

The development of eosinophilic colitis after liver transplantation in children

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Abstract: Tacrolimus-based immunosuppression in pediatric liver transplant recipients is known to be associated with EGID. Our goal was to determine the incidence, risk factors, and characteristics of EGID in our pediatric liver transplantation program. This study was a retrospective analysis of 38 pediatric liver transplant recipients. Rectal mucosal biopsy was performed to evaluate for gastrointestinal PTLT and eosinophilic colitis. There were 14 patients (37%) who were diagnosed with eosinophilic colitis. The mean age at transplantation was 10.8 ± 1.8 months. Those with eosinophilic colitis had a higher incidence of peripheral eosinophilia ($p = 0.003$) during the first two months following transplantation and had a higher EBV infection rate. Symptoms, such as diarrhea, hematochezia, and abdominal pain, became apparent after an average of three months; diagnoses were made at 6.9 ± 2.0 months after transplantation. There were eight patients (57%) with elevated food-specific IgE levels. With food restriction treatment, the symptoms of patients improved. EGID should be considered when clinical symptoms are present, because symptoms of this disorder are similar to those of gastrointestinal PTLT. It should also be considered when peripheral eosinophilia is detected or when EBV seroconversion develops during the first two months following transplantation.

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Tacrolimus (FK506) and cyclosporin A, both calcineurin inhibitors, have been used widely in pediatric liver recipients. The major adverse effects of tacrolimus are neurotoxicity, nephrotoxicity, diabetogenic effects, and infectious and malignant complications (1). Recently, it has been reported that food allergy and EGIDs are also important side effects (2–9). There are two hypotheses regarding the association between a calcineurin inhibitor and the development of EGID; one theory has suggested that the inhibition of interleukin-2, synthesized by the Th1 cells, causes a shift toward Th2-cell immune responses secreting IL-5. Imbalance between Th1 and Th2 cells, with a loss of control of the synthesis of IgE antibodies due to excessive production of IL-4

and IL-13, implies development of allergic disease (10–13). The other theory is that tacrolimus leads to an increase of the intestinal permeability by reduced mitochondrial ATP and thereby promotes the exposure of food allergens (14, 15).

EGID is a descriptive term for a condition characterized by eosinophilic infiltration of one or more regions of the gastrointestinal tract in the absence of parasitic or extraintestinal disease (16, 17). The exact mechanism underlying the association between a calcineurin inhibitor and EGID remains unknown. EGID presents with vomiting, diarrhea, bloody stool, poor oral intake, hypoalbuminemia, anemia, and growth retardation. These problems are very similar to those of one of the most serious complications in liver transplant recipients, gastrointestinal PTLT. It is important that accurate diagnosis of EGID or PTLT be made and adequate treatment be initiated to improve the prognosis of liver transplant recipients.

Abbreviations: EBV, Epstein–Barr virus; EGID, eosinophilic gastrointestinal disorder; PCR, polymerase chain reaction; PTLT, post-transplant lymphoproliferative disorder.

In this report, we discuss the occurrence of eosinophilic colitis after tacrolimus-based immunosuppression following pediatric liver transplantation. The goal of the study was to determine the incidence, potential risk factors, characteristics, and prognosis of eosinophilic colitis.

Materials and methods

Materials

Between May 2001 and May 2005, 50 pediatric patients underwent orthotopic liver transplantation at Samsung Medical Center, Seoul, Korea. Thirty-eight of the 50 pediatric liver transplant recipients had rectal mucosal biopsy for diagnosis of gastrointestinal PTLT or eosinophilic colitis. The 38 patients at liver transplantation ranged from two months to seven yr of age; there were 17 males and 21 females. The primary liver diseases were extrahepatic biliary atresia (29 patients, 76%), hepatoblastoma (one), angiosarcoma (one), Alagille syndrome (one), fulminant hepatitis (three), and cryptogenic liver cirrhosis (two). Of these, 35 received a living-related orthotopic liver transplantation and the other three patients received unrelated deceased donor transplantation. All of the 38 patients received steroids and tacrolimus medication for initial immunosuppression therapy. The duration of steroid treatment ranged from 29 to 552 days (mean 87 days). After the initial combination immunosuppression, only tacrolimus was used as maintenance immunosuppression. A retrospective analysis was performed for all the 38 patients by review of the medical records.

Methods

Rectal mucosal biopsy was performed at six, nine, and 12 months after transplantation to evaluate for the presence of gastrointestinal PTLT, especially in the EBV high-risk group, and eosinophilic colitis. All the parents of the patients studied gave written informed consent. Eosinophilic colitis was defined as increased eosinophilic inflammation of the lamina propria (>15 eosinophils per high-power field) and infiltration of surface or mucosal gland epithelium and crypt invasion with eosinophils on histologic examination (7). Based on the histologic definition, patients were categorized as either the EGID group or non-EGID group. Medical records were reviewed for clinical features, such as age at transplantation, primary liver disease, peripheral eosinophilia at pre- and two months post-transplantation evaluation, history of allergy in the recipient, donor or family, EBV infection and CMV seroconversion at two months after transplantation, PTLT, rejection episodes, level of tacrolimus, duration of steroid treatment, and elevated levels of total IgE, and food-specific IgE (RAST). For continuous data, a two-tailed Student's t-test and Mann-Whitney test were performed. For nominal data the chi-squared test and Fisher's exact test were performed. Values of $p < 0.05$ were considered significant. In the EGID group, we assessed symptoms at diagnosis, association with food-specific IgE, and duration of treatment. In addition, a multiple regression analysis was performed to determine the independent risk factors for EGID. The software program SPSS for windows (version 11.5: SPSS Inc., Chicago, IL, USA) was used for analyses.

Results

Characteristics of patients

Of the 14 patients (37%) who were diagnosed with eosinophilic colitis (EGID group), there were no differences in sex ($p = 0.506$) and age ($p = 0.268$) in comparison with the group without eosinophilic colitis (non-EGID group) between the two groups (Table 1). The most common primary diagnosis of liver disease was extrahepatic biliary atresia (76%). The other primary diagnoses were cancer (hepatoblastoma and angiosarcoma), Alagille syndrome, fulminant hepatitis, and cryptogenic liver cirrhosis. There was also no difference in primary diagnoses of liver disease comparing the two groups ($p = 0.285$).

Peripheral eosinophilia

Peripheral eosinophilia ($>10\%$) at pretransplantation was not significantly different in comparison between the two groups ($p = 0.252$). All of the 14 patients in the EGID group showed peripheral eosinophilia during the first two months post-transplantation; however, only 13 of 24 patients in the non-EGID group presented with eosinophilia. Those with EGID had a higher incidence of peripheral eosinophilia post-transplantation ($p = 0.003$) (Table 2).

Allergic symptoms and history

The number of patients with suspected allergic symptoms at pretransplantation was two in the EGID group and one in the non-EGID group. The number of patients with a donor allergy history were three in the EGID group, and none in the non-EGID group. Those with a family allergy history were three in the EGID group and two in the non-EGID group (Table 2).

Table 1. Characteristics of patients

	EGID group	Non-EGID group	p-value
No. of patients	14 (37%)	24 (63%)	
Sex			
Male	5	12	0.506
Female	9	12	
Age			
≤ 12 months	12	16	0.268
>12 months	2	8	
Primary diagnosis			
Biliary atresia	13	16	0.285
Cancer	1	1	
Alagille syndrome	0	2	
Fulminant hepatitis	0	3	
Liver cirrhosis	0	2	

EGID, eosinophilic gastrointestinal disorder.

Table 2. Comparison between EGID and non-EGID group

	EGID group	Non-EGID group	p-value
Peripheral eosinophilia before transplantation	2 (14)	5 (20)	0.252
Peripheral eosinophilia after transplantation	14 (100)	13 (54)	0.003
Allergy before transplantation	2 (14)	1 (4)	–
Allergy history of donor	3 (21)	0	–
Familial allergy history	3 (21)	2 (8)	–
Rejection	4 (29)	10 (42)	0.501
PTLD	2 (14)	4 (17)	–
EBV risk*			
High	12 (86)	12 (50)	0.039
Low	2 (14)	12 (50)	
EBV PCR positive seroconversion	10 (71)	6 (25)	0.008
CMV antigenemia positive seroconversion	6 (43)	4 (17)	0.127
Duration of steroid treatment (days)	66.00 ± 15.36	99.17 ± 49.77	0.235
Tacrolimus level, mean (ng/mL)	11.67 ± 2.40	11.65 ± 2.57	0.239

*High: donor EBV Ab positive, recipient EBV Ab negative; low: recipient EBV Ab positive or both negative.

Values in parentheses are percentages. EGID, eosinophilic gastrointestinal disorder; PTLD, post-transplant lymphoproliferative disease; EBV, Epstein-Barr virus.

EBV and CMV infection

The EBV high-risk group was defined as EBV-seronegative patients receiving allograft from EBV-seropositive donors. In the EGID group,

12 of 14 patients were in the EBV high-risk group; this was significantly different from the non-EGID group ($p = 0.039$) (Table 2). The incidence of EBV PCR seroconversion post-transplantation in the EGID group (10/12) was higher than that in the non-EGID group (6/24) ($p = 0.008$). CMV infection was not the significant factor when the results were univariately compared between EGID and non-EGID patients, even though CMV positive seroconversion rate was higher in EGID group than in non-EGID group.

Duration of steroid and tacrolimus level

There were no significant differences in the duration of steroid treatment and therapeutic tacrolimus levels between EGID and non-EGID patients.

Characteristics of EGID group

The oldest girl, 33 months of age, without symptoms and the one with mild diarrhea did not have a restricted diet. Three patients presented with only a skin rash. A patient with vomiting showed eosinophilic infiltration in the esophagus and stomach as well as in the rectum (Table 3). Diarrhea was the most common symptom in nine patients with or without bloody stools, poor oral intake, and skin rash. The symptoms of eosinophilic colitis became apparent at 3.9 ± 1.5 months post-transplantation

Table 3. Clinical aspects and treatment of EGID group

Case	Sex	Age (mo)	Symptoms	Symptom onset after LT (mo)	EGID diagnosis after LT (mo)	Age at treatment cessation (mo)	Total IgE (U/ml)	Food-specific IgE	Treatment
1	F	11	Skin rash	7	9	21	244	Soy, wheat	Food restriction
2	M	6	Diarrhea	6	10	–	ND	ND	No treatment
3	F	5	Vomiting	6	10	23	55	Egg white	Hypoallergenic formula, food restriction
4	F	33	–	–	10	–	ND	ND	No treatment
5	M	7	Skin rash	3	7	21	3	Negative	Hypoallergenic formula, food restriction
6	F	7	Diarrhea blood tinged stool	4	7	22	10	Negative	Hypoallergenic formula, food restriction
7	F	7	Diarrhea poor oral intake	4	7	31	365	Egg white, milk	Hypoallergenic formula, food restriction
8	F	8	Skin rash	6	7	32	5	Negative	Food restriction
9	M	10	Diarrhea blood tinged stool	2	3	31	82	Egg white, milk	Food restriction
10	M	18	Diarrhea	2	3	27	57.5	Milk	Hypoallergenic formula, food restriction
11	F	9	Diarrhea	4	9	29	725	Egg white, milk	Hypoallergenic formula, food restriction
12	M	12	Diarrhea poor oral intake	2	6	38	18.9	Egg white, milk	Hypoallergenic formula, food restriction
13	F	7	Diarrhea skin rash	1	3	23	31.3	Soy	Hypoallergenic formula, food restriction
14	F	11	Diarrhea skin rash	4	5	21	ND	ND	Food restriction

EGID, eosinophilic gastrointestinal disorder; LT, liver transplantation; ND, not done.

(range one to seven months); diagnosis was made at 6.9 ± 2.0 months post-transplantation (range 3–10 months); all diagnoses were made within three months after the onset of symptoms. In the EGID group, 11 patients were evaluated for their total IgE levels and common food-specific IgE levels (egg, milk, soy, and wheat). There were three patients with elevation of the total IgE level, and eight patients had a positive result for more than one food-specific IgE. The most common allergens were eggs and milk.

Risk factors for EGID

A logistic multiple regression analysis was performed to determine the independent risk factors for the EGID group with the model including post-transplantation eosinophilia, EBV PCR seroconversion, CMV antigenemia seroconversion, tacrolimus trough concentration (Table 4). The odds ratio of peripheral eosinophilia within two months post-transplantation was 8.926 (95% CI 6.477–11.405) in the EGID group compared with the non-EGID group. The odds ratio of EBV PCR seroconversion post-transplantation was 3.207 (95% CI 1.298–5.116) and that of CMV antigenemia seroconversion was 3.638 (95% CI 1.537–5.739).

Food restriction treatment of EGID group

There were two patients without food restriction treatment in the EGID group, one was a 33-month-old girl, oldest in the group and the other was a 10-month-old boy with mild diarrhea who had improved with weaning from milk (Table 3). The other 12 patients in the EGID group were fed hypoallergenic formula, and major allergens, such as eggs, milk, soy, and seafood, were not given after weaning from milk. With food restriction treatment, the symptoms of patients improved. From 12 months of age, milk products and soy were introduced carefully and eggs were introduced after 24 months of age. Seafood was attempted at three yr of age. Allergic symptoms of most patients disappeared at the age of two to three yr (Table 3). No patient was switched from tacrolimus to cyclosporin A in the EGID group.

Discussion

Many reports have discussed food allergy in pediatric liver transplantation recipients treated with tacrolimus-based immunosuppression previously (2–9). Romero et al. (18) reported that peripheral eosinophilia developed in 28% of 54 pediatric liver transplantation recipients, and gastrointestinal endoscopy and biopsy were performed in 23 patients with gastrointestinal complaints. Of those, six patients were diagnosed with eosinophilic gastroenteritis and all six had peripheral eosinophilia. They suggested that a younger age at transplantation, frequency of rejection episodes, tacrolimus-based immunosuppression, and EBV viral load might be associated with the development of this condition. Granot et al. also reported that eosinophilia is present in up to 50% of children and adolescents receiving tacrolimus immunosuppression (19). In our study, 38 patients had rectal mucosal biopsy for early diagnosis of PTLT or EGID with suggestive gastrointestinal symptoms; of those 27 patients (71%) had peripheral eosinophilia and 14 patients (37%) were diagnosed with EGID. The higher incidence of EGID, compared with previous studies, may be due to the following: (i) all of the liver transplantation recipients received tacrolimus-based immunosuppression in this study; (ii) the rectal mucosal biopsies were performed regularly in most of the patients. Until 2003, EBV quantitative PCR method was not available in our hospital. At that time, we evaluated PTLT with clinical symptoms and EBV *in situ* hybridization, CD20- and CD3-immunostaining from biopsy specimens of GI tract; (iii) younger age at liver transplantation than in previous studies; and (iv) This study cannot reveal the actual incidence of eosinophilic colitis in the wider post-transplant population, because the children who were screened were already symptomatic.

Although tacrolimus has been widely used in adult organ transplantation, reports of the development of allergy have been more common in children; this may be associated with immaturity of immunity and intestinal permeability (20, 21). The age at transplantation has been an

Table 4. Risk factors for EGID

	EGID group	Non-EGID group	OR (95% CI)
Peripheral eosinophilia after transplantation	14 (100%)	13 (54%)	8.926 (6.477–11.405)
EBV PCR positive conversion	10 (71%)	6 (25%)	3.207 (1.298–5.116)
CMV antigenemia positive conversion	6 (43%)	4 (17%)	3.638 (1.537–5.739)

EGID, eosinophilic gastrointestinal disorder; EBV, Epstein–Barr virus; OR, odds ratio; CI, confidence interval.

important factor, but in this study the age was not significant. This may have been due to the fact that most of the enrolled pediatric liver transplantation recipient patients (24 patients, 74%) were under 12 months of age. The peripheral eosinophilia post-transplantation was strongly associated with the development of EGID and this was statistically significant. The relationship between EGID and peripheral eosinophilia is not certain but peripheral eosinophilia may be induced by eosinophilic infiltration of the intestinal wall by increasing intestinal permeability (14). All of the three recipients who received a liver from the donor with an allergy history developed eosinophilic colitis. There are reports that liver transplantation from a donor who has outgrown food allergy to a young recipient with immature regulatory T-cell development can lead to reactivation of that food allergy in the graft recipient (22, 23). In addition, the fact that only liver and bone marrow transplants have been associated with newly acquired food allergy suggests a role for hematopoietic tissue (7, 24).

EGID and EBV had a significant association, which is in accordance with Romero's report (18). Theoretically, EBV and CMV may counteract the effects of each other on the immune system by their different Th1 and Th2 activations. CMV infection elicits a prototype Th1 response by inducing IL-2, TNF- α , and IFN- γ . By contrast, EBV infection may transform human B cells, resulting in the production of IL-5, which in turn may induce a chronic eosinophilic inflammation, promoting allergy, and a preferred Th1 response (25–28). In our study, there was a higher incidence of EGID in the high-risk group of EBV infection or EBV PCR positive seroconversion group, and no association between EGID and CMV infection in a univariate analysis. Interestingly, however, the logistic multiple regression analysis revealed that the both EBV PCR positive seroconversion and CMV antigenemia positive seroconversion were risk factors for EGID. The explanation for this discrepancy may be due to a small sample size, statistic error of interaction between two variables or the immunologic aspects of coinfection with two viruses. Further research on the relationship between EGID and CMV infection is necessary.

The tacrolimus trough concentration during the first three months after transplantation was not significant in comparison between the EGID group and the non-EGID group. This may indicate that in both groups the tacrolimus level was maintained at an optimum level for immunosuppression independent of EGID.

The treatment of the EGID group was based on restriction of allergens in food, prior to weaning. None was switched from tacrolimus to cyclosporin A in this study. Breast milk or hypoallergenic formula were tried and later food allergens were carefully introduced; soy, milk product, and egg products in that order. After three yr, seafood and nuts were permitted. From 21 to 38 months of age, the symptoms of EGID resolved and diet restriction was discontinued. In our study, the response to food restriction treatment without replacement of tacrolimus appears to be good even though dietary manipulation with switching to cyclosporin A is known to be the current best practice (13). A few patients presented with oral allergy and urticaria intermittently. Although some medications are effective for food allergies they are very limited. Antihistamine medication is effective for food allergy and IgE-mediated dermatologic symptoms and anti-inflammatory drugs are helpful for EGID (29, 30). We gave the patients with urticaria antihistamines and did not treat them with anti-inflammatory agents. There is no standard recommendation of duration of food allergen restriction and currently, the American Academy of Pediatrics recommends that major allergens, such as peanuts, nuts, and seafood, be introduced after three yr of age (31, 32). In the future, a food challenge test and a prospective cohort design are needed to search for the specific food allergens, range of food restriction and treatment duration.

In conclusion, EGID should be considered when clinical symptoms, such as vomiting, diarrhea, hematochezia, and abdominal pain, are present, because symptoms of this disorder are similar to those of gastrointestinal PTLT. It should also be considered when peripheral eosinophilia is detected or when EBV seroconversion develops during the first two months following transplantation.

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