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ISAVUCONAZOLE: A QUICK UPDATE FOR CLINICIAN'S

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Isavuconazole, a newly approved triazole antifungal, offers a broad spectrum of efficacy and a favourable safety profile.[1] The FDA and EMA have approved it for the treatment of invasive aspergillosis and mucormycosis. Isavuconazole displays fungicidal actions by disrupting the biosynthesis of ergosterol, which is a key component of the fungal cell membrane.

Antifungal properties: Many *Candida species,* most *Aspergillus species, Mucorales, Cryptococcus spp., Fusarium species,* dermatophytes, and dimorphic fungi are inhibited in vitro. Isavuconazole MICs vary greatly within *mucorales* genera, with some isolates (genus *Rhizopus*) having MIC values as low as 0.12 g/mL and others having MIC values as high as 32 g/mL[2] Isavuconazole resistance has been linked to a mutation in the target gene, CYP51. Cross-resistance between isavuconazole and other azoles has also been hypothesised, although its clinical significance is unknown.

Pharmacology[3]: Unlike voriconazole and posaconazole, the prodrug, isavuconazonium sulphate, is extremely water-soluble; hence, the intravenous formulation does not require cyclodextrin vehicle solubilization. This is advantageous because it reduces the risk of nephrotoxicity from the cyclodextrin carrier. Because of the excellent oral bioavailability, intravenous and oral dosing can be used interchangeably, eliminating the requirement for a repeat loading dose when switching from an IV formulation to an oral formulation. Isavuconazonium is well absorbed and has a high oral bioavailability (98%). While isavuconazole can be taken with or without food, consuming a high-fat meal concurrently reduced C_{max} by 9% and increased AUC by 9%. Following dosing, isavuconazonium undergoes rapid biotransformation to active moiety-isavuconazole via esterase-mediated hydrolysis. Isavuconazole is strongly protein-bound (more than 99%) and has a high mean plasma half-life of 130 hours. Isavuconazole is widely distributed throughout the body, including the brain, liver, lung, and bones. Clinical data supporting brain penetration in humans is limited to case reports showing successful treatment of fungal CNS infections with isavuconazole. Isavuconazole is primarily metabolised by CYP 3A4, CYP 3A5, and subsequently by uridine diphosphate-glucuronosyltransferases (UGT). Isavuconazole clearance is decreased in patients with mild to moderate hepatic impairment (Child-Pugh classes A and B), resulting in increased isavuconazole exposure in patients with liver disease. No dosage changes are advised for these patients. There is no information available for patients with Child-Pugh class C liver disease. No dose adjustment is needed for renal dysfunction

Indications: Isavuconazole is approved and indicated for the treatment of invasive aspergillosis and mucormycosis in patients 18 years of age and older. The drug has been used off label in children as well. The drug is currently not recommended for treatment of invasive candidiasis and antifungal prophylaxis.

Dosage Recommendation: Parenteral and oral dosage schedule are same. Loading dose: 200mg three times a day for first two days followed by maintenance dose: 200 mg once a day. In children below 30 kg it has been dosed at 100 mg thrice daily for 2 days and then 100 mg once daily.

Adverse drug effects: In contrast to the majority of the azoles, isavuconazole caused a dose-related shortening of the QTc interval. When compared to other medicines in the azole class, isavuconazole is well tolerated and has a favourable side effect profile. Nausea, vomiting, and diarrhoea are the most commonly

Message from the Editor

Dear Friends

A warm welcome to the delegates of ISOT 2023 from the Fungal Infection Study Forum. Invasive fungal infections (IFI) are reported in 1-14% of all SOT recipients and are associated with high treatment costs, morbidity and mortality. In this newsletter we begin with a quick review of the newest azole "isavuconazole". Its lower drug drug interactions as compared to voriconazole/ posaconazole make it particularly useful in transplant patients. This review is followed by four interesting cases of IFI. The first a "polyfungal" IFI and the second is mucormycosis in liver transplant recipients. The next two are cases of disseminated Fusariosis and allograft Mucormycosis in renal transplant recipients. These cases highlight the challenges faced in diagnosis and treatment of IFI in SOT recipients.

Finally a reminder to all readers to contribute cases of invasive fungal infections (aspergillosis, mucormycosis and rare/ endemic fungi) to the fungal registry at www.fungireg.in. Contributors are free to publish their submitted cases elsewhere and will receive reimbursement of Rs 2000 per case. They will also have the opportunity to submit the samples to PGI Chandigarh for accurate identification and susceptibility testing.

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About FISF

The purpose of the Fungal Infections Study Forum is to conduct educational activities, undertake epidemiological and clinical studies and to promote research activities on invasive fungal infections. The results of such research would benefit clinicians, mycologists and the general public. The trust was formed in view of emergence of Invasive fungal infections (IFIs) in India which is posing a serious challenge to haematologists, critical care providers, ID specialists, pulmonologists, neurologists, medical mycologists and many other clinicians handling serious and immunocompromised patients.The trust consists of clinicians and mycologists and was instituted on 3rd March 2012 at Mumbai, India.

reported adverse effects. In most cases, the symptoms are not severe enough to necessitate the withdrawal of therapy. Isavuconazole can cause hepatotoxicity; hence, liver enzymes should be monitored while on medication. A few patients have experienced infusion reactions such as sudden respiratory distress, cold, dyspnea, and hypotension. Hypokalemia and peripheral edema are other side effects. Isavuconazole or for that matter all azoles should not be administered to pregnant women. Because the drug was found in the breast milk of lactating rats, it should not be used by women who are breastfeeding.

Drug Interactions[3]: Because isavuconazole is a CYP3A4 substrate, it should not be taken with other drugs that inhibit or induce this enzyme. Isavuconazole serum levels are considerably reduced by CYP3A4 inducers such as rifampin, carbamazepine, and long-acting barbiturates. Ketoconazole and ritonavir are two CYP3A4 inhibitors that could lead to elevated isavuconazole levels. Isavuconazole is a mild CYP3A4 inhibitor, and also inhibitor of P-glycoprotein (P-gp), breast cancer resistant protein (BCRP), human organic cation transporter (OCT2) transporters, which could result in increased levels of medicines such as sirolimus, tacrolimus, cyclosporine, colchicine, and digoxin because of decreased metabolism. If these medicines are given concurrently with isavuconazole, their serum levels should be monitored.

Therapeutic Drug monitoring: Current guidelines (IDSA for aspergillosis and ECIL-6) do not advocate regular TDM for isavuconazole. However patients who are obese, over the age of 18, or have moderate hepatic insufficiency, or those with serious/ CNS infections may benefit from therapeutic drug monitoring (TDM).

Isavuconazole Clinical Pearls

Isavuconazole offers various advantages over other triazole antifungal drugs, including IV and oral formulation, broad range action, predictable pharmacokinetics, and fewer adverse effects.
Current evidence and recommendations place voriconazole/ posaconazole and isavuconazole at the same level for treatment of invasive aspergillosis. However for patients with hematologic malignancies and solid organ transplant where drug-drug interactions and toxicities are a concern, isavuconazole is an excellent alternative to voriconazole for invasive aspergillosis.
For the treatment of mucormycosis, isavuconazole is a viable option as a step down and salvage therapy in patients with refractory disease or those who cannot tolerate amphotericin B &/or posaconazole.
Isavuconazole was not found to be noninferior to caspofungin in the treatment of invasive candidiasis, it is an option for an oral step down therapy when fluconazole is not an option.
The usefulness of isavuconazole in anti-mold prophylaxis in high risk patients is less clear. More research is needed in this area.

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THE FUNGAL RIDDLE: MULTIPLE INVASIVE FUNGAL INFECTIONS IN A LIVER TRANSPLANT RECIPIENT

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A 32 yrs old male, engineer by occupation was diagnosed with ethanol related liver failure. He had a high MELD score prior to transplant. He had undergone multiple episodes of paracenetesis for the ascites management and therapeutic plasma exchange due to high bilirubin. He also received Rituximab for ABO incompatibility prior to transplant. The surgical process was uneventful and he did not require excessive blood products. The graft to recipient weight ratio was 0.8, indicating a reasonable sized graft. He was immunosuppressed with mycophenolate, tacrolimus and steroids.

Post-transplant, his bilirubin rose with increased surgical drain output, which was bilious. He underwent exploratory laparotomy and required multiple blood transfusions as he had liver capsule tear and surface bleed. Biopsy of the liver showed graft rejection and his immunosuppressants were increased along with Bortezomib. Patient developed features of sepsis after 8 days with hemodynamic instability. Patient was taken for reexploration as the imaging showed some peri hepatic collection. Blood cultures demonstrated carbapenem resistant *Klebsiella pneumoniae* and treatment was initiated with Ceftazidime +Avibactam and Aztreonam. His immunosuppressants were withheld for a brief period and restarted in low doses. During this period, he was maintaining hemodynamically and was fed by feeding jejunostomy.

A week later, the patient developed fever and tachycardia with an elevated procalcitonin. Blood cultures from the central venous access yielded *Candida parapsilosis* and the implicated line removed. Anidulafungin was started prior to availability of speciation. At this point, Chest CT revealed bilaterally cavitary lung lesions (Figure 1). He underwent bronchoscopy and BAL cultures had *Aspergillus flavus* growing. He was started on intravenous Posaconazole and his TDM for posa was 2. Repeat blood cultures done to demonstrate clearance of Candidemia grew filamentous fungi which was identified as Fusarium spp. The susceptibility was checked and Posaconazole was continued. After 2 weeks he was changed to oral posa and his repeat levels were only 0.2. It was noted that patient was given tablet in powdered form by feeding jejunostomy and later when changed to oral, following which the levels increased. The patient recovered.

Discussion

SOT populations are at high risk for IFI. The incidence rate may vary from 0.9% to 13.2% and varies with the organ type with lung and bowel having the highest incidence of IFI followed by moderate risk in liver and heart transplants and the lowest risk with renal transplant.

The known risk factors of fungal infections in solid organ transplants are

- Diabetes
- Previous invasive fungal infections
- Prolonged surgery time
- Requiring multiple blood products

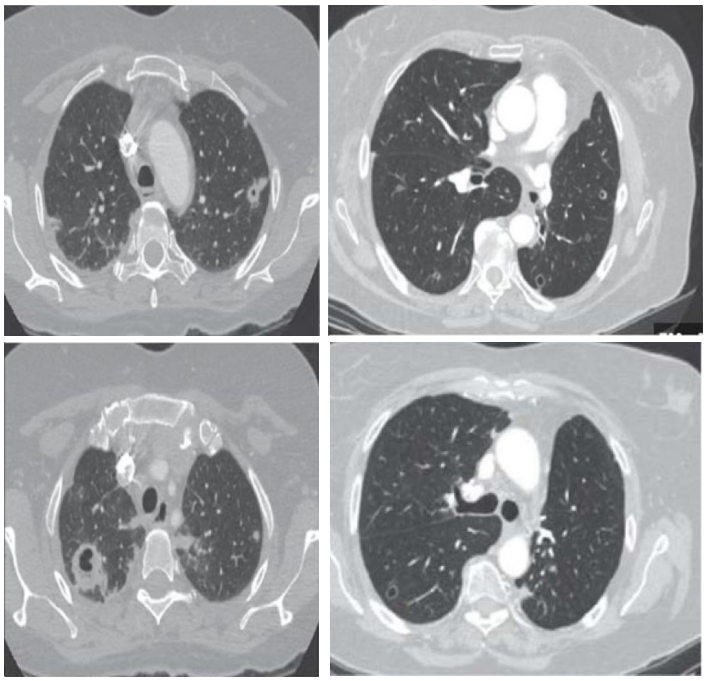

Figure 1: CT showing multiple cavitary lesions

- Prolonged ICU stay
- Graft rejection requiring pulsing /higher dose of immunosuppressants
- Follow up reexploration /retransplant
- post operative dialysis

Factors which may increase the risk of IFI in the Indian setting include suboptimal infection control precautions, high spore count in the hospital environment, contamination of perfusing fluid etc

Our patient also had multiple risk factors including two rexplorations, multiple blood products and use of rituximab, Our patient had three IFI, something not uncommon among highly compromised SOT recipients.

Fusarium species are common soil saprophytes and plant pathogens. Like aspergillus species, Fusarium species have a propensity to invade vessels and can result in tissue necrosis and pulmonary cavitation. Unlike fusarial infection in patients with hematological malignancies, fusarial infection in SOT recipients tends to be localized, occurs later in the post-transplantation period, and has a better outcome. Our patient however had a disseminated fusarial infection early in the post-transplant period probably due to intense immunosuppression. Table 1 highlights differences between Fusarial infection in HSCT recipients versus SOT recipients

Finding	HSCT recipient	SOT recipient
Type of infection	Disseminated	Localized
Incidence of fungemia	20-60%	Uncommon
Time of onset	Early	>9 months post
Mortality	70-100%	33%

Based on EORTC criteria, he had possible invasive Aspergillosis, and treatment was initiated with posaconazole. In this patient who has undergone an SOT and has tested positive for Aspergillus in BAL and Fusarium in blood, it can be concluded that these two are pathogens and are present at the same time, as polymicrobial IFI are seen occasionally. Voriconazole could have been initiated for covering both pathogens, but considering the possible interactions with immunosuppressants, posaconazole was used instead (5). Posaconazole has fewer interactions as compared to voriconazole. Recent literature in respect to invasive Aspergillosis has shown posaconazole is comparable to voriconazole in clinical efficacy. Posaconazole has also been shown to be efficacious in the treatment of Fusariosis.

Ideally, this patient with mold growing in blood cultures should be subjected to brain imaging but in this case as the patient refused further diagnostics, this was not done. Another take away from this case is the use of oral posaconazole when oral feeding is not feasible. In a recent publication on the use of crushed posaconazole tablets through a feeding tube in lung transplant recipients, nearly 30% of the patients had inadequate plasma levels, highlighting the even greater need for therapeutic drug monitoring in such patients.

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A CASE OF GASTRIC MUCORMYCOSIS IN POST LIVER TRANSPLANT RECIPIENT

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A 64 years old male from Tirupathi, carpenter by occupation, diabetic and hypertensive, with NASH related chronic liver disease underwent live donor liver transplant in our centre in April 2023. He had presented symptomatically in the past with ascites, variceal bleed and required multiple large volume paracentesis. The past medical history was also marked by pulmonary tuberculosis treated successfully in 2017. He was Child Pugh stage C with high MELD score when posted for liver transplant surgery. The intra operative period was stormy requiring massive blood transfusion and the operative period was prolonged lasting 13 hours. The immediate post operative period was marked by requirement of ionotropic support, acidosis and acute kidney injury requiring continuous renal replacement therapy. Patient gradually improved and was extubated on post operative day 5. He was on triple immunosuppressants and shifted to post operative ward. Explant hepatectomy showed no evidence of tuberculosis.

Post operatively patient developed progressive elevation of alkaline phosphatase and bilirubin and non-oliguric acute kidney injury (AKI). Abdominal imaging did not show any obvious collection or obstructed system. The patient had episodes of diarrhoea and melena and his AKI component worsened requiring continuous renal replacement therapy. Extensive workup was done to identify cause of gastroenteritis. CMV PCR was negative. Clostridium difficile PCR and toxin was negative. Blood cultures and stool cultures were also negative. Immunosuppressants were optimised- mycophenolate mofetil was stopped. Since the patient continued to have episodes of melena, upper GI endoscopy was done on post operative day 21 which showed a large ulcer in greater and lesser curvature and body of the stomach and was covered with necrotic material (Figure 1). Biopsy tissue was subjected for Gram stain and culture and KOH staining showed broad aseptate hyphae with right angled branching. The patient was started on Liposomal Amphotericin B at dose of 5mg/kg /day and oral posaconazole. Histopathology of the ulcer showed irregular aseptate fungal filaments with tissue and angioinvasion. After detailed discussion with surgical team and patient's family regarding need for surgical excision, patient was taken up for subtotal gastrectomy with gastro-jejunostomy on POD-24. Fungal culture reports were followed which showed growth of Rhizopus species. Liposomal Amphotericin B and posaconazole were continued. Renal functions and serum posaconazole levels were suggested for monitoring. However on POD 27, patient succumbed to Carbapenem resistant *Klebsiella pneumoniae* bacteraemia secondary to ventilator associated pneumonia.

DISCUSSION

Invasive fungal infections contribute to significant morbidity and mortality in solid organ transplant recipients and the risk varies with the organ type. In liver

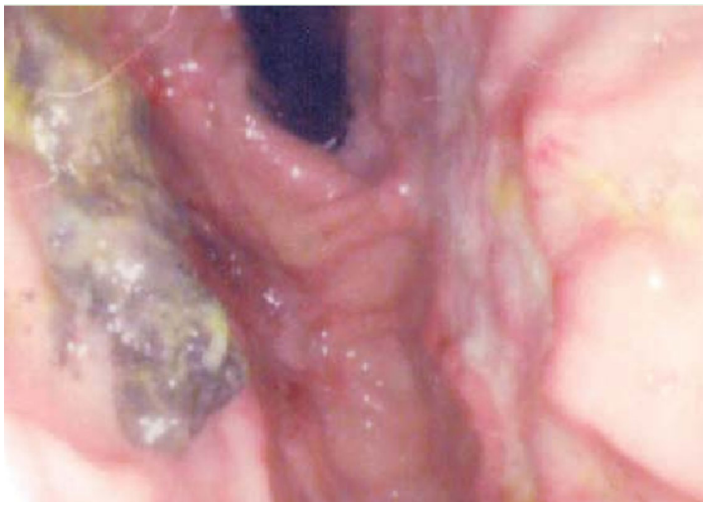

Figure 1: Endoscopic image showing gastric ulcer covered with necrotic slough

transplant recipients IFI are reported in 4 to 40% of patients with mortality rates being very high. Incidence of mucormycosis in liver transplant recipients has been estimated to be 0.4% to 1.6%.

Certain factors impose a high risk for developing IFI in solid organ recipients and include the following:

PREOPERATIVE	INTRAOPERATIVE	POSTOPERATIVE
High MELD	Emergency transplantation	Re-laparotomy
Anti-infective Rx/ Hospitalisation within 90 days prior transplant	Prolonged surgery	Renal replacement therapy
End stage renal disease	Massive transfusion	Biliary leak
Fungal pre colonisation	Donor derived	CMV viremia

Our patient, being a carpenter by occupation, may have been pre-colonised with fungus. Pretransplant risk factors include a high MELD score; intra operative risks of prolonged transplant surgery, and requirement of multiple transfusions; renal replacement therapy in the post-operative period. Review of recent data on risk of IFI post-transplant may not show these as significant risks due to better surgical techniques, reduction in blood product use and transplantation done prior to patient decompensating. The importance of blood products as an immune suppressive is often under recognized. It should be noted that the use of antifungal prophylaxis in the form of fluconazole or an echinocandin may not have had any impact in clinical course of this patient, and this highlights the difficulty in choosing antifungal prophylaxis in high risk patients undergoing liver transplant.

This case also highlights the high risk associated with invasive mold infections in SOT patients, especially gastro-intestinal mucormycosis. There is significant attributable mortality in spite of aggressive medical and surgical therapy. While guidelines do not recommend combination antifungal therapy in patients with combinations are often used in sick patients.

Conclusion

A high index of suspicion, early diagnosis and aggressive management including early surgical intervention are key in the management of invasive mold infection. Despite advances in surgical techniques, diagnostic modalities and antifungal therapeutics, mortality remains high in invasive fungal infection because of poor host immune factors and high risk for hospital acquired infections in such patients.

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FUSARIUM IN THE URINE

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Fusarium species have been reported as causative agents in keratitis, endophthalmitis, onychomycosis, cutaneous infections (particularly of burn wounds, mycetoma), endocarditis, peritonitis, septic arthritis, catheter-associated fungemia, and, rarely urinary tract infections. Disseminated opportunistic infections can occur in immunocompromised hosts. Fusarium-caused urinary tract infection appears to be rare & may occur in the setting of urolithiasis. We describe a case with possible disseminated infection involving the lung, prostate & urine in a renal transplant recipient who also had COVID 19 and TB of the knee. Most cases of fusariosis in renal transplant recipients have been of cutaneous infections.

This is a 45 year old male with hypertension and end stage renal disease who underwent LRKT in Jan 2022. He was on MMF, tacrolimus, prednisolone. He had COVID-19 in Mar and May 2022 when he was treated with Remdesivir and steroids on both occasions. In Jun 2022 he developed fever with knee arthritis. Aspiration revealed Xpert MTB positive, RIF resistance was not detected. INH, PZA, EMB and Levofloxacin were started. Rifampin was not used to avoid the interaction with tacrolimus. Subsequently the patient developed extreme leukocytosis (33,000/ microl) and the creatinine increased from 2.4 to 5.1 mg/dl. Anticipating bacterial UTI, tests were done. The urine showed more than 100 wbc/ hpf and the culture grew Fusarium (Figure 1 and 2). This was a surprise and a search for the focus was carried out. A right upper lobe pulmonary nodule & an abscess in the prostate were found (Figure 3 and 4). It is conceivable that the lung nodule was due to Fusarium which developed in the setting of COVID-19 & receipt of steroids in the transplant recipient and led to dissemination of infection to the prostate.

The Fusarium species identification by MALDI TOF MS and BMD MIC is useful further management since different Fusarium species have different susceptibility. However these were not possible at that time. Besides the exact relevance of MIC to clinical outcome is somewhat uncertain in this infection. Voriconazole is considered as the most useful azole in the treatment of Fusarium infection, perhaps in combination with L AmB. The latter was avoided both because of expense & potential nephrotoxicity. Although voriconazole has no useful urinary levels, it was used in this case because there was a probable prostatic source of infection. RIF had been avoided in the ATT regimen, which was just as well, to prevent subtherapeutic levels of Voriconazole. The dose of tacrolimus was lowered suitably keeping in mind the interaction with Voriconazole. Levofloxacin which was a part of ATT however tends to have an additive effect on QT prolongation along with Voriconazole. A careful watch on QT interval was maintained during treatment.

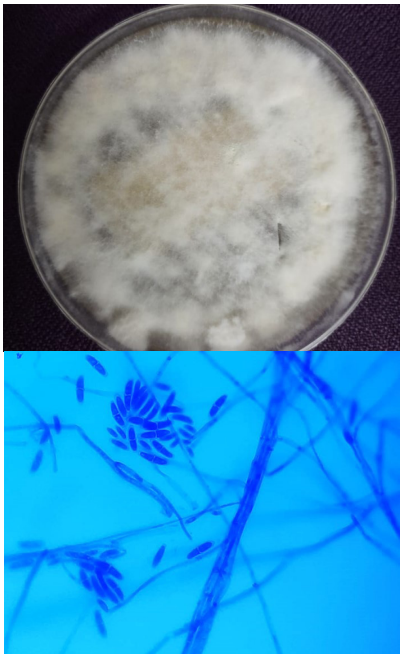

Figure 1 and 2: Petridish and LPCB mount

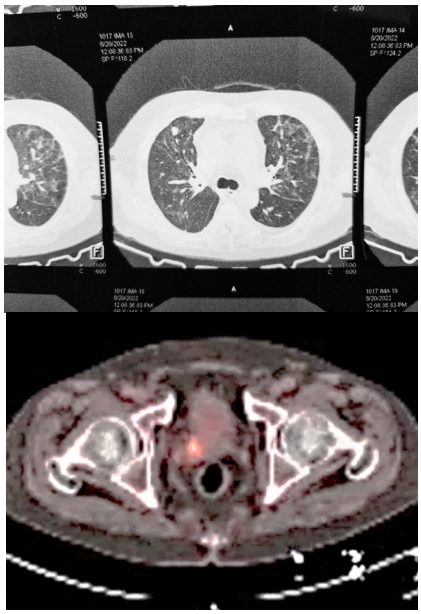

Figure 3 and 4: CT and PET CT images showing nodule in the lung and the prostate

The patient received 6 weeks of therapy which led to symptomatic improvement & negative urine cultures on several occasions. However a PET scan was not been repeated to document resolution of the prostatic lesion. This would have been helpful in supporting our conjecture of that being the source of urinary fusarium. The patient is doing well on follow up. The case highlights the importance of carefully considering drug interactions while using azoles especially when immunosuppressants and anti TB drugs are part of the treatment regimen.

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FATAL MUCORMYCOSIS OF THE RENAL ALLOGRAFT

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Mucormycosis is a rare complication in renal transplant recipients with reported incidence of 0.4-0.5 per 1000 patients.[1] In a recent review summarizing 174 cases of post RT mucormycosis, mucormycosis of the allograft was reported to comprise of 11.5% of all cases and was associated with the highest risk of mortality (55%) second only to disseminated disease (76%).[2] Here we present a deceased donor renal transplant recipient who developed mucormycosis of the graft kidney in the early post-operative period and succumbed despite a graft nephrectomy.

This 70 year old male with history of hypertension, ischemic heart disease and end stage renal disease underwent cadaveric renal transplantin Feb 2015. The intraoperative course was uneventful and patient was extubated the next day. Immunosuppression included prednisolone, MMF and tacrolimus.The urine output failed to improve and creatinine was still 6.1 so the patient was dialysed and a kidney biopsy was done. It showed features of acute tubular necrosis but no rejection. Gradually the urine output increased and creatinine started coming down. However on day 10, the urine output again dropped, white cell count increased to 15,000 and creatinine started rising. Urine, surgical drain fluid and blood cultures were sent. The USG Doppler showed hydronephrosis. On day 12 post-transplant the patient underwent exploration. The kidney looked healthy. The DJ stent was blocked with coagulum and lower ureter looked abnormal. The DJ stent was removed, diseased ureter excised, ureteric re implantation was done with new stent and a graft biopsy was done. On day 15 post-transplant, the urine and drain fluid grew filamentous fungi with broad aseptate hyphae identified as Mucor. The HPE of the excised ureter showed invasive mucormycosis; the graft biopsy was normal. In view of these reports Amphotericin B deoxycholate and posaconazole suspension was initiated and the patient was taken up for a graft nephroureterectomy on Day 16. All the immunosuppression was stopped. The external surface of the graft kidney appeared brownish and rough and had multiple scars. The cut surface showed multiple yellowish white punctate abscesses throughout the cortex, medulla. The pelvis contains brownish soft material and the ureter also appeared thickened and edematous and had brown friable material in its lumen. The HPE showed multiple ribbon like broad aseptate fungal hyphae in the renal cortex, medulla, pelvicalyceal system and ureter. The cultures from the renal bed, urine and tissue all grew Mucor. The patient was extubated the day after surgery and seemed to be improving. However over the next 2 days the patient developed hypotension, fluid overload, severe metabolic acidosis and hyperkalemia for which he was managed with inotropes, dialysis and ventilation. He developed refractory hyperkalemia and repeated episodes of ventricular tachycardia and cardiac arrest from which he could not be revived and died on day 20 post-transplant.

A recent review summarized 29 cases renal allograft mucormycosis reported till date.[3] Infection was assumed to be donor derived in all cases. Only in a few cases was infection clearly linked to the donors who had died after injection drug use/ drowning. Most of the cases happened in low resource settings including India, Pakistan, Egypt often from living unrelated donors. Here contamination during organ processing and transport was most likely. The complications occurred usually within the first 1 month after transplantation in 60% of the cases. The usual presentation was fever, abdominal pain and renal failure mimicking organ rejection. In fact some patients erroneously received anti-rejection therapy before a diagnosis was made.[4] More than half the patients died despite graft nephrectomy and antifungal therapy.

What was the source of infection in our patient? None of the other recipients of the kidney and liver from the same donor were infected suggesting that contamination may have occurred after organ retrieval. An unopened bag of the fluid of the same batch used to perfuse the kidney was culture negative for fungus. The sequence of events in our patient suggests that it was probably an ascending infection from the ureter. Infection occurred first at the ureteric anastomotic site followed by blockage, hydronephrosis, renal failure and then infection of the graft. While amphotericin B deoxycholate was chosen in our patient owing to its superior penetration in the urinary tract, this is unnecessary if the infected kidney is promptly removed. Combination therapy was used in our patient though its role is unproven. Irrigation of the operative bed with amphotericin B deoxycholate has been practised in previous infections but was not done in our patient.[5]

To conclude, careful donor history for risk factors for mold infections, asepsis during organ retrieval, perfusion and transport, high index of suspicion for allograft infection and prompt graft nephrectomy with antifungal therapy is recommended to reduce the risk and mortality of renal allograft MM.

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Fungal India Registry

A Scientific project of Fungal Infection Study Forum

(Fung-I-Reg)

FISF
Fungal Infection Study Forum

Key Points of Fung-I-Reg

1. Pan India Web Based Registry of Fungal infections (Aspergillus, Mucor, Rare Fungi)
2. Advancing knowledge on Epidemiology, clinical manifestations, laboratory parameters, treatment and outcome of Fungal infections
3. India Specific data
4. Validating selected culture results at Reference Laboratory (PGIMER, Chandigarh)
5. Advanced molecular analysis of selected fungal cultures
6. Registry based data analysis
7. Comparison with western data
8. Publication in peer reviewd journals
9. Inclusion of both Private and Public health care sectors
10. Coordinated by Fungal Infection Study Forum (FISF) a not for profit educational trust based at PGI, Chandigarh (Chairperson: Prof Arunaloke Chakrabarti) www.fisftrust.org

Methods

1. One time Registration (No charges)
2. Generate your own password
3. Accept a confirmation e mail
4. Log in with your password
5. Select Case Record Form (CRF) of any of the Gateways :
   - ► CRF Aspergillus
   - ► CRF Mucor
   - ► CRF Rare and Endemic Fungi
6. Fill up the details
7. Submit the form
8. Save a self generated PDF of your form
9. For any query contact Registry Coordinator at -
10. The filled up form will be ratified by the Fung-I-Reg Scientific Board
11. Email for acceptance of your submission will be sent
12. Send your account details for Rs 2000/- per accepted CRF

For details visit www.fisftrust.org OR www.fungireg.in