Published in final edited form as:

J Clin Apher. 2017 August ; 32(4): 279–281. doi:10.1002/jca.21488.

Role of C1q Complement Fixing Antibody Assay In Therapeutic Plasma Exchange Management Of Pediatric Cardiac Antibody Mediated Rejection

Oluwatoyosi A. Onwuemene, MD MS^{1,†}, Deneen Heath, MD², Carol Hartman, MS CPNP-AC², Edward C.C. Wong, MD³

¹Division of Hematology, Duke University Medical Center, Durham, North Carolina

²Division of Cardiology, Children's National Health System, Washington, District of Columbia

³Division of Laboratory Medicine, Children's National Health System, Washington, District of Columbia

Abstract

Pediatric cardiac transplant patients with antibody-mediated rejection (AMR) often undergo therapeutic plasma exchange (TPE) to remove pathologic donor specific antibodies (DSA). In cases where DSA persist, it is unclear how long TPE should be continued. We report a case of a 17-year-old cardiac transplant patient with AMR where use of a C1q complement fixing antibody assay helped guide TPE cessation. This report adds to the existing literature that highlights the potential clinical significance of C1q antibodies in AMR management.

Keywords

Plasmapheresis; heart transplantation; acute rejection; donor specific antibodies; HLA antibodies

INTRODUCTION

In the United States alone, over 400 pediatric cardiac transplants are performed annually [1]. Within the first post-transplant year, about 20% of pediatric cardiac allografts will experience a first episode of acute rejection [1]. Acute antibody-mediated rejection (AMR) is thought to be precipitated by the action of human leukocyte antigen (HLA) antibodies against the donor heart [2]. These so-called donor specific antibodies (DSA) are the target of AMR treatment strategies, which seek to suppress the T- and B-cell response, inhibit DSA production, and remove circulating alloantibodies [2]. Circulating antibodies can be removed by therapeutic plasma exchange (TPE) [2].

It is widely believed that TPE's therapeutic benefit stems primarily from HLA antibody removal [3]. However, TPE improves AMR-induced cardiac allograft dysfunction in some

[†]Corresponding Author: Oluwatoyosi Onwuemene, MD, MS, 40 Duke Medicine Circle, DUMC Box 3422, Durham, NC 27710, Telephone: (919) 684-5350, Fax: (919) 681-1177, Toyosi.Onwuemene@duke.edu.

but not all patients [4]. Limited data exist on which HLA antibodies may be most clinically significant in evaluating TPE response and thereby guide use of TPE for AMR treatment.

CASE REPORT

A 17-year-old male with familial dilated cardiomyopathy who underwent cardiac transplantation about 7 years prior to presentation was admitted for treatment of elevated DSA and decreased left ventricular ejection fraction (EF) of 53.6% (baseline in the 60s). Cardiac biopsy demonstrated International Society of Heart and Lung Transplantation (ISHLT) grade 2R cellular rejection with questionable C4d staining. He was treated with intravenous (IV) immune globulin and pulsed steroids. One month later, he developed worsening EF (42.3%) with increased proBNP (2,300 pg/mL; previously 1,150). He received a single dose of rituximab (375 mg/m²) and IV methylprednisolone (10 mg/kg) bid for 4 days. However, his condition deteriorated and he was transferred to the cardiac intensive care unit with worsening EF (now 35.2%) and increasing proBNP (6,807 pg/mL). IV furosemide and milrinone infusion were initiated. Cardiac biopsy showed ISHLT grade 0R with diffuse C4d staining, concerning for AMR. He initially underwent 5 consecutive days of TPE. All exchanges (1.0 – 2.0 plasma volumes) were performed with either 5% albumin or a combination of 5% albumin and fresh frozen plasma (when signs/symptoms of bleeding were present). TPE was followed by a standard protocol [5] consisting of pre-treatment with rituximab (375 mg/m²), which was then followed by treatment with TPE, methylprednisolone (5 mg/kg), and bortezomib (1.3 mg/m²) on days 1, 4, 7, and 11. TPE was also performed as stand-alone therapy on days 14–16. Over the next 7 months, based on clinical improvement, TPE was weaned from every week (2 months), to every other week (3 months), to every three weeks (2 months). During this time, patient achieved EF in the 57–58% range by the 8th month of TPE. With TPE, there was initial decrease in the titer and mean fluorescent intensity of DSA. Anti-DR4 and anti-DR53 DSA resolved but anti-DQ8 persisted. Subsequently, based on the literature [6], a modified C1qScreen™ assay (One Lambda, Canoga Park CA), which detects only the subset of HLA antibodies capable of binding human C1q with 100% sensitivity and specificity [6], was validated at Georgetown University Hospital Histocompatibility Laboratory. Assay results are typically available within 24 – 36 hours. Therefore, earlier serum samples were retroactively tested for C1q binding. C1q binding, which had been positive early in the clinical course, was found to have been negative during the last two months of TPE (See Figure). Therefore, TPE was held. Follow up cardiac biopsy showed that patient was negative for both cellular rejection and AMR. For 2 years following treatment, despite detectable anti DQ8 titers, which eventually resolved, the C1q assay remained negative. Three years later, patient is doing well with stable EF in the mid 60s.

DISCUSSION

Because much of the literature support is limited to retrospective case series and reports, AMR for pediatric cardiac transplantation remains an ASFA category III indication [3]. However, TPE is increasingly used for AMR management due to the high risk for allograft failure and mortality when cardiac transplant patients develop DSA [7].

One of the ways in which DSA causes endothelial damage and allograft injury is by activation of the complement cascade through complement fixation; however, not all DSA can fix complement [6]. Complement-fixing DSA may be important mediators of allograft injury [8] and can be identified by measurement of C1q binding. The C1q assay is able to detect a subset of antibodies that fix complement and may identify patients at risk for early AMR [6]. C1q positive DSA may confer a higher risk of rejection and graft loss compared to C1q negative DSA [9, 10]. In cardiac transplant recipients, C1q positive DSA were associated with early clinical post-transplant AMR [11]. A study of renal transplant patients with rejection demonstrated that C1q positive DSA are seen more frequently in patients with AMR [8].

It is not clear in this case whether clinical benefit and the negative C1q assay was due to TPE or the immunosuppression protocol used [5]; however, the use of C1q complement fixing antibody assays to assess the clinical significance of putative donor specific antibodies may allow appropriate use and safe withdrawal of TPE in pediatric cardiac transplant patients with AMR who have residual DSA and improving graft function. Prospective studies are needed to confirm these findings.

REFERENCES

1. Colvin M, Smith JM, Skeans MA, Edwards LB, Callahan ER, Snyder JJ, et al. Heart. American Journal of Transplantation. 2016;16:115–40. [PubMed: 26755266]
2. Colvin MM, Cook JL, Chang P, Francis G, Hsu DT, Kiernan MS, et al. Antibody-mediated rejection in cardiac transplantation: emerging knowledge in diagnosis and management: a scientific statement from the American Heart Association. Circulation. 2015 5 5;131(18):1608–39. [PubMed: 25838326]
3. Schwartz J, Winters JL, Padmanabhan A, Balogun RA, Delaney M, Linenberger ML, et al. Guidelines on the use of therapeutic apheresis in clinical practice-evidence-based approach from the Writing Committee of the American Society for Apheresis: the sixth special issue. J Clin Apher. 2013 7;28(3):145–284. [PubMed: 23868759]
4. Jackups R Jr, Canter C, Sweet SC, Mohanakumar T, Morris GP. Measurement of donor-specific HLA antibodies following plasma exchange therapy predicts clinical outcome in pediatric heart and lung transplant recipients with antibody-mediated rejection. J Clin Apher. 2013 8;28(4):301–8. [PubMed: 23426730]
5. Morrow WR, Frazier EA, Mahle WT, Harville TO, Pye SE, Knecht KR, et al. Rapid reduction in donor-specific anti-human leukocyte antigen antibodies and reversal of antibody-mediated rejection with bortezomib in pediatric heart transplant patients. Transplantation. 2012 2 15;93(3):319–24. [PubMed: 22179403]
6. Chin C, Chen G, Sequeria F, Berry G, Siehr S, Bernstein D, et al. Clinical usefulness of a novel C1q assay to detect immunoglobulin G antibodies capable of fixing complement in sensitized pediatric heart transplant patients. The Journal of heart and lung transplantation : the official publication of the International Society for Heart Transplantation. 2011 2;30(2):158–63.
7. Ho EK, Vlad G, Vasilescu ER, de la Torre L, Colovai AI, Burke E, et al. Pre- and posttransplantation allosensitization in heart allograft recipients: major impact of de novo alloantibody production on allograft survival. Human immunology. 2011 1;72(1):5–10. [PubMed: 20971146]
8. Yell M, Muth BL, Kaufman DB, Djamali A, Ellis TM. C1q-Binding Activity of De Novo Donor-Specific HLA Antibodies in Renal Transplant Recipients With and Without Antibody-Mediated Rejection. Transplantation. 2015 4 3.
9. O'Leary JG, Kaneku H, Banuelos N, Jennings LW, Klintmalm GB, Terasaki PI. Impact of IgG3 Subclass and C1q-Fixing Donor-Specific HLA Alloantibodies on Rejection and Survival in Liver

Transplantation. American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons. 2015 4;15(4):1003–13.

10. Susal C, Wettstein D, Dohler B, Morath C, Ruhenstroth A, Scherer S, et al. Association of Kidney Graft Loss With De Novo Produced Donor-Specific and Non-Donor-Specific HLA Antibodies Detected by Single Antigen Testing. Transplantation. 2015 2 12.
11. Zeevi A, Lunz J, Feingold B, Shullo M, Bermudez C, Teuteberg J, et al. Persistent strong anti-HLA antibody at high titer is complement binding and associated with increased risk of antibody-mediated rejection in heart transplant recipients. The Journal of heart and lung transplantation : the official publication of the International Society for Heart Transplantation. 2013 1;32(1):98–105.

Response of Ejection Fraction and Donor Specific Antibodies to Therapeutic Plasma Exchange.

The horizontal axis shows treatment dates. The *left* vertical axis shows the DQ8 donor specific antibody (DSA) titers while the *right* vertical axis shows the antibody mean fluorescent intensity (MFI). The green arrows show when plasma exchange was done while the red arrows demonstrate C1q binding measurements. C1q binding became negative about 2 months following initiation of treatment. Ejection fraction took time to gradually normalize. Anti DR4 and DR53 weakly positive titers (>1024) were last seen on 12/22 and 1/26 then 5/7, respectively.