Organizing pneumonia secondary to *Pneumocystis jirovecii* infection in a kidney transplant recipient: Case report and review of literature

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**ABSTRACT**

Organizing pneumonia (OP), previously known as bronchiolitis obliterans OP, is a diffuse parenchymal lung disease affecting the distal bronchioles, alveolar ducts, and alveolar walls. Pulmonary infections, especially bacterial and viral diseases, are known to be associated with the secondary form of OP. OP secondary to fungal infections is less common. Here, we report a case of OP associated with pneumocystis pneumonia (PCP) in a kidney transplant recipient on tacrolimus-based triple immunosuppression. The index case had developed new lung consolidation toward the end of trimethoprim-sulfamethoxazole therapy for PCP. Spontaneous clinical and radiographic resolution was seen without any increment in the dose of corticosteroids. We review the literature and present a summary of all reported cases of OP associated with PCP to date.

**KEY WORDS:** Organizing pneumonia, *Pneumocystis jirovecii*, renal transplantation, tacrolimus

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**INTRODUCTION**

Organizing pneumonia (OP) is a clinicopathologic entity characterized by buds of granulation tissue within the airspaces associated with varying interstitial inflammation. These lesions occur predominantly in the alveoli, but may also extend into the bronchiolar lumen (previously known as bronchiolitis obliterans).[1] The stages in the development of OP include intra-alveolar fibrin accumulation, migration of fibroblasts from the interstitium, and production of connective matrix proteins forming mature fibrotic intra-alveolar buds. The clinical course may vary considerably according to the etiology and stage of the disease. The diagnosis is usually confirmed by transbronchial or surgical lung biopsy. Treatment is based on corticosteroid therapy, and complete resolution occurs in majority of the cases.

Infections are the common causes of secondary OP, of which bacterial and viral infections constitute the majority.[2] *Pneumocystis jirovecii* is a ubiquitous opportunistic fungus known to cause pneumonia among immunocompromised individuals. The association of pneumocystis pneumonia (PCP) with OP was reported previously in HIV-positive individuals and solid-organ transplant recipients. Here, we present a case of OP associated with PCP in a renal transplant recipient on tacrolimus-based triple immunosuppression.

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transplant recipients (lung and liver). Here, we report a case of OP associated with pneumocystis pneumonia (PCP) in a kidney transplant recipient and review the literature regarding this association.

CASE REPORT

A 36-year-old male, renal allograft recipient, presented with the complaints of fever, dry cough, and loss of appetite of 14-day duration. His fever was of low grade with no diurnal variation. He denied any history of breathlessness, chest pain, hemoptysis, or weight loss. He underwent live-related renal allograft transplantation 6 months back for end-stage renal disease due to IgA nephropathy without any induction immunosuppression (antithymocyte globulin or basiliximab). He had no other comorbid medical illnesses. He was on tacrolimus 3.5 mg, mycophenolate sodium 720 mg, and prednisolone 7.5 mg/day to prevent graft rejection. He had no medication adjustments made in the past 6 months and was never exposed to high-dose corticosteroids. He denied smoking, alcohol, or drug use.

On examination, he was afebrile, hemodynamically stable, and had a respiratory rate of 28/min with saturation of 95% breathing room air. On chest auscultation, he had bilateral inspiratory crackles with normal cardiovascular examination. The examination of other systems was unremarkable. His laboratory parameters were within normal limits (Hb – 14.6 g/dL; total lymphocyte count [TLC] – 9900/µL; Absolute neutrophil count (ANC) – 7720/µL; and platelets – 2.85 lakhs/µL). His allograft function was stable (serum creatinine 1.05 mg/dL), and urine analysis was unremarkable. His arterial blood gases revealed mild hypoxia (PaO₂ – 68 mmHg and alveolar–arterial gradient – 22 mmHg). HIV testing done by ELISA was negative. His chest radiograph revealed bilateral diffuse alveolar infiltrates [Figure 1a]. High-resolution computed tomography scan (HRCT) was performed, which showed bilateral diffuse ground glass opacities (GGOs) with no mediastinal or pleural abnormality [Figure 2a-e].

PCP, Cytomegalovirus (CMV) pneumonia, and atypical bacterial pneumonia were considered in the differential diagnosis. Induction of sputum with nebulized hypertonic saline did not yield adequate sample for analysis. Flexible bronchoscopy and bronchoalveolar lavage (BAL) was performed. Grocott’s Methenamine Silver stain for PCP was positive in the lavage fluid. The fluid was negative for acid-fast bacilli (AFB), CMV inclusion bodies, and fungal hyphae. A diagnosis of PCP was made, and he was started on trimethoprim-sulfamethoxazole (TMP/SMX) 960 mg/day. The dose of prednisolone was changed to 40 mg twice daily for the first 5 days, 40 mg once daily for the next 5 days, and 20 mg daily subsequently. His fever and cough had improved along with radiologic resolution of infiltrates after 2 weeks of therapy [Figure 1b].

After 3 weeks of TMP/SMX therapy, he was completely asymptomatic except for occasional dry cough. TMP/SMX was stopped, and 10 mg of prednisolone was continued. Laboratory investigations revealed leukopenia (TLC 1400/µL and ANC 1050/µL) with other normal cell lines (Hb – 13 g/dL; platelets – 1.75 lakhs/µL), and repeat chest radiograph showed left upper, middle zone infiltrates [Figure 1c]. Repeat HRCT thorax done showed peribronchovascular consolidation in the right upper lobe, left upper lobe, and left lower lobe apical segment with clearance of all GGOs [Figure 2b-f]. A repeat analysis of BAL fluid was negative for AFB, fungus, and PCP. Transbronchial lung biopsy done from the left upper lobe showed alveoli filled with inflammatory debris consisting of granulation tissue and interstitial inflammation. Few areas of intra-alveolar fibrin deposition were also noted [Figure 3]. His trough tacrolimus level was within the target range (9.97 ng/mL). Quantitative polymerase chain reaction for CMV DNA was negative. A provisional diagnosis of OP with drug-induced leukopenia was made. He was observed closely with symptomatic treatment as he had no major symptoms, and tacrolimus was continued.

There was improvement in cough and leukopenia over the next 2 weeks (TLC 4400/µL and ANC 2900/µL). Chest radiograph done 2 weeks after the diagnosis of OP showed clearing of infiltrates [Figure 1d]. The OP was attributed to be associated with pneumocystis pneumonia rather than tacrolimus. The patient remains stable on follow-up at 6 months without any relapse.

DISCUSSION

This article reports a 36-year-old male patient of noncryptogenic OP associated with PCP and reviews additional ten OP patients reported in the literature. PCP and OP were suspected mostly because of clinical, histopathological, and radiological findings. The
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The association between the two diseases is less common and has never been reviewed before.

OP is a parenchymal lung disease which may be idiopathic (cryptogenic OP) or associated with any inciting event. Idiopathic form is the most common form of OP reported worldwide.[2] Infection, drugs, and radiation are the causes of secondary OP, with infections being most common. It may also develop as a manifestation of the immune process associated with connective tissue disease, malignancy, and hematologic disorders. It may follow bone marrow and lung transplantation, usually accompanying acute rejection.[3-5] If OP is related to infection, it occurs as a part of nonresolving pneumonia of the primary causative agent or as an exaggerated inflammatory reaction triggered by that agent after resolution of the primary cause. Fungal infections are less commonly associated with OP, which include Cryptococcus neoformans, Penicillium janthinellum, and P. jiroveci.[6] The association of Pneumocystis infection with OP was previously reported in HIV-positive individuals and in organ transplant recipients (lung and liver).[7,8]

The literature search yielded ten studies reporting on OP/bronchiolitis obliterans OP associated with Pneumocystis infection. Of which eight studies (ten patients) were reviewed [Table 1] and two non-English case reports were excluded.[15,16] All the ten cases were proven OP histopathologically; eight biopsies had demonstrated PCP cysts in the tissue specimen. Of ten cases, five had developed OP during treatment for PCP, two after completion of therapy, and three were diagnosed to have OP and PCP concurrently. The development of OP in all cases of HIV infection was seen after the introduction of antiretroviral therapy (ART) during/immediately after PCP treatment. This is attributed to immune reconstitution phenomenon seen after the initiation of ART.

The treatment strategy for secondary OP includes treatment of the inciting factor and the use of immunosuppressants in refractory cases (glucocorticoids and cytotoxic therapy). The usage of immunosuppression in cases of secondary OP, unlike cryptogenic OP, is not clear. Seven cases have received glucocorticoids for OP; one case received TMP/SMX alone; ART was withheld in one case without any specific therapy. Of the ten cases, one had succumbed to illness,[13] and the rest all had complete recovery. The index case did not receive any glucocorticoid therapy for OP, but he was receiving low-dose prednisolone (10 mg), tacrolimus, and mycophenolate throughout the clinical course.

Tacrolimus is an immunosuppressant drug, which is widely used in organ transplant recipients to prevent graft rejection. Tacrolimus has been reported to cause interstitial lung injury, including OP in renal transplant recipients.[17,18] The contribution of tacrolimus in the development of OP in this case seems unlikely. Clinical improvement was noted despite continuation of tacrolimus. We reviewed three cases of PCP-related OP in post solid organ transplant patients who were receiving sirolimus/tacrolimus. All the three cases were given glucocorticoids, and dose reduction of the drug was done in two cases.[7,10]

Postinfectious OP should be suspected when new lung infiltrates or consolidation develops during the course of infection or after resolution of infection. The diagnosis depends on the demonstration of the typical histopathologic features in a patient with compatible clinical and radiographic features. Treatment is based on the severity of the disease; mild disease can be managed conservatively, whereas severe form of disease requires glucocorticoid administration.
Table 1: Clinical characteristics and management of pneumocystis infection associated with organizing pneumonia reported in the literature

| She | Sex | Background Illness | Biopsy | Diagnosis on HPE | Temporal correlation with PCP | Treatment | Outcome |
|-----|-----|--------------------|--------|------------------|------------------------------|-----------|---------|
| Yousen et al.[9] | NS | NS | DLT | NS | OP with PCP | Concurrent diagnosis | Cotrimoxazole | Good |
| Kleindienst et al.[7] | Male | Male | Post-OLT, tacrolimus | TLB | OP with PCP | On PCP therapy | Reduction of tacrolimus dose + methylprednisolone | Good |
| Wislez et al.[9] | 37 | Male | HIV infection | OLB | OP | After completion of PCP therapy | Withholding of ART | Good |
| Wislez et al.[9] | 47 | Male | HIV infection | TBLB | OP with PCP | On PCP therapy | Withholding of ART and methylprednisolone | Good |
| Verma and Soans[10] | 56 | Male | Postrenal transplant, sirolimus | OLB | OP with PCP | Concurrent diagnosis | Reduction of sirolimus dose + cotrimoxazole + prednisone | Good |
| Godoy et al.[11] | 59 | Male | Post-OLT, tacrolimus | Core biopsy | OP with PCP | On PCP therapy | Methylprednisolone | Good |
| Almaslmani et al.[12] | 36 | Male | HIV infection | Core biopsy | OP with persistent PCP | On completion of PCP therapy | Corticosteroids and clindamycin + primaquine | Good |
| Godoy et al.[11] | 54 | Male | HIV infection | Core biopsy | OP with PCP | Concurrent diagnosis | Cotrimoxazole + prednisone | Good |
| Fernández-Codina et al.[14] | 63 | Male | Seronegative arthritis on methotrexate | TBLB | OP | On PCP therapy | Methylprednisolone | Poor |
| Index case | 36 | Male | Postrenal transplant, tacrolimus | TBLB | OP | Toward the end of PCP therapy | Observation | Good |

AML: Acute myeloid leukemia, ART: Antiretroviral therapy, DLT: Double-lung transplantation, HIV: Human immunodeficiency virus, HSCT: Hematopoietic stem cell transplantation, HPE: Histopathological examination, NS: Not specified, OLT: Orthotopic liver transplantation, OLB: Open lung biopsy, TBLB: Transbronchial lung biopsy, TLB: Thoracoscopic lung biopsy, OP: Organizing pneumonia, PCP: Pneumocystis jiroveci pneumonia

CONCLUSION

OP can complicate the course of pneumocystis pneumonia or may develop after resolution of the infection. Mild cases of OP without respiratory failure can be managed conservatively and do not require glucocorticoid administration. OP associated with PCP has a good prognosis an complete recovery.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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