Pulmonary Hemorrhage in Renal Transplant Recipients

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Dear Sir,

Pulmonary hemorrhage (PH) has a variety of etiologies, including Goodpasture's syndrome [1], systemic vasculitis [2], adverse drug reactions [3], pulmonary infarction [4], necrotizing lung infections [5], and recently diffuse alveolar hemorrhage have been described after autologous bone marrow transplantation [6,7]. We report here the first case of fatal PH after renal transplantation.

A 27-year-old woman received a cadaveric renal transplant (RT) in June 1991. She had started hemodialysis in December 1988 due to chronic glomerulonephritis. Her immunosuppressive therapy consisted of cyclosporine A (CyA) and prednisone. On the 8th postoperative day, acute rejection was diagnosed that did not respond to methylprednisolone therapy (MTP; 1 g/day i.v. for 3 days), and treatment with monoclonal anti-CD3 antibody (OKT3) (5 mg/day i.v. for 14 days) was begun. After OKT3 therapy, serum creatinine remained steady at 240 mmol/l (2.7 mg/dl); she was thus discharged on the 37th day after RT. Fifteen days later, she was admitted again because of progressive dyspnea, hemoptysis and cough. On admission, physical examination showed pallor and tachypnea. Temperature was 36.3°C and blood pressure 120/80 mm Hg. On chest examination, diffuse bilateral rales were noted. The rest of the exploration was normal. Admission laboratory results included: serum creatinine 240 mmol/l (2.7 mg/dl), hemoglobin 5.9 g/dl, hematocrit 17%, platelet count $57 \times 10^9/l$ and white blood count $12.3 \times 10^9/l$. Coagulation studies were normal and schistocytes were not seen. Arterial blood gases in room air showed pH 7.36, pO₂ 31 mm Hg, pCO₂ 30 mm Hg. Urinalysis was normal. A chest roentgenogram showed bilateral alveolar infiltrates. Endotracheal intubation was performed and mechanical ventilation started. Cardiac catheterization showed a main pulmonary artery pressure of 30/15 mm Hg with a pulmonary capillary wedge pressure of 6 mm Hg. Bronchoscopic examination did not detect airway bleeding and bronchoalveolar lavage fluid (BAL) was bloody. Empirical antibiotic therapy with ce-fotaxime and trimethoprim-sulfamethoxazole was started. The CyA dosage was adjusted to maintain the same levels, prednisone dosage was increased from 0.5 to 1 mg/kg/day and MPT was begun. The clinical situation improved

moderately during MPT, but worsened again after MPT withdrawal. Immunological serum tests for antinuclear antibodies, antiglomerular basement membrane antibodies, antineutrophil cytoplasmic autoantibodies and cryoglobulins were negative. Complement levels were normal. Stains, serological studies and cultures for bacteria, mycobacteria, fungus, viruses and parasites were negative. A second course of MPT was given and cyclophosphamide (2 mg/kg/day i.v.) was added. The hemorrhage did not respond to immunotherapy and her clinical condition deteriorated. An open lung biopsy revealed diffuse alveolar damage with alveolar hemorrhage without signs of vasculitis. Plasma exchange therapy was started and CyA was withdrawn but her pulmonary condition continued worsening and she died on the 78th day after renal transplantation.

In our case, the main pulmonary artery pressure permits us to rule out pulmonary thromboembolism as a cause of pulmonary hemorrhage. The results of the BAL analysis for multiple infectious agents as well as the serological studies, were negative and inclusion bodies due to cytomegalovirus infection were not seen on the lung biopsy. These findings did not support an infectious origin of the hemorrhage in our case. Vasculitis is uncommon in renal transplant recipients who receive immunotherapy, and generally it occurs in patients with a recurrent vasculitic process or an infection [8]. In our case, the absence of immunological tests and clinical findings suggestive of vasculitis as well as the histological features do not support the diagnosis of systemic vasculitis or Goodpasture's syndrome. On the other hand, our patient did not receive any drug associated with pulmonary hemorrhage [3]. Although CyA can induce endothelial damage and hemolytic uremic syndrome after renal transplantation [9], no case of pulmonary hemorrhage associated with CyA has been reported. This fact together with the poor response to plasma exchange therapy and the lack of response after the withdrawal of CyA do not suggest a pathogenic role for CyA. Fibrinoid necrosis of the temporal artery has been reported in a heart transplant recipient who received OKT3 therapy [10]. In our patient this situation seems very improbable because the time of pulmonary hemorrhage and OKT3 treatment did not coincide. Diffuse alveolar hemorrhage, for which no specific etiology was found, has been reported after autologous bone marrow transplantation [6,7] but, unlike the cases reported by Chao et al. [11], our patient did not respond to early and intensive steroid therapy. In summary, pulmonary hemorrhage is an exceptional and fatal complication of renal transplantation and should be considered in the differential diagnosis of pulmonary disease in these patients.