Case Report

A severe *Mycoplasma pneumoniae* pneumonia inducing an acute antibody-mediated pulmonary graft rejection

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ABSTRACT

A 40-year-old cystic fibrosis woman with a history of double-lung transplantation 2 years previously was admitted for a progressive respiratory distress. Physical examination revealed fever (39°C) and diffuse bilateral lung crackles. Laboratory findings included severe hypoxemia and inflammatory syndrome. Bronchoalveolar lavage and serological test were positive for mycoplasma pneumonia. As the patient did not improve after 3 days of antibiotics and donor-specific HLA antibodies had been detected, an acute antibody-mediated graft rejection was treated with high-dose corticosteroids, plasma exchange, intravenous immunoglobulin, and rituximab. The patient rapidly improved. Unfortunately, 6 months after this episode, she developed a bronchiolitis obliterans syndrome with a dependence to noninvasive ventilator leading to the indication of retransplantation. This case illustrates the possible relationship between infection and humoral rejection. These two diagnoses should be promptly investigated and systematically treated in lung transplant recipients.

KEY WORDS: Antibody mediated, graft rejection, *Mycoplasma pneumoniae*, pneumonia

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INTRODUCTION

The role of infections in the graft rejection remains unclear. The lung transplant, in contrast with other transplanted organs, can often be infected, notably by respiratory infectious agents. The present case illustrate the potential role of such respiratory infection in organ rejection.

CASE REPORT

A 40-year-old Caucasian woman with a lifelong history of cystic fibrosis was admitted for a progressive respiratory distress upon return by plane from Turkey. The patient had noted over the previous 4 days a progressive onset of fever, dry cough, and dyspnea. She had undergone double-lung transplantation 2 years previously. Sequential bilateral lung transplantation had been performed after the placement of an extracorporeal membrane oxygenation and included immunosuppressive induction with basiliximab. Two months previously, the patient was in good general health including normal pulmonary function test. Because of persistent abdominal pain and diarrhea, trimethoprim-sulfamethoxazole prophylaxis had been stopped and immunosuppressive therapy by mycophenolate mofetil (2 g every day) and tacrolimus (3 mg every day) switched to azathioprine (100 mg every day) and cyclosporin (175 mg bid), associated with corticosteroids at 5 mg every day. Subsequently, digestive symptoms resolved following this medication change.

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Physical examination revealed fever (39°C), diffuse bilateral lung crackles, and no extrapulmonary signs. Arterial oxygen pressure was 51 mmHg. There was an inflammatory biological syndrome with elevated leukocyte count (17 G/L, normal <10 G/L), C-reactive protein (266 mg/L, normal <5 mg/L), and no kidney insufficiency. Hepatic test revealed mild cytolysis with elevated serum glutamo oxaloacetate transferase (83 U/L, normal <34 U/L), normal serum glutamate pyruvate transaminase, and no cholestasis. Cyclosporin residual level was in therapeutic range (133 μg/L). There was no cardiac dysfunction on echocardiography. Chest radiography and computed tomography revealed bilateral pneumonia [Figure 1a] and ruled out pulmonary embolism. After blood culture and bronchoscopy with bronchoalveolar lavage (BAL), empirical antibiotics were started with trimethoprim-sulfamethoxazole, piperacillin-tazobactam, amikacin, and erythromycin. As the acute respiratory failure was worsening, the patient was transferred to the intensive care unit the same day. However, mechanical ventilation was not necessary and high-flow (fraction of inspired oxygen between 50 and 60%) oxygenation was performed with inspired air humidification system (Optiflow®). Mycoplasma pneumonia was detected by polymerase chain reaction (PCR) in BAL samples. No other infectious agent was detected, in particular no *Pneumocystis jirovecii*. After 3 days of antibiotics, as the patient did not improve, i.e., persistent severe hypoxemia, fever, biological inflammatory syndrome, and radiographic diffuse lung opacities; the diagnosis of acute graft antibody-mediated rejection (AMR) was suggested based on the detection of specific HLA antibodies (DSA) anti-DQ4 and anti-DQA1*03 detection (Luminex Technic, kit LSA Class II Immunocor). Because of the severity of the respiratory insufficiency, transbronchial lung biopsies were not performed. Treatment was started associating (i) three boluses of prednisolone (500 mg every day) followed by 1 mg/kg oral prednisone, (ii) seven plasma exchanges, (iii) seven intravenous infusions of polyvalent immunoglobulin after each plasma exchange (0.1 g/kg, except the last at 1 g/kg), and (iv) one rituximab injection (375 mg/m^2) on day 14. Azathioprine was switched for mycophenolate mofetil given its additional anti-B-cell properties. DSA were controlled negative and arterial oxygen pressure improved, oxygen therapy was stopped. Mycoplasma pneumonia serology, initially negative (IgG = 2.5 UI/mL, IgM <8.5 UI/mL), was positive on day 14 (IgG 15.8 UI/mL, IgM <8.5 UI/mL). At day 20 and month 3, computed tomography was still improving [Figure 1b and c]. Unfortunately 6 months after the episode, she developed a bronchiolitis obliterans syndrome (BOS) with a dependence to noninvasive ventilator. Retransplantation was decided and 1 year later, she is still on the waiting list with a grades three BOS.

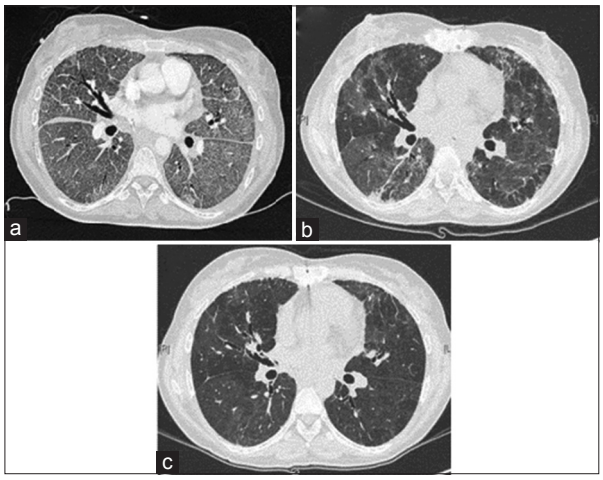

Figure 1: Computed tomography showing at day 1 (a) diffuse bilateral ground glass opacities with thickened septal lines, improved at day 20 (b) and month 3 (c) after antibiotics, corticosteroids, plasmapheresis, intravenous immunoglobulin, and rituximab

DISCUSSION

We report a case of severe *Mycoplasma pneumoniae* pneumonia, inducing an acute pulmonary AMR with favorable outcome following antibiotics and early aggressive immunosuppressive therapy.

The clinical presentation without trimethoprim-sulfamethoxazole prophylaxis in such immunocompromised host was initially suggestive of *Pneumocystis jirovecii* pneumonia, but this diagnosis was ruled out by negative BAL including specific PCR. As the detection of *M. pneumoniae* in respiratory tract could just reflect a colonization,[1] beta-lactam antibiotics were continued until the confirmation of the diagnosis. Here, the diagnosis of *M. pneumoniae* pneumonia can be assessed by a 4-fold increase in IgG antibodies titers in serum and detection of bacteria in the lower respiratory tracts by PCR[2] despite the lack of positive culture.[3] However, despite the administration of a macrolide antibiotic, the respiratory insufficiency, and the inflammatory syndrome did not improve after 3 days. Thus, in the context of recent modification of immunosuppression regimen and detection of DSA, possible AMR[4] was considered although diagnosed lately after transplantation.[5] Indeed, in lung transplantation, the process of allorecognition is likely to be augmented by local innate immune activation through endogenous tissue injury and exogenous infection.[5] Cases of acute rejection after infectious pneumonia had already been observed.[6] Thus, the interaction between infectious pathogens and acute AMR should be further studied. In particular, this is currently increasing evidence for relationship between BOS and *Pseudomonas* or *Aspergillus* infection and/or colonization.[7,8]

The development of DSA has been linked to an increased risk of acute rejection and BOS.[9,10] Experimental studies suggest that HLA antibodies have a pathogenic role and are not merely an epiphenomenon of humoral immunity.[11] Thus, one can speculate that early antibody depletion may favorably influence clinical outcome as suggested by the current case report. The patients who developed DSA and received antibody-directed therapy had a similar incidence of acute rejection and BOS as those who did not develop DSA;

moreover, patients with successful depletion of DSA had greater freedom from BOS and better survival than those who had persistent DSA.[12] However, clinical evolution of AMR is sometimes severe as reported in a retrospective study where plasmapheresis, rituximab, and intravenous immunoglobulin were only administered for patients with declining allograft function.[13] Whatever, a single episode of acute rejection, as well as increased frequency and severity of acute rejection, increases the risk for BOS.[14]

This case emphasizes the interest to detect donor-specific antibodies in atypical or severe respiratory disorder in lung transplant recipients. Specific immunosuppressive therapy should be promptly started and is likely to decrease the risk of BOS. However, concomitant infections should always be investigated using a large panel test because the clinical presentation could be severe and atypical in such immunocompromised patients.

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Conflicts of interest

There are no conflicts of interest.

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