

# **Pneumocystis Carinii and Trichosporon Beigelii Pneumonia following Allogeneic Haemopoietic Stem Cell Transplantation**

Shahid Raza<sup>1</sup>, Parvez Ahmed<sup>1</sup>, Badshah Khan<sup>1</sup>, Khalilullah Hashmi<sup>1</sup>, Sajjad Mirza<sup>2</sup>, Shahid Ahmed Abbasi<sup>2</sup>, Masood Anwar<sup>2</sup>, Iftikhar Hussain<sup>3</sup>, Chaudhry Altaf<sup>2</sup>, Muhammad Khalid Kamal<sup>1</sup>

Armed Forces Bone Marrow Transplant Centre<sup>1</sup>, Armed Forces Institute of Pathology<sup>2</sup>, Combined Military Hospital<sup>3</sup>, Rawalpindi.

### **Abstract**

Pneumocystis Carinii and Trichosporon beigelii are opportunistic infections in immunocompromised patients. We report a case of a young lady who underwent haemopoietic stem cell transplantation for relapsed acute lymphoblastic leukemia. This 25 years old female developed fever, dry cough and rapidly progressive dyspnoea during post transplant neutropenia and was found to be suffering from Pneumocystis carinii pneumonia. She was successfully treated with Co-trimoxazole. The patient again presented with similar symptoms on day 55 post transplant. This time Trichosporon beigelii was isolated from bronchoalveolar lavage and she responded to prompt antifungal therapy. Other complications encountered during the subsequent course were extensive subcutaneous emphysema and spontaneous pneumothorax that required chest intubation and brief hospitalization. The patient is presently nine months post transplant and is asymptomatic.

### **Introduction**

Pneumocystis Carinii pneumonia (PCP) is primarily a disease of immunocompromised host. Although it existed for nearly hundred years, this infection was brought in spotlight in mid and late eighties with AIDS epidemic. Early diagnosis requires very high index of suspicion by clini-

cians and adequately trained lab staff since it can be rapidly fatal if left untreated. Trichosporon beigelii is a fungus that is another rare cause of pneumonia in immunocompromised patients.<sup>1</sup>

Occurrence of both pneumocystis carinii and Trichosporon beigelii pneumonia in a single patient has not been reported in the literature. We report a case of PCP and Trichosporon beigelii pneumonia in a young female who underwent haemopoietic stem cell transplant for relapsed acute lymphoblastic leukaemia.

### **Case Report**

A 25 years old female was diagnosed with acute lymphoblastic leukaemia on 29 May 2001. She received remission induction, intensification and cranial irradiation as per UK ALL X protocol. Post remission, the patient was put on maintenance chemotherapy. She relapsed in May 2003 while still on maintenance. Re-induction was done as per UK ALL 12 protocol in June 2003, followed by three cycles of high dose Methotrexate in September and October 2003. Since the disease was in remission and she was a high-risk patient for relapse, allogeneic haemopoietic stem cell transplant was planned.

She underwent allogeneic peripheral blood haemopoietic stem cell transplantation (SCT) from her



Figure 1. Portable chest X-Ray showing bilateral lung infiltrates.

HLA identical sister on 30th January 2004. Conditioning was done with Busulphan 16mg/kg and Cyclophosphamide 200mg/kg. Graft versus host disease (GVHD) prophylaxis was given with Cyclosporin, Prednisolone and Methotrexate. Total mononuclear cell dose given was  $5.49 \times 10^8$ /kg.

On 3rd day post SCT she developed neutropenic fever. Except for grade III oral mucositis her physical examination including chest auscultation was normal. She was started on Tazobactam and Amikacin along with low dose Amphotericin-B (0.5mg/kg/day) as antifungal prophylaxis. Appropriate culture samples were also taken.

On 5th day post SCT she complained of dry cough and was found to have bilateral crepitations on chest auscultation. Chest x-ray revealed bilateral interstitial shadows and soft opacities in right mid and lower zone and left middle zone. Suspecting the possibility of fungal infection, the dose of Amphotericin-B was increased to 1mg/Kg/day. On 8th day post SCT fever and cough persisted and she also complained of shortness of breath. Oxygen saturation dropped to 80% on air at rest, urea increased to 83.4mg/dl, creatinine to 2.35mg/dl. At this point Cyclosporin was withheld with simultaneous increase in dose of steroids. Tazobactam & Amikacin were replaced with Meropenem and Teicoplanin. Considering the critical condition of the patient and high prevalence of tuberculosis in our population, antituberculosis treatment was also added. All the cultures were repeated and multiple samples of induced sputum were sent for bacterial, fungal and PCP studies. She was also started on G-CSF for early neutrophil recovery.

On day 14 post SCT her temperature was 99°F, she had coarse bilateral chest crepitations (Figure 1), O<sub>2</sub> Saturation fell to 78% on air at rest. The patient was toxic

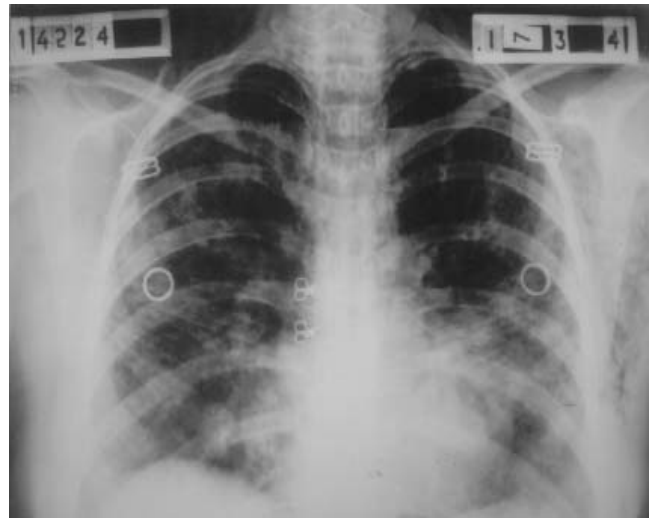


Figure 2. Chest X-Ray PA film showing subcutaneous emphysema more marked on left.

and in severe respiratory distress. Bronchoalveolar lavage (BAL) was attempted at this stage but was unsuccessful due to unstable condition of the patient. At this point patient however, achieved neutrophil recovery and her absolute neutrophil count was  $1.5 \times 10^9$ /l. PCP was considered a strong possibility due to progressively worsening cough, fever and shortness of breath, therefore she was started on tab Co-trimoxazole in therapeutic doses (Trimethoprim 20mg/kg) and dose of prednisolone was increased to 60mg/day. She started improving and in next 2 days her fever settled, O<sub>2</sub> saturation however, took another 2 weeks to improve. Induced sputum was found positive for cysts of *Pneumocystis carinii* on day 20. By day 25 post SCT her oxygen saturation at rest was normal, her Co-trimoxazole was reduced to TMP 12mg/kg and she was discharged from hospital. Bone marrow aspiration done before discharge showed successful tri-lineage engraftment.

She continued twice a week follow up in out door, and made gradual recovery. Co-trimoxazole was changed from therapeutic to prophylactic doses after 5 weeks. On day 45 post transplant she developed subcutaneous emphysema (Figure 2) involving upper chest and neck, was treated conservatively and made complete recovery in a week.

On day 55 post transplant patient again developed fever, cough and severe breathlessness. Chest radiograph showed bilateral diffuse infiltrates. Possibility of PCP relapse and atypical infection were considered. Bronchoalveolar lavage (BAL) was performed which revealed growth of *Trichosporon beigelii*. The fungus was sensitive to Itraconazole. She was given Itraconazole 400mg/day to which she responded in two weeks time. Patient also developed chronic GVHD of skin for which steroids and cyclosporin were continued beyond six months.



Figure 3. Chest X-Ray showing right pneumothorax with complete lung collapse.

Six and a half months later she felt sudden sharp pain in right chest with severe shortness of breath. Chest auscultation revealed absent breath sounds in right chest with hyper-resonant percussion note. Chest x-ray (Figure 3) confirmed large pneumothorax with complete lung collapse; chest tube thoracostomy was done with immediate improvement. Chest tube was removed after three days following complete lung expansion. High resolution computerized tomogram (HRCT) done after recovery showed apical fibrosis and sub pleural bullae on right side.

Presently patient is in complete remission and is asymptomatic (Figure 4). She is on tapering doses of steroids for mild chronic GVHD along with antifungal and PCP prophylaxis.

### Discussion

While genus pneumocystis is known for nearly a century, advent of DNA analysis has brought to light extreme diversity within the genus. In recognition of its genetic and functional distinctness the organism that causes human PCP is now named pneumocystis jiroveci. Changing names however does not preclude the use of acronym PCP because it can be read "Pneumocystis pneumonia".<sup>2</sup> Whereas traditional theory postulates that disease results from reactivation of latent infection, recent data suggest that active acquisition of infection is either through environmental exposure or person-to-person transmission.<sup>3</sup>

Patients at highest risk for PCP are infants with severe malnutrition, children with primary immune deficiencies, patients with hematological malignancies and recipients of solid organ or SCT, those receiving high dose steroids and immunosuppressive therapy.<sup>4</sup>

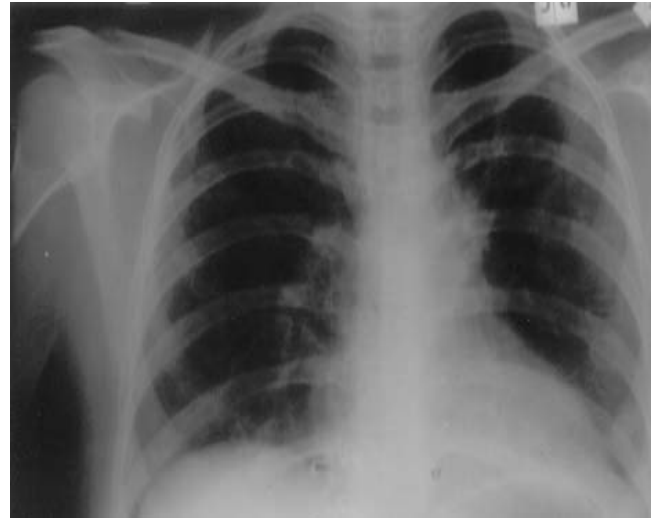


Figure 4. Latest chest X-Ray which is normal.

In 1980's tens of thousands of cases of PCP occurred in persons with AIDS making it most common opportunistic infection. Dual infection with PCP and respiratory viruses following bone marrow transplant (BMT) has also been reported, although our patient developed *Trichosporon beigelii* infection after she was cured of the PCP and was on regular PCP prophylaxis.

In a series of 1454 BMT recipients<sup>5</sup>, 19 developed PCP; 18 of these were not receiving PCP prophylaxis. The mortality in patient developing PCP less than 6 months post BMT was 89% versus 40% in later onset PCP. Lytikken et al.<sup>6</sup> have reported 16 episodes of PCP in 110 BMT recipients with 14 occurring more than 6 months post BMT when these patients were not receiving PCP prophylaxis underscoring the need for prolonged prophylaxis in some patients specially those with chronic GVHD.

Onset of disease is usually insidious and patients present with 2-10 days history of dyspnoea, dry cough, shortness of breath and fever with sweats. Physical examination often reveals increased respiratory rate, tachycardia, cyanosis and fine crackles on auscultation of chest. Chest x-ray show bilateral infiltrates in 50-60% of all patients, although up to 15% may have no or minimal x-ray findings. Other investigations, which assist diagnosis, are assessment of arterial blood gases, which demonstrate hypoxia and increased alveolar-arterial oxygen gradient ( $PAO_2 - Pao_2$ ). There may be reduction in transfer factor, vital capacity, total lung capacity and increased tracer uptake on gallium scan. Serum LDH is usually raised but is non-specific. Bronchoalveolar lavage (BAL) and induced sputum samples are frequently used for the diagnosis of PCP.<sup>7</sup>

*Pneumocystis carinii* infection is not only confined to the lungs but may also be disseminated via lymphatics

and hematogenous routes and commonly involves thyroid, liver, bone marrow, lymph nodes and spleen.<sup>8</sup>

Co-trimoxazole is the first line treatment for PCP. The drug is used for 14-17 days for non-HIV and 21 days for HIV associated PCP.<sup>5,7</sup> Optimum duration of treatment in SCT recipients is less well established in literature and our patient took about five weeks for complete response. Second line treatment for patients intolerant of Co-trimoxazole is with intravenous Pentamidine or Clindamycin with Primaquine or Dapsone with Trimethoprim. Atovaquone and Trimetrexate with Folinic acid may be used as a third line treatment of PCP.<sup>9</sup>

Addition of glucocorticoids to the treatment regimes has shown to reduce the risk of respiratory failure and subsequent need for mechanical ventilation. It also shortens duration of mechanical ventilation and hospital stay.<sup>7</sup>

Mortality rates among individual with non-HIV associated PCP is high, ranging from 34% to 49% in comparison with patients with HIV associated PCP. Mortality as high as 89% has been reported in SCT recipients. Poor prognostic factors are high respiratory rate, high pulse rate, elevated C-reactive protein, elevated serum LDH and mechanical ventilation.<sup>10</sup>

Trichosporon beigelii is a fungus, which is a rare cause of invasive pneumonia or disseminated disease in immunocompromised patients. First case of Trichosporon beigelii was reported in 1970. Over the past decade disseminated disease due to the yeast *T. beigelii* has been increasingly documented in severely immunosuppressed patients. Portals of entry into deep tissues are usually respiratory or gastrointestinal tract and skin. The fungus can cause invasive disease at a single organ site or in a disseminated form in which lungs, kidneys, skin and eyes are the main targets. *T. beigelii* can cause fungemia even in immunocompetent individuals. In these cases, the infection is related either to the presence of a foreign body such as a prosthetic heart valve, an indwelling catheter or to intravenous drug abuse.<sup>1</sup>

Diagnosis relies on clinical suspicion with microbiological confirmation. There have been conflicting results in the literature regarding susceptibilities of this organism to various antifungal agents. Furthermore, the efficacy of antifungal drugs does not always correlate with susceptibility in

vitro. Clinical isolates of *T. beigelii* are generally reported to be susceptible to Amphotericin-B, but sensitivities too can vary. Rarely, *T. beigelii* may be resistant to Amphotericin-B in vitro and Flucytosine also is variably active. There are data suggesting that certain azoles (including Miconazole, Fluconazole and Itraconazole) are active against most *T. beigelii* isolates and should be considered as possible alternative therapeutic agents. Our patient also responded to prolonged Itraconazole therapy. More recently, a new triazole derivative, Voriconazole has been reported to have potent in vitro antifungal activity against yeasts, moulds and filamentous fungi. Although its clinical effectiveness is still to be established, this newer triazole appears to be promising in the treatment of human mycoses.<sup>1</sup>

At present, therapy is not efficacious in all cases of *T. beigelii* and immunological recovery of patient seems to be essential in the resolution of the infection, as confirmed in this report. Clinical suspicion is essential for earlier institution of antifungal therapy, which can decrease the high mortality rate and improve outcome for patients with disseminated trichosporonosis.<sup>1</sup>

## References

1. Eser B, Galimberti M, Lucarelli G, Giardini C, Polchi P, Baronciani D, et al. Trichosporon beigelii: a life threatening pathogen in Immunocompromised hosts. Bone Marrow Transplant 2000;25:745-9.
2. Stringer JR, Beard CB, Wakefield AE, Miller RF. A new name (Pneumocystis jiroveci) for Pneumocystis from humans. Emerg Infect Dis 2002;8:891-6.
3. Morris A, Beard CB, Huang L. Update on epidemiology and transmission of Pneumocystis Carinii. Microbes Infect 2002;4:95-103.
4. Russian DA, Levine SJ. Pneumocystis Carinii pneumonia in patients without HIV infection. Am J Med Sci 2001;321:56-65.
5. Tuan IZ, Dennison D, Weisdorf DJ. Pneumocystis Carinii pneumonitis following bone marrow transplantation. Bone Marrow Transplant 1992;10:267-72.
6. Lyytikainen O, Ruutu T, Lautenschlaager I, Volin L, Jokipii L, Tiittaner L, et al. Late onset Pneumocystis Carinii pneumonia following Allogeneic bone marrow transplantation. Bone Marrow Transplant 1996;17:1057-9.
7. Wazir JF, Ansari NA. Pneumocystis Carinii Infection, update and review. Arch Pathol Lab Med 2004;128:1023-7.
8. Telzak EE, Cote RJ, Gold JW, Campbell SW, Armstrong D. Extra pulmonary Pneumocystis Carinii Infection. Rev Infect Dis 1990;12:380-6.
9. Smego RA Jr, Nargar S, Maloba B, Popara M. A meta-analysis of Salvage Therapy for Pneumocystis Carinii Pneumonia. Arch Intern Med 2001;161:1529-33.
10. Robolt F, Godet C, Le Moal G, Garo B, Faouzi Souala M, Dary M, et al. Analysis of underlying diseases and prognosis factors associated with Pneumocystis carinii pneumonia in immunocompromised HIV-negative patients. Eur J Microbiol Infect Dis 2002;21:523-31.