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The Journal of Heart and Lung Transplantation
http://www.jhltonline.org

Biopsy-diagnosed antibody-mediated rejection based on the proposed International Society for Heart and Lung Transplantation working formulation is associated with adverse cardiovascular outcomes after pediatric heart transplant

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KEYWORDS:
pediatric;
heart transplant;
rejection;
cardiac allograft vasculopathy;
antibody-mediated

BACKGROUND: There is greater awareness of the pathologic features and clinical implications of antibody-mediated rejection (AMR) after heart transplantation (HT). Yet, compared with adults, the lack of routine surveillance for AMR has limited the growth of evidence in the pediatric population. Herein, we compared outcomes of pediatric HT recipients with and without AMR.

METHODS: All recipients ≤18 years of age with at least 1 endomyocardial biopsy (EMB) between 1988 and 2009 were included in this study. Assessment for AMR was routine. AMR severity was assigned retrospectively using the proposed 2011 ISHLT grading schema for pathologic AMR (pAMR). Outcome comparisons were made between patients with histologic and immunopathologic evidence for AMR (pAMR 2), those with severe AMR (pAMR 3), and those without evidence of AMR (pAMR 0) or without both histologic and immunopathologic findings (pAMR 1).

RESULTS: Among 1,406 EMBs, pAMR 2 or higher was present in 258 (18%), occurring in 45 of 76 (59%) patients. Of the 17 episodes of pAMR 3 in 9 patients, 6 (35%) were sub-clinical. Mortality was not different between groups. Patients with at least 1 pAMR 3 episode had lower freedom from cardiovascular (CV) mortality or cardiac allograft vasculopathy within 5 years of HT than those without pAMR 3 (45% vs 91%, $p < 0.001$).

CONCLUSIONS: Biopsy findings of AMR (pAMR 2 or higher) are common after pediatric HT. Like cellular rejection, biopsy grading of AMR seems important to delineate those at risk of adverse events. Our results suggest that pAMR 3 is associated with worse CV outcomes. Widespread surveillance for pAMR with a uniform grading system is an important next step to further validate these findings in the pediatric HT population.

J Heart Lung Transplant 2012;31:686–93

The pathologic description of antibody-mediated rejection (AMR) and its association with poor outcome after heart transplantation (HT) was first reported in 1989.[1] Since then, numerous studies in adult HT recipients have shown a higher prevalence of adverse cardiovascular (CV) events in

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http://dx.doi.org/10.1016/j.healun.2012.03.009

patients with AMR. Cardiac allograft survival is worse in adult HT recipients after recurrent episodes of AMR compared with cellular rejection.[2,3] Studies in adult patients have shown a higher incidence of hemodynamic compromise at the time of AMR[2,4,5] and worse left ventricular function at 1 year after an episode of AMR compared with patients with cellular rejection.[4] AMR after adult HT is associated with a significantly higher incidence of cardiac allograft vasculopathy (CAV) as well as shorter time to CAV.[2,6,7] In adults, repetitive episodes of AMR as well as the pathologic severity of AMR have been associated with incremental increases in CV mortality.[3,8]

In 2004, the pathologic criteria for the diagnosis of AMR were first included by the International Society for Heart and Lung Transplantation (ISHLT) in the standardized nomenclature for the diagnosis of heart rejection.[9] Recently, the importance of a pathologic scoring system for AMR severity, similar to that of cellular rejection, was put forth in an AMR consensus conference report.[10,11] To date, however, the clinical significance of AMR after HT in childhood remains limited due to relatively few pediatric recipients compared with adults and a lack of routine surveillance for AMR.

The purpose of this study was to determine the clinical significance of biopsy-diagnosed AMR with respect to CV mortality and the development of CAV after pediatric HT. Furthermore, we sought to identify predictors for the development of AMR in the pediatric HT population.

Methods

Study population

After approval by our institutional review board, we queried the cardiac transplant database of the Utah Transplant Affiliated Hospitals (U.T.A.H.) to identify all patients who underwent HT at age ≤18 years between January 1, 1988 and December 31, 2009. Patients with at least 1 endomyocardial biopsy (EMB) performed during follow-up at Primary Children's Medical Center were included in the study. Excluded from analyses were patients who died prior to the first EMB and those patients who did not undergo HT at one of the U.T.A.H. Cardiac Transplant Program hospitals such that information pertaining to EMB assessment of AMR was not available from the time of HT.

Although immunosuppression protocols have evolved over time, medical therapies were standardized within a given period. Patients received peri-operative cyclosporine and steroids throughout the study period. Prior to 2007, the primary maintenance regimen consisted of cyclosporine and azathioprine; since that time, tacrolimus and mycophenolate mofetil have been used more commonly. Steroids were tapered over 6 months after transplant. Patients with creatinine clearance <60 ml/min/1.73 m^2 or a positive crossmatch received antibody-based induction therapy consisting of OKT3 antibody prior to 1997 and horse or rabbit antithymocyte globulin thereafter.

AMR surveillance and grading

Biopsies were performed in a time-dependent fashion at weekly intervals for the first 4 weeks, then every other week times 2, and monthly for 2 months. Thereafter, routine biopsies were performed annually or as clinically indicated. Surveillance for AMR was performed routinely within the first 8 to 12 weeks after HT as previously described.[3,12] Thereafter, immunofluorescence (IF) studies were done if there was a history of AMR, vasculitis by light microscopy, or clinical evidence of hemodynamic compromise. A biopsy positive for AMR was determined by prominent HLA-DR staining and the co-localization of immunoglobulin (IgG or IgM) and complement (C3d, C1q or C4d) in a vascular distribution as highlighted using IF staining of frozen tissue sections.

Histologic and immunopathologic findings were recorded prospectively in the pathology database independently of the clinical status of the patient and the function of the graft, as defined elsewhere.[3,6,13] The pathology database includes not only the overall vascular score but also details multiple histologic and immunopathologic findings on a 5-point scale such that there is sufficient information to score the findings as external grading systems change over time, as occurred with the newly proposed ISHLT scoring system. Thus, all EMBs in this study were assigned a grade of pAMR 0, 1, 2 or 3, based on detailed descriptors of the histologic and immunopathologic findings rather than a simplistic conversion from one grading scale to another. Examples of pAMR severity as put forth by the ISHLT AMR working group are displayed in Figure 1.[10] Herein, we refer to patients with pAMR 2 or 3 as being positive for AMR. Those patients with no evidence for AMR (pAMR 0) and those with either histologic evidence alone or immunopathologic findings alone of AMR, but not both (pAMR 1), were considered not to have fulfilled the criteria for a diagnosis of AMR and are included in the "no AMR" group for the analyses.[10,11,14] A diagnosis of AMR at our institution did not require the ISHLT clinical requisite of allograft dysfunction and, thus, patients with asymptomatic episodes of AMR were included.

For outcome and risk factor analysis, patients were grouped according to the absence of both histologic and immunopathologic findings of AMR (no AMR = pAMR 0 or 1) and AMR severity with patients having at least 1 episode of pAMR 2 or higher in the ≥1 pAMR 2 group and those with at least 1 episode of pAMR 3 in the ≥1 pAMR 3 group.

Data collection

Data regarding demographics, clinical characteristics and outcome are entered prospectively at listing, at transplant, and at the time of clinical events into the transplant database. Additional information pertaining to clinical parameters at the time of AMR was collected retrospectively for purposes of this study. These data included the presence of echocardiography abnormalities as defined by the new finding of at least moderate mitral insufficiency, pericardial effusion, or decline in left ventricular ejection fraction (LVEF) to <50%. Hemodynamic data were considered abnormal when the cardiac index was <2 liters/min/m^2 or the pulmonary artery wedge pressure (PAWP) was >15 mm Hg. The medical record was also reviewed for clinical findings of heart failure at the time of an episode of AMR, including a new gallop or jugular venous distension.

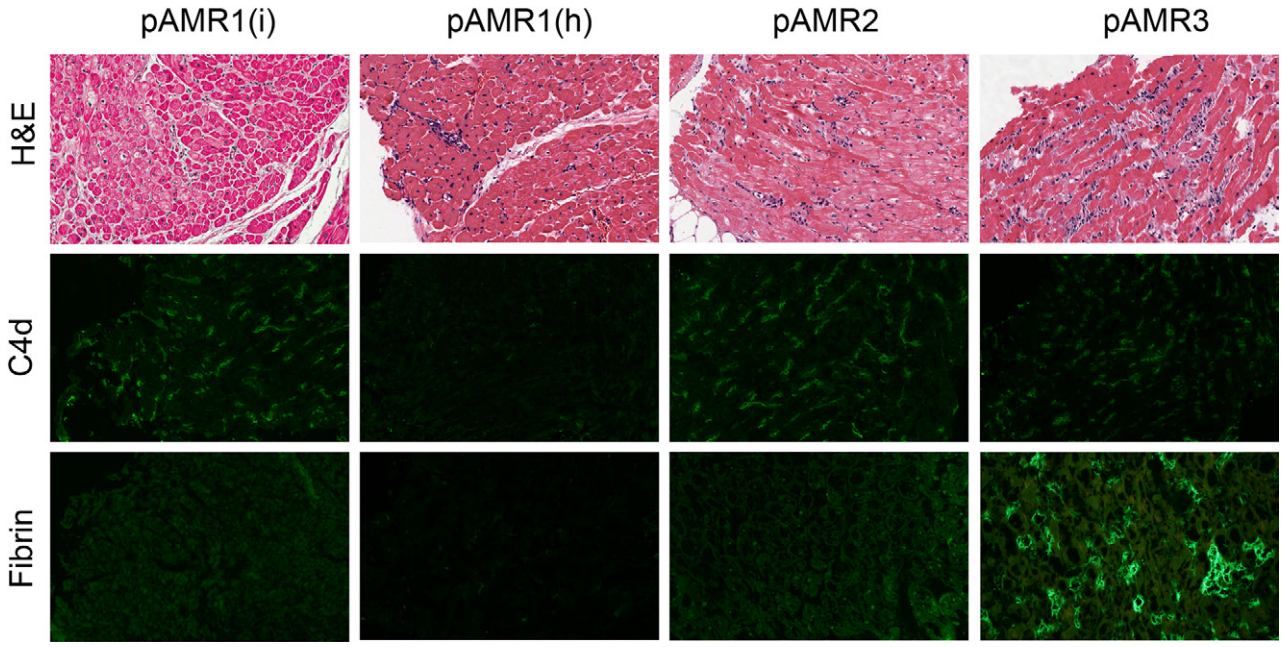

Figure 1 Grading of AMR according to the ISHLT 2010 working formulation. An array of representative bright-field and fluorescence photomicrographs demonstrating the characteristic features of AMR grades in the 2010 ISHLT working formulation is shown: pAMR1(i) is characterized by normal histology, but immunopathologic evidence of complement deposition (positive immunoflourescence [IF] staining for C4d) with negative staining for fibrin (top: hematoxylin–eosin [H&E], original magnification ×200; middle: C4d IF stain, original magnification ×200; bottom: fibrin IF stain, original magnification ×200); pAMR1(h) demonstrates histologic features of AMR (endothelial swelling and intravascular mononuclear cells) with negative immunopathologic studies (top: H&E stain, original magnification ×400; middle: C4d IF stain, original magnification ×200; bottom: fibrin IF stain, original magnification ×200); pAMR 2 is characterized by both histologic and immunopathologic features of AMR, but without extensive myocyte necrosis or fibrin extravasation (top: H&E stain, original magnification ×400; middle: C4d IF stain, original magnification ×200; bottom: fibrin IF stain, original magnification ×400); pAMR 3 is severe AMR with diffuse myocyte injury by histology and bright interstitial staining for fibrin (top: H&E stain, original magnification ×400; middle: C4d IF stain, original magnification ×200; bottom: fibrin IF stain, original magnification ×400).

CV events of interest

CV mortality was defined as death resulting from acute rejection, myocardial infarction, congestive heart failure, graft failure, arrhythmia or CAV. Retransplantation was also included in the end-point of CV mortality. Cause of death was determined by the primary HT physician at the time of death or by autopsy. Routine coronary angiography was performed 4 to 6 months after HT and then annually in all patients. Any degree of narrowing in a primary vessel or diffuse narrowing of branches of the coronary arteries detected by angiographic imaging was considered abnormal, consistent with the current ISHLT CAV nomenclature.[15]

Statistical analysis

We compared clinical characteristic differences of patients with and without AMR using the chi-square test for categorical variables and Wilcoxon's rank-sum test for continuous variables. Descriptive statistics presented include counts and percentages for categorical data. Continuous variables are described using the mean and standard deviation, or the median and interquartile range (IQR, 25th to 75th percentile), as appropriate. The end-points of interest were time to all-cause mortality, CV mortality and CAV or CV mortality. Kaplan–Meier survival curves were constructed for each of the 5 groups. A significance level of 0.05 was used for all analyses.

Results

Clinical characteristics of study cohort

Between January 1, 1988 and December 31, 2009, there were 85 pediatric HT recipients followed at the Primary Children's Medical Center, of whom 76 had at least 1 EMB for review. Among the 9 patients excluded, 5 patients died from primary graft failure at <1 week, 2 died suddenly within 1 month of HT without an EMB or autopsy, and 2 died due to pulmonary hemorrhage. Follow-up was complete through December 31, 2010. The median age at HT was 9.8 years (IQR 1.1 to 14.4 years). Recipients were mostly male (n = 44, 58%). The diagnosis leading to HT was congenital heart disease (CHD) in 43 (57%) patients and cardiomyopathy in 33. The panel-reactive antibody (PRA) level was >10% in 15 (20%) patients, and 3 (4%) transplants were performed with a positive retrospective crossmatch. Median follow-up time was 5.1 years (IQR 1.2 to 9 years).

Episodes of AMR

During the study period, 1,406 EMBs were performed among the cohort. The number of EMBs obtained per pa-

Table 1 Patients' Characteristics According to Presence of Biopsy-diagnosed AMR

	No AMR ($n = 31$)	AMR[a] ($n = 45$)	p-value
Male	17 (55%)	27 (60%)	NS
CHD diagnosis	15 (48%)	28 (62%)	NS
Age at HT, mean (years)	5.7	10.0	0.010
PRA >10%	6 (19%)	9 (20%)	NS
Positive crossmatch	1 (3%)	2 (4%)	NS
Induction used	13 (42%)	21 (47%)	NS

AMR, antibody-mediated rejection; CHD, congenital heart disease; HT, heart transplant; PRA, panel-reactive antibody.
[a]Includes all patients with at least 1 episode of pAMR 2 or 3.

tient ranged from 1 to 61 with a mean of 13 per patient and a median of 11 per patient (IQR 3 to 18). There were 258 EMBs consistent with findings of pAMR 2 or higher, including 17 with histologic and immunopathologic findings of pAMR 3. Forty-five (59%) patients had at least 1 episode of pAMR 2 or 3. The clinical characteristics of these patients are presented in Table 1. The time from HT to first pAMR 2 ranged from 7 days to 6.5 years, with a mean time from HT of 1.2 years, median of 38 days and IQR of 20 days to 1.3 years. The time from HT to first pAMR 3 ranged from 12 days to 3 years with a mean time from HT of 319 days, median of 39 days and IQR of 19 days to 1.3 years. The 17 episodes of pAMR 3 occurred in 9 patients. Among the 17 episodes of pAMR 3, 10 (59%) were associated with only mild (ISHLT Grade 1R) or no evidence of cellular rejection, and 3 (18%) were accompanied by evidence of severe cellular rejection (ISHLT Grade 3R). Thirty-five percent (6 of 17) of the biopsy-diagnosed episodes of pAMR 3 were sub-clinical and without apparent echocardiography, hemodynamic or clinical abnormalities. Patients' characteristics, timing of pAMR 3 and outcomes are shown in Table 2. Two episodes were manifest by a new pericardial effusion without tamponade. Depressed function, as measured by echocardiography, was present at the time of 5 biopsy-diagnosed episodes of pAMR 3, with elevated left ventricular end-diastolic pressure (LVEDP) and clinical signs of heart failure in 3 patients. The remaining 4 episodes of pAMR 3 were characterized by an elevated LVEDP and a gallop or jugular venous distension on examination without apparent echocardiographic abnormalities.

Cardiovascular outcomes

Overall survival for the entire cohort at 5 years post-transplant was 81%. Figure 2a shows that actuarial survival was similar in patients with no AMR, those with ≥1 episode of pAMR 2 and those with ≥1 episode of pAMR 3. Figure 2b shows that freedom from CV mortality at 5 years after transplant was 91% for patients with no AMR, 90% for patients with ≥1 episode of pAMR 2, and 62% for those with ≥1 episode of pAMR 3. However, with longer follow up, the event-free survival of the groups was not statistically different ($p = 0.16$). The composite outcome of CV mortality or the development of CAV (CV event-free survival) is depicted in Figure 2c. CV event-free survival was worse for patients with pAMR 3 compared to those with no AMR and those with pAMR 2. Freedom from CV mortality or CAV at 5 years post-HT was only 45% in patients with at least 1 episode of pAMR 3 compared with 91% for those without any episodes of AMR ($p < 0.0001$). The time from first pAMR 3 to CV death or CAV ranged from 0 days to 9 years, with a mean time to CV event of 3.3 years, median of 332 days and IQR of 135 days to 5.3 years.

Risk factors for pAMR 3

As pAMR 3 correlated with adverse CV outcome, factors associated with at least 1 episode of pAMR 3 were the focus of the risk factor analysis. There were 9 patients who had at least 1 episode of pAMR 3. Comparisons were made between patients with at least 1 episode of pAMR 3 and those with no AMR. Only older age at transplant was associated with a greater likelihood for the development of pAMR 3 (Table 3).

Discussion

This study of AMR in pediatric HT recipients includes a review of over 1,000 EMBs at a single center with routine

Table 2 Characteristics, Timing and Outcome of Those Patients With Asymptomatic pAMR 3

Patient[a]	Diagnosis	Time from HT to asymptomatic pAMR 3	Recurrent pAMR 2 or 3[b]	Time to next pAMR 2 or 3[c]	Time to CAV[d]	Time from HT to CV death
9-year-old girl	CM	1 month	Yes	3 years		11 years
16-year-old boy	CM	1 year	Yes	2 months		2 years
14-year-old girl	CM	1 month	No			Alive
13-year-old girl	CM	1 month	Yes	2 months		Alive
1-year-old girl	CHD	2 months; 2 years	Yes	2 years	1 year	3 years

[a]Age at HT and gender.
[b]Recurrent is defined as ≥3 episodes of pAMR 2 or 3 after the episode of asymptomatic AMR.
[c]Time from asymptomatic pAMR 3 to the next episode of pAMR 2 or 3.
[d]Time from asymptomatic episode of pAMR 3 to CAV.

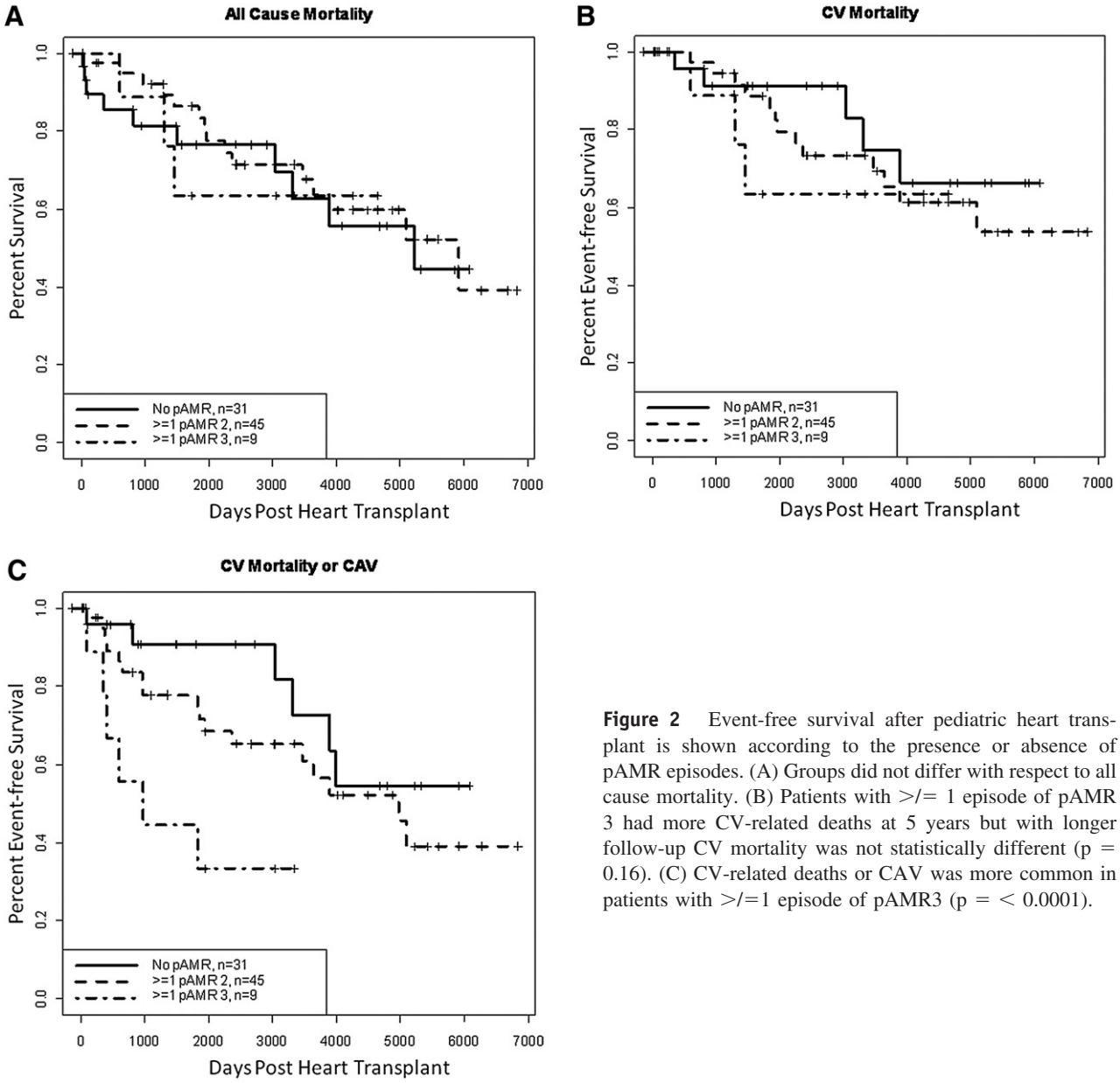

Figure 2 Event-free survival after pediatric heart transplant is shown according to the presence or absence of pAMR episodes. (A) Groups did not differ with respect to all cause mortality. (B) Patients with >/= 1 episode of pAMR 3 had more CV-related deaths at 5 years but with longer follow-up CV mortality was not statistically different ($p = 0.16$). (C) CV-related deaths or CAV was more common in patients with >/=1 episode of pAMR3 ($p = < 0.0001$).

surveillance for and standardized grading of AMR. Thus, the findings add important information to the limited fund of knowledge regarding AMR after HT in childhood and provide the first clinical outcomes relevant to the currently proposed ISHLT pAMR grading system.

Biopsy findings for pAMR 2 were common in this series of patients, seen in >50% of the grafts at some time-point. Using this definition of AMR, the prevalence of AMR (59%) after pediatric HT in this study is higher than the 35% prevalence previously reported in pediatric HT recipients by Casarez et al in 2007.[16] The prevalence is also higher than that reported by the majority of adult HT centers in a recent survey (<5%) focusing on AMR.[17] With respect to the lower prevalence cited by adult centers, routine surveillance for AMR is not widespread such that lower detection rates are not surprising, especially when episodes are asymptomatic. The reason for this nearly 2-fold difference in AMR between the two pediatric studies to date does not appear to be related to more vigilant routine biopsy surveillance, as the biopsy schedule was similar in both studies. With regard to routine surveillance at the time of biopsy for AMR using IF or immunohistochemistry staining, both centers performed this when vasculitis was identified by histologic features. However, the disparity may in part be due to differences in the threshold for determining vasculitic changes that triggered subsequent staining for AMR. Florid vasculitis has been found to be highly specific but insensitive in a study among our adult patient population.[13] Thus, in our study, IF staining was regularly performed within the first 8 to 12 weeks on all samples, irrespective of the light microscopy findings. Routine staining for immunopathologic evidence of AMR in the absence of histologic findings is proposed by the current ISHLT working group as is the classification of AMR as either pAMR 1h (histology-positive) or pAMR 1i (immunopathology-positive). The proposed revision to the ISHLT biopsy grading system will

Table 3 Analysis of Patients' Characteristics Associated With Development of ≥1 Episode of pAMR 3 Referenced to Patients Without AMR

	Odds ratio/ difference	95% confidence interval	*p*-value
Male	4.4	0.75–34	0.06
CHD diagnosis	0.33	0.04–1.87	0.25
Mean age at HT, difference	5.9 years	1.2–10.5	0.015
PRA >10%	1.7	0.13–14.2	0.617
Induction used	0.40	0.035–2.62	0.44

Positive crossmatch could not be analyzed as only 3 transplants were performed with a positive crossmatch and none of these developed pAMR 3. Only older mean age at HT was significantly different.

provide a common framework for evaluating and grading AMR severity, which is vital to our understanding of this entity, its prevalence and its clinical impact.

Our detection rate of AMR and the pattern of AMR scores were consistent over time. The percentage of patients with AMR did not change despite a known shift in immunosuppressive regimens, including a change in the type and usage of induction therapy and the primary choice of maintenance medications. Notwithstanding, the choice of immunosuppressive medications in this cohort of patients may have contributed to the aforementioned difference in AMR prevalence within our population compared with the findings by Casarez and colleagues. Our maintenance regimen included the use of cyclosporine and azathioprine in earlier years, whereas the study population described by Casarez et al used tacrolimus in conjunction with mycophenolate mofetil. When myocophenolate mofetil was utilized by our institution in later years, the dose given was lower, 600 mg/m^2 vs 750 mg/m^2. Similarly, the duration of steroid use was likely shorter in our patient population as steroids are generally discontinued within 6 months at our center as opposed to 6 to 12 months in their study. Randomized trials in kidney transplant recipients and in adult HT recipients have shown a decrease in acute cellular rejection with the use of tacrolimus instead of cyclosporine.[18–20] Mycophenolate mofetil has also been demonstrated to reduce acute rejection and improve survival after renal transplantation, and its use is associated with a reduction in coronary intimal thickening in HT recipients.[21,22] Although these medications are potentially more efficacious in the prevention of AMR, the role of various medical regimens to prevent and treat AMR could not be assessed by either pediatric study and they remain a target for future research.

Regarding outcomes after HT in children with AMR, those with at least 1 episode of pAMR 3 after HT had a higher rate of CV events, as defined by the development of CAV or CV death, than those without any episodes of pAMR 3. The association of CAV and CV mortality with AMR has been well described in the adult literature. In a study by Wu et al, the 5-year freedom from CAV in adult patients with AMR who were asymptomatic and untreated was lower (52%) compared with the freedom from CAV in patients without AMR (79%).[7] We have previously shown in analyses of primarily adult patients that AMR severity scores are associated with an incremental risk of CV mortality. Adult HT recipients with moderate or severe AMR (corresponding to pAMR 2 or 3) have a >10-fold risk of CV mortality when referenced against those without AMR and against those with severity grades that correspond to only mild or borderline AMR (pAMR 1).[3] In pediatric HT recipients, the study by Casarez et al indicated a higher rate of CV events in children with AMR in the first year after HT, namely more graft failure at 3 years (47% with AMR vs 29% without AMR, $p = 0.06$). The results, however, did not reach statistical significance, and no difference in CAV was detected between groups, occurring in 19% of both. Consistent with the previous results, CV mortality was worse at 3 years after HT in patients, also showing at least 1 episode of pAMR 3 in our study population. With longer follow-up, however, there was no difference in CV mortality alone between any of the groups. Nevertheless, freedom from CV mortality or the development of CAV was worse and remained statistically different with long-term follow-up between those with at least 1 episode of pAMR 3 and those without pAMR 3.

Our results corroborate the utility of biopsy surveillance after pediatric HT, routine assessment for AMR, and biopsy grading of AMR severity. The adverse impact of a biopsy diagnosis of pAMR 3 on CV outcome, despite the fact that more than one-third of the episodes were sub-clinical, underscores the benefit of routine surveillance for AMR by biopsy and appropriate immunostaining. In contrast, patients with lesser degrees of vasculitis and less severe immunopathologic findings (pAMR 2) had CV outcomes similar to those without any episodes of AMR. As is the case with cellular rejection, we found that pathologic grading of AMR may identify findings associated with worse CV outcome. This observation should be validated in a larger population of pediatric patients. Furthermore, it remains unknown how treatment should be altered in the setting of these findings with a well-functioning graft. Whether lesser degrees of pAMR (1h, 1i and 2) become quiescent over time or herald progression to pAMR 3 will also require a larger study population with more episodes of pAMR.

Older age at transplant was the only clinical factor found to predict development of pAMR 3 in our study. This is consistent with previously published age-related differences after HT in childhood, which include an increased risk of rejection within the first year, increased risk of rejection with severe hemodynamic compromise, greater prevalence of CAV, and shorter transplant half-life in older vs younger HT recipients.[23–27] Likewise, other investigators have found a trend toward younger transplant age and the presence of donor-specific antibodies (DSA) in pediatric HT recipients with a significant association between older donor age and the prevalence of DSA.[28] Future studies on the immunologic changes that occur with age may be important to understanding the pathophysiology of AMR.

Information pertaining to circulating DSA was not routinely collected in our work. It is debatable whether or not

the documentation of circulating DSA is required for a diagnosis of AMR. Furthermore, AMR can result from non-HLA antibodies for which screening is even less customary.[29–31] Nevertheless, evidence is emerging that circulating DSA in HT recipients is associated with worse graft survival.[28,32] Thus, the coupling of DSA monitoring to biopsy results with grading of AMR may aid in understanding the clinical consequence of the individual test results.

Limitations

A retrospective re-grading of EMB rather than a prospective re-grading is a limitation of our study. Nevertheless, only 7 pathologists and 1 senior pathologist have graded the EMBs since 1985, with only 3 pathologists at any one time. The senior pathologist provided consistent oversight and instruction of histologic and IF scoring throughout the study period. Instruction included double review by the senior pathologist with each individual pathologist for the first 6 months of grading prior to independent review by the new pathologist. Further education was provided as needed to minimize inter-observer variability. Any EMBs with findings that were merely suspicious of AMR were reviewed with at least 1 other pathologist to verify the grading. Accordingly, we believe that the variability of grading of individual elements that collectively define the AMR grade was reduced, and therefore we have not performed a formal, large-scale inter-observer study other than that described.

Another limitation is the small size of the population studied in this single-center pediatric analysis. The EMB features of pAMR 3 were infrequently present, and the prevalence of CV end-points of interest was low. Moreover, there were few patients with previously identified risk factors for rejection, such as sensitization or positive crossmatch. Thus, the ability to detect a significant difference in outcome between groups was potentially limited, as was our ability to identify risk factors for AMR. Low event rates and small sample size also hindered our ability to study potential confounding variables such as cellular rejection. Notwithstanding, the presence of AMR with cellular rejection has previously been shown in the adult population to be associated with similar CV mortality when compared with AMR alone. Both AMR with cellular rejection and AMR alone have been associated with worse CV outcome than cellular rejection without AMR.[33] Our study does not include information pertaining to circulating DSA. We recognize that circulating antibody information may provide additional insight.

In conclusion, our study of pediatric HT recipients builds upon the ISHLT's 2010 consensus conference conclusion supporting the routine assessment of biopsies for AMR and grading of AMR severity. Our findings suggest that pathologic AMR is clinically relevant in the pediatric HT population. Children with at least 1 episode of pAMR 3 had a higher prevalence of CAV and CV mortality compared to those with no AMR. Routine surveillance for AMR and the pathologic grading of AMR severity are important steps toward improved understanding of the clinical significance of AMR and the effects of anti-rejection therapies in children after HT.

Disclosure statement

The authors have no conflicts of interest to disclose.

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