



Research Article

Post-transplant eosinophilic gastrointestinal disorders and lymphoproliferative disorder in pediatric liver transplant recipients on tacrolimus

Paul Wasuwanich^{a,1}, Irini Batsis^{b,1}, Supharerk Thawillarp^c, Mary K. Alford^b, Douglas Mogul^b, Robert A. Wood^d, Wikrom Karnsakul^{b,*}

^a University of Florida College of Medicine, Gainesville, FL, USA

^b Division of Pediatric Gastroenterology, Hepatology, and Nutrition, Department of Pediatrics, Johns Hopkins University School of Medicine, Baltimore, MD, USA

^c Department of Health Policy and Management, Bloomberg School of Public Health, Johns Hopkins University, Baltimore, MD, USA

^d Division of Pediatric Allergy and Immunology, Department of Pediatrics, Johns Hopkins University School of Medicine, Baltimore, MD, USA

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ABSTRACT

Aim: To examine and characterize post-transplant eosinophilic gastrointestinal disorders (PTEGID) and post-transplant lymphoproliferative disorder (PTLD) in pediatric liver transplant recipients.

Methods: This is a single center retrospective study of all liver transplant recipients aged 0–18 years from 1999 to 2019 who received tacrolimus as their primary immunosuppressant. Demographic data and clinical/laboratory data including PTEGID, PTLD, liver transplant types, Epstein-Barr virus status, and blood eosinophil count were reviewed. Analysis was done with logistic regression and Mann-Whitney *U* test.

Results: Ninety-eight pediatric liver transplant recipients were included with median age at transplantation of 3.3 years (IQR: 1.1–9.3). The major indication for transplantation was biliary atresia, 51 (52%) cases. Eight (8%) children had PTLD and 14 (14%) had PTEGID. Receiving liver transplantation at an age of ≤ 1 year was associated with developing PTEGID (OR = 11.9, 95% CI = 3.5–45.6, $p < 0.001$). Additionally, eosinophilic count of $\geq 500/\mu\text{L}$ was associated with having PTLD (OR = 10.7, 95% CI = 1.8–206.0, $p = 0.030$) as well as having at least one liver rejection (OR = 2.8, 95% CI = 1.2–7.0, $p = 0.024$). The frequency of food-induced anaphylaxis significantly increased post-transplantation ($p = 0.023$).

Conclusions: PTEGID and PTLD are common in this cohort and are associated with certain risk factors that help screen children to improve recipient survival. Further studies are needed to evaluate the clinical benefits of these findings.

1. Introduction

Over the past decades, with advances in surgical technique and improvements in immunosuppression, the graft and patient survival for pediatric liver transplants have steadily increased [1–3]. However, as mortality rates decrease, focuses have shifted to improving the quality of life by reducing morbidity in these patients. Immunosuppressants by their nature have significant trade-offs; they are required to maintain the transplanted organ to treat the original morbidities, but they also create

new ones such as lymphoproliferative disorder, frequent/opportunistic infections, kidney dysfunction, and diabetes. Tacrolimus has become the preferred immunosuppressant in pediatric liver transplant recipients due to its superior ability to prolong liver graft survival; however, its mechanism of action has also been considered to play a pivotal role in the development of allergic and immunologic diseases along with susceptibility to infection or malignancy [4].

In the general population, eosinophilic gastrointestinal disorders (which include eosinophilic esophagitis, eosinophilic gastritis,

Abbreviations: IQR, Interquartile Range; PTEEGE, Post-Transplant Eosinophilic Esophagitis/Gastritis/Enteritis; PTEGID, Post-Transplant Eosinophilic Gastrointestinal Disorders; PTLD, Post-Transplant Lymphoproliferative Disorder.

* Corresponding author at: Division of Pediatric Gastroenterology, Hepatology, and Nutrition, Department of Pediatrics, Johns Hopkins University School of Medicine, CMSC-2, 600 North Wolfe Street, Baltimore, MD 21287, USA.

E-mail address: wkarnsa1@jhmi.edu (W. Karnsakul).

¹ Co-first authors.

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eosinophilic enteritis, eosinophilic gastroenteritis, and eosinophilic colitis) are a very rare condition. In the United States, the prevalence of eosinophilic esophagitis was reported to be 25.9 per 100,000 persons while the prevalence of eosinophilic colitis was reported to be 2.1 per 100,000 persons with the prevalence of other forms of eosinophilic gastrointestinal disorders being in between [5,6]. While eosinophilic gastrointestinal disorders are not currently known to increase mortality, they can significantly impact morbidity with a symptomology that affect patients' daily well-being such as persistent dysphagia for patients with eosinophilic esophagitis [7].

Post-transplant lymphoproliferative disorder (PTLD) is a serious condition that can occur in solid organ transplant recipients including liver transplant recipients [8]. The incidence of PTLD can be up to 15% in pediatric liver transplant recipients, much greater than in adults which is only up to 2.8% [9]. Additionally, in pediatric patients, PTLD results in high mortality rates of 18–42% [10–12]. Epstein-Barr virus infection is known to be a major risk factor for developing PTLD [8]; however, these studies typically analyze solid organ transplants in general, and rarely focus on or isolate the liver, especially in pediatric studies. The suppression of T cells from tacrolimus therapy can not only impair Epstein-Barr virus-specific T cell-mediated immunity and contribute to the development of PTLD, but also promote allergic diseases [13]. Thus, we aim to investigate the incidence and the risk factors associated with post-transplant immunologic diseases including post-transplant eosinophilic gastrointestinal disorders (PTEGID) and PTLD in pediatric liver transplant recipients on tacrolimus therapy.

2. Materials and methods

2.1. Study population

This was a retrospective cohort study of pediatric liver transplant recipients approved by the institutional review board of Johns Hopkins University School of Medicine. Liver transplant recipients who received transplantation between 0 and 18 years of age at the Johns Hopkins Hospital between 1999 and 2019 were included. Only patients who received tacrolimus as their primary immunosuppressant were included. Patients with substantially incomplete or fragmented medical records were excluded. Patients were followed for at least one year after transplantation.

We extracted demographic data including age, sex, and race/ethnicity for each patient. We also extracted clinical and laboratory data including diagnosis of PTLD, diagnosis of PTEGID (i.e. eosinophilic esophagitis, eosinophilic gastritis, eosinophilic enteritis, eosinophilic gastroenteritis, and eosinophilic colitis), gastrointestinal symptoms (e.g. abdominal pain, nausea, dysphagia, odynophagia, hematemesis, gastroesophageal reflux disease, diarrhea, constipation, or hemochezia), the indications for liver transplantation, type of liver transplantation (i.e. orthotopic, heterotopic, live donor, deceased donor, segmental, split, or whole), history of liver rejection, history of esophagogastroduodenoscopy, history of colonoscopy, Epstein-Barr virus status of donor and recipient (pre-transplantation and post-transplantation), and peripheral blood eosinophilic count (the highest value). Additionally, we examined reports of eczema, asthma, and food-induced anaphylaxis of each patient before and after transplantation. For this study, we grouped the diagnoses made by esophagogastroduodenoscopy (i.e. post-transplant eosinophilic esophagitis, eosinophilic gastritis, eosinophilic enteritis, and eosinophilic gastroenteritis) together as post-transplant eosinophilic esophagitis/gastritis/enteritis (PTEEGE).

2.2. Statistical analysis

Data were summarized using frequencies and percentages or medians and interquartile ranges (IQRs). Associations between clinical outcomes and risk factors were analyzed with logistic regression;

univariate results were reported. Continuous data were compared using the Student's *t*-test or the Mann-Whitney *U* test. Paired data were compared using McNemar's test for categorical data and Wilcoxon signed-rank test for continuous data.

Normality was tested with the Shapiro-Wilk test with $p < 0.05$ indicating non-normal data. Non-normal data were reported with median and interquartile range (IQR). Missing data were assumed to be missing at random. All reported *p*-values are two-tailed *p*-values. Statistical significance was defined as $p < 0.05$. Statistical calculations were performed using RStudio (R Core Team (2020). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria.) and STATA software (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP).

3. Results

Ninety-eight children were included in this study. Of those, 50 (51%) were female and 48 (49%) were male. Their median age at transplantation was 3.3 years (IQR: 1.1–9.3). The racial/ethnic distribution was 56 (57%) White, 19 (19%) Black, 10 (10%) Asian or Pacific Islander, 9 (9%) Hispanic, and 4 (4%) other/unknown. The major indication for liver transplantation for this cohort was biliary atresia at 51 (52%) cases (Table 1). Twenty-eight (29%) of the 96 children had live donor liver transplantation.

Of the 98 children, 39 (40%) reported having gastrointestinal symptoms. The most common being diarrhea at 15 (38%) cases followed by abdominal pain at 14 (36%) cases. The least common were hematemesis and odynophagia at 1 (3%) case each (Table 1).

Twenty-five (26%) children had undergone both esophagogastroduodenoscopy and colonoscopy, 6 (6%) had undergone only esophagogastroduodenoscopy, and 5 (5%) had undergone only colonoscopy. Endoscopic exploration found 14 (14%) of those 98 children to have PTEGID and of those 14, 12 (86%) had PTEEGE and 6 (43%) had post-

Table 1
Clinical characteristics of cohort of pediatric liver transplant recipients.

Clinical Characteristics	Patient Sample (N = 98)
<i>Indication for Liver Transplantation</i>	
Alpha-1-Antitrypsin Deficiency, N (%)	3 (3)
Acute Liver Failure, N (%)	15 (15)
Autoimmune Hepatitis, N (%)	6 (6)
Biliary Atresia, N (%)	51 (52)
Budd-Chiari, N (%)	1 (1)
Cystic Fibrosis, N (%)	2 (2)
Congenital Hepatic Fibrosis, N (%)	1 (1)
Cryptogenic Cirrhosis, N (%)	2 (2)
Hepatic Cancer, N (%)	3 (3)
Idiopathic Cirrhosis, N (%)	1 (1)
Idiopathic Neonatal Cholestasis, N (%)	1 (1)
Methylmalonic Acidemia, N (%)	1 (1)
Primary Sclerosing Cholangitis, N (%)	3 (3)
Progressive Familial Intrahepatic Cholestasis, N (%)	7 (7)
Unspecified Metabolic Disease, N (%)	1 (1)
<i>Gastrointestinal Symptoms</i>	
<i>Upper Gastrointestinal Symptoms</i>	
Abdominal Pain, N (%)	14 (14)
Dysphagia, N (%)	2 (2)
Emesis, N (%)	4 (4)
Gastroesophageal Reflux Disease, N (%)	1 (1)
Hematemesis, N (%)	1 (1)
Nausea, N (%)	2 (2)
Odynophagia, N (%)	1 (1)
<i>Lower Gastrointestinal Symptoms</i>	
Blood in Stool, N (%)	4 (4)
Constipation, N (%)	2 (2)
Diarrhea, N (%)	15 (15)
Rectal Bleeding, N (%)	1 (1)
<i>Other</i>	
Failure to Thrive, N (%)	1 (1)

transplant eosinophilic colitis. The most common sub-diagnosis of PTEEGE in our cohort was eosinophilic esophagitis. The median time for diagnosis of PTEEGE was 1.9 years (IQR: 0.8–3.5) post-transplantation and the median time for diagnosis of eosinophilic colitis was 0.5 years (IQR: 0.4–1.4) years post-transplantation. In these children, we found that receiving liver transplantation at an age of 1 year or younger was associated with developing PTEGID (OR = 11.9, 95% CI = 3.5–45.6, $p < 0.001$). Additionally, White race, versus non-white race, was associated with decreased odds having PTEGID (OR = 0.2, 95% CI = 0.1–0.8, $p < 0.027$) (Table 2).

Eight (8%) children had PTLT. Four (50%) had monomorphic PTLT, 2 (25%) had polymorphic PTLT, and 2 (25%) had non-specified PTLT. The median tacrolimus trough level was 4.8 ng/mL (IQR: 3.2–6.5) at the time of PTLT diagnosis. At that time, 7 (88%) were on tacrolimus therapy and 1 (13%) was on sirolimus, but tacrolimus was still detectable in that patient. The median time for diagnosis of PTLT was 1.9 years (IQR: 1.5–3.2) post-transplantation. We found a peripheral blood eosinophilic count of greater than or equal to 500/ μ L was associated with having PTLT (OR = 10.7, 95% CI = 1.8–206.0, $p = 0.030$). The median peripheral blood eosinophilic count was 1070/ μ L (IQR: 552–1502) in children with PTLT while 350/ μ L (IQR: 160–870) in children without PTLT ($p = 0.012$). Additionally, Epstein-Barr virus positivity in the recipient post-transplantation was found to be associated with having PTLT (OR = 17.1, 95% CI = 3.6–97.1, $p < 0.001$) (Table 3). The sites of involvement of PTLT were varied; 2 (25%) involved the liver, 2 (25%) involved the general abdomen, 2 (25%) involved lymph nodes, 1 (13%) involved the neck, and 1 (13%) was only lymphoma. Treatments used for the PTLT varied by patient, the most common was rituximab which was used in 4 (50%) patients. All 8 children had successful outcomes after treatment. The odds for acquiring PTLT or PTEGID was found to be independent of liver transplant type (live versus deceased donor), sex of the recipient, and Epstein-Barr virus positivity in the donor or recipient pre-transplantation ($p > 0.05$). Of the 98 children, 8 (8%) received livers from donor positive for Epstein-Barr virus, 10 (10%) were positive for the virus prior to transplantation, and 13 (13%) were positive for the virus after transplantation.

We also found that a peripheral blood eosinophilic count of greater than or equal to 500/ μ L was associated with having at least one episode of acute liver rejection (OR = 2.8, 95% CI = 1.2–7.0, $p = 0.024$).

In these children, we found that developing anaphylaxis to foods post-transplantation was associated with developing asthma post-transplant (OR = 18.8, 95% CI = 1.8–177.7, $p = 0.009$). The presence of eczema, asthma, and food-induced anaphylaxis was compared before and after liver transplantation. There were no differences in the presence of eczema and asthma before and after liver transplantation. However, the presence of food-induced anaphylaxis was greater post-

Table 2

Clinical and demographic risk factors for post-transplant eosinophilic gastrointestinal disorder (PTEGID).

Risk Factor	Odds Ratio (95% CI)	P-Value
<i>Demographics</i>		
Age (≤ 1 Year vs > 1 Year)	11.9 (3.5–45.6)	< 0.001
Sex (Female vs Male)	1.9 (0.6–6.6)	0.289
Race (White vs Non-White)	0.2 (0.1–0.8)	0.027
<i>Clinical</i>		
Liver Transplant Status (Live vs Deceased)	2.9 (0.9–9.3)	0.076
Donor EBV Status (Positive vs Negative)	N/A	0.991
Recipient EBV Status Pre-Transplant (Positive vs Negative)	0.6 (0.0–3.6)	0.624
Recipient EBV Status Post-Transplant (Positive vs Negative)	2.0 (0.4–7.9)	0.338
PTLD (Yes vs No)	2.2 (0.3–10.7)	0.376
<i>Laboratory</i>		
Elevated Eosinophil Count (≥ 500 vs < 500)	1.0 (1.0–1.0)	0.075

Table 3

Clinical and demographic risk factors for post-transplant lymphoproliferative disorder (PTLD).

Risk Factor	Odds Ratio (95% CI)	P-Value
<i>Demographics</i>		
Age (≤ 1 Year vs > 1 Year)	1.3 (0.2–6.4)	0.737
Sex (Female vs Male)	1.7 (0.4–8.5)	0.502
Race (White vs Non-White)	1.3 (0.3–6.5)	0.750
<i>Clinical</i>		
Liver Transplant Status (Live vs Deceased)	1.0 (0.1–4.7)	0.957
Donor EBV Status (Positive vs Negative)	N/A	0.994
Recipient EBV Status Pre-Transplant (Positive vs Negative)	2.9 (0.4–15.2)	0.240
Recipient EBV Status Post-Transplant (Positive vs Negative)	17.1 (3.6–97.1)	< 0.001
PTEGID (Yes vs No)	2.2 (0.3–10.7)	0.376
<i>Laboratory</i>		
Elevated Eosinophil Count (≥ 500 vs < 500)	10.7 (1.8–206.0)	0.030

transplantation compared to pre-transplantation, increasing from 0 (0%) to 7 (7%) cases ($p = 0.023$). Of those who developed food-induced anaphylaxis post-transplantation, 4 (57%) was due to nuts, 1 (14%) due to eggs, 1 (14%) due to wheat, and 1 (14%) due to fish. Gastrointestinal symptoms improved in those patients after diet restrictions/modifications.

4. Discussion

A recent study by Marcus et al. on solid organ transplant recipients reported Epstein-Barr virus infection as well as female sex to be risk factors for post-transplant allergy, autoimmunity, and immune-mediated disorders in children; however, in our study, we did not find any significant associations with developing PTEGID due to those factors [14]. In our cohort, we also found an association between Epstein-Barr virus infection in the recipient post-transplantation and the development of PTLT; however, we did not find any associations with the pre-transplantation Epstein-Barr virus status in the donor or recipient. Dharnidharka et al., in a large study of over 40,000 liver transplant recipients from a national registry, reported that Epstein-Barr virus negativity in the recipient pre-transplantation was associated with increased risk of PTLT; however, while statistically significant, the association was not strong [15]. This suggests that a large sample size may be required to observe this association. Epstein-Barr virus negativity in the recipient pre-transplantation is thought to leave the patient vulnerable to Epstein-Barr virus infection post-transplantation due to the lack of antibodies to neutralize the virus and lack of virus-specific T cells to control proliferation of infected B cells [16]. Similar to Dharnidharka et al., we did not find associations between Epstein-Barr virus positivity in the donor and development of PTLT [15].

In our study, receiving a liver transplant at a young age (≤ 1 year) strongly associated with developing PTEGID. This finding is consistent with prior studies on pediatric liver transplant recipients [14,17,18]. Compared to adults, the development of the immune system in infants start out with a larger ratio of Th2 to Th1 lymphocytes [19,20]. Th2-type cytokines are known to promote eosinophilic responses, and an introduction to tacrolimus at this early stage may interfere with a natural decrease in Th2 to Th1 ratio, leading to the increased odds of PTEGID development. IL-5, a recruiter and activator of eosinophils produced by Th2 lymphocytes, is known to be greatly increased in solid organ transplant recipients on tacrolimus, even compared to those on cyclosporin (Fig. 1) [21–23]. Many studies suggest that the immature immune responses play an important part in their predisposition to allergic disease in early childhood particularly in infants less than 1 year of age at the time of transplantation. Their allergic mechanism might be explained by their limited exposure to dietary antigens [24,25]. Therefore, these young children with immature immunoregulatory

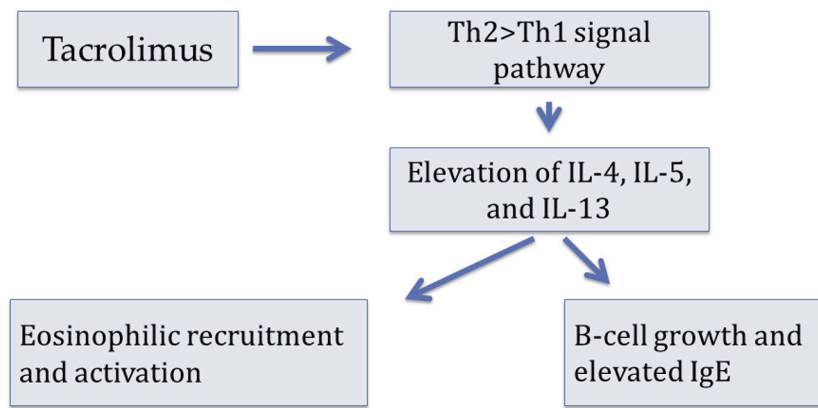


Fig. 1. Proposed mechanism of development of post-transplant eosinophilic gastrointestinal disorders and post-transplantation lymphoproliferative disorder in pediatric liver transplant recipients on tacrolimus therapy.

responses may fail to suppress the clinical expression of new food allergies [23]. Clinicians attempt to prevent infants with chronic liver disease such as biliary atresia from developing end stage liver disease in the early infantile period. Delaying liver transplantation in early infancy is as almost impossible in many cases such as biliary atresia with failed portoenterostomy. However, clinicians may consider delaying transplantation until the child's growth and nutrition are improved and some immunizations before 1 year of age including live vaccines are completed [26–28].

We found that high maximal peripheral blood eosinophilic count was strongly associated with developing PTLT in our cohort. After a literature search, peripheral blood eosinophilic count does not appear to have been studied in the context of PTLT in liver transplant recipients. In 2006, Granot et al. reported asymptomatic eosinophilia in pediatric liver transplant recipients on tacrolimus, but PTLT was not examined, though some cases of PTEGID were reported [29]. More recently, Barış et al. reported eosinophilia in some children with PTLT but were unable to make any associations [30]. Due to the severity of PTLT, this risk factor could become very useful as a low-cost screening method; however, additional studies are needed.

PTEGID and PTLT are both very rare conditions in the general population [5,6,31]. In our cohort, 14% developed PTEGID and 8% developed PTLT. The cumulative incidence of PTLT was comparable to similar studies [32]; however, and our cumulative incidence of PTEGID was over four times that of Wisniewski et al. who reported only 3% in a cohort of pediatric liver transplant recipients [25]. A possible explanation for the discrepancy is the difference in the frequency of esophagogastroduodenoscopy or colonoscopy between studies; we had nine times the rate of esophagogastroduodenoscopy or colonoscopy compared to Wisniewski et al. [25]. This suggests that several cases of PTEGID could have been missed.

We found that the prevalence of food-induced anaphylaxis increased post-transplantation in our cohort, and also developing food-induced anaphylaxis was also associated with developing asthma. Compared to other solid organ transplants, liver transplant recipients appear to be more prone to developing allergies and allergy-related complications [17,25,26,33]. Tacrolimus may select against Th1 lymphocytes by IL-2 inhibition while promoting Th2 lymphocyte proliferation, contributing to the development of allergies in children [29]. IL-13, produced by Th2 lymphocytes, is greatly increased with tacrolimus treatment. IL-13 can induce IgE secretion from B cells and contribute to IgE-mediated allergies or allergy-related complications (Fig. 1) [23,34]. Another possible mechanism is an increase in allergenic protein exposure due to increased intestinal permeability [23]. Gabe et al. reported increased intestinal permeability and increased endotoxin levels in blood compared to healthy controls in liver transplant recipients on tacrolimus therapy [35]. Parents of children who receive liver transplantation may

potentially benefit from being informed of the increased risk of allergies and allergy-related complications.

A limitation of this study is that due to the retrospective nature of this study, many transplant recipients were not evaluated for PTEGID with esophagogastroduodenoscopy and colonoscopy as they could have milder symptoms or were even asymptomatic, thus, our cumulative incidence of PTEGID may not be representative of the cohort. Also, we have not explored a role of the family history of atopy in this current study as another risk factor for transplantation-acquired atopic diseases. Additionally, the lack of change in asthma before and after transplantation may be due to the difficulty of diagnosing asthma at very young age.

5. Conclusion

PTEGID and PTLT are common in this cohort and are associated with certain risk factors. PTEGID is associated with transplantation at a young age, 1 year or less, and PTLT is associated with high maximal peripheral blood eosinophilic count. Food-induced anaphylaxis increases in prevalence after transplantation. Risk factors for PTEGID and PTLT may be helpful as an inexpensive way to screen children with liver transplants for those potentially severe conditions. Parents may potentially benefit from being informed of the increased risks of food-induced anaphylaxis after their child receives liver transplantation. Further studies are needed to evaluate the clinical benefits of these findings on a larger scale.

Disclosures

We have no conflicts of interests or funding to disclose.

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