**Case Report**

**Cutaneous aspergillosis as a first manifestation of systemic infection in allogeneic haematopoietic stem cell transplantation**

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**Abstract**

Infections are one of the major causes of morbidity and mortality after stem cell transplantation (SCT). Opportunistic infections of varying severity with bacterial fungal and viral organisms occur in > 90% of patients after allogeneic SCT. Fatal opportunistic infections have been reported in 4-15% of related transplant recipients and 12-28% of unrelated transplant recipients. More than half of the transplant patients affected by invasive aspergillosis die despite treatment. Cutaneous aspergillosis has been rarely reported in transplant patients.

During last five years 154 patients underwent allo SCT at our centre for various haematological disorders. Aspergillus infection was observed in six patients. Three patients had systemic aspergillosis whereas other three patients had primary cutaneous aspergillosis infection. Patients with primary cutaneous aspergillosis are presented here as case report.

**Introduction**

Fungal infections with aspergillus species are a significant cause of morbidity and mortality after allogeneic stem cell transplantation (allo-SCT). More than half of the transplants patients are affected by aspergillosis and die from these fungal infections. The most common manifestation of an aspergillus infection in these patients is invasive pulmonary aspergillosis. Haematogenous dissemination as a secondary event occurs in 20-50% of these patients commonly involving central nervous system and gastrointestinal system. Secondary skin involvement due to systemic aspergillosis is extremely rare in transplant patients however aspergillus infection more frequently present as primary solitary extra pulmonary aspergillus infection involving maxillary sinuses, which can lead to endogenous spread in the lungs causing invasive pulmonary aspergillosis. Cutaneous aspergillosis is a poorly described entity in transplant patients. Rare sites of skin infections are central venous lines entry site. With this background, we describe three patients, who developed aspergillus infection in different post transplant period either presenting as a solitary skin lesion or primarily involving skin with secondary invasive pulmonary aspergillosis as well as simultaneous involvement of skin and lung tissue.

**Patient - 1**

A 9 years old girl with aplastic anaemia, underwent allogeneic-SCT from her HLA matched sibling brother in October 2003. She was conditioned with cyclophosphamide 50mg/kg for 4 days and ATG (lymphoglobulin- sangstat, Lyon France) 15mg/kg for 3 days. Mononuclear cell dose was 4.5x10⁸/kg body weight of patient. She achieved uneventful allogeneic engraftment. She remained stable for 7 months Post-SCT. While her cyclosporine being tapered off, she rejected the graft. She received second transplant in August 2004 from the same sibling after conditioning with Fludarabin 30mg/m², cyclophosphamide 300mg/m² for 4 days and ATG (Rabbit, Fersineus) 3.75mg/kg for 3 days. Mono-nuclear cell dose was 7.0x 10⁸/kg body weight of patient. She developed swelling around right nostril also involving right maxillary region during conditioning. Swelling was warm, firm tender to touch and measuring 3 x 2cm in size. She was initially treated with broad spectrum antimicrobials consisting of Pipperacillin, Tazobactam (Tazocin), Amikacin and Teicoplanin. Inspite of comprehensive antibiotic cover, swelling further increased in size and she started having severe frontal headache. Later on the lesion became necrotic and started discharging dirty grey coloured fluid. Culture specimen of the discharging fluid was sent for microbiological examination and she was put on intravenous Amphotericin - B (1mg/kg daily) and Itraconazole (400mg daily) along with

![Figure 1. Primary skin involvement by aspergillus infection.](image)
topical 1% amphotericin-B nasal spray. Cultures from the site of lesion revealed the growth of Aspergillus fumigatus. Meanwhile the nasal lesion on the outer surface of right nostril also became necrotic. Necrotic debris were removed and sent for histopathological examination which also revealed the presence of Aspergillus in the necrotic lesion.

Lesion started regressing in size after early neutrophil recovery 0.5x10⁹/L and ultimately healed by secondary union with a scar mark as shown in Figure 1. She was discharged from the hospital on day 21 and rest of her post transplant period remained uneventful.

**Patient - 2**

A 10 years old boy with aplastic anaemia received allogeneic stem cell transplant (MNC dose 4.5x10⁸/kg body weight) from his HLA identical younger sister. He was conditioned with cyclophosphamide (500mg/kg for 04 days) and antithymocyte globulin (lymphoglobulin sangstat Lyon - France) (15mg/kg for 03 days). He received methotrexate and cyclosporine as Graft Versus Host Disease (GvHD) prophylaxis prophylactic antimicrobial therapy started from day 2 of conditioning. On day 9 an oval warm red swelling measuring 1.5 x 2.0 cm appeared on his right inguinal region with no focus of infection in area of lymphatic drainage. Patients was initially treated with cefipime and teicoplanin, however lesion rapidly increased in size (7.5cm x 3.5cm) and became extremely painful and tender. Amphotericin-B was increased to 1.5mg/kg/day I.V. On day 14 lesion extended in to lower abdomen in the region of right liac fossa. The central area of the lesion became necrotic and started discharging haemorrhagic fluid, which was sent for microbiological examination. However, no microorganism was isolated. Patient did not achieve early haematological recovery till day 30 and remained severely immunosuppressed with primary graft failure. He started having high grade fever (39°C) Lesion gradually involved whole of the right iliac fossa and converted into large gaping wound with necrotic tissue at the base and started discharging greenish black thick fluid. Debridement of necrotic tissue was done. Both necrotic tissue and fluid were sent for microbiological/ histopathological examination. Aspergillus fumigatus was isolated from the necrotic tissue as well as from the fluid. Voriconazole was added to amphotericin B initially at the dose of 400mg twice daily for one day followed by 400mg daily. On day 35, post SCT patient developed persistent cough and X-ray chest revealed pneumonitis of left lung and soft opacities in the right paracardiac region (Figure 2). Aspergillus fumigatus was again isolated from bronchoalveolar lavage. Blood culture revealed the growth of Pseudomonas aeruginosa. However, patient did not respond to antifungals and antipseudomonal therapy and died on day 46 post SCT due to pulmonary complication.

**Patient - 3**

A 22 years old male with Philadelphia positive chronic myeloid leukemia (CML) received allogeneic SCT from his HLA matched sibling brother in March 2003. He received conditioning with Bu16/cy200, methotrexate and cyclosporine were used for GvHD prophylaxis. Prophylactic antimicrobials were started 02 days before transplant as per protocol. On day 4, he developed neutropenic fever and was started on empirical first line antibiotics consisting of Piperaciline / Tazobactum and Amikacin. On day 7 post SCT, he developed diffuse swelling in left maxillary area also involving the lower eyelid. X-ray left maxillary sinus was hazy on radiological examination. Amphotericin-B was added to the therapy as blood cultures at this stage were negative. Patient became afebrile within a week and became symptom free. He was discharged from hospital on 19th post SCT day after neutrophil recovery and was on regular weekly follow-up in out patients department.

One month post SCT, patient was admitted with dyspnoea and cough along with bilateral crepitations in the chest and splenic enlargement. Beside this, he was also having multiple non tender well circumscribed swellings of variable sizes (largest measuring 4 x 3cm) on right arm, right thigh and left groin. High resolution computed tomography revealed multiple shadows in both lungs and spleen suggesting aspergillosis. Aspergillus Spp was isolated on histopathological examination of both Fine Needle Aspiration (FNA) and excision biopsy of nodular swellings as well as...
from bronchoaveolar lavage. He was initially treated with amphotericin 1mg/kg daily and itraconazole 400mg daily and his skin lesions started improving. However chest symptoms further worsened with cytomegalovirus (CMV) pneumonitis for which gancyclovir was added and itraconazole was replaced with voriconazole 400mg daily. However he did not respond to therapy and died of respiratory complications after 7 months post SCT.

Discussion

Fungal infections cause significant morbidity and mortality in bone marrow transplant patients. Candida and Aspergillus spp are the most common pathogens in transplant patients, although new fungal opportunistic organisms, Pseudallescheria boydii, Curvularia, Bipolaris, Exserohilum, Alternaria spp, Penicillium marneffei and Fusarium dimerum may occasionally cause local and systemic infections. Two types of aspergillus infections have been described: primary cutaneous aspergillus infection and secondary cutaneous aspergillus infection (as a result of haematogenic dissemination of aspergillus). Primary skin infections result from local trauma or skin maceration (caused by adhesive tapes) around surgical wounds or indwelling catheters particularly in neutropenic post transplant patients. Secondary cutaneous aspergillus infections result from haematogenous spread and are extremely rare (< 5%).

Schimmelpfenning et al\(^6\) have reported two cases of primary cutaneous aspergillus infection as first manifestation of systemic aspergillosis where as Kardori et al\(^7\) also reported five cases of primary cutaneous aspergillosis having typical areas of skin discoloration with central necrosis or necrotizing ulcer as a clinical presentation. Our first patient developed typical primary cutaneous ulceration over the nose which ultimately became necrotic ulcer and later on after antifungal therapy healed by secondary union leaving a big scar mark.

Our second patient developed cutaneous fungal lesion on day 9 (Post-SCT) and did not have any evidence of haematogenous spread from any other primary site. As our patient was severely neutropenic with primary graft failure, the risk of developing secondary pulmonary aspergillosis remained very high, however no clue could be obtained from conventional radiological examination till day 35. In this case high resolution computed tomography (HR-CT) of chest would have been beneficial for early detection and treatment.\(^8\) Unfortunately, the condition of our patient was highly unstable and HR-CT examination could not be done.

Our third patient at 5 months post SCT, simultaneously developed multiple skin lesions and pulmonary aspergillosis. This patient was already on heavy immunosuppressive therapy for grade-III acute GvHD skin. In this case, it was very difficult to decide whether patient had a primary cutaneous fungal infection with secondary pulmonary aspergillosis or he had a primary fungal infection of the lungs with secondary skin involvement through haematogenous dissemination. However reactivation of old lesion in maxillary sinus might be the cause of haematogenous spread. We used combinations of amphotericin - B and voriconazole in therapeutic doses in second and third patient. However, both of these patients died of fungal pneumonias. Whereas, our first patient who had solitary skin lesions, responded to antifungal therapy. As per our transplant protocol we used fluconazole 100mg daily in all patients from day 2 of the conditioning as antifungal prophylaxis. From these results, we can draw the conclusion that leveraging fungal infections are increasingly recognized in transplant settings. Early detection techniques like detection of antibodies against aspergillus sp or aspergillus antigen by PCR would help in early management strategies. Recently more sensitive diagnostic tests based on the detection of fungal cell wall components and aspergillus specific DNA sequences with very high sensitivity and specificity have been developed for early detection of fungal infection.\(^10\) The above mentioned early detection techniques are definitely very helpful in early management of these patient, which will reduce the fungal infection related morbidity and mortality in post SCT, but unfortunately these PCR based techniques are not available in Pakistan.

References