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Original Research Article

Fearsome four- Fungal infections in renal transplant recipients

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ABSTRACT

Aim: To study the clinical presentation, diagnostic methods, treatment and outcomes of Invasive Aspergillosis Cryptococcal infection, Mucormycosis and Histoplasmosis in renal transplant recipients.
Materials and Methods: We performed a retrospective analysis of renal transplant recipients with four major fungal infections from January 2000 until December 2022 at a tertiary care centre in Southern India. This study was approved by the institutional ethical committee. We have identified these cases from the electronic records of the microbiology department and renal transplant outpatient clinic.
Results: A total of 1970 patients underwent renal transplantation at this institute during study period. A total of 25 patients were diagnosed as having invasive Aspergillosis - 20 patients had pneumonia, three had right maxillary sinusitis, one each had left chronic suppurative otitis media, and skull base osteomyelitis). There were 20 patients with cryptococcal infection of which eight had disseminated infection, seven had meningitis, four had cutaneous cryptococcosis and one had pulmonary cryptococcosis. Mucormycosis was diagnosed in 14 patients, twelve of which had pulmonary mucormycosis, one had oculo-cerebral mucormycosis and one patient had acute invasive fungal maxillarysinusitis. Histoplasmosis was diagnosed in four patients, two of whom had disseminated histoplasmosis and two had cutaneous histoplasmosis. In this study, mortality was highest with mucormycosis (57%) followed by 33.3% with invasive Aspergillosis and 20% with Cryptococci infection.
Conclusion: Currently, there is no standard serological test available for the routine identification of invasive fungal infections in patients. Initial cultures may yield negative results due to slow fungal growth and variations in colony appearance. Therefore, it is essential to pursue aggressive sampling methods when fungal infection is suspected. Invasive procedures such as bronchoscopic lavage and abscess aspiration play a crucial role in reaching a diagnosis. In summary, maintaining a high level of suspicion and employing thorough investigations in post-renal transplant recipients are vital for early diagnosis, prompt treatment initiation, prevention of disease spread, and reduction of mortality risk.

1. Introduction

Renal transplantation (RT) stands as the preferred treatment for patients grappling with end-stage renal failure, significantly enhancing both their quality of life and survival rates.[1] Representing approximately two-thirds of all solid-organ transplantations (SOTs), RT holds its place as the most prevalent form of such procedures.[2,3] Fungal infections account for roughly five percent of all infections observed in renal-transplanted patients, with Aspergillus infections ranking as the second most frequent fungal infection following candida infections.[4] Increased

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immunosuppression, as well as environmental factors are some of the risk factors involved in this increased incidence of fungal infections in SOTs. This immunosuppressive state allows infectious complications leading to a high mortality rate. Currently, overall mortality due to invasive fungal infections in solid organ transplant (SOT) recipients' ranges between 25 and 80%. Most fungal infections occur in the first 6 months after transplantation due to optimum dose of various immunosuppresants. The symptoms of systemic fungal infections are nonspecific. Early diagnosis and appropriate timely management of these fungal infections plays decisive role in reducing mortality. This study was carried out in a single centre to find out the prevalence, clinical profile, diagnostic procedures, treatment modalities and final outcome of four major fungal infections viz Aspergillosis, Cryptococcal infection, Mucoymycosis and Histoplasmosisis in Renal transplant recipients.

2. Materials and Methods

We performed a retrospective analysis of renal transplant recipients with four major fungal infections from 01 January 2000 to 31 December 2022 at a tertiary care centre in southern India. This study was approved by the institutional ethical committee. This vide Institutional Review Board (IRB) minute number 13641 dated 02.12.2020). We identified these cases from the electronic records of the microbiology department and renal transplant outpatient clinic. A case was identified as an individual aged 18 years or older who had received a renal transplant, with laboratory confirmation of fungal species from any location alongside clinical signs indicative of infection. Data collected included demographics, antibiotic prophylaxis, immunosuppressive regimens, and episodes of rejection, time from date of transplantation, clinical presentation, diagnosis, treatment, and outcome. The results were analysed in using Microsoft Excel 2021, (v16.0). Categorical variables expressed as frequencies and proportions. Continuous variables expressed as mean with standard deviation or median with interquartile range.

3. Results

During the study period, a total of 1970 patients underwent renal transplantation at this institute. Among them, 25 (1.26%) patients were diagnosed with invasive Aspergillosis, 20 (1.01%) with cryptococcal infection, 14 (0.7%) with mucormycosis, and 4 (0.2%) with Histoplasmosis. Invasive Aspergillosis (IA) accounted for 1.26% of all fungal infections in this research. The mean age of patients at diagnosis of IA was 43.5 ± 10.2 years, with a male-to-female ratio of 8:1. The mean duration after transplantation for developing invasive Aspergillus infection was 4.3 ± 2.1 years, ranging from within one month to a maximum of 14 years post-transplantation. Four patients received kidneys from deceased donors, and 21 from living related donors. In 80% of patients with invasive Aspergillosis, the infection was confined solely to the lungs. Clinical presentations included right maxillary sinusitis in three patients, orbital cellulitis in one patient, and left chronic suppurative otitis media with lower motor neuron facial palsy in one patient, and skull base osteomyelitis in another. Additionally, six patients had a history of pulmonary tuberculosis. All patients (21/25) 84% with pneumonia required bronchoalveolar lavage (BAL) and transbronchial lung biopsy (TBLB) for the diagnosis. BAL Galactomannan and serum Galactomannan were positive in all patients. In the remaining patients, Aspergillus grew from aspirate obtained from purulent discharge from the respective affected sites.

The species identified were A. fumigatus in eight patients (32%), A. flavus in six patients (24%), A. niger in two patients (8%) and A.terreus (8%) in two patients. In the remaining seven cases (28%), the species could not be identified.Concomitant infections of mucormycosis in two patients, Nocardiosis infection in two patients and pneumocystis jerovici pneumonia in one patient were present. Graft function was stable in 14 patients (56%) during infection with a mean serum creatinine of 1.8+0.4mg/dl. At the time of infection, the mean Tacrolimus Co level was 7.4 + 1.8ng/ml, Cyclosporine Co level was 160.3 + 102.2 ng/ml and Mycophenolate area under curve (AUC) was 55.3 +2.5 mg.h./L, appropriate levels for the time after transplantation. Twenty patients (80%) were treated with intravenous liposomal Amphotericin monotherapy at 3 mg/kg for at least 6 weeks followed by oral azoles like Itraconazole, Voriconazole or Posaconazole for a minimum period of one year. Four patients were treated primarily with Voriconazole (administered at 6 mg/kg IV twice a day on day 1, followed by 4 mg/kg twice daily for at least seven days followed by oral dosing at 200 mg orally twice daily. One patient was treated with a combination therapy of Voriconazole and Anidulafungin. Eight of the 25 patients (32%) who developed acute kidney injury due to severe infection expired with refractory septic shock and multi-organ dysfunction syndrome. A patient developed massive hemoptysis which required Bronchial artery embolization for stabilization.

A total of 20 cases of Cryptococcosis were diagnosed with an incidence of 1.01%. The mean age of patients at diagnosis was 47 ±13.1 years, with a male-female ratio of 19:1. On average, the time taken to develop cryptococcal infection post-transplantation was 4.2 ± 2.1 years, with the earliest occurrence documented within three months and the latest observed up to 20 years after transplantation. All were living related donor transplant recipients. Eighteen patients had received Basiliximab induction and two patients received Anti Thymocyte Globulin (ATG) induction. In this study 11 out of 20

(55%) patients had cryptococcal meningitis, four (20% had cutaneous nodules, two (10%) had cryptococcal arthritis and one each had graft pyelonephritis, generalised lymphadenopathy, and non-resolving pneumonia. All patients underwent cerebrospinal fluid (CSF) analysis irrespective of presentation to look for disseminated disease. CSF Cryptococcal antigen was positive in all cases of cryptococcal meningitis. The patients with non-resolving pneumonia required bronchoscopy, BAL and TBLB for establishing the diagnosis. The mean Tacrolimus level was 8.2 ±1.6 ng/ml, Cyclosproine level was 162.3 ±102.2 ng/ml and Mycophenolate area under curve (AUC) was 55.3 ± 4.5mg.h./L at the time of infection which were higher for duration after transplantation. In our study, the six patients with cryptococcal meningitis and one patient of graft pyelonephritis, received 4 weeks of induction therapy with intravenous liposomal amphotericin B (3mg/kg intravenously per day) and Flucytosine administered as 100 mg/kg/day orally in four divided doses (adjusted for renal function). In view of leucopenia, the remaining five patients with meningitis received induction therapy treated with liposomal amphotericin B (3 mg/kg intravenously per day) and Fluconazole (800 mg per day orally) for two weeks of induction therapy. All these patients received maintenance therapy with oral fluconazole 200 mg once daily for 12 months. In patients with cutaneous cryptococcosis, two patients had disseminated disease and they received induction therapy with liposomal amphotericin B and Fluconazole for four weeks followed by maintenance therapy with oral fluconazole 200 mg once daily for 12 months. In view of cytopenias flucytosine was not considered for induction therapy. Two patients who had only localised skin disease received oral fluconazole for 12 months. One patient with Cryptococci arthritis had evidence of disseminated disease and received liposomal Amphotericin and Flucytosine for four weeks followed by Fluconazole maintenance therapy for 12 months. The one patient who had elbow bursitis and generalised lymphadenopathy received only oral Fluconazole for 6 month. The serum electrolytes and graft function were closely monitored in all patients who received liposomal amphotericin. In patients who received Fluconazole, the dose of Calcineurin inhibitors (CNIs) was adjusted as per therapeutic drug monitoring. Four of the 20 patients (20%) succumbed due to sepsis disseminated intravascular coagulation and acute kidney injury. In the remaining 16 (80%) patients, the graft function remained stable and the mean serum creatinine was 1.7 ± 0.5mg/dl.

In our study, a total of 14 patients were diagnosed with Mucormycosis with an incidence of 0.71%. The mean age at presentation was 38.2 ± 15.2 years and the time of presentation after renal transplantation was 2.5 ± 1.2 years. Ten of the 14 recipients had received kidneys from living related kidney donors and the remaining four from deceased kidney donors. Six patients had received induction with ATG and remaining had received Basiliximab induction. Eleven patients received maintenance immunosuppression with Prednisolone, Tacrolimus and Mycophenolate, two patients received Prednisolone, Cyclosporine and Azathioprine. One of the patients was on steroid monotherapy in view of Mycophenolate induced cytopenias and recurrent infections. Tacrolimus was stopped in view of Tacrolimus toxicity. The mean Tacrolimus level was 8.4 ± 2.5 ng/ml, Cyclosproine level was 250.4 ± 110.2 ng/ml and Mycophenolate area under curve (AUC) was 56.4 ± 22.4 mg.h./L at the time of Infection which are at higher normal range level as per transplant duration. The most common presentation was pulmonary involvement seen in in 12 of the 14 (85.7%) patients, one patient presented with oculo-cerebral mucormycosis and one patient presented with invasive fungal sinusitis. In patients with pulmonary involvement, eight patients (66%) required bronchoscopy, BAL and TBLB for diagnosis and in four patients (33.3%), required CT guided lung biopsy for establishing the diagnosis. The remaining two patients required functional endoscopic sinus surgery (FESS) for debridement and the aspirated pus grew Rhizopus species mucorales. All patients were treated with intravenous liposomal amphotericin B at the dose of 5 mg/kg body weight for minimum of 3 weeks followed by oral posaconazole therapy (300 mg every 12 hours on the first day, then 300 mg once daily) in stable patients. In severe infection, the duration of amphotericin was extended to 6 weeks. Seven patients with pulmonary mucormycosis and one patient with occulo-cerebral mucormycosis succumbed to their illness. Two patients required lobectomy, out of which one succumbed to illness.

In our study, four patients were diagnosed with histoplasmosis, with two presenting with disseminated histoplasmosis and the other two with cutaneous histoplasmosis. The mean age of patients was 39.2 ±12.2 years and the mean time of presentation post-transplant was 8.5±1.7 years. All these patients had live related donor renal transplantation. They had received Basiliximab induction followed by maintenance immunosuppression with Prednisolone, Tacrolimus and Mycophenolate. The mean Tacrolimus level was 4.2±1.8 ng/ml, and Mycophenolate area under curve (AUC) was 45.3±5.8mg.h./L at the time of Infection which were at appropriate as per duration after transplantation. The patient with disseminated histoplasmosis were treated with Liposomal Amphotericin B 3 mg/kg/day IV for 3 weeks followed by oral Itraconazole at a loading dose of 200 mg every eight hours for the first three days followed by 200 mg twice daily for a total of 12 months with close monitoring of graft function, electrolyte abnormalities and therapeutic drug monitoring of the calcineurin inhibitor drug. The patients with cutaneous

diseases were treated with oral Iatraconazole 200 mg every eight hours for the first three days, then 200 mg twice daily for a total of 12 months. All patients had stable graft function.

The clinical feature, transplant details treatment details and outcomes of these fungal infections were mentioned in Table 1. The graphical representation of clinical features were depicted in Figure 1.

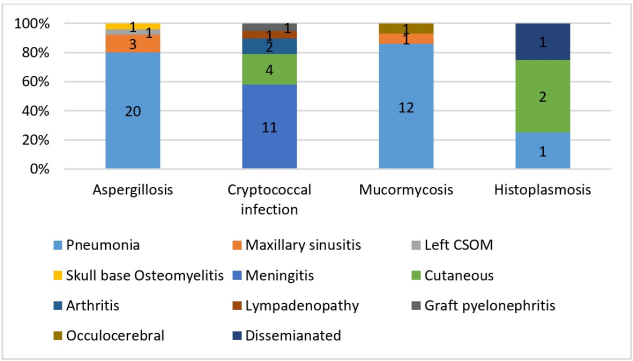

Figure 1: Clinical features of fungal infections in Kidney transplant recipients

The excision biopsy of left elbow bursa showing necrotising granulomatous inflammation as depicted in Figure 2 and showing many small spherical or ovoid yeasts, 2–6 μm in size, characterized by the ability to enter host macrophages and survive was shown in Figures 3 and 4.

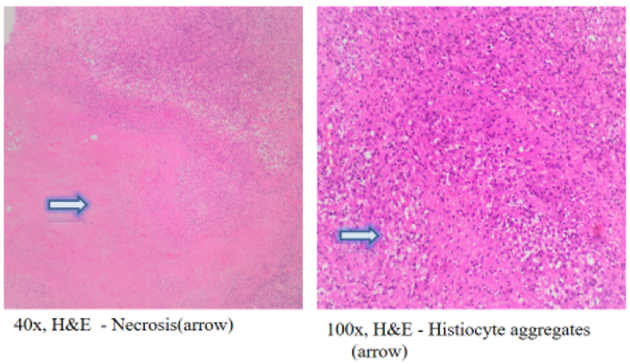

Figure 2: Excision biopsy of left elbow bursa showing Necrotising granulomatous inflammation

In this study, the highest mortality rate was observed in patients with mucormycosis (57%), followed by 33.3% in those with invasive Aspergillosis and 20% in cryptococcal infection cases with no mortality for histoplasmosis.

4. Discussion

Invasive aspergillosis (IA) poses a significant threat as a life-threatening opportunistic fungal infection, particularly among immunocompromised patients, such as renal

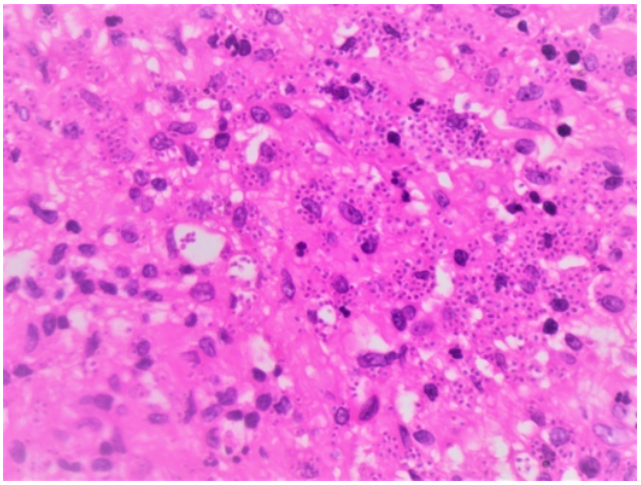

Figure 3: HPE of left elbow bursa- 400x, H&E: Many small spherical or ovoid yeasts, 2–6 μm in size, characterized by the ability to enter host macrophages and survive

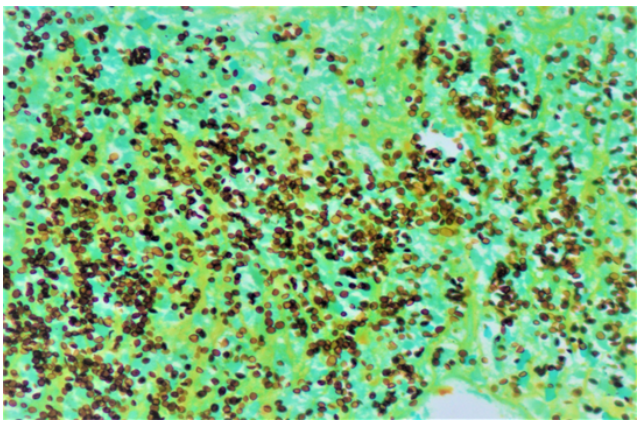

Figure 4: HPE of left elbow bursa- 400x GMS stain -Highlighting yeast

transplant recipients.[5] In our study, this is the most common infection constituting 40% of the cases with pneumonia as predominant presentation as consistent with previously published studies.[5] All patients with pneumonia 84% (21/25) required bronchoalveolar lavage (BAL) for diagnosis. By maintaining a high index of suspicion, employing aggressive diagnostic techniques, and promptly administering appropriate antifungal treatment for the correct duration, 17 out of 25 patients (68%) experienced symptomatic improvement alongside stable graft function.

The trends in the incidence of cryptococcosis among transplant recipients are not as clearly defined. Cryptococcosis ranks as the third most prevalent invasive fungal infection in Solid Organ Transplant (SOT) recipients. It is estimated that 20–60% of cryptococcosis cases in non-HIV infected individuals in the United States[6] and 17.4% in France[7] occur in SOT recipients. The overall

Table 1: Clinical features, transplant & treatment details and outcomes of fungal infections in kidney transplant recipients

	Invasive Aspergillosis		**Cryptococcal infection**		**Mucormycosis**		**Histoplasmosis**	
Number of patients n (%)	25 (1.26%)		20 (1.01%)		14 (0.7%)		4 (0.2)	
Male/Female n	23/2		19/1		10/4		3/1	
Mean age (years)	43.5±10.2		47 ±13.1		38.2 + 15.2		39.2 +12.2	
Live/Deceased donor	21/4		20/0		10/4		4/0	
Induction IS (Basiliximab/ATG)	19/6		18/2		8/6		3/1	
Maintenance IS	P+T+M	15	P+T+M	13	P+T+M	11	P+T+M	03
	P+T+A	04	P+C+A	04				
	P+C+M	02	P+A	02	P+C+M	01		
	P+C+A	02						
	P+E+M	01	P+C+M	01	P+T	01	P+T	01
	P+A	01						
Timing of infection since transplant (years)	4.3 ± 2.1		4.2 ± 2.1		2.5 ± 1.2		8.5+1.7	
Clinical features	Pneumonia	20	Meningitis	11	Pneumonia	12	Cutaneous	02
	Maxillary sinusitis	03	Cutaneous	04				
	Left CSOM	01	Arthritis	02	Maxillary sinusitis	01	Pneumonia	01
	Skull base Osteomyelitis	01	Lympadenopathy	01				
			Graft pyelonephritis	01	Occulo-cerebral	01	Disseminated	01
			Pneumonia	1				
Number of invasive diagnosis (BAL/TBLB/biopsy) n (%)	21 (84%)		09 (45%)		14 (100%)		04 (100%)	
Antifungal treatment Induction – 6 weeks	LipAmph	20	LipAmph + Flucytosine	8	All received LipAmph 02 patients required Lobectomy		LipAmph	02
	Voriconazole	4	LipAmph+ Fluconazole	12			Itraconazole	02
	Voriconazole + Anidulafungin	1						
Antifungal treatment Maintenance	Oral Itraconazole	14	Oral Fluconazole		Oral Posaconazole		Oral Itraconazole	
	Oral Voricoazole	02						
	Oral Posaconazole	01						
Mortality n (%)	8 (32%)		4 (20%)		8 (57.1%)		Nil	
Graft function (Serum Creatinine – mg/dl) during infection for alive patients	2.3±0.8		1.9±0.4		2.5 +1.8		1.2+0.4	

A- Azathiprine, ATG- Anti Thymocyte Globulin, BAL- Broncho alveolar Lavage, C- Cyclosporine, E- Everolimus, IS- ImmunoSuppression, LipAmph- Liposomal Amphotericin, M- Mycophenolate**,** P- Prednisolone, T- Tacrolimus, TBLB- Transbronchial lung biopsy

incidence of cryptococcosis in SOT recipients' ranges from 0.3–5%, with approximately 2.8% reported.[8] In immunocompromised patients, the disease primarily results from the reactivation of latent infection.[9] While central nervous system disease, particularly meningoencephalitis, is the most common manifestation of systemic cryptococcosis, lung involvement is also frequent.[10] Cryptococcal lesions, known as cryptococcomas, may localize in affected organs and have been documented in unusual sites.[11,12] Typically, localized cryptococcal lesions coincide with systemic disease. According to Singh N et al, 61% of SOT recipients had disseminated disease, with 54% exhibiting pulmonary involvement, and 8.1% presenting with skin, soft-tissue, or osteoarticular cryptococcosis.[13] Approximately one-third of SOT recipients with cryptococcosis exhibit pulmonary-limited disease. Pulmonary cryptococcosis may be incidentally detected in asymptomatic patients.[14] However, when presenting as acute respiratory failure,

pulmonary cryptococcosis carries a grave prognosis. Cutaneous cryptococcosis can manifest as papular, nodular, or ulcerative lesions, or as cellulitis.[15,16] While cutaneous lesions typically indicate hematogenous dissemination, the skin has also been identified as a Cryptococcus species entry point and a potential source of subsequent disseminated disease in SOT recipients.[17] In our study, the most common presentation was disseminated infection followed by meningitis, cutaneous and pulmonary involvement with mortlity of 20%. Only two patients had rare presentations in the form of generalised lympadenpathy and graft pyelonephritis without any systemic features.

Mucorales are widely distributed in nature and typically do not cause disease in individuals with intact immune systems, except in specific circumstances such as uncontrolled diabetes mellitus,[18] significant exposure as seen in natural disasters,[19] and only exceptionally without identifiable predisposing factors.[20,21] Infection typically occurs through the inhalation of spores or, less commonly, through direct skin contact. The invasive hyphae of pathogenic mucorales lead to angio-invasion, resulting in hemorrhagic necrosis, vascular thrombosis, and tissue infarction.[22] The primary site of infection varies depending on the individual's health status. Among diabetic patients, localized sino-nasal or sino-orbital disease involving the brain accounts for 66% of mucormycosis cases. However, pulmonary infection is predominant in Solid Organ Transplant (SOT) recipients,[23] who are at heightened risk due to multiple predisposing factors. Among various patient populations, diabetes mellitus remains the foremost risk factor. Immunocompromised states, particularly due to potent T-cell depleting agents[24,25] and neutropenia,[26] also significantly elevate the risk. In our study, the predisposing factor of Diabetes was present in 10/14 (71.4%) of patients.

In renal allograft recipients, mucormycosis is exceedingly rare, with an incidence ranging from 0.2% to 1.2%.[27,28] It represents a rapidly fatal complication, especially in cases where patients have received aggressive anti-rejection therapy.[29,30] Renal transplant recipients face a heightened risk of mucormycosis due to chronic immunosuppression, frequent use of broad-spectrum antibiotics, and underlying metabolic disorders such as uremia and post-transplant diabetes mellitus (PTDM).[31] In our study the mortality was 57% which is highest when compared to other fungal infections.

Histoplasmosis is caused by the intracellular dimorphic fungus Histoplasma capsulatum.[32] The disease is categorized into acute, disseminated, and chronic pulmonary histoplasmosis. Disseminated histoplasmosis predominantly affects immunocompromised patients, including transplant recipients.[33] Among transplant recipients, kidney transplant recipients, in particular, appear to be at elevated risk for disseminated histoplasmosis.[34,35] The clinical presentation of disseminated histoplasmosis often mimics that of tuberculosis, necessitating a definitive diagnosis typically based on the identification of the fungus in tissue samples and body fluids. Various laboratory techniques, such as molecular identification, antibody responses, and histopathology, can be utilized for this purpose.[36,37] Despite being rare, clinical disseminated histoplasmosis in Solid Organ Transplant (SOT) recipients has an estimated incidence of less than 0.5%, even in endemic areas.[38] The most common presentation involves disseminated disease with pulmonary involvement, with the highest risk period occurring within the first year after transplantation, although cases have been documented up to 20 years post-transplantation.[39,40] In our study, this is the least common infection without any mortality.

Elderly age, the net state of immunosuppression at the time of infection and presence of diabetes are the important risk factors for developing infection in this study. All patients required reduction of immunosuppression especially antimetabolite agents like Mycophenolate and Azathioprine and subsequently stopped in patients with severe infection. The empirical therapy in the transplant patients should be avoided when facilities for definite diagnostic methods like BAL/TBLB and biopsy from the respective infected sites are available. The timely diagnosis and appropriate antifungal therapy for optimum duration prevented mortality in most of cases. The Liposomal amphotericin B was the drug of choice in systemic fungal infections and required careful monitoring of graft function and serum electrolytes. The Cryptococcal infection required induction and maintenance regimens for eradication. The Liposomal Amphotericin B along woith flucytosine was used as induction flowed by Fluconzaole. In patients with cytooenias, Fluconazole was used for Induction. Balancing immunopsuression and antibiotic therapy is the utmost importance for graft outcome and preventing mortality as the antifungal agents like fluconazole has significant interaction with Calcineurin inhibitors (CNI). The disseminated infection with secondary bacterial sepsis especially in invasive in aspergillosis and Mucormycosis are responsible for mortality.

5. Conclusion

Currently, there is no standard serological test available for the routine identification of invasive fungal infections in patients. Initial cultures may yield negative results due to slow fungal growth and variations in colony appearance. Therefore, it is essential to pursue aggressive sampling methods when fungal infection is suspected. Invasive procedures such as bronchoscopic lavage and aspiration of deep seated abscesses play a crucial role in reaching a diagnosis. In summary, maintaining a high level of suspicion and employing thorough investigations in post-renal transplant recipients are vital for early diagnosis, prompt treatment initiation with appropriate antifungal

for optimum duration, prevention of disease spread, and reduction of mortality risk.

6. Ethical Approval

This study had approval of Institutional ethical Committee vide minute number 13641 dated December 2, 2020.

7. Source of Funding

No funding received from any agency.

8. Conflicts of Interest

The authors declare no conflicts of interest.

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