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Brief communication

Antibody-mediated rejection in a lung transplant recipient after acute stroke☆,☆☆,★,★★

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ABSTRACT

Antibody-mediated rejection (AMR) is becoming a more recognized problem in lung transplantation. We present a case of late onset AMR in a lung transplant recipient after an acute embolic stroke requiring thrombolytic therapy, who previously had a completely unremarkable course for over 3 years.

1. Introduction

Antibody-mediated rejection (AMR), or also termed humoral rejection, was recognized early in the history of organ transplantation as hyperacute rejection caused by the presence of preformed antibodies to blood group ABO or human leukocyte antigen (HLA) antigens. Hyperacute rejection, which is the more severe form of AMR, occurs when pre-existing donor-specific antibodies (DSAs) immediately lead to complement activation and rapid loss of the allograft shortly after the transplant. The use of ABO compatible donors and the development of pre-transplant crossmatch techniques have significantly reduced the incidence of hyperacute rejection. Efforts [1–3] focused on improving crossmatching between the donor and recipient with the development of the panel-reactive antibody (PRA) to identify DSAs have dramatically improved outcomes, including significant reduction in the incidence of hyperacute rejection in all organ transplants [4–12]. Moreover, studies have identified a definite correlation between DSAs and complement deposition on the allograft with C3d and C4d staining in patients with AMR [13–15].

Although virtual crossmatches are performed with intentions to avoid unacceptable antigens, patients with positive pre-transplant PRAs are at higher risk for post-transplant complications [16]. Moreover, patients with negative PRAs prior to transplant can develop DSAs or *de novo* non-DSAs after transplant while patients with PRAs before transplant, can remain stable after transplant or increase via generation of either DSAs or non-DSAs [16]. We present an interesting case of AMR diagnosed 3 years after lung transplant in a patient who suddenly experienced a significant increase in DSAs in the presence of allograft dysfunction and C3d

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and C4d deposition on immunohistochemical staining of allograft tissue after an embolic stroke treated with tissue plasminogen activator (t-PA).

2. Case report

19-year-old female who underwent bilateral sequential lung transplant 3.25 years earlier for advanced bronchiectasis due to cystic fibrosis was diagnosed with an ischemic infarct of the right cerebral hemisphere and basal ganglion in the distribution of the right middle cerebral artery. While at home, she suddenly developed expressive aphasia and left-sided weakness of the face, arm, and leg. Upon presentation to a local emergency department 45 min later, she was treated with t-PA. Her only risk factor for stroke was mild hypertension that was diagnosed after lung transplant and was well-controlled on single drug therapy with lisinopril 5 mg daily. With no identifiable risk factors and the reported risk of stroke with tacrolimus, we speculated that the stroke was related to her medical regimen and her immunosuppressant regimen was changed from tacrolimus 1 mg twice daily to sirolimus 1 mg daily with continuation of mycophenolate 750 mg twice daily and prednisone 5 mg daily.

Forty-eight hours after treatment of the acute stroke, PRAs demonstrated an acute elevation of Alloscreen Class 2 at 82% while Class 1 was 0%. Our transplant program routinely monitors annual PRAs, so her most recent levels were 0% for both Classes 1 and 2 two months earlier. Due to the stroke and the thrombolytic therapy, allograft function assessment by spirometry and tissue biopsy was delayed. Regarding her immunosuppressant therapy over the past three years, she had done well with stable tacrolimus trough levels between 9.0 and 11.8 ng/mL (reference range 5–20 ng/mL). With the change to sirolimus, trough levels were monitored and ranged from 8.7 to 11.4 ng/mL (reference range 4–12 ng/mL).

She was subsequently hospitalized for 1 week due to the stroke and then transferred to a rehabilitation facility for 2 weeks for inpatient physical therapy. The day after discharge from the rehabilitation facility, she was evaluated in the lung transplant clinic with her having no respiratory symptoms and no changes on physical examination other than residual left-sided facial, arm, and leg weakness. Her pulmonary function on spirometry was at normal post-transplant baseline measurements, forced vital capacity (FVC) 3.03 L (90% predicted) and forced expiratory volume in 1 s (FEV_1) 2.48 L (83% predicted). Chest radiograph was clear with post-surgical findings that were unchanged from previous radiographs.

Two weeks later, she had sudden development of non-productive cough and subtle dyspnea during exertion, so she was evaluated with the physical examination being unchanged with normal vital signs. Spirometry was dramatically reduced with an FVC of 1.92 L (58% predicted) and an FEV_1 of 1.71 L (58% predicted). Chest radiograph was once again clear. To assess for acute allograft rejection, a bronchoscopy with transbronchial biopsies was immediately performed. The anastomoses were intact with the left side being slightly stenotic and the lower airway mucosa being mildly inflamed bilaterally. Bronchoalveolar lavage fluid and tissue cultures were negative for bacteria, fungi, virus, and acid-fast bacteria. Histologic analysis of the allograft tissue showed no cellular rejection but found significant deposition of both C3d and C4d on immunohistochemical staining (Figs. 1 and 2) with this being a new finding with no previous C3d or C4d on previous biopsies. Due to these acute changes, PRAs were obtained and demonstrated an elevation at 84% for Alloscreen Class 2 while Class 1 was 0% with the DSAs DQ2 and DQ7 being 16,996 and 18,298 mean fluorescence intensity (MFI), respectively. An aggressive treatment regimen was immediately started with pulse intravenous (IV) corticosteroids (10 mg/kg) days 1–3, plasmapheresis for 5 days, IV bortezomib (1.3 mg/M^2) on days 1, 4, and 8 after completion of plasmapheresis, and IV rituximab (375 mg/M^2) weekly on weeks 1–4. One month into the treatment course, the Alloscreen Class 2 decreased to 63% but returned to 84% after the treatment course was completed. Additionally, peripheral blood immunophenotyping demonstrated reduced B cells at 0.1% and plasma cells at 0% as determined by CD19 and CD38/CD138, respectively. Weekly IV IgG replacement (2 mg/kg) for 4 weeks was given after the last dose of bortezomib. Despite the immediate reduction in both B cells and plasma cells, there was no impact upon DSAs. Repeat transbronchial biopsy demonstrated complete resolution of C3d and C4d deposition by immunohistochemical staining 2 months after presenting with the acute reduction in her pulmonary function. However, her clinical course continued to decline over the next 2 months despite further therapy with IV rituximab, IV IgG, and plasmapheresis as well as treatment with a dose of IV alemtuzumab 30 mg.

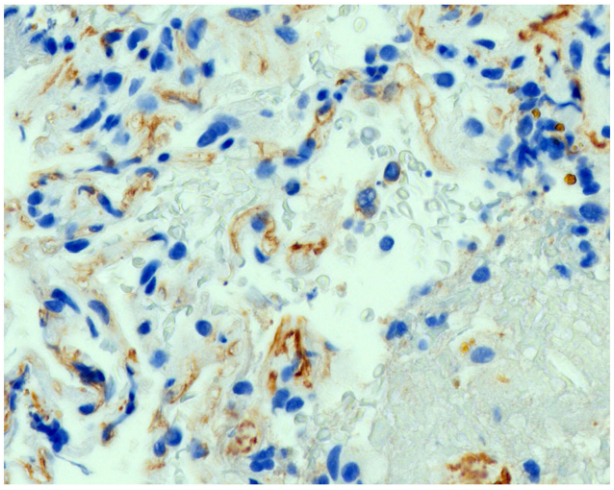

Fig. 1. Immunohistochemical staining of lung tissue demonstrating significant C3d deposition (400× magnification).

The HLA type of the donor for Class 1 was A1, A3, B7, B8, Bw6 positive and Class 2 was DR17, DR11, DR52 positive, DQ2, and DQ7 while the recipient HLA type for Class 1 was A2, A3, B35, C4, Bw6 positive and Class 2 was DR1, DR13, DQ5, DQ6, and DR52 positive. While awaiting transplant, the recipient had an elevation of Alloscreen Class 2 at 2% on a single occasion 2 months before transplant while corresponding DSAs had peak levels of 1672 and 349 MFI for DQ2 and DQ7, respectively. There was no elevation in PRAs on annual evaluations after transplant. At the time of the original diagnosis of AMR, there were no changes in her menstrual period with her not being sexually active and thus a spontaneous abortion was unlikely while laboratory evaluation also included both urine pregnancy test and serum human chorionic gonadotropin that confirmed no evidence of pregnancy. Due to abstinence, she was not on any form of contraception, and she does not use tobacco products. Furthermore, she

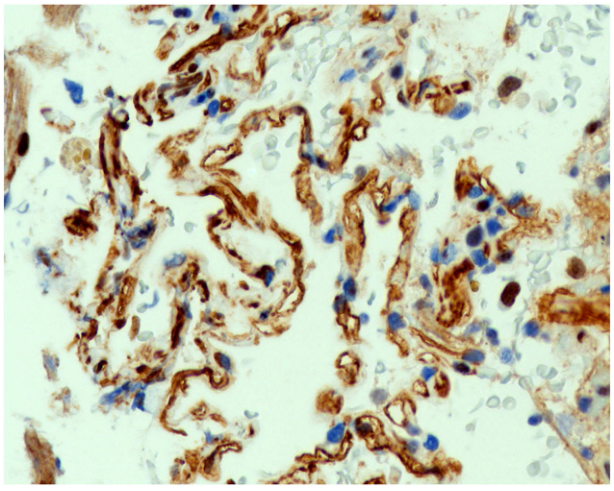

Fig. 2. Immunohistochemical staining of lung tissue demonstrating significant C4d deposition (400× magnification).