Fulminant hyperacute rejection after unilateral lung transplantation

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Abstract
Hyperacute rejection (HAR) is a well-known complication in renal and cardiac transplantation, but rare in lung recipients. We present a case of HAR of the lung graft with a fatal outcome of a male patient with preformed class II anti-HLA antibodies.

Keywords: Hyperacute rejection • Preformed antibodies • Lung transplantation

INTRODUCTION
Lung transplantation is a fully established treatment for patients with terminal respiratory pathologies [1, 2]. Many complications cast a shadow over the prognosis and survival after lung transplantation. Some of these arise immediately after surgery and, although rare, can have high mortality. This is the case with hyperacute rejection (HAR) [3].

HAR is associated with the presence of preformed antibodies in the recipient against either the blood antigens of the ABO system or against the human leucocyte antigens (HLA) of the donor. This is a well-known complication in renal or cardiac transplants [4], but it is rare in lung transplant.

CASE REPORT
The recipient was a 62-year-old male (0-Rh+) diagnosed with emphysema who was listed for left unilateral transplant. Single-lung transplantation was performed from a 49-year-old, male, brain-dead donor (0-Rh+). Due to PaO2/FiO2 below 300, we carried out an ex vivo evaluation (normothermic and with Steen® solution [5]). During this evaluation, oxygenation improved (PaO2/FiO2 was 503 and 497 at 120 and 180 min, respectively) and we proceeded with the transplantation (total ischaemic time: 7 h).

Thirty minutes after reperfusion, the graft developed pulmonary oedema. The patient developed grade 3 primary graft dysfunction (PGD), refractory to nitric oxide and mechanical ventilation manoeuvres. We initiated veno-venous lung assistance (consisting of respiratory assistance—a Novalung®—connected to a centrifugal pump) without any improvement. A chest X-ray showed a massive consolidation of the left lung (Fig. 1a). Forty-eight hours later, the patient still had a poor PaO2/FiO2 ratio, X-ray consolidation and systemic inflammatory response syndrome with oligaunuria, coagulopathy, thrombocytopenia and maintained hypotension. The patient died 77 h after transplantation.

IMMUNOLOGY
The recipient HLA typing was: A*01,*32; B*38,*49; DRB1*01,*13; DRB3*01; DQB1*05, *06; DQA1*01:GN, DQA1*01:03. But HLA typing on the donor showed the antigens: A2, 11; B44, 62; DR4, 7; DQB1*02, *03; DQA1*02:01, DQA1*03:01:01.

A pre-transplant test was performed based on complement-mediated cytotoxicity, and 2 positives were obtained out of 40 cells studied (panel-reactive antibody (PRA) was 5%). Consecutively, an analysis was performed based on flow cytometry, which was negative for the both type I and type II anti-HLA antibodies.

After the transplant, a new analysis was performed in another centre and with the pre-transplant serum of the recipient, based on the flow cytometry over the spheres conjugated to HLA (type I, type II) and MICA molecules (Gen-Probe SA class I, class II, MICA; lot 03118A, 07-2010). The results were positive for IgG antibodies against the HLA-DQA1 (HLA type II) molecules, specifically against the heterodimers formed by DQA1*3:02 with any of the DQB1*2:02, *03:01, *03:02 or *03:03 alleles. Moreover, the heterodimer DQA1*03:02–DQB1*03:02 enlisted the C3d component of the complement system with the same technique (Fig. 1f).

DISCUSSION
We ruled out the usual causes of early graft failure (blood group discordance, ischaemia–reperfusion damage and technical defects in vascular anastomosis). We also considered that the graft was initially from a marginal donor and could contribute to PGD development, but we performed an ex vivo system reconditioning getting a suitable organ for transplantation.

The pathological examination is described in Fig. 1b–e.

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circulating antibodies, C4d deposition, compatible histology and clinical dysfunction [4]. In our case, the clinical findings were characterized by the consequences of PGD plus the development of a systemic inflammation response syndrome: immediate graft oedema, hypoxia, coagulopathy, thrombocytopenia, oligoanuria and haemodynamic instability, as have been described [6–8]. The histological alterations based on oedema, capillaritis, non-lymphocytic inflammatory infiltrate and the subendothelial deposition of C4d also indicate the diagnosis.

Concerning the preformed antibodies, although the first screening test based on flow cytometry was negative, the fact is that PRA showed 5% positivity. Hence, a low PRA should not be interpreted as a weak sensitization, but as a probability of developing these entities if the donor, by chance, has the sensitizing antigen. Therefore, a consistent PRA should not be ignored, even

<table>
<thead>
<tr>
<th>Author</th>
<th>Sex/age</th>
<th>Indication</th>
<th>Tx</th>
<th>PRA</th>
<th>Crossmatch</th>
<th>Evolution</th>
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<tr>
<td>Frost et al. [3]</td>
<td>Female/48</td>
<td>COPD</td>
<td>33%</td>
<td>+: Anti-B8</td>
<td>Died: 13th DPO</td>
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<td>Choi et al. [6]</td>
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<td>+: unidentified</td>
<td>Died: 4 h</td>
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<td>Bittner et al. [8]</td>
<td>Female/57</td>
<td>COPD</td>
<td>33%</td>
<td>+: Anti-A2</td>
<td>Survives</td>
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<tr>
<td>Scornik et al. [10]</td>
<td>Female/?</td>
<td>Not available</td>
<td>Negative</td>
<td>+: Anti-DR11</td>
<td>Died: 48 h</td>
<td></td>
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<tr>
<td>de Jesus Peixoto Camargo et al. [9]</td>
<td>Female/60</td>
<td>COPD</td>
<td>Negative</td>
<td>+: Anti-A2</td>
<td>Died: 24 h</td>
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<tr>
<td>Masson et al. [7]</td>
<td>Female/53</td>
<td>COPD</td>
<td>Negative</td>
<td>+: Anti-B7-B81</td>
<td>Died: 9th DPO</td>
<td></td>
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<tr>
<td>Our case</td>
<td>Male/62</td>
<td>COPD</td>
<td>5%</td>
<td>+: Anti-DQA1</td>
<td>Died: 77 h</td>
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Figure 1: (a) Post-transplant chest X-ray. (b) Cut surface of the graft after its extraction showing widespread red hepatization, consistency increase, glossy and haemorrhagic cut. (c) Alveolar haemorrhage and septal inflammation with capillaritis. (d) The presence of neutrophils in the septa and oedema. (e) Immunostaining of the C4d component of the complement: diffuse linear staining along septal capillaries. (f) The graph shows the Mean Fluorescence Intensity of the positive reaction for IgG antibodies against the HLA-DQA1 (HLA type II) molecules, specifically against the heterodimers formed by DQA1*3:02 with any of the DQ8B1*2:02, *03:01, *03:02 or *03:03.
Table 1 shows the documented cases of antibody-mediated HAR. The majority of cases described to date confirm the presence of preformed antibodies against type I HLA [3, 7–9], but there is one in which the antibodies were against type II HLA [10]. Therefore, the idea, taken from kidney transplants, that the anti-HLA type II antibodies are ‘less’ dangerous cannot be extrapolated to lung transplantation.

A striking fact is that in all of the cases, the recipients were women, except ours. In the article by Scornik et al. [10], being a woman was identified as a risk factor for developing pre-transplantation antibodies. All patients had a COPD diagnosis, but it is difficult to say if this entity has a role in the anti-HLA antibody development.

This case contributes, as an innovation, to the clinical presentation of preformed antibodies anti-HLA type II in a male recipient with no risk factors for the pre-transplant development of anti-HLA antibodies.

Ideally, a pre-transplant crossmatch (virtual or real) could be carried out with all those receivers in whom the presence of preformed antibodies has been detected. However, in the case of lung transplantation, a real crossmatch is performed if the donor is nearby, to avoid a long period of ischaemia. A virtual crossmatch could solve this problem, as well as an early retrospective crossmatch, even during the transplant surgery. Although there is no proven effective treatment for these clinical symptoms (of all the cases listed in Table 1, only one survived, having been treated with plasmapheresis, cyclophosphamide, anti-thymocyte immunoglobulin and steroids [8], any positives in this retrospective test could be treated early on.

An alternative is to attempt a preventive treatment on the possible clinical symptoms with different strategies: reduce the circulating antibodies with plasmapheresis or immunoadsorption, as well as the production of these with treatments, such as rituximab. We did not suspect the clinical entity and that is why we did not indicate treatments used in other groups/protocols (plasmapheresis, rituximab or IVIG).

In summary, this case once again highlights the high mortality of HAR. It is essential to establish as a routine, a screening method that is more sensitive and has the highest negative predictive value possible. Currently, these methods are based on flow cytometry. In patients who have an increased risk of developing anti-HLA antibodies, these screening methods should be repeated while they are on the waiting list. It is advisable to develop a protocol for the management of these patients with known preformed antibodies and, ideally, a pre-transplant crossmatch should be performed. If this is not possible, alternatives must be established.

Conflict of interest: none declared.

REFERENCES