Therapeutic Failure in a Renal Transplant Patient with *Pneumocystis Jiroveci* Pneumonia: A Case Report

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Abstract

Objectives: **Pneumocystis jiroveci pneumonia is common in immunocompromised individuals.**

Patients: **This case report describes an immunosuppressed patient who acquired *P jiroveci* pneumonia 6 months after renal transplant surgery.**

Results: **The patient experienced many pneumonia-related complications and adverse effects from drug therapy, and despite treatment with various antibiotic agents, he died on the 62nd day after his admission to the intensive care unit.**

Conclusions: **The therapeutic failure of the drug of choice (co-trimoxazole) was evident.**

This case raises questions about the development of *P jiroveci* resistance to current therapies.

Key words: *Renal transplant, Immunosuppression, Antibiotics, Treatment, Resistance*

Renal transplant recipients are at high risk for infections caused by opportunistic pathogens such as *Pneumocystis jiroveci (Pneumocystis carinii)*. Most cases of pneumonia associated with *P jiroveci* infection develop within the first 6 months after transplant surgery, when patients receive high doses of immunosuppressive agents. We present the case of a renal transplant recipient with severe *P jiroveci* pneumonia who died despite all efforts with antibiotic therapy.

Case Report

A 44-year-old white man was admitted to our hospital with a 4-day history of fever and dyspnea. Seven days later, his condition deteriorated, and he was transferred to the intensive care unit. His medical history included renal failure caused by polycystic renal disease, renal transplant surgery 6 months earlier, and satisfactory graft function. His immunosuppressive regimen consisted of initial treatment with antilymphocyte globulin (1.5 mg/kg/day) and subsequent therapy with cyclosporine (8 mg/kg/day), prednisolone (15 mg/day), and mycophenolate mofetil (2 g/day). He did not receive prophylaxis against *P jiroveci*.

The results of a chest radiograph on admission and a subsequent computed tomographic scan revealed bilateral diffuse infiltrates. *P jiroveci* pneumonia was highly suspected, and empiric intravenous treatment was initiated with co-trimoxazole (trimethoprim-sulfamethoxazole ratio, 1:5; trimethoprim [20 mg/kg] and sulfamethoxazole [100 mg/kg] daily) as well as hydrocortisone (125 mg 3 times daily). Additional treatment included ceftriaxone, erythromycin, and ganciclovir as prophylaxis against bacterial or viral infection.

After his admission to the intensive care unit, this patient underwent intubation and mechanical ventilation (fraction of inspired oxygen: 0.7; positive end-expiratory pressure, 0.98 kPa [10 cm H_2O]). His biochemical laboratory values were within normal limits, except for an elevated level of serum L-lactate dehydrogenase (> 460 U/L). A diagnosis of *P jiroveci* pneumonia was confirmed by the detection of cysts in the bronchoalveolar lavage fluid, and cyclosporine therapy was discontinued. Quantitative colony counts from bronchial secretions and bronchoalveolar lavage fluid cultures were negative. Cell analyses demonstrated increased alveolar macrophage and lymphocyte counts but a decreased number of polymorphonuclear neutrophils (Table 1). Cellular immunity was evaluated, and flow cytometry was used to determine lymphocyte

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Experimental and Clinical Transplantation (2009) 2: 129-132

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Table 1. Bronchoalveolar lavage fluid analysis in a renal transplant patient with *Pneumocystis jiroveci* pneumonia.

Bronchoalveolar Lavage Fluid Analysis	Value (%)
Alveolar macrophages	65
Polymorphonuclear neutrophils	5
Lymphocytes	25
Bronchial epithelial cells	5

*Total number of cells: 100 000/mL

subpopulations (Table 2). Corticosteroid therapy was tapered off over a 17-day period and then discontinued. The patient's condition deteriorated suddenly after the development of right-sided pneumothorax caused by cavitating parenchymal lesion ruptures. A thoracic tube was inserted. The results of blood and urine cultures were negative, as was an evaluation for extrapulmonary pneumocystosis of the eye. A repeat computed tomographic scan revealed bilateral interstitial pulmonary infiltrates, pneumothorax, cavitating lesions, and pleuritic fluid. The fluid was aspirated by pleurocentesis and with ultrasonographic guidance. The results of a cytologic analysis were unremarkable and the cultures were negative; however, the concentrations of *P jiroveci* in bronchial secretions and pleuritic fluid were significant. The serum levels of L-lactate dehydrogenase remained high.

Table 2. Lymphocyte subpopulations determined by flow cytometry in a renal transplant patient with *Pneumocystis jiroveci* pneumonia.

Lymphocyte Subpopulations	Value
Lymphocytes	742/μL
CD4 cells	401/μL
CD8 cells	178/μL
CD4/CD8 cells	2.25

After 4 weeks of ineffective therapy with co-trimoxazole, treatment with that agent was discontinued and intravenous pentamidine (4 mg/kg/d) was prescribed. One week later, the pentamidine caused episodes of torsades de pointes, which resolved after therapy with that drug had been discontinued. Treatment with co-trimoxazole was resumed, but the patient's condition deteriorated, and surgical intervention became necessary. A right thoracotomy revealed severe lobar parenchymal damage and multiple cavitating and noncavitating abscesses. A right upper lobectomy and a middle lobectomy were performed. The patient's respiratory function deteriorated postoperatively, and significant hypercarbia was noted. Analysis of the right upper and middle lobular pustules revealed only *P jiroveci*, and the results of culture were negative for other pathogens. Eight days after surgery, *P jiroveci* was once again identified in the patient's bronchial secretions, and dapsone (100 mg/d) via a nasogastric tube was added to co-trimoxazole therapy. The deterioration of the patient's condition seemed to be irreversible. On the 62nd day after his admission to the intensive care unit, a pulmonary hemorrhage occurred, and he died.

Discussion

Opportunistic infections often occur in renal transplant recipients. Studies on *P jiroveci* pneumonia in immunosuppressed patients have documented risk factors, prognostic indicators (1-5), conventional and alternative therapies (4,6), statistics on outcomes and mortality rates. *P jiroveci* resistance against antibiotics has not been extensively studied, and its effect on mortality rates remains unclear.

During the long course of this case, we observed changes in factors and indicators related to the outcome, several therapy-related complications, and the death of the patient, which was associated with treatment failure to which *P jiroveci* resistance might have contributed.

The incidence of *P jiroveci* pneumonia in renal transplant recipients seems to correlate with the degree of immunosuppression. Aggressive anti-rejection agents, such as cyclosporine, have been associated with an increased risk for *P jiroveci* pneumonia (7). Our patient was receiving cyclosporine but not prophylactic treatment with co-trimoxazole against *P jiroveci*. Cellular immunodeficiency and defective T-cell and B-cell immunity are the primary risk factors for the development of *P jiroveci* infection. As several studies have shown, patients with a CD4+ cell count lower than 200/μL are at great risk for *P jiroveci* infection, regardless of underlying disease (1,2,8,9).

Our patient had received cyclosporine, which was discontinued after the diagnosis of *P jiroveci* pneumonia was confirmed. Moreover, his CD4+ counts were higher than 200/μL. Although this patient was in critical condition during the course of his pneumonia, the results of his laboratory examinations are not supported in the literature.

It has been suggested that alveolar macrophages have an essential role in the clearance of *P jiroveci* (10). Studies of cellular changes in the bronchoalveolar lavage fluid of immunocompromised patients have documented a decrease in the number of alveolar

macrophages and increased numbers of lymphocytes and polymorphonuclear neutrophils. Identifying cysts in bronchoalveolar lavage fluid is a more sensitive method for diagnosing *P jiroveci* pneumonia than is an analysis of induced sputum, which may yield false-negative results. Bronchoalveolar lavage is usually performed early in the course of *P jiroveci* pneumonia, when the patient's clinical condition permits that intervention. At that time, the presence of polymorphonuclear neutrophils and leukocytes in the lavage specimens may indicate the first stage of an alveolar inflammatory reaction (11). In our patient, bronchoalveolar lavage was performed early, and cytologic analysis of the fluid showed an increase in the alveolar macrophage and lymphocyte counts and a decrease in the number of polymorphonuclear neutrophils.

It is also interesting to note that *Cytomegalovirus* is considered a risk factor for *P jiroveci* pneumonia but does not affect the prognosis or outcome (7,10). Our patient's serologic and antigenic laboratory analyses were negative for *Cytomegalovirus*, herpes simplex virus, varicella-zoster virus, Epstein-Barr virus, *Cryptococcus*, *Candida*, *Aspergillus*, and *Legionella*. The results of the Mantoux skin test and Ziehl-Neelsen staining of bronchial secretions were negative for *Mycobacterium tuberculosis*. Bronchoalveolar lavage cultures for bacteria, respiratory viruses, fungi, *Legionella*, and *Mycobacterium tuberculosis* were negative. The results of a postoperative histologic examination, a urine antigen test for *Legionella*, and polymerase chain reaction analyses for herpes simplex virus, varicella-zoster virus, and *Mycobacterium tuberculosis* in the patient's bronchoalveolar lavage fluid and *Cytomegalovirus* in his blood were negative. A computed tomographic scan revealed no sign of aspergillosis (fungal balls, nodules, perinodular halo, cavities, consolidation) or tuberculosis (upper lung cavities, lymphadenopathy, tuberculous pleurisy).

Concurrent pulmonary infections (typically bacterial diseases and *Cytomegalovirus* pneumonia) have been observed in 35% to 45% of patients with *P jiroveci* pneumonia (7). Our patient's blood and bronchial cultures were negative for other microorganisms that could have contributed to his death. Moreover, he received a macrolide for protection against atypical microorganisms and ceftriaxone and antiviral therapy as part of his initial treatment, because even though pulmonary infections in immunocompromised patients are primarily opportunistic, bacterial or viral pneumonia is also a possibility.

In patients with *P jiroveci* pneumonia, the following factors have a significantly negative correlation with survival: a partial pressure of oxygen in arterial blood value of lower than 9.33 kPa (70 mm Hg), an alveolar-to-arterial oxygen difference of more than 6 kPa (45 mm Hg), an increased microbial load, a questionable polymorphonuclear neutrophil count in bronchoalveolar lavage fluid, radiographic findings typical of that disease, an elevated serum L-lactate dehydrogenase level, and a low albumin level. Mutations in the *P jiroveci* gene, age older than 36 years, and a low CD4+ cell count are also associated with a poor prognosis. Positive indicators for survival are prompt admission to an intensive care unit and mechanical ventilation, if required. Of the biochemical markers for *P jiroveci* pneumonia, L-lactate dehydrogenase is considered a sensitive but not specific indicator. Nevertheless, the degree of L-lactate dehydrogenase elevation is associated with the severity of the *P jiroveci* infection (1). In the patient we describe, we observed a steady increase in the level of L-lactate dehydrogenase.

Our patient was unsuccessfully treated with antimicrobials for *P jiroveci* pneumonia. Co-trimoxazole (trimethoprim and sulfamethoxazole) was the therapeutic agent of choice; sulfamethoxazole, which targets dihydropteroate synthase, is the agent active against *P jiroveci*. According to some studies, point mutations identified in the dihydropteroate synthase gene of *P jiroveci*, under selective drug pressure, may be related to resistance of *P jiroveci* to sulfa, because that phenomenon has been confirmed in other pathogens (*Escherichia coli*, *Plasmodium*) with mutations at homologous positions (3,12-14). It has not yet been proven that those mutations confer drug resistance to *P jiroveci*, because human *P jiroveci* cannot be routinely cultured in vitro, and multifunctional folic acid synthase gene analysis is difficult (3, 12-16).

Because the course of pneumonia and the ineffectiveness of treatment in this patient were not in accordance with the literature or with prognostic factors, we speculated that therapeutic failure could have been due to *P jiroveci* drug resistance to co-trimoxazole, even though there was no evidence to support that theory. Whether mutations translate into clinical resistance is unknown; thus we could not determine if co-trimoxazole resistance occurred in

our patient. In addition, no analysis of the folic acid synthase gene for *P jiroveci* could be performed; thus no molecular evidence of that type of resistance existed.

Alternative treatments for *P jiroveci* pneumonia may be effective in cases of co-trimoxazole resistance. Atovaquone is one such alternative drug with a different target (cytochrome b), but unfortunately, there are also reports of *P jiroveci* resistance to atovaquone (8). It seems that *P jiroveci* resistance to first-line and second-line drugs could become a concern for immunosuppressive patients.

Pentamidine, which causes well-known cardiovascular adverse effects, was administered to our patient after the initial failure of co-trimoxazole therapy. Pentamidine was discontinued because torsades de pointes arrhythmia developed. The resolution of that arrhythmia after therapy with pentamidine was terminated suggested that pentamidine was the cause. The early discontinuation of that drug did not enable us to confirm whether it would have been effective. In our patient, every therapeutic intervention failed.

The treatment failure in this patient could have been due to *P jiroveci* drug resistance, but other factors also contributed to the course of disease and fatal outcome. Significant immune suppression, which was definitely an issue, could have contributed to the deterioration of his condition. In addition, he had a high burden of infection that was likely exacerbated when the pneumothorax seeded the infection into the pleural space (a sequence of events evidenced by the identification of *P jiroveci* in the pleural fluid).

The number of immunosuppressed patients admitted to intensive care units has increased, and clinicians should be aware of associated opportunistic infections that can lead to serious complications or death. Mortality rates for patients with *P jiroveci* pneumonia who are admitted to the intensive care unit are high, but whether those high death rates result from the severity of infection, immunosuppression, complications, concurrent infections, or treatment failure remains unclear. The clinical failure in our patient was probably multifactorial, but *P jiroveci* drug resistance to co-trimoxazole and alternative drugs may be a problem and requires further investigation.

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