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Restoration of Gluten Tolerance Following Heart Transplantation in a Child With Celiac Disease

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Celiac disease (CD) is a common, lifelong disorder of the small bowel, stemming from an autoimmune response to gluten proteins found in wheat, barley, and rye. Confirmation of the diagnosis is followed by establishment of a lifelong gluten-free diet, the only scientifically proven therapy for CD. We describe a child with biopsy-proven CD achieving remission following heart transplantation, despite a lack of dietary gluten exclusion.

CASE

A child with hypoplastic left heart syndrome completed 3-stage repair at 15 months of life. He underwent median sternotomy with tricuspid valve replacement at the age of 3 years and again at 7 years. Postoperatively, his weight dropped from the 25th to below the 3rd percentile. At the age of 8 years, onset of abdominal distension and chronic diarrhea led to concern for protein-losing enteropathy and supplementation with total parenteral nutrition. Further workup revealed a tissue transglutaminase (tTG) IgA antibody level of >100 U (normal <20 U) and deamidated gliadin peptide (DGP) IgG antibody level of 70 U (normal <20 U; Figure 1). A diagnostic upper endoscopy was performed, and histologic examination revealed diffuse villous blunting and increased intraepithelial lymphocytes in the second portion of the duodenum, confirming a diagnosis of CD. A colonoscopy done at the same time was visually within limits, and the results of the histopathologic examination was read as normal. Genetic testing revealed the presence of DQ2.2 and DQ8 heterodimer, confirming permissibility for CD. No family history of CD or autoimmune disease was reported. After 2 years on a gluten-free diet, CD antibodies of the patient had normalized. With continued poor weight gain, an upper endoscopy was repeated, showing normal biopsies in the small intestine (Figure 2).

At the age of 14 years, he underwent orthotopic heart transplantation. The postoperative course was complicated by ventricular tachycardia, atrioventricular block requiring pacemaker placement, cytomegalovirus viremia, adrenal insufficiency, hypothyroidism (pretransplant thyroid studies were normal), and excision of an extramedullary spinal tumor. Chronic weight loss after transplantation led to placement of gastrostomy tube and introduction of overnight formula feeding, prompting a 20 kg weight gain over the next 3 years.

At the age of 17 years, frustrated by a limited diet and prolonged dependence on tube feeding, the patient independently reintroduced gluten into his diet (estimating over 20 g/day). He presented for follow-up of CD 6 months later. Serology revealed a tTG IgA antibody level of 23 U, a DGP IgG antibody level of 10 U with a negative Endomysial IgA antibody titer. Biopsies obtained from endoscopy displayed intact duodenal villi without the presence of intraepithelial lymphocytes. At subsequent follow-up 22 months after reintroduction of gluten, he remained asymptomatic, with a tTG IgA antibody level of 14 U and a DGP IgG antibody of 8 U. Immediately posttransplant, he was started on antirejection therapy with high dose steroids (wean completed by 3 months), tacrolimus 1 mg twice a day and mycophenolate mofetil 10 mg/kg twice a day. A year later, with concern for side effects, the mycophenolate mofetil was discontinued, and the subject was transitioned to azathioprine 25 mg daily. At the time of this report, he continues on immune suppression with tacrolimus 1.5 mg twice a day and azathioprine 75 mg daily.

DISCUSSION

We report histologic remission of biopsy-proven CD in a child 5 years after heart transplantation, despite reintroduction of a gluten-containing diet for 22 months. Historically, relapse can be expected to occur within 2 years of gluten reintroduction (1). Although this remains a possibility, considering the long history of poor growth prior to gluten restriction, severity of symptoms prompting CD diagnosis, and current unrestricted gluten intake, a delayed relapse is less likely to explain the clinical picture.

Instead ongoing remission may be, in part, related to posttransplant immune suppression with tacrolimus and azathioprine. Azathioprine, a medication that disrupts purine synthesis and causes downregulation of T- and B-cell clonal expansion, has been successfully used to induce remission in adult patients with refractory CD (2). This effect is also described in a cohort of patients with end-stage liver disease and positive tTG and EMA IgA antibodies and undergoing liver transplantation. In these cases, antibody levels normalized following successful transplantation, despite the subjects consuming a gluten-containing diet (3). The authors hypothesize that this finding may be driven by a combination of immunosuppression along with correction of structural and functional anomalies following transplantation, such as improved intestinal permeability. The latter may also be an important mechanism of remission in the case presented here. It is worth noting that these authors also describe cases of silent CD posttransplant eventually progressing to intestinal lymphoma, suggesting that resolution of symptoms and normal serologies may

Received June 10, 2020; accepted July 23, 2020.

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The authors report no conflicts of interest.

JPGN Reports (2020) 1:2(e004)
ISSN: 2691-171X
DOI: 10.1097/PG9.0000000000000004

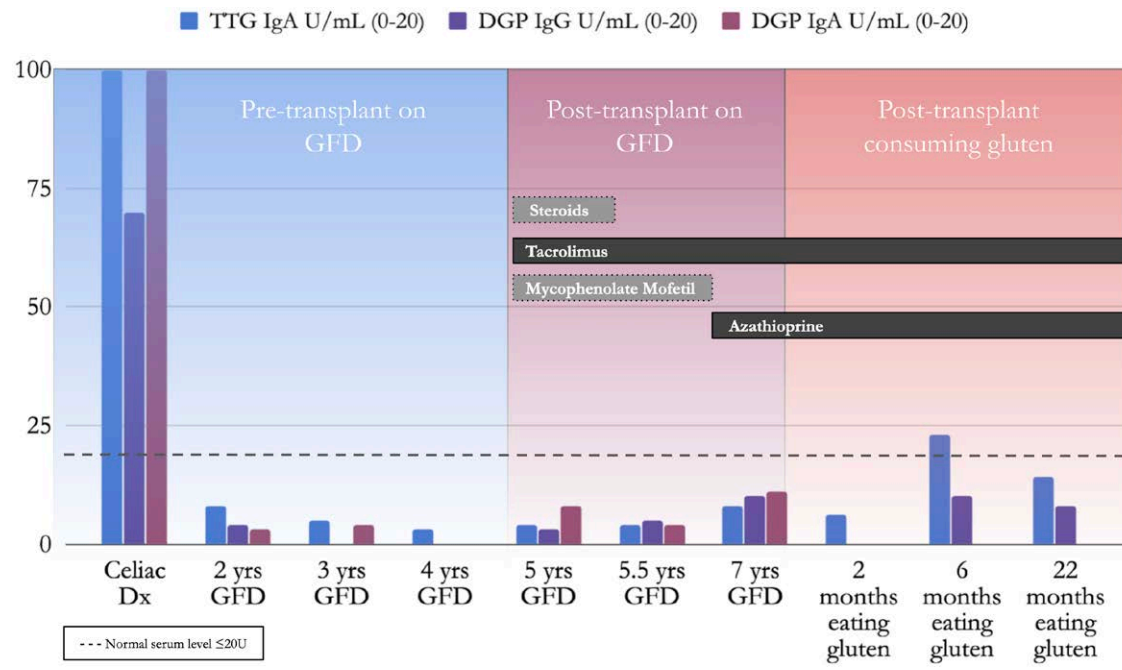

FIGURE 1. Celiac antibody levels on the y axis over distinct periods of time (x axis): pretransplant on gluten-free diet (shaded blue), posttransplant on gluten-free diet (shaded plum), and posttransplant after resuming gluten in diet (shaded coral). Post-transplant immune suppression is shown in closed rectangles, with current medications in black and previous medications in gray. DGP = deamidated gliadin peptide; dx = diagnosis; GFD = gluten-free diet; TTG = tissue transglutaminase.

not be sufficient for determining remission. While tacrolimus is not explicitly studied in refractory CD, another calcineurin inhibitor, cyclosporine, has shown efficacy, likely mediated by inactivation of cytotoxic T cells (4).

Examples of restored gluten tolerance in patients with comorbid CD have been described following hematopoietic stem cell transplantation (HSCT). For instance, in a child undergoing allogenic HSCT for acute myelogenous leukemia, clinical remission of CD has been reported at 4 years posttransplantation (5). In addition, CD remission has also been described in allogenic HSCT derived from umbilical cord blood of a partially human leukocyte antigen-matched matched sibling (6). In this child with chronic granulomatous disease and CD, clinical remission was sustained on a gluten-containing diet 8 years after transplantation. In adult subjects with refractory CD with aberrant T cells (RCD type II), autologous HSCT has demonstrated clinical and histologic improvement (7). The mechanism for gluten tolerance in these cases may be mediated through reconstitution of T-cell lymphocyte lineages following transplantation. These findings are highlighted in a case series of allogenic HSCT of 2 children with B-thalassemia major and sustained histologic remission of CD 2 years after reintroduction of gluten (8).

Though, the benefits of HSCT for CD may be well characterized, to our knowledge, this is the first report describing histologic remission of CD following solid organ transplantation. As CD is a lifelong disorder affecting people of all ages across the globe, this finding is relevant for any patient with CD and comorbid disease requiring solid organ transplantation. Of particular importance, in pediatric subjects, when growth failure becomes a challenge following transplantation, liberalization of the diet to include gluten may be a safe, reasonable consideration. However, this should only be implemented if appropriately monitored with periodic endoscopic surveillance, as CD antibodies may be unreliable in the setting of immune suppression.

ACKNOWLEDGMENTS

The subject of this case report and their parents provided informed consent to publish the included information.

Joseph Runde, DO, as guarantor accepts full responsibility for the conduct of the article and had access to all data, as well as final control on decision to publish. Joseph Runde, DO, is responsible for acquisition, analysis, interpretation of data for the work, drafting the article, revising the article, and final approval of version to be published. Ram Al-Sabti, MD, is responsible for the interpretation of data for the work, production of figure containing histopathologic findings, and final approval of the version to the published. Valentina Discepolo, MD, PhD, is responsible for the conception and design of work, interpretation of data for the work, critical manuscript revision for intellectual content, and final approval of the version to be published. Stefano Guandalini, MD, is responsible for the contributions to the design of work, critical manuscript revision for intellectual content, and final approval of the version to be published. Ruba Azzam, MD, MPH, is responsible for the conception and design of work, interpretation of data for the work, critical manuscript revision for intellectual content, and final approval of the version to be published.

There is no potential conflict of interest, real or perceived, on the part of any author. There are no commercial products mentioned in the manuscript. There are no prior publications or submissions with significant overlapping information. This work is not and will not be submitted to any other journal while under consideration by the *Journal of Pediatric Gastroenterology and Nutrition*.

REFERENCES

1. McNeish AS, Harms HK, Rey J, et al. The diagnosis of coeliac disease. A commentary on the current practices of members of the European Society for Paediatric Gastroenterology and Nutrition (ESPGAN). *Arch Dis Child* 1979;54(10):783–786.

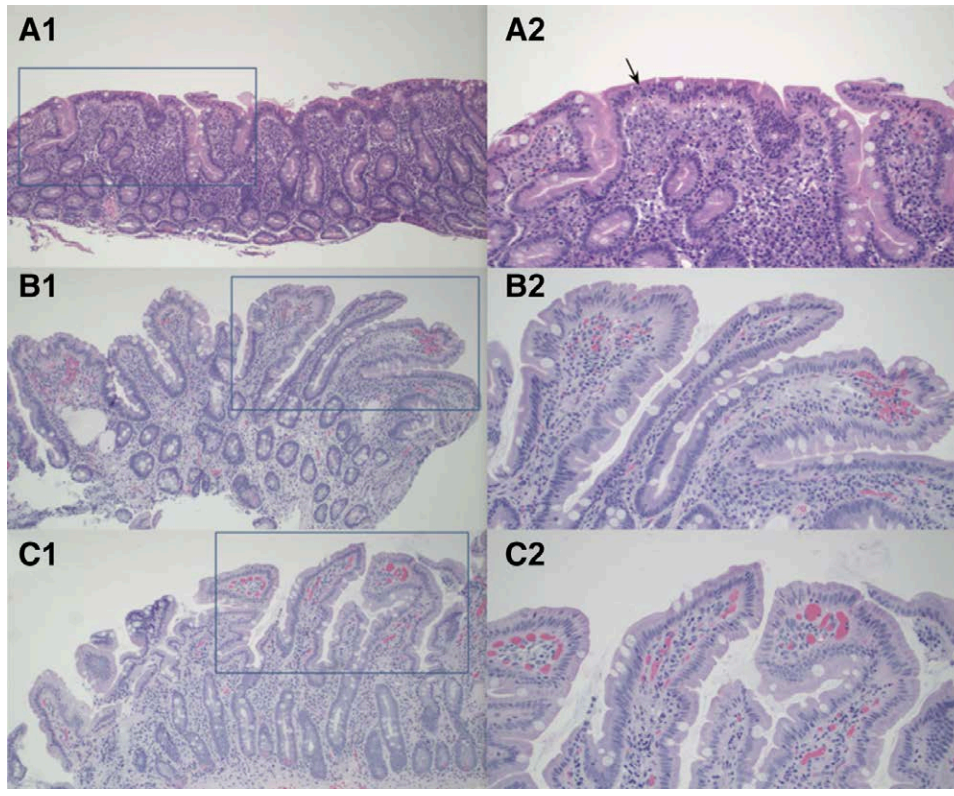

FIGURE 2. Duodenal biopsies at distinct time points. A1 and A2, Diagnosis of Celiac disease showing increased intraepithelial lymphocytes (black arrow) and villous blunting at low and high power (section contained within box). B1 and B2, Two years on a gluten-free diet with normalization of villi and clearance on intraepithelial lymphocytes. C1 and C2, Sustained remission of Celiac disease with restoration of gluten tolerance following heart transplantation.

2. Maurino E, Niveloni S, Cherñavsky A, et al. Azathioprine in refractory sprue: results from a prospective, open-label study. *Am J Gastroenterol* 2002;97(10):2595–2602.
3. Rubio-Tapia A, Abdulkarim AS, Wiesner RH, et al. Celiac disease autoantibodies in severe autoimmune liver disease and the effect of liver transplantation. *Liver Int* 2008;28(4):467–476.
4. Bernstein EF, Whitington PF. Successful treatment of atypical sprue in an infant with cyclosporine. *Gastroenterology* 1988;95(1):199–204.
5. Kline RM, Neudorf SM, Baron HI. Correction of celiac disease after allogeneic hematopoietic stem cell transplantation for acute myelogenous leukemia. *Pediatrics* 2007;120(4):e1120–e1122.
6. Janeczko-Czarnecka M, Kalwak K, Ussowicz M. Familial Celiac disease remission as a result of a full donor immunologic recovery after sibling cord blood transplantation for chronic granulomatous disease: a case report. *Transplant Proc* 2019;51(9):3155–3158.
7. Tack GJ, Wondergem MJ, Al-Toma A, et al. Auto-SCT in refractory celiac disease type II patients unresponsive to cladribine therapy. *Bone Marrow Transplant* 2011;46(6):840–846.
8. Ciccocioppo R, Bernardo ME, Russo ML, et al. Allogeneic hematopoietic stem cell transplantation may restore gluten tolerance in patients with celiac disease. *J Pediatr Gastroenterol Nutr* 2013;56(4):422–427.