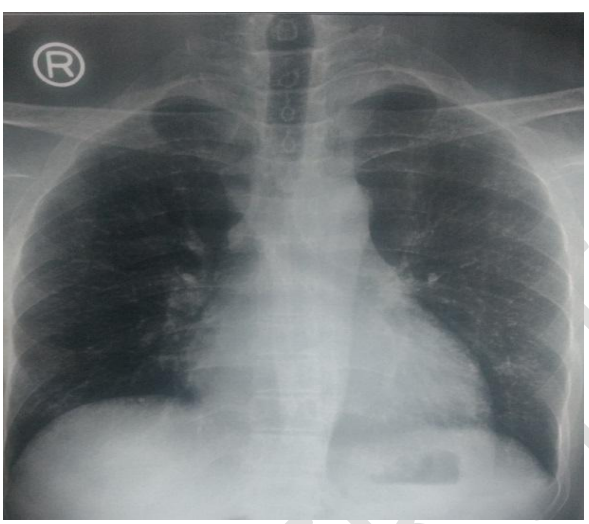
Case 1- Figure 1. a a peripheral well-defined solid mass lesion in the left upper lobe apical posterior segment with a thin rim of pleural effusion **Case 1- Figure 1. b-**. Gomori's silver Methenamine staining and Mucicarmine staining were carried out which confirmed the presence of cryptococcal infection

MUCORMYCOSIS

Case2-A 24-year-old male presented with progressive generalized weakness and fever for 1 month after receiving a living unrelated kidney transplant for end-stage kidney disease of unclear aetiology. He was maintained on hemodialysis for 5 years prior to the transplant. The patient was on maintenance therapy of immunosuppression consisting of mycophenolate mofetil, tacrolimus, and corticosteroids, in addition to trimethoprim/sulfamethoxazole and valganciclovir for microbial prophylaxis. An evaluation of the transplanted kidney using showed a mass lesion in the transplanted kidney. ct scan of the abdomen was done, which confirmed the mass lesion of 4x5cms as shown in **figure (2. a)** and uppercuts of ct also showed a mass lesion in the right lower lobe basal segments of the lung. A kidney biopsy showed evidence of acute tubular necrosis. CT-guided transthoracic biopsy of the mass lesion was also performed, which revealed mucormycosis. CT of the head showed no involvement of the sino-orbital areas or the brain. The patient was started on liposomal amphotericin B (5 mg/kg daily i.v o.d) with syrup posaconazole per oral 200mg thrice a day for mucormycosis. A cumulative dose of 3 grams of liposomal amphotericin b was administered over 2 weeks. Mycophenolate and tacrolimus were discontinued and the dose of prednisone was reduced. The patient had an acute increase in levels of serum creatinine levels which was treated with dialysis every third day during treatment with amphotericin b. he became asymptomatic within 3 days of starting the treatment and the lesion showed regression in size repeat ct scan was done after completion of cumulative dose. The patient is on regular follow-up and required dialysis only twice after cumulative dose in 1 month and the patient's serum creatinine level is stable now.





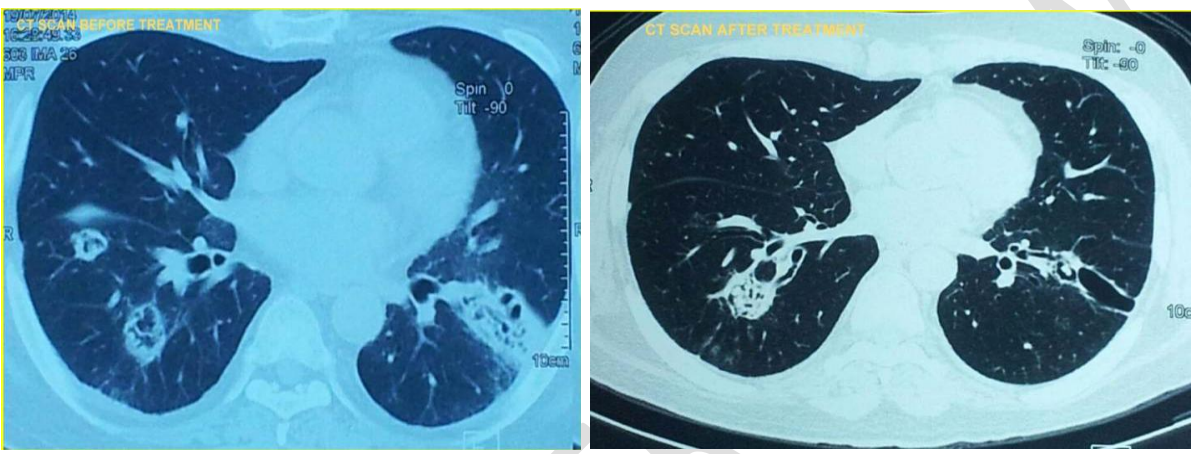


CASE 2 -FIGURE 2. a, 2.b-CT scan of the abdomen confirmed the mass lesion of 4x5cms as shown in figure 2. b and uppercuts of CT also showed a mass lesion in the right lower lobe basal segments of the lung in figure 2. a

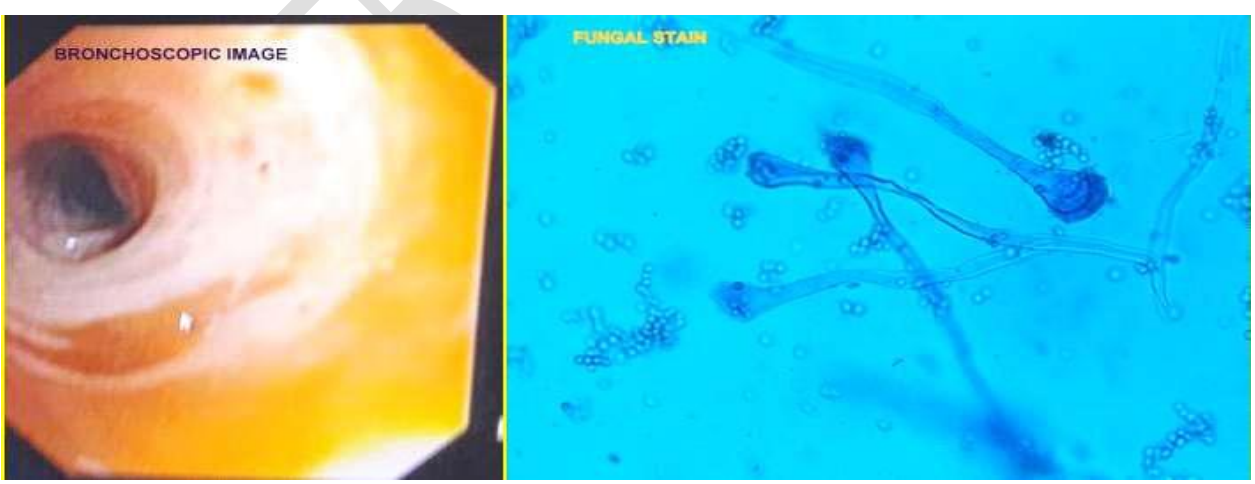
Invasive pulmonary aspergillosis

Case report 3:- Case2-A 43-year-old male presented with cough with expectoration, fever, and heamoptysis for 15 days after 4 years of receiving a cadaver kidney transplant for end-stage kidney disease. The patient was on maintenance therapy of immunosuppression consisting of cyclosporine and corticosteroids. Vital signs in the emergency department were temperature 100.8F, blood pressure 144/66 mm Hg, heart rate 80/min, respiratory rate 30/min, and oxygen saturation 99% on room air. Clinical examination revealed fine crepitations in the bilateral infrascapular area. Laboratory data showed a white cell count of 7000 cells/dl with 82% neutrophils, haemoglobin 10 g/dl, hematocrit 25%, blood urea nitrogen 77 mg/dl, and serum creatinine 3.5 mg/dl. Liver function tests and electrolytes were normal. Electrocardiogram was normal and the chest X-ray showed a b/l cavitary lesion in the lower lobes. The peak expiratory flow rate

was 200 L/min. ct scan confirmed the cavitating macro nodules with a halo sign in both lower lobes. Serum mycoplasma antibody, urine legionella antigen, nasal swab for respiratory syncytial virus and influenza antigen, and rapid streptococcal throat tests were negative. Bronchoscopy revealed whitish plaques in the lower lobe bronchus. Bal b-galactomannan was highly positive, bronchial washing showed branching hyphae and cultures showed green colour Aspergillus fumigatus. Hence the diagnosis of IPA was confirmed. He was treated with incremental doses of amphotericin b followed by voriconazole 200 for 6 months, follow-up ct scan and clinical improvement were satisfactory.



CASE 3 -FIGURE 3. A- cavitating macro nodules with a halo sign in both lower lobes.



CASE 3 -FIGURE 3. B-, bronchial washing showed branching hyphae and cultures showed green colour Aspergillus fumigatus

DISCUSSION

The presented cases highlight the occurrence of different fungal infections in solid organ transplant recipients, specifically cryptococcosis, mucormycosis, and invasive pulmonary aspergillosis. These cases emphasize the challenges in diagnosing and managing fungal infections in immunocompromised patients.

In Case 1, a renal transplant recipient developed cryptococcal pneumonia. The patient presented with respiratory symptoms, and imaging studies revealed a solid mass lesion in the left upper lobe of the lung. Histopathological examination confirmed the presence of cryptococcal infection. The patient received treatment with Amphotericin B followed by Fluconazole, leading to symptom resolution but persistent radiological opacity. This case highlights the importance of considering cryptococcal infection as a potential cause of respiratory symptoms in post-renal transplant patients and the need for prompt diagnosis and appropriate antifungal therapy.

Case 2 involves a renal transplant recipient who developed mucormycosis. The patient presented with generalized weakness and fever. Imaging studies revealed a mass lesion in the transplanted kidney and the lung. Biopsy confirmed the diagnosis of mucormycosis, and the patient was treated with liposomal Amphotericin B and Posaconazole. The patient showed regression of the lesions and improvement in symptoms. This case underscores the importance of considering mucormycosis as a potential infection in renal transplant recipients, particularly in the presence of immunosuppressive therapy, and highlights the need for prompt diagnosis and aggressive antifungal treatment.

In Case 3, a kidney transplant recipient developed invasive pulmonary aspergillosis (IPA). The patient presented with respiratory symptoms and imaging studies revealed cavitary lesions in the lower lobes of the lungs. Bronchoscopy and microbiological analysis confirmed the diagnosis of IPA. The patient received treatment with Amphotericin B followed by Voriconazole, resulting in clinical improvement. This case emphasizes the challenges in diagnosing IPA in post-kidney transplant patients and highlights the importance of considering this infection in the differential diagnosis of respiratory symptoms.

These cases collectively demonstrate the importance of early recognition and appropriate management of fungal infections in solid organ transplant recipients. Prompt diagnosis, initiation of antifungal therapy, and close monitoring are crucial in improving patient outcomes. Additionally, these cases underscore the need for further research to enhance diagnostic methods, explore novel treatment strategies, and identify preventive measures to reduce the incidence of fungal infections in this vulnerable patient population.

IPA

The diagnosis of IPA is challenging due to the nonspecific nature of the symptoms and is often delayed due to lack of clinical suspicion in patients without classic risk factors. Tissue biopsy with histopathologic demonstration of tissue invasion by fungal hyphae is considered the 'gold standard' (9). Invasive aspergillosis can be a catastrophic complication in SOT recipients and is associated with high rates of graft loss and death. Data from 15 centers involved in a prospective cohort study indicate that mortality at 12 months for SOT recipients with aspergillosis exceeds 50% [1 The most common infecting species is *Aspergillus fumigatus*. Infections due to *Aspergillus flavus*, *Aspergillus niger* and *Aspergillus terreus* are less common [67,68]. However, obtaining tissue specimens from critically ill, often intubated, and hemodynamically unstable patients is not always feasible. Identification of Aspergillus species in the sputum could represent colonization, especially in immunocompetent patients (1, 10). On the contrary, isolation of Aspergillus from sputum in patients with leukemia, or in those who have undergone SOT, has a positive predictive value of 80-90% for the presence of IPA (1, 11, 12). Nosocomial transmission leading to colonization and even infection has been described [71]. In one notable case, debridement and dressing of wounds from a patient with aspergillosis resulted in aerosolization of spores and airborne person-to-person transmission in a transplant ICU [72]. Diagnosis of invasive aspergillosis can be challenging and frequently require histological evidence for infection and culture. Specimens (e.g., smears and tissue) can be stained with Gomori's Methenamine Silver and periodic acid-Schiff or with fluorescent dyes such as Calcofluor white [84]. Immunohistochemistry techniques are another promising diagnostic modality, but are not in widespread use as of yet With regard to imaging studies, Patterson et al., in their review of 595 cases of IPA, reported that 85% of the cases had computed tomographic (CT) scan findings suggestive of IPA (13). HRCT is recommended in all cases of suspected IPA. Pulmonary nodules are the most commonly seen abnormality whereas the 'halo sign' is relatively more specific with a high predictive value for IPA in patients with neutropenic fever after SOT (14). Laboratory tests to detect Aspergillus antigens in body fluids, either serum or bronchoalveolar lavage fluid (BAL), are increasingly helpful in the diagnosis of IPA. Galactomannan (GM) testing or Aspergillus polymerase chain reaction (PCR) assay in BAL has good sensitivity and specificity for IPA (2, 15). BAL GM testing is part of the diagnostic criteria for IPA (16). The mortality rate of IPA continues to be very high, exceeding 50% in neutropenic patients (14), and 90% in SOT recipients (18). Amphotericin used to be the preferred antifungal, until a large randomized clinical trial comparing amphotericin with voriconazole for primary treatment of IPA showed a better response rate and higher survival (71 vs. 58%) at 12 weeks of therapy in the voriconazole group. Voriconazole also has a better side effect profile and is generally better tolerated. Echinocandins, such as caspofungin, are used as salvage therapy in patients not responding to or not tolerating first-line therapy (1). Due to differences in their mechanisms of action, combination therapy with azoles, trienes, and echinocandins could be a strategy to treat IPA (1). At present, voriconazole is considered the therapy of choice (19). Prolonged and high-dose corticosteroid therapy is an established risk factor for the development of IPA (1, 2). Steroids inhibit macrophage killing of Aspergillus by nonoxidative mechanisms (20). Steroids may also promote the growth of Aspergillus (21). Although IPA is seen in patients with chronic lung diseases on long-term steroids, it is rarely seen with short use of corticosteroids (1, 2, 22).

Mucormycosis

The most form of disease was rhino-cerebral , followed by pulmonary . Overall mortality rate was 52%, particularly in recipients with pulmonary infection (100%); however, the mortality rate in rhino-cerebral form of disease was low (30.8%). There was no statistically significant difference in mortality rate between male and female . In addition, no significant differences were seen in mortality rate with age of patients and time of diagnosis since transplantation . Pulmonary infection was more seen in recipients received azathioprine compared to those on mycophenolate mofetil .Mucorales are ubiquitous in nature and rarely cause disease in immunocompetent hosts, except in the settings of uncontrolled diabetes mellitus[7], heavy exposure as in natural disasters, [8, 9] or rarely without apparent predisposing factors [7, 10, 11]. Recipients of SOT are at higher risk given their multiple predisposing factors. Diabetes mellitus remains the leading risk factor among all studied patient populations, as 36% of Roden etal.'s 929 cases were diabetic, mostly type 2, and in the setting of ketoacidosis [7]. Thus it remains an independent risk factor even in the presence of other predisposing factors [12]. Another major risk factor is the state of immunosuppression, especially the use of potent T cell depleting agents [13, 14] Use of tacrolimus was associated with a 4-fold reduction in the risk of developing mucormycosis [6]. This could be explained by the synergy demonstrated in vitro between calcineurin inhibitors and triazole antifungals against some species of mucormycosis [18, 19] In the reported literature, the species of Mucorales accounting for most of the cases is variable, likely reflecting regional and hospital variability. *Rhizopus* species is the most common, accounting for 35%–73% of cases, followed by *Mucor* (13%–37%) and *Mycocladus* (0%–13%) [4, 6, 7, 15]. The infection is acquired through inhalation of spores or rarely through direct contact with the skin. The hyphae of pathogenic Mucorales are angioinvasive, whichlead to hemorrhagic necrosis, vascular thrombosis, and tissue infarction [1, 9].The primary site of infection varies according to the host's condition. Localized sinonasal or sino-orbital disease with involvement of the brain accounts for 66%of mucormycois in diabetic patients. However, pulmonary infection is the predominant site affected in recipients of SOT [4, 7], accounting for 39% of cases with involvementof other organ sites in 48% [6].

In the SOT population, disseminated disease occurs in 9–26% of cases, with the highest incidence among liver transplant recipients (26–55%), followed by lung (11–25%), heart (11–20%), and kidney transplant recipients (9–13%) [6, 7, 12, 15]. The unique factors that increase the risk of dissemination in specific organ transplant groups remain undefined. The risk of dissemination based on the primary site of infection among SOT recipients is unknown but has been reported among all cases of mucormycosis, including but not exclusive to SOT [7]. About 50% of patients with pulmonary infection suffered from dissemination [7]. The diagnosis of mucormycosis is challenging and often delayed [29, 36], as the clinical presentation is not specific and symptoms and signs are often muted by the blunted immune response. Timely diagnosis and treatment are crucial due to the aggressive course of mucormycosis that may eventually lead to tissue necrosis and dissemination. The diagnosis is confirmed by a A high index of suspicion and suggestive signs and symptoms are combination of radiological, histological, and microbiological studies. Plain or contrast enhanced CT or magnetic resonance imaging (MRI) of the head, sinuses, brain, chest, and abdomen may show some suggestive radiological signs [1, 13]. CT features of pulmonary mucormycosis in SOT recipients commonly include consolidation or mass-like lesions, nodules, or cavities in about 25% of cases. The etiological diagnosis, and direct identification of the organism by culture or

histopathology is the gold standard. The hyphae of Mucorales are broad, irregularly branched, thin-walled, and sparsely septate (Figure 1).

Molecular diagnostic tests for identification of Mucorales are increasingly used for early detection of infection and identification of genus even in cases when cultures are negative. Qualitative and quantitative PCR has been used to detect infection in lung tissue, bronchoalveolar lavage fluid, and serum samples [39]. Whether these techniques can be recommended for routine use remains unclear, although PCR testing should be considered in cases where the histopathology is suggestive of Mucorales, but cultures are negative [39–41]. Mucorales do not release β-D-glucan during their growth, so a positive galactomannan serum assay indicates coinfection with *Aspergillus* [4] Timely initiation of treatment is crucial and associated with better survival [36]. The optimal management of mucormycosis is based upon early recognition and initiation of treatment, surgical resection of necrotic tissue if possible, and reversal of predisposing factors, such as uncontrolled glycemia, IS, and neutropenia. Surgery is an essential part of the management of localized disease, such as rhino-orbito-cerebral disease, and surgical resection and debridement are associated with improved outcomes [7]. Lobectomy and nephrectomy were reported to be successful in isolated pulmonary [29, 43] and renal disease, respectively [22]. Salvage hepatic resection and retransplantation have also been reported [44]. Amphotericin B (AmB) and posaconazole are the only antifungal agents currently available that are active against Mucorales. AmB is considered the drug of choice. Lipid formulations of AmB are thought to have better activity and safety profile compared to conventional AmB. Treatment with AmB lipid complex (ABLC) was reported to be successful in 8 of 14 (57%) SOT recipients with mucormycosis [6, 29], compared to 16 of 17 patients (94%) treated with liposomal AmB (LAmB) [6]. The reduced nephrotoxicity associated with standard doses of LAmB would make it the primary agent for treatment in SOT recipients, as these patients are usually receiving other potentially nephrotoxic agents such as calcineurin inhibitors. LAmB would also be preferred in renal transplant recipients where nephrotoxicity can result in graft failure.

Posaconazole is available in oral formulation only and has been used as an oral step-down agent after successful response with AmB or for salvage therapy in case of refractory disease or intolerance to side effects of AmB [32, 33]. In a retrospective study, 91 patients with mucormycosis (including 10 SOTs) received at least 30 days of enteric posaconazole at 400mg twice a day as a salvage therapy. At 12 weeks, total response rate was 60%, of which complete and partial responses accounted for 14% and 46%, respectively. The disease remained stable in 21% of patients and progressed in 17%, and the outcome in the remaining 2% was not known [32]. The initiation of posaconazole as first-line therapy for the treatment of serious fungal infections remains problematic. Posaconazole is presently available for oral administration only.The oral bioavailability is enhanced when administered with a fully fatty meal and with a lower stomach acid pH[47]. Hence posaconazole has to be administered soon after a full meal especially with fatty foods, liquid nutritional supplements, or an acidic carbonated beverage [48]. Therapeutic drug monitoring may be important in optimizing outcomes due to erratic absorption resulting in unpredictable levels. This is especially true in the presence of a concentration effect relationship [47]. The dietary requirements for optimal absorption and achievement of therapeutic drug levels can be difficult in transplant recipients receiving several other oral medications. Various outcomes have been reported using different combination therapies with a small number of patients. Combination of LAmB with posaconazole was no more effective than LAmB alone in a murine model of

mucormycosis [49]. Although echinocandins are reported to have no to moderate activity against Mucorales [30, 50–54], the use of an echinocandin in combination therapy has been attempted. Combined with a median of 2 surgical procedures per patient, Reed et al. [30] reported a 100% success rate (6/6) with the combination of caspofungin with a lipid AmB, compared to 45% (14/31) success rate for those treated with ABLC monotherapy. Isavuconazole is a new broad-spectrum triazole antifungal agent that has good *in vitro* activity against clinically important yeasts and molds including *Aspergillus* and Mucorales.The drug has a favorable pharmacokinetic profile, is available as an intravenous and oral formulation, and has the advantage of less drug-drug interaction than voriconazole and posaconazole. It is presently in phase III clinical trials for the treatment of invasive aspergillosis and other molds [55].
Mucormycosis occurs in patients with iron overload, as host iron availability is important for the pathogenesis of mucormycosis. Adjunctive therapy with deferasirox iron chelation and LAmB had shown improved outcomes in the diabetic mouse model of mucormycosis. However, a small clinical trial of 20 patients (DEFEAT Mucor Study) using LAmB and deferasirox demonstrated worse outcomes in the deferasirox arm [56]. Currently, there are no recommendations regarding routine prophylaxis against fungal infections in kidney transplant recipients.

The overall mortality rate of mucormycosis ranges from 38% to 56.5%. The primary site of infection plays a major role in determining the outcome, with marked increase in mortality when dissemination occurs, reportedly up to 100%.Mortality has been reported from33% to 60% for isolated pulmonary infection, but 95% when disseminated.

Conclusion & future perspective

Invasive fungal infections are a significant problem for people who have received solid organ transplants. These infections can cause severe illness and even death. This study provides important information about how these infections occur, how they are diagnosed, and how they are treated. It emphasizes the need to consider factors related to the person receiving the transplant and the environment in which they live when thinking about fungal infections.The study shows that certain types of transplants, such as small bowel and lung transplants, carry a higher risk of fungal infections compared to other types of organ transplants. This information is crucial for doctors to assess the risk for each patient and develop strategies to prevent infections.

The study also reveals that the way fungal infections present and develop can vary depending on the type of transplant. Understanding these differences can help doctors develop targeted ways to monitor and prevent infections. The study includes examples of patients who developed fungal infections after their transplants, providing important insights into how these infections are diagnosed and managed.The study highlights the importance of starting antifungal treatment early in suspected cases, even before laboratory tests confirm the infection. Early treatment is essential for better outcomes and to prevent complications. The study also emphasizes the need to adjust the doses of antifungal drugs in patients who have received kidney transplants to reduce the risk of kidney damage.

In conclusion, this study emphasizes the significant impact of invasive fungal infections on people who have received solid organ transplants. It highlights the need for better ways to diagnose and treat these infections. The study suggests that future research should focus on developing new diagnostic tools, evaluating combinations of different drugs for treatment, and understanding how the risk of these infections may change over

time. Improving our understanding and treatment of fungal infections will help improve outcomes and reduce the harm caused by these infections in transplant recipients.

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