


## Letter



# Late Cardiac Antibody-Mediated Rejection: A Only Heart Duel

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### Conflict of Interest

The authors have no financial conflicts of interest.

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Heart transplantation is an arduous and continuous treatment rather than a definitive solution. Even with optimal immunosuppression therapy, acute allograft rejection is a frequent complication and is associated with increased morbidity and mortality.<sup>1)</sup> Antibody-mediated rejection (AMR) is a less common type of rejection but is increasingly diagnosed each year due to higher awareness.<sup>2)</sup>

AMR develops when recipient antibodies are directed against human leukocyte antigen (HLA) on the endothelial layer of the allograft; this leads to complement system activation, prompting innate and adaptive immune responses of the allograft vessels. It may occur early after transplantation, if the recipient is already presensitized to donor HLA, with a high risk of hemodynamic compromise.<sup>3)</sup> Late AMR represents more than half of AMR cases, being associated with poor short-term prognosis.<sup>4)</sup>

The diagnosis combines both histologic (such as myocardial capillary injury with intravascular macrophage accumulation on light microscopy) and immunopathologic findings (in particular, the presence of complement components—C4d, C3d, and/or C1q within the capillaries and macrophage immunofluorescence staining for CD68). Presence of serum antibodies directed against donor's HLA class I reinforces AMR diagnosis.<sup>5)</sup> According to the combination of such findings, a nomenclature for the severity of AMR has been proposed<sup>5)</sup>: pathologic AMR 0 (pAMR0) if both histologic and immunopathologic studies are negative; pAMR1 if either histologic or immunopathologic findings are present; pAMR2—when both tests are positive; and is considered pAMR 3 (rare) if gross myocardial damage or destruction exist.<sup>5)</sup>

When both graft dysfunction—usually presenting with heart failure clinic—and diagnostic criteria for AMR are present, it seems to be reasonable to start therapeutic promptly. However, optimal treatment is still a matter of debate.<sup>5)</sup> While hemodynamic compromise may be improved by plasmapheresis with immunosuppressors (either corticosteroids, cyclophosphamide and/or tacrolimus), rescue therapies, such rituximab, are used for refractory cases.<sup>6)</sup> AMR is associated with a worse prognosis than cellular rejection, evolving with higher mortality, greater rate of graft loss due to acute rejection and increased risk of transplant vasculopathy.<sup>7)</sup>

In this clinical case, we aim to expose a challenging case of AMR, and describe the overt improvement of clinical status after rituximab treatment. We also review the current literature of AMR management, emphasizing the use of rituximab in these patients.

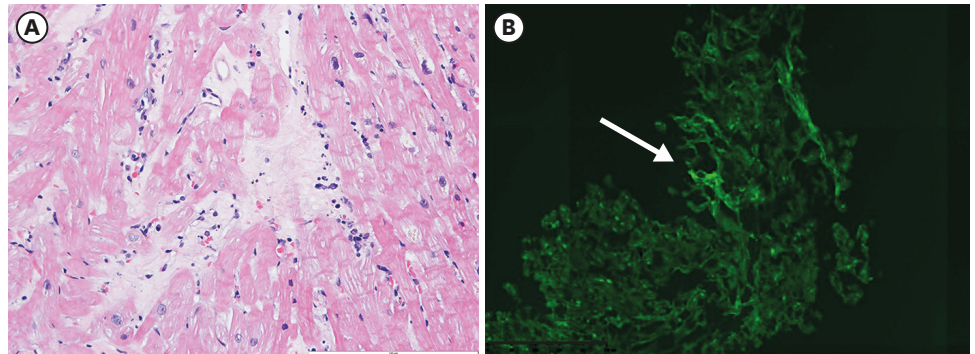
Fifty-five-year-old women had been submitted to heart transplant in 2008 due to valvular cardiomyopathy. During follow-up, she had some cellular rejections grade 1R and one asymptomatic grade 2R rejection in 2013, with normal ventricular function, treated with oral pulse of prednisolone. Last echocardiogram (2019) showed normal systolic biventricular function. Her usual immunosuppressant regimen was azathioprine 50 mg/day, ciclosporin 75 mg + 100 mg/day prednisolone 2.5 mg/day; however she admitted taking medication irregularly.

On 20th February 2020, she presents with pulmonary edema, B-type natriuretic peptide (BNP) of 2,300 ng/L and left ventricular ejection fraction (LVEF) of 24%, severe right ventricular (RV) dysfunction and moderate tricuspid regurgitation. She had no significant elevation hs-cTnT elevation (maximum 30 ng/L). Acute allograft rejection was suspected and the patient was admitted at our institution (**Figure 1** for timeline of events).

Methylprednisolone pulses (1 g/day for 3 days) were promptly performed; azathioprine was switched to mycophenolate mofetil (MMF) 1,000 mg bid and cyclosporine to tacrolimus 3 mg bid (target level of 5–10 ng/mL). On the next day of admission, the patient performed coronary angiography, which did not show vasculopathy. Endomyocardial biopsy (EMB) showed interstitial lymphocytic infiltrate without myocyte damage (1R) and positive



**Figure 1.** Timeline of events, including immunosuppression schemes and main diagnostic studies performed. AZA = azathioprine; COVID = coronavirus disease; Cyclo = cyclosporine; DSA = donor specific antibodies; EMB = endomyocardial biopsy; IVIg = intravenous immunoglobulin; LVEF = left ventricular ejection fraction; MFI = mean-fluorescence intensity; MMF = mycophenolate mofetil; MP = methylprednisolone pulses; R = rituximab.



**Figure 2.** Histology and immunofluorescence study. (A) Interstitial lymphocytic infiltrate without myocyte damage (1R), focal interstitial fibrosis with scarce infiltrate of lymphocytes and plasmocytes, hematoxylin and eosin staining histologic study. (B) C4d presence in immunofluorescence staining (white arrow).

immunofluorescence staining for C4d (**Figure 2**), making the diagnosis of AMR (AMR1). Serum donor specific antibodies (DSA) later obtained corroborated this diagnosis: anti-HLA A68 of 1720 and anti-HLA DQ7 of 18508 (cut-off >1,000 mean-fluorescence intensity [MFI]). Plasmapheresis sessions followed by intravenous immunoglobulin (IVIg) were performed (5 sessions, 120 g IVIg). Meanwhile, severe pancytopenia developed, and MMF had to be suspended. Cell lines improved without need of colony stimulating factor drugs and MMF was re-introduced in a lower dosage (250 mg bid).

One month later left systolic dysfunction (LVEF of 26%) and RV dysfunction persisted. DSA evaluation showed similar titers (anti HLA A68 of 1097 MFI, anti-HLA DQ7 of 18459 MFI), and after performing a new EMB, positive C4d was maintained. So, 15 days after, methylprednisolone pulses were repeated and a trial with rituximab (600 mg, 375 mg/m<sup>2</sup>) was performed. Prophylaxis was made with cotrimoxazole, fluconazole and valganciclovir. Two months later a significant clinical recovery occurred, with BNP decreasing to 232 ng/L and a partial improvement of LVEF to 46%, persisting moderate RV dysfunction with mild tricuspid regurgitation. A new course of IVIg (100 g) and Rituximab (600 mg, 375 mg/m<sup>2</sup>) was performed. One month later, the patient showed an improvement in LVEF to 52%, with only minimal mitral regurgitation, mild RV dysfunction and minimal tricuspid regurgitation.

During follow-up, the patient returned to New York Heart Association class I, serial echocardiograms performed showed a complete recovery in LVEF (LVEF >60%) and a normal right ventricle function.

In November 2020 she was hospitalized by a severe severe acute respiratory syndrome coronavirus 2 pneumonia requiring mechanical ventilation. She maintained normal biventricular function and had an admission BNP of 334 pg/mL. Long after ventilatory recovery, on 5th January, she died due to a multiresistant *Pseudomonas aeruginosa* bacteriemia.

Diagnosing and treating of AMR may lead to challenging decisions, often diverging among centers.<sup>5,8)</sup> Early diagnosis and treatment of AMR may be important to reduce chronic inflammation leading to development of myocardial fibrosis and cardiac allograft vasculopathy. There is clearly a need for more effective surveillance for AMR and routine monitoring of DSA may be helpful as well as functional assays of antibodies with C1q.<sup>8)</sup>

Considering that AMR presentation may vary from mild heart failure to cardiogenic shock, stabilization of the hemodynamically compromised patient may extend to the use of inotropic and vasopressor support as well as mechanical circulatory support. Simultaneously, in order to reduce circulating alloantibodies, different approaches can be used, often in combination: 1) suppression of the T-cell response, similarly to cellular rejection, using corticosteroids, MMF, anti-lymphocyte antibodies, photopheresis, or total lymphoid irradiation; 2) through elimination of circulating antibodies by plasmapheresis—the corner stone of AMR; 3) inhibition of residual antibodies with IVIGs; 4) suppression or depletion of B cells either with corticosteroids, rituximab, or splenectomy; 5) suppression or depletion of plasma cells with bortezomib; or 6) inhibition of complement (e.g., eculizumab, intravenous gamma globulin [IVIg]).<sup>5)</sup>

Indications to start treatment are not clear enough. Therapies are initiated for AMR2/3, especially in the setting of hemodynamic compromise; however, there are few studies in AMR1, as the patient described.

Our patient offered several demanding decisions: firstly, an exhaustive diagnostic work-up was performed and the disproportion of clinical manifestation vs. histologic findings were unexpected. Secondly, considering the poor clinical status, poor ventricular function, and high levels of DSA, it was decided to perform plasmapheresis and IVIg in a patient with pAMR1 diagnosis and stratification (as explained no formal indication to start treatment in pAMR1). Finally, the unsatisfactory response made necessary to undergo a rescue trial and we decided to perform rituximab, which was followed by clinical and echocardiographic recovery. Unfortunately, our patient died one year later after coronavirus disease 2019 infection and we cannot exclude a higher risk of infection after several months after the last rituximab dose (despite our patient undergone a prolonged prophylactic therapy).

Rituximab is a genetically engineered monoclonal antibody against the pan B-cell marker CD20 and was first introduced for the treatment of B-cell non-Hodgkin lymphoma but is also used for the treatment of autoimmune disease.<sup>6)</sup> Recommended dosage is 375 mg/m<sup>2</sup> (smaller people) to 1g weekly, repeated maximum for 4 weeks. Main adverse reactions include fever, chills, nausea, headache, myalgia, and rash. When used for the management of AMR or as desensitization therapy, rituximab has largely been used in combination with other therapies, though there are series of patients with AMR treated with rituximab as monotherapy.<sup>6)</sup> Ravichandran et al compared in a retrospective analysis of cardiac transplant patients with a diagnosis of AMR from 2001 to 2011, treated with rituximab (13 patients) or not (control group, 20 patients). They showed through Kaplan-Meier curves for a 3-year follow-up period that Rituximab improved survival ( $p=0.0089$ ), with no increase in infection, change in EF, or rehospitalization.<sup>9)</sup> In AMR refractory cases, there are also multiple case reports of the successful use of rituximab as salvage therapy after failure of combination therapy with cytolytic antibodies, corticosteroids, plasma exchange, and cyclophosphamide.<sup>5)</sup> It is described a clinical case of refractory humoral cardiac rejection successfully treated with a single dose of rituximab with no further relapses within 2 years of follow-up.<sup>10)</sup>

In this complex case, with few clinical evidence available, clinical recovery and absence of relapse during the follow-up was achieved after optimization of immunosuppression. Even that a cause-effect relation cannot be proven, this clinical case supports the role of rituximab has a rescue treatment in refractory AMR.

## REFERENCES

1. Chang DH, Kittleson MM, Kobashigawa JA. Immunosuppression following heart transplantation: prospects and challenges. *Immunotherapy* 2014;6:181-94.  
[PUBMED](#) | [CROSSREF](#)
2. Coutance G, Ouldamar S, Rouvier P, et al. Late antibody-mediated rejection after heart transplantation: mortality, graft function, and fulminant cardiac allograft vasculopathy. *J Heart Lung Transplant* 2015;34:1050-7.  
[PUBMED](#) | [CROSSREF](#)
3. Chang H, Youn JC, Dilibero D, Patel JK, Kobashigawa JA. Heart transplant immunosuppression strategies at Cedars-Sinai Medical Center. *Int J Heart Fail* 2021;3:15-30.  
[CROSSREF](#)
4. Clerkin KJ, Restaino SW, Zorn E, Vasilescu ER, Marboe CC, Mancini DM. The effect of timing and graft dysfunction on survival and cardiac allograft vasculopathy in antibody-mediated rejection. *J Heart Lung Transplant* 2016;35:1059-66.  
[PUBMED](#) | [CROSSREF](#)
5. Colvin MM, Cook JL, Chang P, et al. Antibody-mediated rejection in cardiac transplantation: emerging knowledge in diagnosis and management: a scientific statement from the American Heart Association. *Circulation* 2015;131:1608-39.  
[PUBMED](#) | [CROSSREF](#)
6. Garrett HE Jr, Duvall-Seaman D, Helsley B, Groshart K. Treatment of vascular rejection with rituximab in cardiac transplantation. *J Heart Lung Transplant* 2005;24:1337-42.  
[PUBMED](#) | [CROSSREF](#)
7. Costanzo MR, Dipchand A, Starling R, et al. The International Society of Heart and Lung Transplantation guidelines for the care of heart transplant recipients. *J Heart Lung Transplant* 2010;29:914-56.  
[PUBMED](#) | [CROSSREF](#)
8. Chih S, Tinckam KJ, Ross HJ. A survey of current practice for antibody-mediated rejection in heart transplantation. *Am J Transplant* 2013;13:1069-74.  
[PUBMED](#) | [CROSSREF](#)
9. Ravichandran AK, Schilling JD, Novak E, Pfeifer J, Ewald GA, Joseph SM. Rituximab is associated with improved survival in cardiac allograft patients with antibody-mediated rejection: a single center review. *Clin Transplant* 2013;27:961-7.  
[PUBMED](#) | [CROSSREF](#)
10. Baran DA, Lubitz S, Alvi S, et al. Refractory humoral cardiac allograft rejection successfully treated with a single dose of rituximab. *Transplant Proc* 2004;36:3164-6.  
[PUBMED](#) | [CROSSREF](#)