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Case Report

Immediate and Catastrophic Antibody-Mediated Rejection in a Lung Transplant Recipient With Anti–Angiotensin II Receptor Type 1 and Anti–Endothelin-1 Receptor Type A Antibodies

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Preexisting donor-specific anti-HLA antibodies (DSAs) have been associated with reduced survival of lung allografts. However, antibodies with specificities other than HLA may have a detrimental role on the lung transplant outcome. A young man with cystic fibrosis underwent lung transplantation with organs from a suitable deceased donor. At the time of transplantation, there were no anti-HLA DSAs. During surgery, the patient developed a severe and intractable pulmonary hypertension associated with right ventriular dysfunction, which required arteriovenous extracorporeal membrane oxygenation. After a brief period of clinical improvement, a rapid deterioration in hemodynamics led to the patient's death on postoperative day 5. Postmortem studies showed that lung specimens taken at the end of surgery were compatible with antibody-mediated rejection (AMR), while terminal samples evidenced diffuse capillaritis, blood extravasation, edema, and microthrombi, with foci of acute cellular rejection (A3). Immunological investigations demonstrated the presence of preexisting antibodies against the endothelin-1 receptor type A (ET_AR) and the angiotensin II receptor type 1 (AT_1R), two of the most potent vasoconstrictors reported to date, whose levels slightly rose after transplantation. These data suggest that preexisting anti-ET_AR and anti-AT_1R antibodies may have contributed to the onset of AMR and to the catastrophic clinical course of this patient.

Abbreviations: AMR, antibody-mediated rejection; AT_1R, angiotensin II receptor type 1; CF, cystic fibrosis; CO, cardiac output; CT, computed tomography; DSA, donor-specific antibody; ECMO, extracorporeal membrane oxygenator; ET_AR, endothelin-1 receptor type A; ICU, intensive care unit; NO, nitric oxide; PAH, pulmonary artery hypertension; PAP, pulmonary artery pressure; RV, right ventricle, right ventricular

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Introduction

Antibody-mediated rejection (AMR) represents a serious obstacle to long-term graft survival (1). AMR has been reported after the transplantation of any type of organ, although the majority of data available to date have been primarily generated in the field of kidney transplantation (2). AMR may occur early or late after transplantation, and its occurrence appears to be invariably associated with premature failure of renal, heart, lung, and even liver transplants (3–6).

AMR has been historically associated with the presence of anti-HLA antibodies, and many efforts have been made by transplant professionals in the past decade to gain better insight into this immunological event that harms the graft. First, technological advancements have enabled the development of new tests that are able to accurately detect the presence of anti-HLA antibodies with a level of sensitivity that is much higher than that of the conventional complement-dependent cytotoxicity assays (7). Second, transplant pathologists have defined organ-specific criteria to diagnose AMR and detect it in a timely manner and with a certain degree of confidence (4,8,9). Third, clinicians have come to appreciate that AMR predicts poor long-term graft survival independent of whether AMR is clinically evident or subclinical (3,10).

Recently, investigators have also reported that antibodies with specificities others than HLA may also cause AMR.

These non-HLA specificities include endothelin type A receptor (ET_AR), angiotensin II type 1 receptor (AT_1R), vimentin, MHC class I chain-related gene A (MICA), and many others (11). With regard to anti-AT_1R antibodies, it has been previously demonstrated that in renal transplant recipients with no anti-HLA antibodies, such antibodies may contribute to the onset of refractory AMR episodes associated with malignant hypertension (12). Further, preexisting anti-AT_1R antibodies are observed in up to 47% patients waiting for a renal transplant, and their presence has been associated with an increased risk of early acute rejection episodes and with graft failure from the third year after transplantation on (13). Anti-AT_1R antibodies have also been detected in cardiac transplant recipients, in whom their presence has been correlated with that of anti-ET_AR antibodies and with increased risk of AMR (14). As far as lung transplantation, the presence of anti-AT_1R and anti-ET_AR antibodies has been observed in graft recipients both pretransplantation and postransplantation, especially in patients affected by cystic fibrosis (CF) or chronic obstructive pulmonary disease (15). However, to date, anti-AT_1R and anti-ET_AR antibodies have not been associated with any ill effect after lung transplantation.

Here, we report the first case of lung transplantation where the presence of preexisting anti-AT_1R and ET_AR antibodies was associated with an immediate and catastrophic clinical course, with immediate intraoperative pulmonary artery hypertension (PAH) and patient death occurring within the first week after lung transplantation.

Case Report

Recipient characteristics

A 34-year-old man with end-stage CF (ΔF508 mutation) was listed for lung transplantation in July 2013. The most important patient characteristics are listed in Table 1. He presented with chronic colonization by multidrug-resistant *Pseudomonas aeruginosa* (three strains), with an incidental finding of atypical mycobacteria and previous history of allergic bronchopulmonary aspergillosis. In 2007 and 2014, he underwent bronchial embolization for episodes of hemoptysis with no need for blood transfusion. The patient also had type 1 diabetes, chronic prostatitis, and osteoporosis. At the time of transplantation, the patient was in good clinical condition with satisfactory muscle mass and no need for oxygen supplementation.

Donor characteristics and lung retrieval

In June 2015, a 21-year-old man who was declared to be brain dead after a road traffic accident, was offered as a donor. His main characteristics are reported in Table 1. His medical records revealed a previous neurosurgical intervention for removal of a brain astrocytoma with full recovery and no other relevant diseases. The thoracic computed tomography (CT) scan performed the day before graft harvesting showed the presence of bilateral parenchymal opacities in the lower lobes suggestive of pulmonary contusions. Surgical exploration confirmed the presence of minor, clinically irrelevant contusive areas exclusively confined to the apical segment of the lower lobes with no signs of edema in the rest of the lung parenchyma and a satisfactory lung collapse test. The organ retrieval took place according to standard procedure with harvesting of the double-lung block that was subsequently soaked in cold ice storage for preservation.

Table 1: Main recipient and donor characteristics

Recipient	
Age (years)	34
Sex	Male
Blood type	A Rh+
HLA	A*11, 24; B*18, 39; DRB1*16; DQB1*05
Height	168 cm
Weight	52 kg
CMV status	Negative
LAS score	32.1
Final LAS score	31.1
Pulmonary function	
FEV_1 (%)	1.54 L/s (42)
FVC (%)	4.08 L (95)
FEF 25–75%	0.39 (9)
Perfusion scan	
Right lung	58.8%
Left lung	41.2%
PAP	
At the inscription in list	17 mmHg (mean)
At the induction	21 mmHg (mean)
At the left pulmonary artery clamping	30 mmHg (systolic)
At the right pulmonary artery clamping	75 mmHg (systolic)
Donor	
Age (years)	21
Sex	Male
Blood type	A Rh+
HLA typing	A*2; B*37, 51; DRB1*7, 11; DQB1*3, 2
Cause of death	Head injury
CMV status	Negative
ICU stay	3 days
Ventilation time	67 h
Bronchoscopy	Unremarkable
CT scan	Positive
Pao_2/Fio_2 ratio at the call	398 mmHg
Final Pao_2/Fio_2 ratio	489 mmHg
Oto score (28)	3

CMV, cytomegalovirus; CT, computed tomography; $FEF_{25–75\%}$, average forced expiratory flow during the mid [25–75%] portion of the FVC; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; ICU, intensive care unit; LAS, lung allocation score; PAP, pulmonary artery pressure.

Lung transplantation

On confirmation of the donor suitability, the recipient was put under light sedation, and an epidural catheter was positioned at the T5-6 intervertebral space. Anesthesia induction was uneventful, with no hemodynamic impairment. Cardiac output (CO) and mean pulmonary artery pressure (PAP) were 3.3 L/min/m^2 and 21 mmHg, respectively. After a double anterior thoracotomy access with sternal sparing, left pneumonectomy was performed first according to perfusion scan. Soon after left pulmonary artery clamping, the systolic PAP reached 30 mmHg and there was no need for hemodynamic support. Bronchial, arterial, and venous anastomoses were completed with no apparent difficulties. However, on left graft reperfusion, the sudden occurrence of severe hypotension and reduced CO required the infusion of inotropic and vasoactive support (dobutamine [5 μg/kg/min]–epinephrine [0.5 μg/kg/min] and norephinephrine [0.2 μg/kg/min]). Hemodynamics transiently improved, and the right

pneumonectomy was started. Soon after clamping of the right pulmonary artery, the systolic PAP increased abruptly (to ~75 mmHg) with sudden and severe right ventricular dysfunction, which was not amenable to reversal with increased infusion of amines and NO inhalation (40 ppm). In the presence of imminent severe deterioration of the patient's conditions, femorofemoral venoarterial extracorporeal membrane oxygenation (ECMO) was instituted to complete the sequential double-lung implantation. The cold ischemia time was 265 and 530 min for the left and the right lung, respectively. At the end of the surgical procedure, a small for cause lung biopsy (~2 cm^2) was performed on the left implanted lung. An attempt to wean the patient from ECMO support turned out to be ineffective, and the patient was admitted to the intensive care unit (ICU) with nearly 50% of cardiocirculatory extracorporeal assistance.

Detection of anti-HLA, anti-AT_1R, and anti-ET_AR antibodies

Specific information regarding the methodology used to determine anti-HLA, anti-AT_1R, and anti-ET_AR antibodies is provided in Data S1.

Results

Clinical course

Neither gas exchange abnormalities nor reperfusion edema was recorded in the immediate postoperative period. On the first postoperative day, under ECMO assistance, cardioactive drug administration was progressively reduced and inhaled NO, oral sildenafil, and intravenous levosimendan infusion were started to reduce the PAP. Given the improvement of both chest radiograph and hemodynamic status, a slow weaning from ECMO was initiated, and within a few hours, the ECMO was completely discontinued. Transesophageal echocardiography performed during the weaning from ECMO assistance did not show signs of right ventricular (RV) or biventricular heart failure, and systolic PAP was 30 mmHg. However, in the first few hours after ECMO discontinuation (on postoperative day 2), a recurrence of pulmonary hypertension (mean PAP of ~35–45 mmHg), associated with an increase in pulmonary vascular resistance, and RV dilatation were observed. CO and gas exchanges were not significantly affected initially but were so after a few hours. Primary graft dysfunction scores at 0, 24, 48, and 72 h were 3, 0, 0, and 0, respectively (16). On postoperative day 4, the lung CT scan was unremarkable (Figure 1). However, during the following hours, development of a severe and rapid-onset shock along with the persistence of a severe pulmonary hypertension, RV dilatation, and consequent biventricular failure was responsible for systemic hypotension, oliguria, and distant organ hypoperfusion. PAH combined with progressive impairment of the RV was unquestionably the primary cause of the unresponsive hemodynamic picture in our patient. Coexistence of sepsis, however, could not be definitely ruled out. Indeed, while blood cultures were persistently negative and infectious laboratory markers remained scarcely indicative, *P. aeruginosa* and *Staphylococcus aureus* were eventually isolated although only in the bronchoalveolar lavage. With regard to hemodynamics, the most relevant parameters recorded can be found in Data S1. Refractory vasoplegia and the impending onset of multiorgan failure precluded the reinstitution of ECMO. The patient died on postoperative day 5 due to irreversible multiorgan failure.

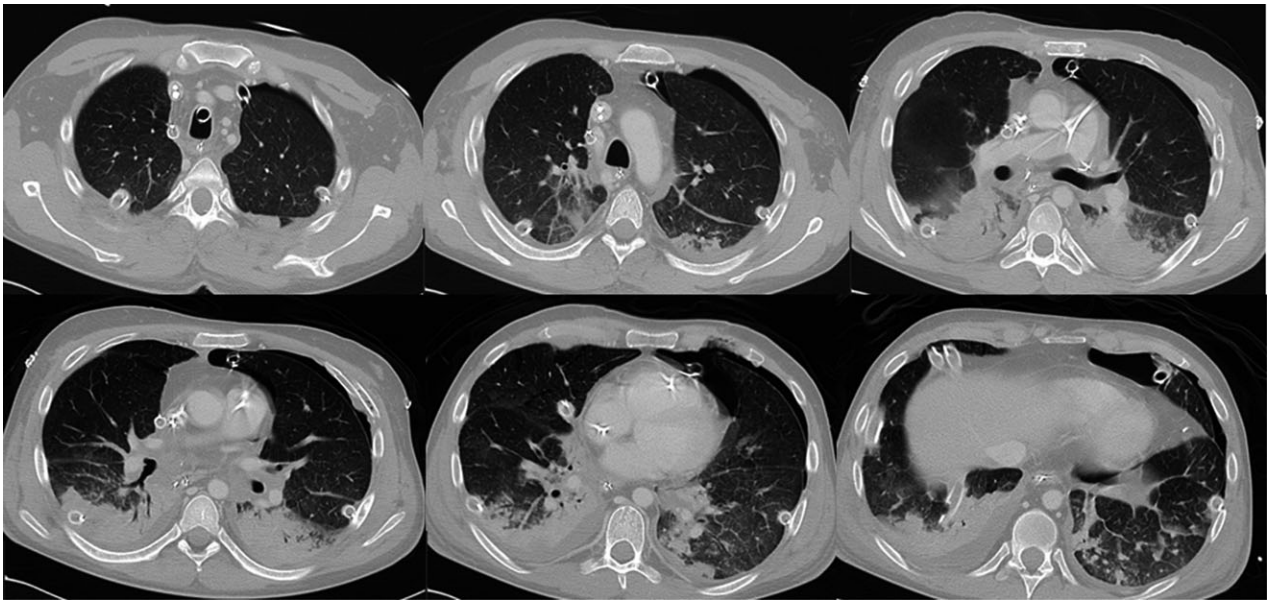

Figure 1: Recipient chest computed tomography scan performed on postoperative day 4 showed the absence of intraluminal filling defects in the pulmonary artery with presence of pleural effusion flap bilaterally, also with intrafissural component associated with atelectasis of the adjacent lung parenchyma. Areas of parenchymal consolidation with aspect of ground-glass and air bronchogram are evident in both lower lobes.

Immunological evaluation and immunosuppression

The patient had no history of prior transfusion or transplantation. The donor had seven HLA mismatches with the recipient (Table 1), but neither class I nor class II HLA DSAs were detected at the time of transplantation, when the recipient only had anti–B-locus non-DSAs (mean fluorescence intensity, <2200). T cell CDC crossmatch was negative, and the immunosuppressive regimen consisted of cyclosporine A, mycophenolate mofetil, and steroids with no induction therapy. No elicited anti-HLA class I or class II antibodies were detected in the serum on postoperative day 4.

In contrast, anti-AT_1R and anti-ET_AR antibodies measured in the only two serum samples available revealed the presence of both antibodies before transplantation. These increased on postoperative day 4 from 12.8 to 15.2 units/mL and from 15 to 18.4 units/mL for anti-AT_1R and anti-ET_AR antibodies, respectively (Figure 2).

Histopathological studies

The biopsy performed 180 min after reperfusion showed blood congestion with significant leukocyte margination and transmigration (Figure 3A). Immunohistochemistry was negative for C4d but diffusely positive for both phosphorylated S6K (p-S6K) and S6RP (p-S6RP) on capillary endothelial cells. In particular, capillaries were strongly positive for p-S6K (Figure 3B). In this regard, it is noteworthy that both p-S6K and p-S6RP have recently been reported as independent diagnostic markers of cardiac AMR, even in C4d-negative biopsy specimens and in the absence of HLA DSAs (17). Positivity for macrophages was not considered.

At autopsy, there was an increased weight of both lungs (2700 g) with a dark-red color and firm consistency (Figure 3C). The cut surface showed patchy and poorly defined areas of hemorrhagic consolidation. All anastomosis sites were intact and widely patent. At histological examination, lung samples showed diffuse capillaritis associated with blood extravasation, edema, and microthrombi (Figures 3D and E). Other areas showed foci of acute cellular rejection (A3) (Figure 3F). The peribronchial regions were substantially free of inflammation (B0). There were no signs of bronchopneumonia even after special staining for microorganisms. No specific findings were observed in the other organs. Immunohistochemistry examinations for C4d, p-S6K, and p-S6RP performed at postmortem were found to be unreliable due to diffuse red blood cell extravasation and hemosiderin deposits.

Discussion

AMR after lung transplantation has been reported as a potentially life-threatening immunological complication occurring soon after transplantation whose prompt identification is of critical importance to timely initiate an adequate clinical approach (18). In this context, however, the most appropriate treatment option has yet to be defined. Indeed, current therapeutic strategies are associated with varying results and, in many cases, poor long-term outcomes. In particular, in the first year after the onset of lung AMR, patients undergo premature chronic allograft dysfunction or untimely death in 70% and 30% of cases, respectively.

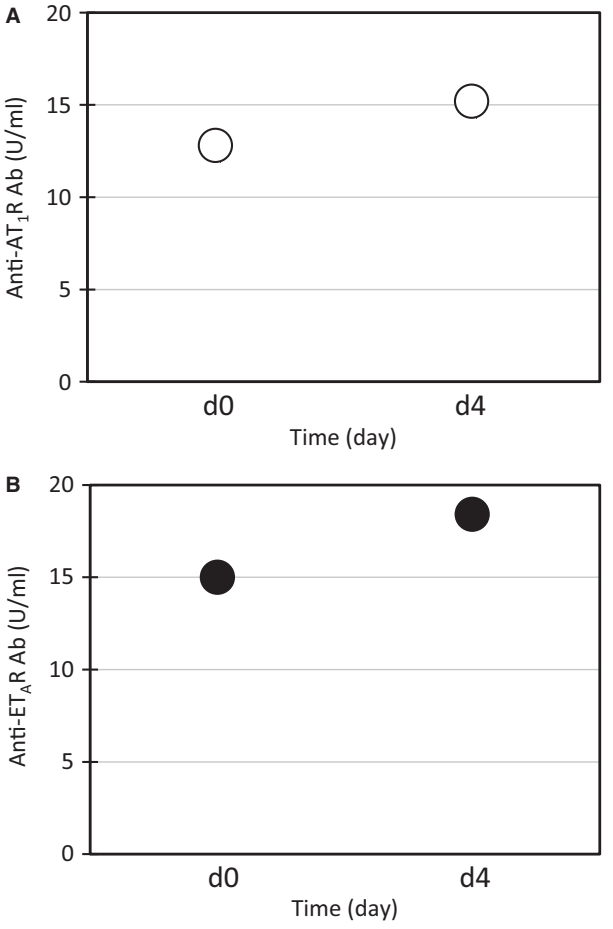

Figure 2: Levels of anti–angiotensin II receptor type 1 (AT_1R; A) and anti–endothelin-1 receptor type A (ET_AR; B) antibodies determined retrospectively in the serum samples collected before transplantation and on postoperative day 4. The cut-off of 10 U/mL was adopted to define a positive detection for both anti-AT_1R and anti-ET_AR antibodies (13,29).

To date, anti-HLA DSAs are the only antibodies that have been associated with lung AMRs, although antibodies with other specificities have been reported in the case of AMR in other organs (11,12,14,19).

In this patient, the histological findings were highly suggestive of AMR. However, C4d staining turned out to be negative. In the search for an additional element to comfort us in our suspicion of AMR, we reasoned that, as

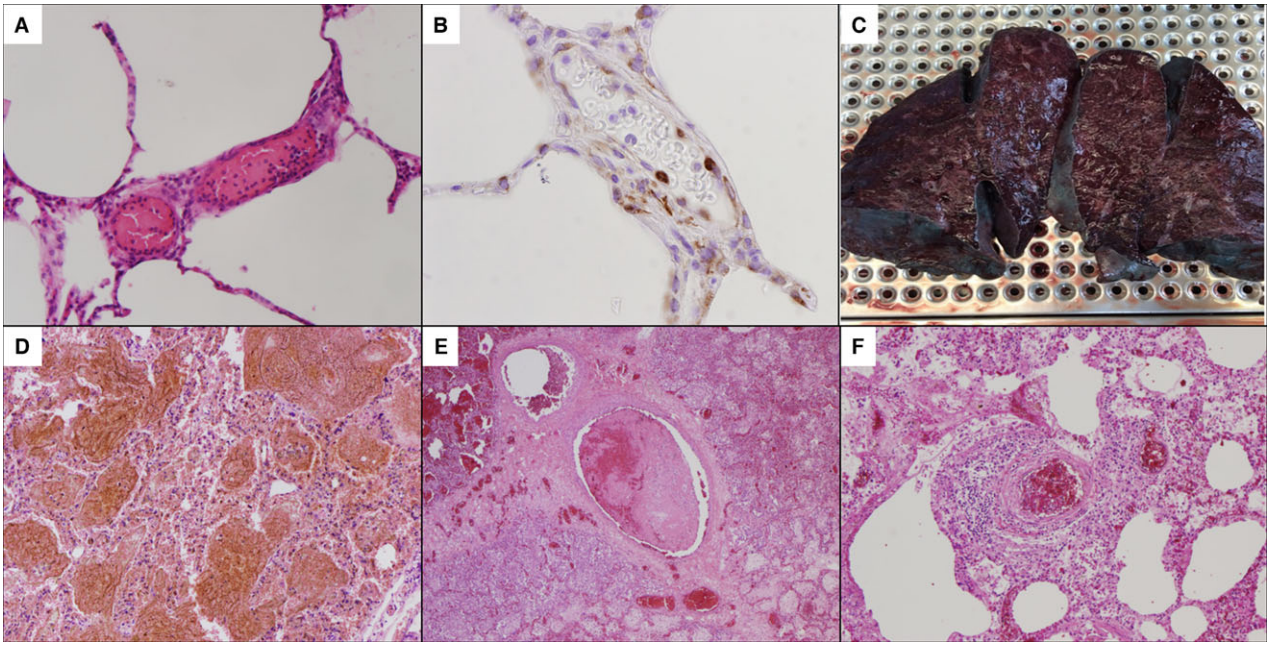

Figure 3: Histology and immunohistochemistry examination of the lung. The biopsy performed 180 min after reperfusion shows blood congestion with significant leukocyte margination and transmigration (A), associated with a strong cytoplasmic endothelial cell staining for p-S6K (B). Postmortem findings are also shown: gross appearance of both lungs (C); histology at that time showing capillaritis with diffuse blood extravasation (D) and thrombosis inside a small artery (E); and lymphomonocyte infiltration around a small artery compatible with acute cellular rejection (A3) (F).

for cardiac transplantation, p-S6K and p-S6RP could indeed represent a valid supplementary tool to corroborate our hypothesis (18). In this regard, while phosphorylation of S6K and S6RP has been associated with HLA class I antigen ligation by antibodies and ultimately activation of the mammalian target of rapamycin complex 1 pathway (20), there is convincing evidence suggesting that additional and yet-unidentified S6K and S6RP phosphorylation pathways must exist. Such a statement is supported by the evidence that HLA DSAs could not be detected in at least 36% of patients with cardiac AMR with p-S6K expression in capillary endothelial cells (17).

In this light, we believe that diffuse expression of both p-S6K and p-S6RP in this patient's biopsy specimen should be regarded as a confirmatory marker of AMR in the transplanted lung. Further, our findings provide additional data in support of the usefulness of p-S6K and p-S6RP staining in cases of equivocal of AMR.

In the absence of anti-HLA antibodies, we hypothesized that preexisting antibodies with specificities other than HLA, possibly provided with some vasoconstrictive activity, may have concurred to the dramatic clinical course.

We were intrigued by several recent observations. In particular, in several autoimmune disorders, such as systemic sclerosis and systemic lupus erythematosus, the presence of PAH has been associated with the existence of autoantibodies directed against ET_AR (and against AT_1R in the case of systemic sclerosis) (21). In addition, endothelin-1 and angiotensin II are two of the most potent vasoconstrictors with a synergistic effect on the development of blood hypertension (22). Further, autoantibodies directed against ET_AR and against AT_1R are elevated in patients with end-stage CF (15), the ultimate cause of the lung disease in our patient.

These observations encouraged us to extend our immunological investigations to evaluate the presence of such autoantibodies in the sera of our patient. Interestingly, the analyses undertaken revealed that the patient had moderately high levels of autoantibodies against ET_AR and against AT_1R before transplantation and that the circulating levels of such antibodies were slightly increased on day 4. In addition, it is highly relevant that anti-ET_AR and anti-AT_1R antibody–driven AMR is frequently C4d negative (19,23).

Although levels of anti-AT_1R antibodies were moderately elevated, those observed in our lung recipient are compatible with AMR and early graft dysfunction after transplantation. Indeed, in the recent series, four of the 11 patients who developed C4d-negative AMR in the presence of anti-AT_1R antibodies did so early after transplantation (between days 3 and 5), in the presence of graft

dysfunction (DGF in 2 cases), and—more importantly—in the presence of moderately high pretransplantation anti-AT_1R antibody levels (between 10.3 and 15.1 U/mL) similar to those observed in our case (19). Further, Giral and colleagues, who, as in our report, recently adopted the significance level of >10 U/mL, showed increased incidence of acute rejection episodes in the first 4 months after transplantation in patients with anti-AT_1R antibodies exceeding such a threshold (13). This observation suggests that patients with such levels of anti-AT_1R antibodies are indeed more susceptible to early immunological events consisting of AMR in one-third of cases. Finally, in a recent study, all the patients presenting with pulmonary hypertension (even in the context of idiopathic PAH) had anti-AT_1R antibody levels inferior to those measured in our patient (21). Interestingly, in the same series of patients, even the levels of anti-ET_AR antibodies did not reach those observed in our case. Taken together, existing data suggest that even intermediate levels of preexisting anti-AT_1R (and anti-ET_AR) antibodies such as those in our lung transplant recipient may increase the risk of AMR and early graft dysfunction. In addition, it is a possibility here that both anti-AT_1R and anti-ET_AR antibodies synergized in the ultimate biological effects observed.

Although our findings are from a different transplantation context, they present several similarities with the observations previously reported by Dragun et al in renal transplant recipients (12). In particular, in both studies, no HLA DSAs were observed at the time of rejection. Further, the clinical picture was heavily dominated by a severe vasoconstriction that occurred in the presence of agonistic autoantibodies directed against vascular receptors. In this regard, our findings substantially replicate the pathophysiological mechanisms underlying Dragun et al's observations—that is, in both circumstances, non-HLA antibodies hit an ischemic vascular bed. Last, the outcome of our patient was poor as it was for the vast majority of Dragun et al's renal recipients who did not received losartan combined with plasmapheresis and intravenous immunoglobulins.

On the other hand, several aspects differentiate our observations from those of Dragun et al's report. In particular, while we found elevated titers of both anti-ET_AR and the anti-AT_1R antibodies, the renal study measured anti-AT_1R antibodies only. Also, while we could evaluate such autoantibodies before transplantation, in the Dragun et al report, such measurements took place only prospectively after the onset of the rejection episodes. Finally and most importantly, the hypertensive picture we observed in our case was not systemic but was limited to the transplanted lungs, a finding that could be explained by the involvement of diverse mechanisms of vasoconstriction in the onset of these two forms of hypertension.

Other concerns are why anti-ET_AR and anti-AT_1R antibodies may be observed in individuals in the complete absence of pulmonary (or systemic) hypertension and why pulmonary hypertension suddenly occurred in the donated lungs. At least three mutually nonexclusive hypotheses could be envisaged to explain such an unexpected finding. First, because a gene polymorphism has been reported for both ET_AR and AT_1R (24–26), it is possible that our patient had only anti-ET_AR and/or anti-AT_1R antibodies recognizing epitopes solely expressed by the donor's receptors. Antigenic determinants of AT_1R and ET_AR, however, have not yet been characterized, precluding firm conclusions on the possible role of a putative alloimmune response (23,27). On the other hand, polymorphism is associated with alternative splicing and, ultimately, with important consequences in terms of both AT_1R levels and functions. For instance, it may well be that the donor lung expressed a specific AT_1R polymorphism (e.g. lacking exon 2 or exon 3) whose presence was associated with elevated AT_1R levels and function, ultimately unleashing the untreatable PAH observed in our patient. Second, we cannot rule out that the donor organ may have expressed specific ET_AR and/or AT_1R polymorphisms more prone to vasoconstriction compared with the native receptors. Alternatively, as speculated by Dragun et al, we cannot rule out at this stage that ischemia–reperfusion injury may have altered the intragraft expression of AT_1R (and perhaps also that of ET_AR), in terms of either receptor density or conformational changes (12,23). We believe that such a scenario may indeed be a possibility, especially in the light of the evidence that human anti-AT_1R antibodies infused in a uninephrectomized renal transplantation model may cause lesions compatible with AMR exclusively in the grafted kidney but not in the native counterpart (12).

Clearly, with the benefit of hindsight, we are firmly convinced that anti-AT_1R and anti-ET_AR antibodies present preoperatively contributed to the dramatic clinical course of this patient and that immediate implementation of appropriate treatment measures would have most probably benefitted and rescued our patient. We are not advocating that lung allograft recipients should undergo routine anti-AT_1R and anti-ET_AR antibody assessment before transplantation. However, as many lung transplant recipients will have such antibodies preoperatively, we recommend to our colleagues that for future similar cases presenting with an otherwise unexplainable and intractable PAH intraoperatively, such a causative hypothesis be seriously considered. Accordingly, it is our view that even in the absence of readily available antibody measurements, such patients should undergo immediate and aggressive treatment. In particular, in the light of the existing literature, therapy in such cases should be based primarily on effective removal of the antibodie(s) putatively involved by means of plasmapheresis or

immunoadsorption, intravenous immunoglobulins, and timely specific treatment of PAH (23).

In conclusion, our data suggest that, similar to other forms of transplantation, anti-AT_1R (and possibly also anti-ET_AR) autoantibodies may play a detrimental role in recipients of lung transplants. These autoantibodies may lead to subclinical or clinical AMR, possibly associated with unusual symptoms that may include PAH. In particular, anti-AT_1R and anti-ET_AR autoantibodies should be kept in mind as possible causative agents when patients undergoing lung transplantation develop immediate and intractable PAH so that appropriate treatment measures can be timely implemented.

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Disclosure

The authors of this manuscript have no conflicts of interest to disclose as described by the *American Journal of Transplantation*.

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Supporting Information

Additional Supporting Information may be found in the online version of this article.

Data S1: Supplementary material.