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Fungal Infections in Renal Transplant Patients

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SUMMARY

Three cases of systemic fungal infections in renal transplant patients are described here. One patient had mucormycosis. The second patient had aspergillosis and the third patient had candidiasis. All three patients died inspite of treatment. These fungal infections and their treatment is discussed.

The success of renal transplantation depends on a compromise between achieving sufficient immunosuppression to avoid rejection of the graft and maintaining a level of immunocompetence sufficient to protect the recipient from infections. Although the incidence of serious infections and the mortality from infections after transplantation has decreased during the last decade[1] but this problem of infection still remains a major hazard for the transplant patients. It contributes substantially to the morbidity and mortality of the transplant patients. Incidence of infections in these patients have been reported to be 32%, 58% and 80%[2-4]. Infections account for 11-40% of all post transplant deaths[1]. Overall about 50% of infections are caused by viruses, 30% by bacteria and 5% by fungi. In 15% of cases infection are polymicrobial[5].

Three fatal cases of systemic fungal infection complicating renal transplantation admitted at Shaikh Zayed Hospital are described here.

Case No.1

M.S 47 years old insulin dependent diabetic, and hypertensive male was admitted to Shaikh Zayed Hospital with history of high grade fever with chills and rigors one and a half month after renal transplantation. He also had diarrhoea with large volume stools with mucus but no blood. He also complained of burning sensation on urination. He was receiving cyclosporine and prednisolone as immunosuppressive treatment. On examination at the time of admission he was febrile, temperature being 99.8°F. Blood pressure was 170/110 mmHg. Lungs were clear on auscultations. Ear, nose and throat were normal. Abdomen was soft with mild tenderness over the renal graft. Laboratory investigations revealed blood urea nitrogen 24 mg/dl, creatinine 2.6 mg/d, Hemoglobin 12 gram/dl, WBC count 4000/mm^3 with normal differential count, blood sugar 331 mg/dl, urine and blood cultures showed no growth. Patient had fever up to 101°F next morning. He was given plain insulin according to blood sugar levels and antidiarrhoeal medications. Syrup cyclosporine and prednisolone were continued. As the patient remained febrile he was started on injection cephloridine. Six days after admission he complained of pain and bleeding from gums. He was seen by oral surgeon who thought that the patient had oral candidiasis with mucosal ulceration. Oral nilstat suspension and oral metronidazole were added to the treatment. His blood sugar remained 200-450 mg/dl inspite of best efforts. Two days later patient complained of pain in the left nasal wall. Next day he developed pain and swelling of left cheek. ENT consultation was sought. Diagnosis of maxillary sinusitis was made. Injection cephlordine and oral metronidazole were continued. The swelling and pain of left cheek increased. Left nasal wall turned black and ulcerated. At this stage gram stain of the nasal swab showed biseptate hyphae. Clinical diagnosis of mucormycosis was made. The patient was started on armphoterecin B infusion. His renal function remained stable. Two days later the left lateral wall of the nose became gangrenous and the gangrene spread rapidly to left lower eyelid and left cheek. Patient also developed cough with expectoration along with rise in temperature. C.T. scan showed soft tissue swelling around the left orbit and left maxillary area. Left maxillary antrum was partly opaque and showed air fluid level. Medial wall of the left maxillary antrum showed erosin. No involvement of orbit or brain was seen. Chest X-ray showed infiltration in both lung fields. Cultures of scrapping from skin lesion and sputum confirmed the growth of the mucorales. Amphotericin B was continued but patient's condition did not improve. He became progressively drowsy and finally developed respiratory arrest. Resuscitative measures failed and the patient expired.

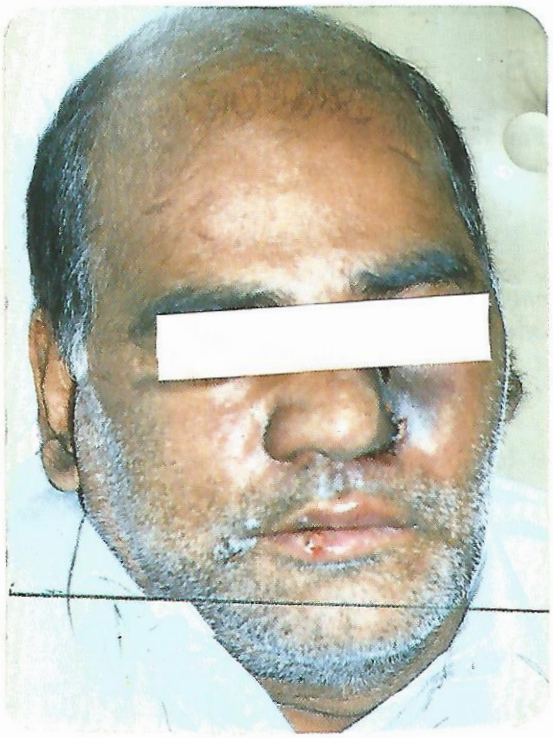

Fig. 1a: **Patients picture showing blockening nasal wall with slight ulcerations.**

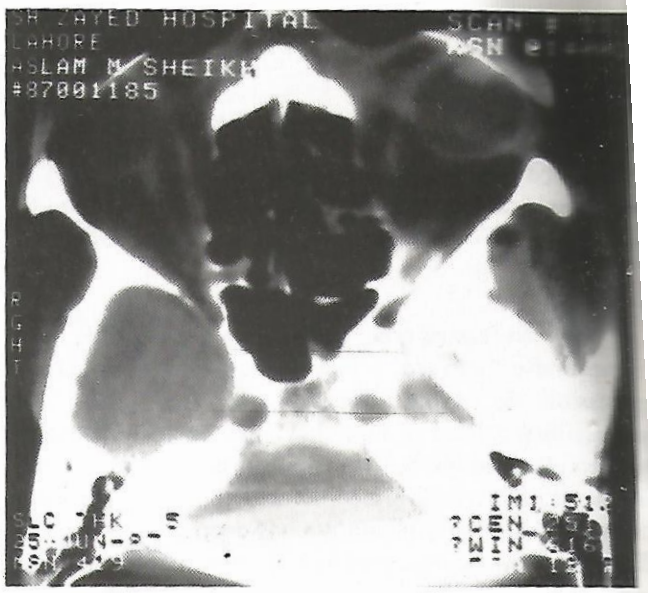

Fig. 2: **C.T. scan showing involvement of left maxillary antrum.**

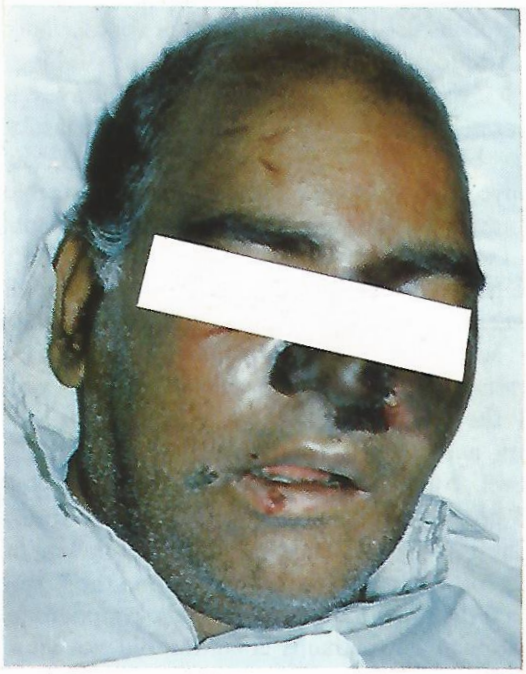

Fig. 1b: **Two days later nose, left check a left lower eyelid becoming gangrenous**

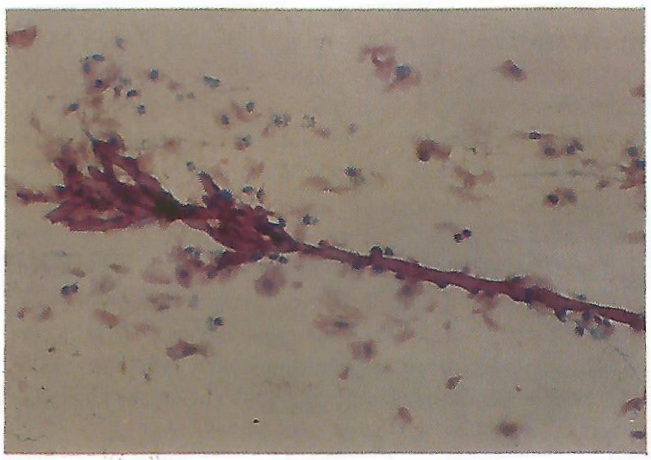

Fig. 3: **Mucorales isolated from culture of skin serappings**

Case No. 2

Forty years old male, had cadaveric kidney transplant in June, 1986, for chronic interstitial nephritis with end stage renal disease.

Eight months later in Feb. 1987, he developed sore throat and a productive cough with high grade fever and chills. He was admitted in Hamad General Hospital, Doha and was investigated. Diagnosis of disseminated aspergillosis and aspergillus pneumonia was made. Intravenous amphotericin B was initiate along with continuation of cyclosporine and prednisolone. Imuran was stopped as the patient developed jaundice.

During his hospital stay he developed right sided hemiplegia with aphasia.

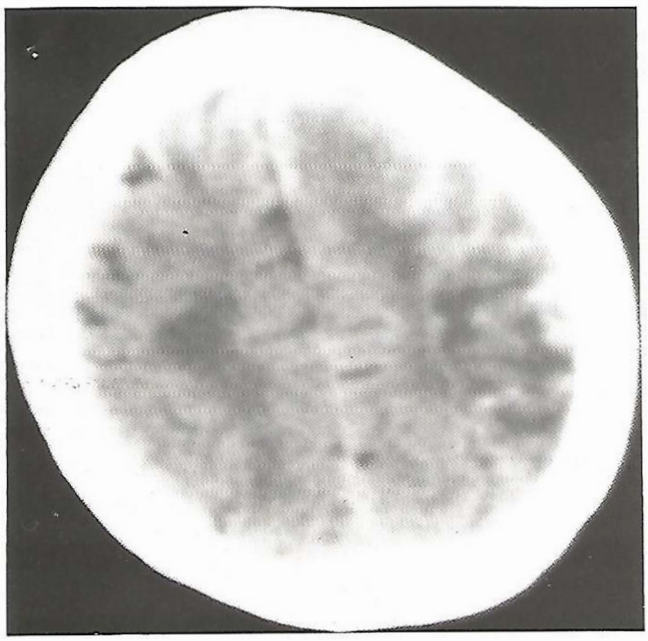

Fig. 5: C.T. scan showing multiple cerebral infaract in left tempro-parietal region.

In March, 1987 he was admitted Shaikh Zayed Hospital, Lahore for reassessment. At that time his temperature was 100°F. Blood pressure was 130/70 mmHg. Pulse was 120 per minute. He looked pale. Jugular venous pressure was not raised. There was no lymph node enlargement. On examination of central nervous system, he was found to be aphasic, drowsy but arousable on maximal painful stimuli and hemiplegic on right side. Examination of chest revealed diffuse scattered coarse crepitations. C.T. Scan showed multiple cerebral infarcts in left parietal lobe. There was a space occupying lesion in left tempro-parietal region idenling the left anterior horn of third ventricle with surrounding cerebral edema.

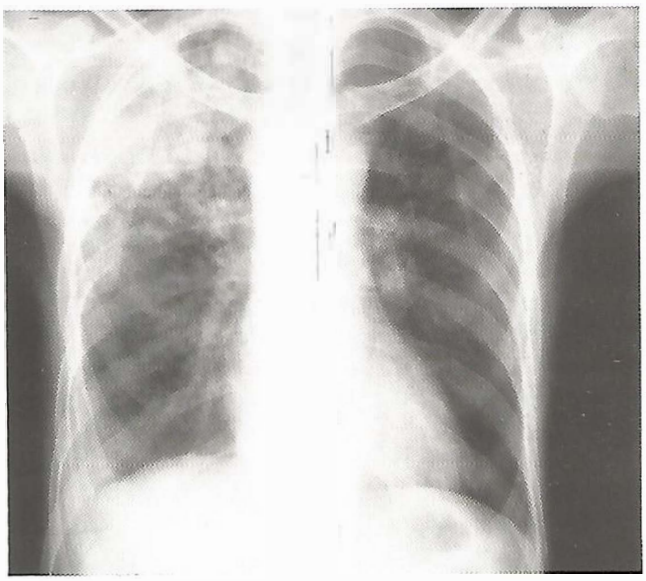

Fig. 6: Chest X-ray showed infiltrate in right lung.

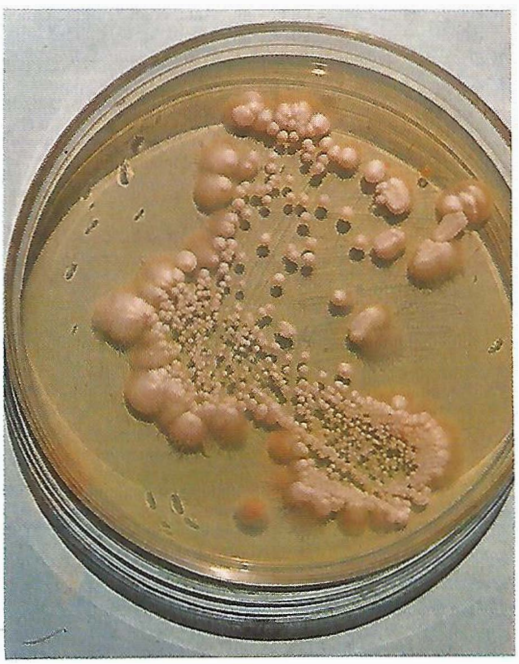

Fig. 7: Culture plate showing growth of Candida Albicans

Radioisotope renal scan and renogram showed good perfusion of the transplanted kidney without any evidence of obstruction. Ultrasound abdomen revealed appearances of early renal failure in transplanted kidney.

Chest X-ray showed consolidation in left lower zone with an associated pleural effusion. He was continued on immunosuppressive drugs and intravenous Amphoterecin B. Butt his condition gradually became worse and finally he died.

Case No. 3

Thirty two years old male, hypertensive with hypertensive renal disease and chronic renal failure had live related renal transplant done in May, 1988. In September, 1988 he came with history of fever for 2 months and productive cough for 3 weeks. Fever was high grade (103°F-104°F) associated with palpitation, regors and sweating.

Work up for fever was negative. He did not respond to different antibiotics and remained febrile.

Repeat chest X-ray showed infiltrate in right lung. Fibreoptic bronchoscopy was done, which showed left upper lobe bronchus exudating pus and chronic atrophic changes. Changes were consistent with chronic inflammation, possible tuberculosis. Biopsy and Bronchial washings were taken. Anti-tuberculosis therapy was started. Sputum was sent for culure and sensitivity repeatedly. He continued to have high grade fever, vomiting, diarrhea, dyspnoe and cough. Culture of bronchial secretions shoed growth of nocardia and sputum culture report revealed candida albicans. Anti tuberculosis therapy was discontinued. Intravenous amphotericin B and oral co-trimoxazole were started. His temperature kept fluctuating. On 7th day of initiation of this therapy he became severely dysponcic and developed cardiopulmonary arrest. He was intubated and put on respirator but had a cardiac arrest again, on the same day. All the efforts to resuscitate him failed.

Comments

Renal transplant patients are susceptible to infection for 3 main reason (a) they have undergone and major surgical operation. (b) they are uremic, and already immunosusppressed. (c) they receive immunosuppressive drugs which have adverse effects on immunecompetence.[50].

The most significant risk factors related to injection are high dose cortico-steriod therapy and leukopenia (granulocyte counts < 100/ mm3) in large number of patients who develop serious infection[6,7]. Other risk factors include diabetes, hyperglycemia, poor graft function, hepatitis and spleenectomy[5]. No sex or race predominance has been observed to be associated with infection., Infections can be divided into 2 major categories: (a) infection complicating the immediate post operative period, being related directly infectious conditions present before surgery or specific complications of surgery and the post operative stat e itself. (b) infections which owe their genesis to intensive immunosuppressive therapy for rejection[8].

Infections in the first 4 weeks after transplantation are usually caused by bacteria. Oportunistic organisms such as legionells, pneumocystis, nocardia, fungi and cytomegalovirus rarely cause problem before the first month after transplantation but occur through the first year when immunosupopression is maximal[8]. Although systemic viral infections, may be documented in over 50% of transplant patients, they are only rarely, directly responsible for fatalities, while bacteria and opportunistic fungi can be incriminated in 90% of deaths from infection[8].

Although fungi are uncommon pathogens in transplant recipients they must regularly be excluded as a cause of fever and penumonia. Definitive diagnosis and decisions about appropriate therapy can be difficult.

In the three cases described here, organisms isolated were mucorales, aspergillus and candida and nocardia respectively.

First patient had mucormycosis which is an acute, often fulminating fungal infection, caused by one of the phycomycetes. It is invariably rapidly progressive and fatal illness[9-10]. Its incidence is increasing and this has been attributed to several predisposing conditions like leukemias, diabetes mellitus, acidosis, malnutrition, and immunosuppressive therapy[9-12]. Several different clinical types have been described. Those include pulmonary, gastrointestinal, central nervous system, subcutaneous, disseminated and miscellaneous localized infections[11,13]. The fungus may enter through conjunctiva, nasal mucous membranes, lungs, gastrointestinal tract, skin and less commonly other organs. The primary infection is common in lungs for paransal sinuses and it is due to inhalation of through the orbital tissues to the brain and meninges. This form is called rhinocerebral mucormycosis. Characteristically the fungus grows along tissue plains, especially in the lumens and wall of vessels causing septic thrombosis and infarctions. Cavernous sinus artery thrombosis are frequent complications. As the orbital involvement progress, loss of function second, third, forth and sixth

nerves may occur resulting in the proptosis, pulillary dilatation and vision loss. The fifth and seventh nerve may become involved. Orbital involvement may extend intraocularly. The most serious complication of this disorder is brain involvement which arises mainly from infarction due to direct vascular invasion by micro organism[11].

Patient No.2 had aspergillosis. Aspergillosis species are the cause of invasive aspergillosis in the immunocompromised host. The disease usually starts with a pneumonia as in our patient, before disseminating to brain, skin, kidney and gut.

There is usually evidence of a progressive destructive bronchopneumonia. The radiological signs include a patchy infiltration often in the upper lobes, consolidation resulting in a pulmonary infarct and abscess formation. Bronchoscopy and biopsy specimens are more reliable than sputum for diagnosing invasive pulmonary aspergillosis. Serology is unhelpful. Aspergillus CNS infections are not oriously difficult to diagnose prior to postmortem examination. It rarely causes a frank meningitis, but rather most often present with localizing signs, fever, headaches confusion and perhaps seizures due to vascular occlusion and perhaps seizures due to vascular occlusion and infarction. Because of slowly progressive symptoms it may resemble brain tumors or abscess[7].

Patient No.3 had systemic candidiasis. Among infections with fungi, candida species predominate throughout the transplant period[1]. It is common particularly in debilitated patients and those with leucopenia, diabetes, or those recently treated with high doses of steroids. Infections are usually localized but occasionally invasive, the identifications of which can be difficult[2]. Stomatitis responds to local nystain. Patients with systemic candidiasis are usually very ill with evidence of infection in lungs, eyes, gut, joints and skin[2]. Candida pneumonia is a lethal infection and is frequently mixed with other pathogens. Our patient had concurrent nocardia infection. This is usually caused by the acid fast bacterium nocardia asteroides and presents as an illness with tendency to spread to the brain[5].

The management of fungal infection encompasses antifungal chemotherapy as well as the treatment of predisposing factors, where possible. The antifungal drugs belong to a number of different chemical families.

Poleyne antifungals are macorlide drugs directed against the structure of cell membrane leading to increased permeability. Of the existing drugs only amphotericin B can be given systemically. It is the drug of choice for treatment of many systemic infections despite a high side effect profile, which range from pyrexia, severe malaise and hypertension in the early phase of treatment, to reduction of renal blood flow and tubular dysfunction as well as hypokalemia. It is possible to lessen their impact by a number of different strategies ranging from the pre-infusion administration of antihistamines to a gradual build up of daily amphotericin B dosage[15].

The second big group is the azole series. These drugs are imdiazole and derivatives like ketoconazole and miconazole (given intravenously). Other antifungals used systemically include flucytosine and griseofulvin. The most pressing problems in the management of systemic fungal infections are seen in the immunocompromised patient. The result of treating neutropenic patients with candida and aspergillus infection, in particular, are notably poor[15].

The assessment of new drugs in the systemic opportunistic infections such as aspergillus, candidiasis, mucormycosis is a formidable problem because of the relative rarity of cases which can be assessed objectively and the difficulty in proving the diagnosis. Generally, the mainstay of treatment for these infections remains amphotericin B given intravenously in doses ranging between 0.3-0.5 mg/kg and 0.8-1.2 mg/kg depending on the infection.

The antifungal agents most recently available (fluorocytosine, clotrimazole and miconazole) have no consistent in vitro or in vivo activity against the mucorales and should not be used alone in the treatment of mucormycosis[15]. Thus amphotericin B remains the most reliable single agent for mucormycosis the rate of amphotecrecin B administration depends on severity of the infection. Traditional dose recommended is a 1 mg test dose in 5% dextrose in water on the first day of therapy followed by escalation of dose by daily increments of 5 mg until a daily dose of 1 mg/kg of body weight is reached. However, in seriously ill patients and most patients with mucormycosis it is recommended that 1 mg test dose over several hours to be followed by repeated doses every 12 hours at 10-15 mg increments until a daily dose of about 0.7-1mg/kg is reached which is given over 6 hours. This dose is usually continued until the patients' condition stabilizes or improves and then the same daily dose can be given every other day. Local irrigation of infected sinuses has also been done by investigators but this procedure is not advocated routinely[11].

The importance early and if necessary repeated surgery in the treatment of mucormycosis emphasized by the reports of surgical excision alone curing several

patients with rhinocerebral, pulmonary, cutaneous or gastrointestinal mucormycosis in whom infections were localized and diagnosed early[10] with more widespread infection surgery should be combined with amphotecin B therapy.

Procedures used for rhinocerebral mucormycosis include drainage of sinuses and abscesses, enucleation or evisceration of necrotic orbital contents and palatectomy. Correction of diabetic ketoacidosis to cure mucormycosis in a diabetic patient is very important. Not only has a single case of mucormycosis of the ethmoid sinus with orbit been cured by diabetic regulation alone but also several cases of rhinocerebral mucormycosis occurring in well controlled diabetes mellitus have been localized and more readily responsive to treatment[3]. In patients with mucormycosis complicating malignancy or renal transplantation, it is recommended to reduce or temporarily withhold immunosuppressive therapy until the infection has been modified or brought under control.

Treatment of candidiasis is with amphotercin B and fluorocytosine but the prognosis is poor. Treatment of nocardia is with sulphonamide alone or in combination with fusidic acid, ampicilin and erythromycin. Treatment in the proven cases of aspergillosis is with amphotericin B5-Flurocytosine is effective against only a small percentage of cases.

The use of antifungals as a prophylactic agents has been a logical development in immunocompromised patients because it has proved difficult to recognize the onset of fungal infection in this group either by clinical or serological methods. At present however, there is insufficient data on the value of their prophylactic use[15].

Although fungal infections are uncommon in transplant recipient but these are associated with high morbidity and mortality. Great awareness and eary diagnosis are prerequisites for successful treatment. But definitive diagnosis about appropriate therapy can be difficult. Systemic mycosis should be regularly excluded as a cause of fever and phneumonia in transplant patients.

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