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## Case Report

# Rejection and graft vasculopathy secondary to effects of Crohn's disease in a heart-transplanted child



Shannon Oliver<sup>1,2,\*</sup>, Jennifer Conway<sup>1,2</sup>, Darren Freed<sup>1,3,4</sup>, Anne Halpin<sup>5,6</sup>,  
Hien Huynh<sup>1,7</sup>, Michael Khoury<sup>1,2</sup>, Cheryl Kluthe<sup>7</sup>, Esme Dijke<sup>5,6</sup>, Lori West<sup>1,2</sup>,  
Simon Urschel<sup>1,2</sup>

<sup>1</sup> Department of Pediatrics, University of Alberta, Edmonton, AB, Canada

<sup>2</sup> Division of Pediatric Cardiology, Stollery Children's Hospital, Edmonton, AB, Canada

<sup>3</sup> Division of Pediatric Cardiac Surgery, Stollery Children's Hospital, Edmonton, AB, Canada

<sup>4</sup> Department of Cardiac Surgery, University of Alberta, Edmonton, AB, Canada

<sup>5</sup> Alberta Precision Laboratories, Edmonton, AB, Canada

<sup>6</sup> Department of Laboratory Medicine and Pathology, University of Alberta, Edmonton, AB, Canada

<sup>7</sup> Division of Pediatric Gastroenterology, Stollery Children's Hospital, Edmonton, AB, Canada

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## ABSTRACT

Patients require immunosuppression after heart transplantation. Conditions such as Crohn's disease can impact tacrolimus absorption and pharmacokinetics. Subtherapeutic tacrolimus levels can lead to rejection and development of donor-specific antibodies (DSA), resulting in the development of cardiac allograft vasculopathy. We present a boy who underwent an ABO blood group incompatible heart transplant at 10 months of age, and developed diarrhea and subtherapeutic tacrolimus levels with subsequent development of de novo DSA, and then acute cellular and antibody-mediated rejection. He was diagnosed with Crohn's disease, which required vedolizumab for control. Despite aggressive reduction of his DSA, he developed rapidly progressive cardiac allograft vasculopathy and required retransplant, with a high prevalence of plasma cells in the explanted heart. Donor-directed blood group antibodies remained negative. This case demonstrates the importance of early consideration of inflammatory bowel disease for patients with diarrhea and subtherapeutic tacrolimus levels, as prompt diagnosis and treatment may prevent secondary graft injury.

**Abbreviations:** ACR, Acute cellular rejection; AMR, antibody-mediated rejection; CAV, cardiac allograft vasculopathy; CYP3a, cytochrome P450, family 3, subfamily A; CMV, cytomegalovirus; DSA, donor-specific antibodies; EAT, ectopic atrial tachycardia; ECG, Electrocardiogram; HLA, human leukocyte antigen; HTx, heart transplant; IBD, inflammatory bowel disease; ISHLT, International Society for Heart and Lung Transplantation; IVIG, intravenous immunoglobulin; MMF, mycophenolate mofetil.

\* Corresponding author. Shannon Oliver, Division of pediatric cardiology, Stollery Children's Hospital, 8440 112 St, Edmonton AB, T6G 2B7, Canada. Tel.: 780-407-4848.

E-mail address: [shannonoliver2020@gmail.com](mailto:shannonoliver2020@gmail.com) (S. Oliver).

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## 1. Introduction

Cardiac allograft vasculopathy (CAV) develops in approximately one-third of pediatric heart transplant (HTx) patients within 10 years post-HTx.<sup>1</sup> The development of CAV involves the complex interplay between immunological and non-immunological factors.<sup>1</sup> Development of donor-specific antibodies (DSA) can lead to acute antibody-mediated rejection (AMR), which is associated with increased risk of CAV.<sup>2</sup> In contrast, ABO blood group incompatible HTx is not associated with increased risk of rejection or CAV compared with ABO-compatible HTx.<sup>3</sup>

Crohn's disease is a form of inflammatory bowel disease (IBD) that typically affects the terminal ileum and proximal colon.<sup>4</sup> It rarely occurs in children on immunosuppression, as agents such as tacrolimus have been shown to be effective in the management of Crohn's disease.<sup>5</sup> Tacrolimus is part of the standard post-HTx immunosuppression regimen and is metabolized by P-glycoprotein and CYP3a in the small intestinal wall and the liver.<sup>6,7</sup>

We present a case in which a pediatric recipient of an ABO-incompatible HTx developed Crohn's disease, with subsequent reduced tacrolimus absorption. As a consequence of this, he developed de novo DSA and rapidly progressive CAV and graft failure in the absence of anti-donor ABO antibodies.

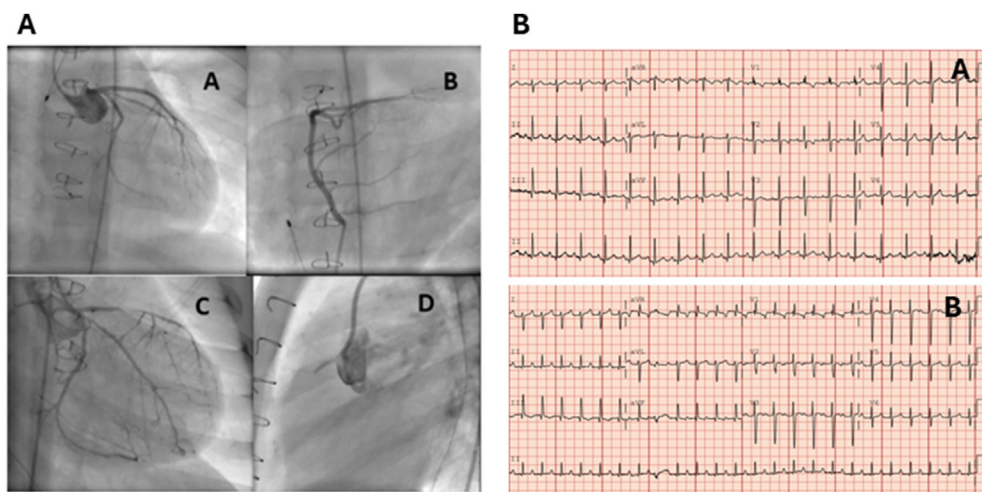
## 2. Case

A 10-month-old boy underwent an ABO-incompatible (donor blood group ABO-A, recipient ABO-O) HTx for dilated cardiomyopathy. He had an uncomplicated early post-HTx period with no evidence of DSA, acute cellular rejection (ACR), AMR, or CAV at his 1-year post-HTx review. He asymptotically acquired cytomegalovirus (CMV) at around this time with a negative viral load. He developed diarrhea and a perianal abscess 15 months post-HTx, with tacrolimus trough levels dropping to 4 ng/mL (target: 6–8 ng/mL) and remained there for 4 weeks, despite dose increases and no medication adherence concerns. His

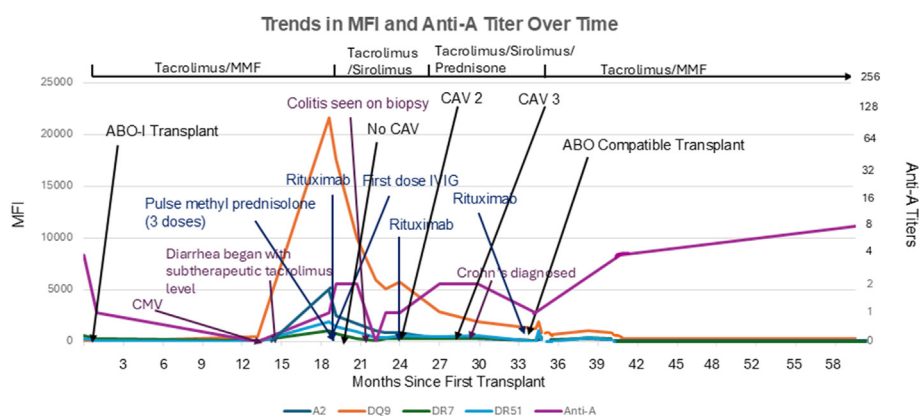
mycophenolate mofetil doses were above 20 mg/kg/day. He developed persistent tachycardia and new electrocardiogram changes in keeping with an ectopic atrial tachycardia (Fig. 1), 18 months post-HTx, raising concerns for rejection. A biopsy demonstrated International Society for Heart and Lung Transplantation criteria for ACR 2R and AMR 2. De novo DSA was detected against human leukocyte antigen A2, DR7, DR51, and DQ9. His anti-A antibody titer remained at 1:1. He underwent AMR therapy as demonstrated in Figure 2, with repeat biopsy 1 month later showing ACR 0R and AMR 0. Coronary angiography at this time revealed no CAV. Within 9 months of this angiogram, he rapidly progressed to the International Society for Heart and Lung Transplantation classification CAV 3 (Fig. 1). He had ongoing arrhythmias and developed evidence of diastolic dysfunction on the echocardiogram. His immunosuppression therapy was escalated from tacrolimus/mycophenolate mofetil to tacrolimus/sirolimus to reduce CAV progression. He was additionally commenced on oral steroids at higher than usual post-HTx doses in context of his gastrointestinal issues.

In parallel to this, he developed a second perianal abscess, with ongoing intermittent diarrhea and underwent 2 colonoscopies and biopsies, resulting in a diagnosis of Crohn's disease, 1-year after the onset of symptoms, in the context of a family history negative for IBD or other associated autoimmune conditions. His Crohn's disease proved steroid-dependent, despite the use of sulfasalazine, however responded well to vedolizumab, an alpha-integrin inhibitor.

With worsening cardiac status, he was listed and underwent retransplantation 3 years after the primary transplant, from an ABO-compatible donor with a negative crossmatch. The explanted heart demonstrated a high burden of plasma cells despite the confirmed absence of B cells in peripheral blood. Now, 5 years post-retransplant, he has no evidence of rejection or CAV, his gastrointestinal symptoms remain controlled on monthly vedolizumab and sulfasalazine therapy, and tacrolimus levels remain within the therapeutic target. He has not developed DSA to his second graft and his anti-A antibody titer has increased to 1:8.



**Figure 1.** Cardiac investigations at baseline and after development of de novo DSA. Figure 1A Cardiac angiograms at baseline and at 9 months after the development of de novo donor-specific antibodies (DSA). (A) Selective coronary angiogram 1 year post-transplant demonstrating a normal left coronary artery. (B) Selective coronary angiogram 1 year posttransplant demonstrating a normal right coronary artery. (C) Selective coronary angiogram 9 months after the detection of de novo DSA demonstrating >50% stenosis of both branches of the left coronary artery. (D) Selective coronary artery angiogram 9 months after detection of de novo DSA demonstrating complete occlusion of the right coronary artery. Figure 1B Electrocardiograms (ECGs) at baseline and at time of development of de novo DSA (A) Baseline ECG at 1 year posttransplant demonstrating sinus rhythm. (B) ECG at time of development of de novo DSA demonstrating ectopic atrial tachycardia.



**Figure 2.** DSA and anti-A antibody trends. Demonstrates the trend of de novo donor-specific antibodies (DSA) and anti-A antibodies over time and response to anti-rejection therapy with steroids (for acute cellular rejection component), B cell depletion with rituximab and immune modulation with intravenous immunoglobulin (IVIg), and the evolution of baseline immunosuppression. It further examines the impact of an ABO-incompatible (ABO-i) transplant on anti-A antibodies, and how they develop following removal of the ABO-A graft when an ABO-compatible transplant was performed. It additionally highlights the key points in the development of CAV and Crohn disease.

### 3. Discussion

Crohn's disease in a pediatric HTx recipient is rarely reported and is unusual to develop in a child receiving immunosuppression. This comorbid condition was the likely cause of his subtherapeutic tacrolimus levels, subsequent rejection, development of de novo DSA, and rapid CAV progression.

Subtherapeutic tacrolimus levels can be detrimental to graft survival, with patients being 6.9 times more likely to experience acute rejection within 2 weeks after a subtherapeutic tacrolimus level and 6.1 times more likely to experience acute rejection within 3 months.<sup>6</sup> Children presenting with diarrhea (usually infectious) typically have elevated tacrolimus levels due to reduced CYP3a activity along the intestinal wall causing increased tacrolimus absorption. In contrast, in our patient with diarrhea as a symptom of IBD, reduced tacrolimus absorption appeared to be the dominant effect. The gut microbiome has been demonstrated in animal models to be associated with tacrolimus absorption, potentially associated with alterations in the expression of P-glycoprotein.<sup>7</sup> As Crohn's disease is known to alter the gut microbiome,<sup>8</sup> it is possible that in this case the alterations resulted in increased expression of P-glycoprotein and subsequently reduced tacrolimus absorption and development of rejection.

A diagnosis of Crohn's was particularly challenging to make in our patient, given the negative family history. What is of interest is that he acquired CMV several months prior to the development of diarrhea and his first perianal abscess. There is some evidence in adult literature that acute CMV infection may trigger the development of IBD, so potentially this was the trigger, despite the absence of a CMV viral load or presence of CMV in the biopsy samples.<sup>9</sup>

In our patient, despite early and intense DSA-reducing therapies and the absence of AMR in subsequent biopsies, we were unable to prevent the progression of CAV and subsequent graft loss. The presence of plasma cells in the explanted heart, despite complete depletion of peripheral B cells, demonstrates that the highly activated plasma cells in the graft, with continuous antigen stimulation, may not be eradicated by B cell depleting and immune-modulating therapies. As presence of plasma cells in coronary biopsies is associated with CAV,<sup>10</sup> this highlights the

need for aggressive management. Treatment with proteasome inhibitors (eg, bortezomib) is typically not first-line due to the risks of peripheral neuropathy<sup>11</sup> (although in our case, this was being considered at the time of retransplant); however, in light of the histopathology, we would consider earlier use of this or anti-CD38 antibodies (eg, daratumumab), should we be presented with this case again. We additionally wonder whether the proinflammatory state from Crohn's disease may have contributed to the rapid development of CAV, given the difficulty with gaining control of his disease,<sup>12</sup> or whether the microbiota, which is known to be associated with graft outcome in solid organ transplants,<sup>13</sup> may have been altered by his Crohn's disease to unfavorably impacted his graft survival.

It is also notable that despite the immune activation against his heart graft, antibodies against his donor blood group were not stimulated; his anti-A titers remained absent until explant of the heart, following which they began to develop after implantation of a blood group O heart. This is in keeping with previous literature, which suggests that for patients who receive an ABO-incompatible HTx, there is modulation of the normal isohemagglutinin response independent of B cell suppression, which persists as long as the donor heart remains in the recipient.<sup>14</sup>

Suitability for retransplantation is challenging, especially in patients with earlier graft failure.<sup>15</sup> By identifying Crohn's disease as the cause of his tacrolimus malabsorption and controlling his symptoms with vedolizumab, the gastrointestinal situation did not represent a contraindication to retransplantation. The clear association of the CAV with the AMR and de novo DSA allowed for the hypothesis that selection of a second graft that did not express these human leukocyte antigen specificities would provide an acceptable immunological risk and likely absence of AMR recurrence. The 5-year course without AMR, absence of DSA to the second graft, and absence of CAV supports the clinical decision to offer retransplantation. In addition, we would advocate for having a low threshold for referring patients to gastroenterology services for further investigations in the event of patients presenting with low tacrolimus levels and gastrointestinal symptoms. Prompt diagnosis of an underlying IBD and effective treatment may result in prevention of subtherapeutic immunosuppression and subsequent graft injury.

## Declaration of competing interest

The authors of this manuscript have no conflicts of interest to disclose as described by *American Journal of Transplantation*.

## Data availability

All data generated or analyzed during this study are included in this article and the supplementary material. Further inquiries can be directed to the corresponding authors.

## ORCID

Shannon Oliver  <https://orcid.org/0009-0007-1294-8164>

Hien Huynh  <https://orcid.org/0000-0002-7295-7595>

Michael Khoury  <https://orcid.org/0000-0001-6112-6860>

Lori West  <https://orcid.org/0000-0002-1990-3651>

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