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Case Report

An unusual pulmonary complication of cytomegalovirus infection in a renal transplant recipient

Jeremy Jacques, Aymeric Dallocchio, Zara Dickson, Frederique Bocquentin, Hela Jebali, Jean-Claude Aldigier, Marie Essig and Jean-Philippe Rerolle

Department of Nephrology and Renal Transplantation, CHU Dupuytren, Limoges, France

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Introduction

Bronchiolitis obliterans organizing pneumonia (BOOP) is a clinicopathological entity occurring in the clinical setting of interstitial pneumonia [1]. Occurrence of BOOP in the post-transplant period has been well described in lung [2] or bone marrow transplantation [3] but remains rare in renal transplantation [4]. We report here, to the best of our knowledge, the first case of BOOP secondary to CMV infection in a renal transplant recipient. Intravenous (IV) ganciclovir was effective in eradicating the virus but ineffective in improving the pulmonary status of the patient. After prednisone therapy, the patient's pulmonary symptoms and radiographic findings rapidly improved.

Case report

A 59-year-old woman with end-stage renal failure due to systemic lupus erythematosus was admitted to our unit in October 2003 for her first renal transplantation. Her past history was uneventful. She was a non-smoker.

The donor was a 31-year-old woman and there were five HLA donor–recipient mismatches. Initial immunosuppression consisted of sequential quadruple therapy using induction by antithymocyte globulins followed by steroids, mycophenolate mofetil and tacrolimus (FK). The cytomegalovirus (CMV) status was donor positive and recipient negative. Prophylactic treatment by valacyclovir was then given for the first 3 months post-transplant. Apart from an acute episode of functional renal insufficiency, the post-transplant period was uncomplicated. Baseline creatinine level was 0.95 mg/dl (84 μmol/l).

Correspondence and offprint requests to: Jean-Philippe Rerolle, Service de Transplantation Rénale, CHRU Dupuytren, 2 Avenue Martin Luther King, 87000 Limoges, France. Tel: +33-5-55056464; E-mail: jean-philippe.rerolle@chu-limoges.fr

Fifteen days after valacyclovir withdrawal, the patient developed neutropaenia (1440/mm^3) and thrombopaenia (123 000/mm^3). At this time, clinical examination was extremely poor with only a slight cough. CMV antigenaemia was highly positive (705/200 000 cells). The diagnosis of CMV infection post-renal transplantation was then established. Treatment by IV ganciclovir was then started and a rapid improvement was noted. White blood cell count increased from 1440/mm^3 to 3000/mm^3 and platelet count from 128 000/mm^3 to 181 000/mm^3 in 6 days and CMV antigenaemia decreased to 425/200 000 cells in 4 days.

Seven days after the introduction of IV ganciclovir, the patient developed dyspnoea, a severe dry cough and fever (39°C). Hypoxaemia was noted (SaO_2 85%). The clinical examination of the patient showed acute respiratory insufficiency with diffuse crackles. Chest X-rays showed diffuse interstitial patchy and nodular opacities involving all the pulmonary lobes. Chest computed tomography revealed that these opacities were bronchocentric and predominantly located at the peripheral part of the lung and showed small nodules and thickening of the wall of multiple bronchi (Figure 1). Laboratory tests revealed an inflammatory syndrome (C reactive protein: 179 mg/l). Lymphocyte count was 3100/mm^3. Plasma creatinine level remained normal. The results of the latex test, antinuclear antibodies and antineutrophil cytoplasmic antibodies were all negative. CMV antigenaemia was still decreasing at 152/200 000 cells. Repeated sputum and blood cultures, and urinary test for legionella antigen were negative. Empirical antibiotherapy using ceftriaxone and ofloxacine was then started. This treatment was inefficient. Thus, flexible bronchoscopy and bronchial washing were performed. Cellularity analysis of the bronchoalveolar fluid showed 650 000 cells/ml with 72% of lymphocytes, 8% of neutrophil polynuclears, 13% of macrophages and 7% of unidentified cells. Special staining showed no acid-fast bacilli, *Pneumocystis carinii* or other microorganisms. However, the polymerase chain reaction (PCR) for CMV was positive in bronchial fluid. Diagnosis of CMV-induced BOOP post-CMV pneumonitis was suspected. To confirm this diagnosis, transbronchial biopsies were performed. Unfortunately, biopsy specimens were not contributive because of their small size and

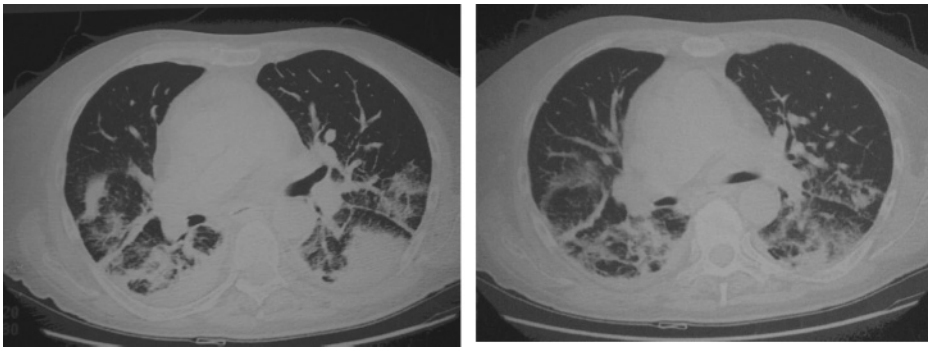

Fig. 1. Chest computed tomography showing diffuse interstitial patchy and nodular opacities involving all the pulmonary lobes and predominantly located at the peripheral part of the lung.

open-lung biopsy was not considered because of the respiratory state of the patient.

Antibiotics were stopped and corticotherapy immediately started at 1 mg/kg per day. The clinical status of the patient then dramatically improved. Apyrexia was obtained in 24 h and normal respiratory function was recovered within 10 days. Inflammatory syndrome disappeared in 10 days and CMV antigenaemia was negative after 22 days of ganciclovir therapy. Steroids were progressively tapered off and stopped after 1 month of treatment. Four years later, no other pulmonary problems have occurred, and the patient has done well.

Discussion

CMV infection is a relatively frequent complication after renal transplantation with an incidence of 10–25% [5]. Clinical manifestations of the disease are numerous including fever, flu-like syndrome, leucothrombopaenia, hepatitis and colitis. CMV pneumonitis is a rare entity in renal transplant recipients [6] with some fatal cases described.

BOOP is a major reparatory response of the pulmonary tissue to an aggression consisting of an incomplete resolution of inflammation in the alveoli and the distal terminal bronchioles. BOOP may be idiopathic or have varied aetiologies as summarized in Table 1. Histologically, BOOP appears in the peri-bronchiolar areas with alveolar filling by loose fibroblastic tissue. Progressively, the lesions may become more organized and diffuse but with preserved adjacent areas and preserved lung architecture. Thus, a lung biopsy is necessary to confirm the diagnosis of BOOP. A transbronchial biopsy is frequently inadequate and an open-lung biopsy is needed.

The occurrence of BOOP in the post-transplant period has been well described in lung [1,2] or bone marrow transplantation [3] but remains rare in renal transplantation [6,7], with only a few cases described, most of them following the use of proliferation signal inhibitors [8]. As transbronchial pulmonary biopsies were not contributive in our patient, we cannot confirm the diagnosis. However, clinical set-up, radiological findings, cytology of bronchoalveolar fluid, the absence of improvement of pulmonary symptoms despite effective therapy for CMV infection (eliminating simple CMV pneumonitis) and the dramatic improvement of the patient's pulmonary status after steroid therapy were clearly in favour of this diagnosis. Moreover, the search for a differential diagnosis of interstitial lung injury was twice negative in this case. An open-lung biopsy was not

Table 1. Classification of BOOP

Idiopathic BOOP	
Postinfection BOOP	Chlamydia, legionella and mycoplasma
	Adenovirus, cytomegalovirus, human immunodeficiency virus and influenza virus
	Malaria and pneumocystis
	Cryptococcus
Drug-related BOOP	Antibiotics: amphotericin B, cephalosporins, minocyclines, nitrofurantoin, sulfasalazine, sulfamethoxypyridazine
	Bleomycine, methotrexate
	Rapamycin
	Gold
	Amiodarone
	Cocaine
	Ltryptophan
	Phenytoin
	Carbamazepine
	Ticlopidine hydrochloride
Rheumatologic or connective tissue BOOP	Lupus erythemathosus
	Rheumatoid arthritis
	Sjoegren's syndrome and Sweet syndrome
	Polymyositis-dermatomyositis
	Scleroderma
	Ankylosing spondylitis
	Behçet syndrome
Immunologic disorder BOOP	Common variable immunodeficiency syndrome
	Cryoglobulinaemia
Organ transplantation BOOP	Bone marrow lung and renal
Radiotherapy BOOP	
Environmental exposures	Textile printing dye
	Penicillium mould dust
	House fire
Miscellaneous BOOP	Inflammatory bowel disease
	Lymphoma and cancer
	Myelodysplastic syndrome
	Chronic thyroiditis
	Primary biliary cirrhosis
	Coronary artery bypass

performed due to respiratory distress syndrome and the probable need for mechanic ventilation after biopsy.

Physiopathology of BOOP after solid-organ transplantation remains to be clarified. If the implication of CMV has been suspected in the physiopathology of BOOP after lung transplantation [9], nothing has been published so far for kidney transplantation. We report here, to the best of our knowledge, the first case of BOOP secondary to CMV pneumonitis in a renal transplant recipient.

In our observation, BOOP occurred in the days following CMV infection, and PCR for CMV in the bronchoalveolar fluid was positive. Simultaneity between CMV infection and the occurrence of lung injury in this particular case seems to be in favour of post-viral BOOP disease. Moreover, no other cause of BOOP was found at the time of the investigation.

The dramatic improvement of pulmonary symptoms and chest CT after steroid therapy is consistent with the results previously published. In a recent publication concerning 57 patients with BOOP, Krishnamohan *et al.* found 59% of complete resolution and 30% of partial resolution after steroid therapy [10].

In conclusion, BOOP is a rare entity after renal transplantation and its exact incidence and prevalence is not known. Diagnosis must be prompt because of the need of specific treatment and of its potential severity. However, BOOP may be overlooked by physicians because of unfamiliarity, nonspecific presentation and the need for biopsy to diagnose the condition. Therefore, clinicians should be aware that unexplained and atypical pulmonary manifestations in a renal transplant patient could be due to BOOP.

Conflict of interest statement. None declared.

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