Antibody-mediated Rejection in Heart Transplantation

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Abstract Heart transplantation is an excellent long-term treatment that confers functionality and longevity in select patients with end-stage heart failure. Yet, allograft rejection continues to pose a significant threat, especially in high-risk recipients and soon after transplantation. Of the two prevailing pathologic types of acute rejection in cardiac allografts, antibody-mediated rejection (AMR) had been variably defined and poorly understood for the past three decades when compared to cellular rejection. As a result, progress in understanding its pathologic and clinical behavior and the ability to find effective therapies had been hindered. Recent years have seen a renewed interest in cardiac AMR with efforts from pathologists, immunologists, and clinicians leading to a standardized diagnostic nomenclature.

Keywords Antibody-mediated Rejection · Humoral Rejection · Vascular Rejection · Heart Transplantation

Introduction

The initial indirect report of a possible humoral recipient response, detrimental to the cardiac allograft and manifesting as arteriolar vasculitis, surfaced in the late 1980's from Johns Hopkins [1]. Soon after in 1989, Hammond et al., in Utah followed with the first comprehensive description of the pathological features and clinical outcomes of vascular or humoral rejection in heart transplantation [2]. The next two decades saw a lot of uncertainty and skepticism as to whether cardiac antibody-mediated rejection (AMR) even existed and, if so, how to best define it. Under the auspices of the International Society of Heart and Lung Transplantation (ISHLT), multidisciplinary consensus meetings including pathologists and clinicians recently succeeded in the standardization and refinement of diagnostic criteria for AMR in heart transplantation. Despite this important milestone, therapies for cardiac AMR and their outcome are still limited to individual transplant centers' experience, and there is a need of rigorous prospective testing on a larger scale.

Associated Risk Factors

In adult heart transplants, AMR is more frequent in young [2, 3] and female recipients [3–7]. In pediatric heart transplants congenital heart disease is a frequent predictor of AMR [8, 9].

The formation of antibodies against Human Leukocyte Antigen (HLA) in sensitized patients is a main predisposing

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factor for AMR [2•, 4, 6]. However, pathological AMR can also occur in the absence of preformed antibodies [9], and the presence or absence of donor-specific antibodies (DSA) does not confirm or exclude the diagnosis of AMR. Therefore, in the 2011 ISHLT consensus report, DSA detection supports the diagnosis of AMR, but it is not essential for diagnosis [10•]. Conditions associated with sensitization include previous transfusions, pregnancies, transplantations, and mechanical circulatory support [3, 11–13]. Prior transplantation stimulates the production of de-novo anti-HLA [14–16], and the development of non-HLA antibodies directed against cardiac myosin and vimentin, which have also been associated with the development of AMR [17]. The growing practice of bridging heart transplant recipients with left ventricular assist devices (LVAD) is known to promote the development of alloantibodies, probably from interaction between the LVAD surface and the immune system. Additionally, the transfusion of platelet products during LVAD support is associated with the development of HLA class I IgG antibodies [12, 18–21]. The type of circulatory support is related to the degree of sensitization as the first-generation LVADs with pulsatile flow and biomaterial surfaces produced more allosensitization compared to second generation LVADs with continuous-flow mechanisms [19, 22].

Several observational studies have linked the presence of a positive crossmatch between donor cells and recipient serum with subsequent development of AMR [2•, 6, 7, 23, 16, 24]. More specific and sensitive antibody-detection assays and the use of virtual crossmatching before transplantation have decreased the frequency of positive donor-recipient crossmatches.

Prolonged allograft ischemic time is a known factor for decreased survival after heart transplantation. The ischemia/reperfusion injury is a complex inflammatory response [25] that triggers the host immune system in a potentially similar way observed during AMR [26]. Despite a potential mechanistic role, prolonged ischemia has not to date been associated with higher frequencies of AMR [7, 27].

Preoperative seropositive status for cytomegalovirus (CMV), and the grafting of organs from seropositive donors or a postoperative CMV infection, are associated with an increased risk of AMR, chronic rejection, and allograft vasculopathy [28, 29].

Immunology/Pathways of Cardiac AMR

The pathogenesis of AMR involves the activation of the innate and the adaptive immune systems, mostly targeting the endothelium of the cardiac microvasculature. New data also suggest a preponderant role of ischemia/reperfusion injury of the cardiac allograft.

The Innate Immune System

The innate immune system is the evolutionary first line of defense against invaders/injury. It is nonspecific and involves several mobile and stationary cells (dendritic cells) that inspect the extracellular space and cytoplasm for the presence of pathogen-associated molecular patterns (PAMPs) as well as damage-associated molecular patterns (DAMPs) [30]. The system involves pattern recognition receptors (PRRs) on these cells that respond to specific pathogens or injury associated molecular profiles [26, 31–34]. The recognition of antigens triggers an inflammatory response, which includes cytokine signaling, complement activation, and leucocyte chemotaxis. Similar to the recipient, the donor immune system can also be activated by pathogens, toxins, and reactive oxygen species (ROS) released during brain death conditions [30].

The Adaptive Immune System

By contrast, adaptive immunity is highly specific and is triggered by the recognition of specific antigens [35–38]. T and B lymphocytes recognize foreign antigen and proliferate, with subsequent B-lymphocyte activation to memory cells and antibody-producing plasma cells. Fully activated B lymphocytes possess surface markers CD 19, part of the antigen receptor, and CD 20, which is a marker of complement activation [39–41]. Plasma cells produce large quantities of an antigen-specific antibody, are incapable of antigen recognition, and do not possess the usual B-cell markers, CD19 and CD20 [42–44].

The endothelium is the main site of action during AMR. Antibodies bind to MHC antigens on the vascular endothelium and may or may not fix complement, which can accelerate the level of injury of the endothelium. C4d and C3d are split products that bind covalently to endothelium and can be used as reliable markers for complement activation [38]. Importantly, the antibodies also can bind to other immune effector cells with receptors for the Fc portion of the immunoglobulin molecule, including macrophages, NK cells, B lymphocytes, neutrophils, and platelets, which further accelerate allograft injury [31, 34, 36, 45, 46]. Overall, the adaptive immune system generates specific effector mechanisms including antibody production, complement activation, coagulation, and CD8 mediated cytotoxicity in the endothelium.

Ischemia/Reperfusion Injury of the Allograft

Ischemia-reperfusion-injury (IRI) is a complex inflammatory response that involves both the innate and adaptive immune systems. It has been described during organ transplantation, trauma, autoimmune diseases, and revascularization [25]. Post-ischemic-reperfusion damage is postulated to occur from the combined release of ROS from donor-derived vascular

cells and from recipient-derived neutrophils entering the graft during reperfusion. The release of ROS is the main mechanism of cell injury and death. The production of DAMPs is then identified by PRRs triggering inflammatory responses of the innate and adaptive systems with the potential of subsequent AMR [25, 30].

Pathology of Cardiac AMR

2013 ISHLT Working Formulation for Cardiac AMR

Recognition of cardiac AMR has evolved over the past three decades from controversial single-center reports [2•, 47] to consensus guideline defined criteria. In 2010, an international multidisciplinary effort was initiated by the ISHLT with the aim of standardizing terminology, definitions, and practices to help facilitate multicenter clinical trials [48]. In a departure from the previous 2005 ISHLT working formulation (WF), the pathologic diagnosis of AMR was separated from the clinical and serologic aspects [49]. The new grades of pathologic AMR were given a "p" prefix to indicate that only pathologic criteria are considered [50••]. The 2013 WF AMR grades were also broadened from a binary present/absent (AMR0/AMR1) to a graduated scale as shown in Table 1.

Surveillance Strategies and Biopsy Handling

The morphologic, immunopathologic, serologic, and clinical features of AMR may fluctuate over time and do not always coincide [51]. The histopathologic features should be assessed in every biopsy. If not done on every biopsy, then at a minimum immunopathology should be done when there is clinical graft dysfunction or when histologic or serologic features suggest AMR. During the first year after the post-transplant, routine immunopathology should be included, if biopsies are done, for biopsies at two and four weeks after transplant and again at three, six, and 12 months [50••].

Both frozen section immunofluorescence (IF) and paraffin section immunoperoxidase (IP) are acceptable immunopathology techniques. For frozen IF, a separate unfixed biopsy piece is required. Sections of the frozen tissue should be examined by routine histology along with the fluorescence stained slides. For IF, the recommended stains include C4d and C3d. For IP, C4d and CD68 are recommended. Other optional stains are also outlined in the 2013 WF document [50••]. Proper assay optimization, validation, and controls are critical.

Histopathologic Features

The first suggestion of AMR by histopathology may be a "busy" hypercellular appearance of the interstitium at low

magnification. On closer inspection the conspicuous cells are largely confined to distended lumens of capillaries and venules and consist of enlarged "swollen" endothelial cells with rounded rather than flattened nuclei along with macrophages and other mononuclear inflammatory cells (Fig. 1). The chromatin patterns of activated endothelial cells and macrophages are similar and not readily distinguishable in many cases, so the 2013 WF terms these "intravascular activated mononuclear cells". If CD68 staining is not routinely done, cases with even focally prominent intravascular mononuclear cells should prompt staining for CD68 [50••]. Other less common features of AMR by light microscopy include edema and hemorrhage in the interstitium. Extravascular inflammation is more prominent in severe AMR, along with edema, hemorrhage, endothelial cell pyknosis/karyorrhexis, and extensive myocyte damage [52].

Immunopathologic Features

The hallmark immunopathologic features of AMR include detecting complement cascade activation by staining for complement split products (e.g., C3d and C4d), and confirming the presence of intravascular macrophages using monocyte lineage antigen (CD68) staining [50••] (Fig. 2). Complement staining and CD68 positive macrophage accumulation are usually concomitant, but one may precede the other in some cases [53].

Interpretation of immunopathology findings can be challenging. The 2013 ISHLT WF outlines an approach incorporating tissue specificity, intensity, and distribution of staining. Regarding tissue specific staining, only myocardial capillary staining is considered significant. In terms of intensity and distribution, specific scoring schemes are outlined. Intensity is scored subjectively as 0 (negative), 1 (weak), and 2 (strong), and distribution is reported as 0 (negative; <10 % of vessels in the total surface area), 1 (focal; 10–50 %), and 2 (multifocal/diffuse; >50 %). Complement staining is considered positive if the intensity is >0 and the distribution is 2 regardless of technique. For CD68, intensity is not a consideration, but positive is defined as any score >0 [50••].

Biopsy Mimics of AMR

The histologic features of AMR are not entirely specific [49] and complement activation in the graft can occur through mechanisms other than rejection [54]. Biopsy grading may be challenging during the first two weeks after transplant because endothelial injury associated with harvesting ischemia/reperfusion overlaps significantly with AMR, and may have some complement activation. The use of the murine anti-CD3 antibody OKT3 can also incite a reaction mimicking AMR [55]. Macrophages are components of other processes besides ACR, and the 2013 ISHLT WF stipulates

Table 1 The 2013 ISHLT Working Formulation for Pathologic Diagnosis of Cardiac AMR

Grade	Definition	Criteria
pAMR 0	Negative for pathologic AMR	Histologic and immunopathologic findings are both absent
pAMR 1 (H+)	Histopathologic AMR alone	Histologic findings are present and immunopathologic findings are absent
pAMR 1 (I+)	Immunopathologic AMR alone	Histologic findings are absent and immunopathologic findings are present
pAMR 2	Pathologic AMR	Histologic and immunopathologic findings are both present
pAMR 3	Severe pathologic AMR	Interstitial hemorrhage, capillary fragmentation, mixed inflammatory infiltrates, endothelial cell pyknosis, and/or karyorrhexis, and marked edema with immunopathologic findings are present.

ISHLT, International Society for Heart and Lung Transplantation; AMR, antibody-mediated rejection

that CD68 (and C4d) should be assessed on intact myocardium away from areas of cellular rejection, Quilty lesions, biopsy site scars, and areas of ischemic-related damage or necrosis [50••].

Controversies in the Pathology of AMR

While as a concept AMR has gained near universal acceptance in the cardiac transplant field, there are still substantial gaps in understanding the pathogenic mechanisms and

especially the prognostic weight of individual (or combined) pathologic AMR features. For example, there is some evidence that detection of both C3d and C4d deposition (as opposed to C4d alone) in biopsies is more ominous; presumably because C3 cleavage signals the failure of complement regulators to halt progression down the complement cascade [56]. The relative significance of pAMR1 versus pAMR2 rejection patterns also needs further study [57]. The combined presence of both cellular rejection and AMR is increasingly recognized and deserves attention in terms of possible cross-

Fig. 1 Histopathology of Cardiac AMR **a**) Low-power photomicrograph of a transplant endomyocardial biopsy showing a “busy appearance” in the interstitium, typical of AMR (H&E stain, 20×; courtesy Desley Niel, MD). **b & c**) Higher power photomicrographs showing cross-sections of capillaries and venules with prominent swollen endothelium and activated intravascular mononuclear cells (H&E stain, 400×). **d**) High-power photomicrograph of a biopsy showing severe AMR with interstitial edema and extensive capillary injury and karyorrhexis (H&E stain, 200×)

Fig. 2 Immunopathology of Cardiac AMR **a)** Fluorescence photomicrograph of a transplant endomyocardial biopsy frozen section stained by C4d immunofluorescence showing diffuse strong capillary “donut” staining (IF stain, 100×). **b)** Fluorescence photomicrograph showing a positive C3d immunofluorescence pattern (IF stain, 200×). **c)** High-power photomicrograph of a biopsy paraffin section stained by C4d immunoperoxidase showing diffuse strong capillary “donut” staining (IP stain, 400×). Photomicrograph of a CD68 stained paraffin section showing aggregation of intravascular CD68 positive macrophages (IP stain, 400×)

reacting immune mechanisms as well as the most appropriate therapeutic strategies for "mixed" rejection.

Clinical Features

It is likely that cardiac AMR is underreported since screening in asymptomatic patients is not routinely done. While its true incidence remains unknown, the prevalence of lone AMR is around 10 % to 15 %, and is conceivably higher when diagnosed concomitantly with cellular rejection (mixed rejection) [58–61].

A number of clinical features are characteristic of AMR. It tends to occur early especially in sensitized patients and the risk of recurrence is high particularly in recipients who have three or more separate AMR episodes in the first three months after transplant. Most AMR occurrences are mild but symptomatic patients are more likely to present with hemodynamic compromise and cardiac dysfunction when compared to cellular rejection. The course of cardiac AMR

depends on its severity and the time of diagnosis. More severe cases and those happening early after transplant are less likely to recover and/or resolve, and the associated outcomes are worse. Cardiac AMR, whether clinically silent or symptomatic, has uniformly been associated with cardiac allograft vasculopathy, chronic graft dysfunction, and higher mortality. In some cases sudden cardiac death is still seen despite successful therapy of the acute AMR with pathological and clinical resolution; in these cases we have usually found an aggressive and diffuse form of cardiac allograft vasculopathy at autopsy [2•, 4, 5, 7, 15, 24, 60, 62–72].

Management of Cardiac AMR

After a diagnosis of AMR is made by pathological findings, the decision of whether to treat requires consideration of the patient's clinical presentation, allograft function, biopsy grade, and the presence of donor-specific antibodies. General recommendations for the treatment of AMR were published by the ISHLT in 2010 [73]. Overall, the treatment of AMR is

complex as there are multiple therapeutic targets in the allo-antibody response, including T-cell and B-cell activity, antibody removal and production, and antibody effect.

ISHLT Guidelines*[73]

Class IIa

1. The following treatments can be used to disrupt the immune-mediated injury of the heart allograft in AMR: (1) high-dose intravenous (IV) corticosteroids; and (2) cytolytic immunosuppressive therapy.
2. The following treatments may be used to remove circulating anti-HLA antibodies or decrease their reactivity: (1) plasmapheresis; (2) immune apheresis (immunoadsorption); and (3) IVIg.
3. The following treatments are used to maintain adequate cardiac output and systemic blood pressure: (1) IV inotropes and vasopressors; and (2) mechanical circulatory support.
4. When AMR is suspected, EMB examination should be expanded to include immunohistochemistry stains for complement split products and possible antibodies.
5. Recipient serum should be screened for presence, quantity, and specificity of anti-donor (HLA) antibodies.
6. Follow-up EMB should be performed one to four weeks after initiation of therapy and should include immunohistochemistry examination.
7. Adjustment of maintenance immunosuppressive therapy may be considered. This can include increase in the dose of current immunosuppressive agent(s), addition of new agent(s) or conversion to different agent(s).

Class IIb

1. Systemic anticoagulation may decrease intravascular thrombosis in the heart allograft.
2. Emergent retransplantation may be considered if the above measures do not restore acceptable heart allograft function, but outcomes in this situation are unfavorable.

*All recommendations are Level of Evidence C.

Antibody removal and inhibition

Immunoadsorption (IA), plasmapheresis (PP), and therapeutic plasma exchange (TPE) effectively and quickly remove circulating antibodies and have been used for desensitization and treatment of AMR [43, 68, 74–76]. No randomized trials of these therapies have been done

in cardiac transplantation, and the small number that have been performed with kidney transplant recipients have had mixed results [77–81]. When used, additional therapies targeting antibody activity or production are often given concurrently to minimize the rapid rebound in antibody titers that can occur following treatment. The activity of circulating antibodies can also be targeted, most commonly with intravenous immunoglobulin (IVIg). Potential mechanisms by which IVIg may be effective in the treatment of AMR include the expansion of regulatory T cells, upregulation of the inhibitory FcγRIIB receptor on B cells, and the suppression of complement activation [82–84]. There is very little data from clinical trials examining the use of IVIg in transplants; however, it is commonly used for treatment of AMR, often in combination with PP and/or agents that target antibody production [85–87]. Finally, eculizumab is an antibody directed against the complement component C5 that effectively blocks the antibody-triggered complement cascade. Case reports describe successful use in the treatment of AMR in renal and lung transplant recipients; however, additional data is needed prior to routine use in cardiac transplantation [88–94].

Antibody production

Therapies to decrease the production of antibodies target B cells and plasma cells. The anti-CD20 antibody rituximab, which acts through the elimination of peripheral B cells, has been increasingly used. The efficacy of rituximab for the treatment of AMR has been difficult to assess as it is always part of a multitherapy strategy. Its therapeutic effect may have limits as CD20 is not present on pro-B cells or mature plasma cells; therefore, rituximab does not prevent the regeneration of B cells and may not directly decrease immunoglobulin levels. Data of its efficacy in the treatment of AMR in cardiac transplant recipients consists of case reports and retrospective observational studies [64, 95–101]. Results are mixed, with the most recently published series showing a survival benefit in those treated with rituximab [101].

B-cell depletion is also achieved with the administration of antibodies, which bind other antigens expressed on the surface of B cells and include the anti-CD52 antibody alemtuzumab as well as antithymocyte globulin [102–106]. Potential future agents target other B-cell inhibitory and costimulatory receptors [107–118]. With all of these agents, an awareness of the potential unwanted effects of B-cell depletion is needed [119]. For example, regulatory B cells may play an important role in promoting tolerance. Further research is needed to identify

optimal treatment regimens that balance the effects of B-cell depletion with rejection and graft survival.

Plasma cells are an additional, and perhaps preferred, target to reduce antibody production. Case reports describe the use of bortezomib, a proteasome inhibitor that preferentially targets alloantibody-producing plasma cells, in the successful treatment of AMR in cardiac transplant recipients [120–124]. As with other agents, toxicities have been reported, and randomized controlled trials are needed prior to widespread adoption.

T-cell inhibition

B-cell activity is tightly regulated by T-cells; therefore, therapy targeting T-cell activity is an important aspect of treatment for AMR. Antithymocyte globulin (ATG) has multiple T-cell targets, and may also be effective in the treatment of AMR beyond its inhibition of T-cells as it contains antibodies to B-cell and plasma cell antigens [125, 126]. It is generally used in moderate to severe cases of AMR associated with graft dysfunction and/or hemodynamic compromise. Unlike with ATG, there is no conclusive evidence for activity on T-cell-independent B-cell antibody production with the calcineurin inhibitors. The mTOR inhibitors such as rapamycin, however, may inhibit B-cell antibody production and proliferation via T-cell-independent mechanisms [127, 128]. Therefore, changing from MMF to rapamycin or the addition of rapamycin is a reasonable strategy in a patient with AMR.

Glucocorticoids bind to glucocorticoid receptors on T cells, antigen presenting cells, and immunosuppressive effects are many and varied. For AMR associated with hemodynamic abnormalities, high-dose corticosteroids (methylprednisolone 1000 mg IV daily for three consecutive days) should be used. In less severe cases, an oral bolus dose may be used.

In our experience, fatal acute AMR seems to be a prothrombotic state with microvascular thrombi often seen on necropsy, yet whether systemic anticoagulation helps in outcome remains unsettled.

Conclusion

Cardiac AMR now has ISHLT-sanctioned defining pathologic criteria. Consensus publications also recommend periodic monitoring of DSA especially early after transplantation and in high-risk recipients. Successes with therapies for cardiac AMR are moderate at best and limited to case reports and small series. The field is in much need of prospective randomized trials to standardize an optimal management approach to

this vexing clinical problem in heart transplantation. Emerging animal models of AMR will further our understanding of its pathophysiology and possibly help in devising new treatment strategies.

Compliance with Ethics Guidelines

Conflict of Interest AG Kfoury, D Budge, J Nativi-Nicolau, RA Alharethi, MEH Hammond, and DV Miller all declare no conflicts of interest.

Human and Animal Rights and Informed Consent All studies by the authors involving animal and/or human subjects were performed after approval by the appropriate institutional review boards. When required, written informed consent was obtained from all participants.

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- Of major importance

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