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De Novo Inflammatory Bowel Disease after Pediatric Kidney or Liver Transplant

Melissa A. Fernandes, MD¹, Hillary J. Braun, BA², Kim Evason, MD Ph.D³, Sue Rhee, MD¹, and Emily R. Perito, MD¹

¹Division of Pediatric Gastroenterology, Hepatology, and Nutrition, Department of Pediatrics, Benioff Children's Hospital San Francisco, University of California San Francisco

²School of Medicine, University of California San Francisco

³Department of Pathology, University of California San Francisco

Abstract

A subset of children who receive a liver and/or kidney transplant develop de novo inflammatory bowel disease-like chronic intestinal inflammation, not explained by infection or medications, following transplant. We have conducted a single-center, retrospective case series describing the unique clinical and histologic features of this IBD-like chronic intestinal inflammation following solid organ transplant. At our center, nine of 327 kidney or liver recipients developed de novo IBD following transplant (6 liver, 2 kidney, 1 liver-kidney). Most children presented with prolonged hematochezia and diarrhea, and were treated with aminosalicylates. At time of diagnosis, five were not currently using mycophenolate mofetil for transplant immunosuppression. Histologic and endoscopic findings at IBD diagnosis included inflammation, ulcerations, granulomas, and chronic colitis. Since diagnosis, no patients have required surgical intervention, or escalation to biologic therapy, nor developed stricturing or perianal disease. In this case series, de novo post-transplant IBD developed in 4% of pediatric liver and/or kidney recipients; however, it often does not fit the classic patterns of Crohn's Disease or Ulcerative Colitis.

Please address correspondence to: Melissa Fernandes, M.D., UCSF Box 0136, 550 16th Street 5th Floor, San Francisco, CA 94143, Tel 415 476 5892, Fax 415 476 1343, melissa.fernandes@ucsf.edu.

Dr. Fernandes (Department of Pediatrics UCSF) made substantial contributions to this manuscript. She participated in design of the study, and was instrumental to acquisition and analysis of data. She participated in drafting the manuscript and associated tables and revisions. She approved the final version and has agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Ms. Braun (UCSF School of Medicine) substantially contributed to this work by doing data collection and analysis. She approved the final version and has agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Dr. Evason (Department of Pathology UCSF) made substantial contributions to data acquisition and analysis for this manuscript. She reviewed histologic findings for the included patients in the study. She participated in revising the manuscript for important intellectual content. She approved the final version and has agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Dr. Rhee (Department of Pediatrics UCSF) substantially contributed to this work. She participated in study design and revisions of the manuscript. She approved the final version and has agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Dr. Perito (Department of Pediatrics UCSF) substantially contributed to this work. She contributed to study design, assisted with data collection and interpretation. She critically revised earlier versions of the final manuscript for important intellectual content. She approved the final version and has agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflicts of Interest

The authors report no other conflicts of interest

Keywords

Colitis; Immunosuppression; Solid Organ Transplant; diarrhea

Introduction

Inflammatory bowel disease (IBD) is a chronic inflammatory disorder that primarily involves the gastrointestinal tract. IBD has been described in a variety of immune-dysregulated states, including common variable immunodeficiency disease, as well as chronic granulomatous disease, which has gastrointestinal findings that closely resemble Crohn disease (CD). (1-3) As with other patients, the trigger for IBD onset in transplant recipients remains unclear, although some posit that transplant recipients' immunosuppressive medications may play a role in intestinal inflammation. In adult studies, the annual incidence of de novo IBD following solid organ transplant has been estimated at 20 cases per 100,000. (4) IBD has also been described in a few patients who are immunosuppressed following pediatric solid organ transplant. (5-7) We describe nine pediatric patients with de novo IBD following liver or kidney transplant. We hypothesize that de novo IBD following solid organ transplant has histologic findings and treatment responses that make it distinct from classic categories of IBD such as Ulcerative Colitis (UC) or CD. Future research and management of this pathologic process could be aided by identifying unique disease characteristics of de novo IBD after solid organ transplant and allow for larger studies that examine the role of immunosuppressive medications.

Patients & Methods

We reviewed the records of all pediatric patients who underwent liver, kidney or combined liver-kidney transplant at the Benioff Children's Hospital San Francisco at the University of California San Francisco (UCSF) from 2004-2015. The Committee for Human Research at UCSF approved this review (IRB Submission 14-12961, approved on June 6th 2014). Three hundred twenty-seven solid-organ transplant recipients (138 liver, 186 kidney, and 3 combined) were identified. Three patients, all liver recipients, had a pre-transplant diagnosis of ulcerative colitis or primary sclerosing cholangitis. Two hundred ninety-six transplant recipients (126 liver, 170 kidney, 3 combined) continue to be followed at UCSF either in the pediatric or adult transplant clinics, or have passed away prior to developing IBD like enteritis. Twenty-eight patients have been lost to follow up, with a majority of those patients undergoing transplant in 2004-2006. From our chart review, 9 cases of post-transplant de novo IBD were identified. The 9 identified patients received all of their transplant related care at UCSF during this time period. All cases of IBD-like enteritis were diagnosed after clinical presentation, including persistent abdominal pain, persistent diarrhea, and some with hematochezia, and after infections were ruled out. Infectious workup included *Salmonella*, *Shigella*, *Campylobacter* and *Clostridium difficile* stool testing which was negative for all subjects. *Cytomegalovirus* testing was negative in all patients documented by PCR serology and via mucosal biopsy. Diagnosis was confirmed by clinical history, radiography, and endoscopy with intestinal biopsy after undergoing a kidney, liver or combined transplant. Patients with primary sclerosing cholangitis, known to be associated with IBD were

excluded (8,9) Demographics, transplant history, presentation of symptoms and associated pathology findings were abstracted from the medical record. We considered the date of confirmatory histology to be the date of diagnosis. All diagnoses were reviewed by one author (MF) and confirmed by two additional authors (EP, SR). One pathologist reviewed all diagnostic intestinal biopsies to provide histologic descriptions and confirm diagnosis (KE).

Results

Nine children (6 liver transplant, 2 kidney transplants, 1 combined liver-kidney) were diagnosed with de novo, chronic post-transplant IBD-like enteritis following solid-organ transplant. Eight of the nine were exposed to the same immunosuppressive regimen following transplant: tacrolimus, prednisone, and mycophenolate mofetil. The ninth received cyclosporine in lieu of tacrolimus immediately following transplant; however, was soon converted to tacrolimus and remained on it at time of enteritis diagnosis. None received induction therapy such as thymoglobulin or basilixumab. At the time of diagnosis, five of the nine were no longer on mycophenolate mofetil, with a range of 1 to 61 months off of the medication. The remaining four were on mycophenolate mofetil in combination with other immunosuppressive medications at the time of diagnosis. Mean tacrolimus levels for all patients the year prior to enteritis diagnosis were 6.6 ± 2.2 and 6.5 ± 2.1 for the year following transplant.

Post-transplant IBD was diagnosed 1 month to 11 years following transplant. None had a family history of IBD. Prolonged non-infectious diarrheal illness was the main symptom for six of the nine. Eight of the nine children had at least one hospital admission for either abdominal pain or diarrhea that was deemed not related to infection, medications or other etiology prior to diagnosis of IBD. One child presented with poor growth and nutritional status, with height at the 4th percentile and BMI less than 10th percentile for age a year prior to diagnosis. Following diagnosis and initiation of treatment for IBD with aminosalicylates, that child had improvement of his height to the 16th percentile for age and BMI restored to the 50th percentile for age. Including the aforementioned child, four of the nine experienced improvement in weight percentiles when comparing one-year prior with one-year post diagnosis. Six of the nine children dropped height percentiles at time of IBD diagnosis when compared to a year prior. Three of the children dropped weight percentiles in that year as well, all of who improved weight percentiles following diagnosis. Five children were at appropriate weight percentiles before and after IBD diagnosis. Overall, de novo post-transplant IBD, appears to impact growth parameters of children; however, changes in height percentiles seem to be more notable than weight, though these findings do not account for confounding diagnoses or treatments.

As part of their evaluation for de novo post-transplant IBD, seven of the nine children underwent radiologic evaluation (Table 1), but only one had findings consistent with IBD: a stricture in the ileum. All post-transplant IBD diagnoses were confirmed with intestinal biopsies obtained during esophagogastroduodenoscopy or colonoscopy. Diagnostic histologic findings included granulomas, chronic and active colitis, and architectural distortion. (Table 2)

Initial management varied. Five of the nine children were started on an aminosalicylates in addition to their transplant immunosuppression. The steroid dose was increased in one patient. The two kidney transplant recipients also had their baseline immunosuppression changed from mycophenolate mofetil to azathioprine. Since diagnosis, follow up time ranging from one to eight years, six patients have ongoing symptoms including abdominal pain, hematochezia and diarrhea. (Table 2). Of the symptomatic children, four are not currently on any medications specifically for IBD; however, their primary solid organ transplant immunosuppression was been adjusted, with a temporary increase in steroids, to manage ongoing enteritis symptoms. Providers remained cautious about over suppressing patients' immune systems. On average, the nine children have had two endoscopies for disease diagnosis and evaluation, with one child having 5 endoscopies. None of the children has required surgical intervention or escalation of medical therapy to include biologic therapy. None has progressed to perianal, structuring, or fistulizing disease phenotypes. Instead, diarrhea and abdominal pain are the main characterization of these patients' post-transplant IBD.

Discussion

This is a retrospective case series of nine children who developed de novo, chronic post-transplant IBD-like illness following a solid organ transplant, representing almost 4% of all liver and kidney recipients transplanted at our pediatric institution. In comparison, recent studies have estimated the prevalence of CD and UC in children younger than 20 years is 43 per 100,000 (95% confidence interval (CI), 40-45) and 28 (95% CI, 26-30), respectively. (10) Our study suggests that the prevalence of IBD-like enteritis is higher in the solid organ transplant recipient; however, this would need to be further explored and confirmed with multicenter data.

The majority of the patients in this series presented with prolonged, non-infectious diarrhea and hematochezia and additionally had histologic findings classically associated with IBD such as granulomas (Table 2). While non-infectious diarrhea is often attributed to immunosuppressive medications such as mycophenolate mofetil, in this case series at least five children developed symptoms with no current exposure to this medication. This suggests that immunosuppressive medications are not solely responsible for development of IBD symptoms.

Recent studies have associated tacrolimus immunosuppression with the development of de novo food allergy and eosinophilic gastritis. (10,11) Only two of the nine patients developed de novo food allergies post-transplant, in both cases mild peanut allergies. Post-transplant eosinophilic gastroenteritis has also been described. Despite a similar clinical presentation as IBD, with non-infectious diarrhea and abdominal pain, 15 to 65 eosinophils per high power field are generally used to define eosinophil-predominant disease. (12,13) While many of our patients did have eosinophils noted on biopsies, it was often in combination with other findings such as architectural distortion or Paneth cells, which are more suggestive of chronic changes of IBD. Eosinophilia remains a non-specific finding, with elevated levels found in IBD as well. (14) Additionally, in a recent case report by Dhawan, et al. post-transplant eosinophilic gastroenteritis was diagnosed in the setting of an escalation of

immunosuppression out of concern for organ rejection. (15) Our patients varied in onset of enteritis symptoms and none developed symptoms that appeared to be triggered by an increase in their immunosuppression.

While immunosuppressive medications might contribute to the development of IBD, immunosuppressive regimens following transplant are highly protocolled, making it unclear why a subset of children develop IBD despite similar exposures. Treatment strategies included addition of aminosalicylates and increase in transplant immunosuppression medications, but only one-third had complete remission. This may represent a combination of differences in the IBD and inflammatory drivers themselves as well as reluctance by clinicians to over-immunosuppress pediatric transplant recipients.

This study is a single-center, retrospective chart review. Sample size is small, but IBD diagnosis was histologically confirmed clinically at diagnosis and again at data analysis to ensure that we captured cases accurately. Cases were identified by retrospective chart review at our pediatric institution; thus, we were unable to identify if any patients who had underwent transplant at our institution but had transitioned to adult care or another transplant center had gone on to develop IBD-like enteritis. While this hinders the ability to provide an accurate incidence of this phenomenon, we are still able to share the clinical experience of these 9 cases. De novo, post-transplant IBD should be considered in the workup of persistent, non-infectious diarrhea in pediatric transplant recipients, and additional medications aimed at controlling intestinal autoimmune inflammation may be needed to achieve remission. Larger, multi-center prospective studies are needed to elucidate risk factors and optimal management of de novo post-transplant IBD after pediatric solid organ transplant.

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Table 1

Patient Characteristics

	Inflammatory Bowel Disease History							
ID	Demographics & Transplant ¹	Presentation of IBD	Immunosuppression at Diagnosis (trough) ²	Radiology Studies ³	IBD Medications		At Last Follow Up	
1	Male, Methylmalonic Acidemia Age at Liver Transplant: 9m Donor: Deceased	Age: 2y Sx: Diarrhea, Failure to Thrive Fever Symptom Duration: 1m	Tacrolimus (8.9)	SBFT: No evidence of IBD	Initial: 5ASA Prednisone	Current: 5ASA Budesonide	Years since IBD Dx: 9 Symptoms: Asymptomatic	
2	Male, Biliary Atresia Age at Liver Transplant: 11m Donor: Living related	Age: 3y Sx: Hematochezia, Leg Pain Symptom Duration: 4m	Tacrolimus (4.5)	SBFT: No evidence of IBD	Initial: 5ASA	Current: 5ASA	Years since IBD Dx: 4 Symptoms: Abdominal Pain	
3	Male, Mesangial Sclerosis Age at Renal Transplant: 3y Donor: Deceased	Age: 6y Sx: Diarrhea Symptom Duration: 6m	Tacrolimus (7.9) MMF Prednisone	SBFT: No evidence of IBD	Initial 5ASA MMF stopped	Current: 5ASA Prednisone Azathioprine	Years since IBD Dx: 4 Symptoms: Asymptomatic	
4	Male, Neonatal Hemochromatosis Age at Liver Transplant: 4m Donor: Deceased	Age: 6y Sx: Diarrhea and Emesis Symptom Duration: 12m	Tacrolimus (3.9)	No imaging	Initial: None	Current: None	Years since IBD Dx: 2 Symptoms: Diarrhea	
5	Female, Autoimmune Hepatitis, Graves/PTU toxicity Age at Liver Transplant: 7y Donor: Deceased	Age: 9y Sx: Diarrhea, Hematochezia, Anemia, Abdominal Pain, Rash Symptom Duration: 24m	Tacrolimus (5.0) Prednisone	SBFT: Stricturing and ulcerations in the ileum	Initial: 5ASA Prednisone (Increased)	Current: None	Years since IBD Dx: 8 Symptoms: Hematochezia	
6	Female, Alpha-1-Antitrypsin Deficiency and Wilson's disease. Age at Liver Transplant: 12y Donor: Deceased	Age: 11.7y Sx: Diarrhea, Abdominal Pain Symptom Duration: 6m	Tacrolimus (7.9) MMF	MRE: No evidence of IBD	Initial: Budesonide	Current: None	Years since IBD Dx: 1 Symptoms: Diarrhea	
7	Female, Autoimmune Hepatitis Age at Liver Transplant: 10y Donor: Deceased	Age: 12y Sx: Hematochezia, Abdominal Pain Symptom Duration: 6m	Tacrolimus (4.4)	MRE: No evidence of IBD	Initial: None	Current: None	Years since IBD Dx: 7 Symptoms: Diarrhea	
8	Male, Posterior Urethral Valves Age at Renal Transplant: 2y Donor: Living related	Age: 13y Sx: Diarrhea, Failure to Thrive Symptom Duration: 2m	Tacrolimus (9.8) MMF Prednisone	No imaging	Initial: Prednisone MMF stopped	Current: Prednisone Azathioprine	Years since IBD Dx: 1 Symptoms: Asymptomatic	
9	Male, Autosomal Recessive Polycystic Kidney and Congenital Hepatic Fibrosis Age at Liver/Renal Transplant: 12y Donor: Deceased	Age: 14y Sx: Hematochezia, Abdominal Pain Symptom Duration: 2m	Tacrolimus (4.7) MMF	CT: No evidence of IBD	Initial: 5ASA	Current: Budesonide	Years since IBD Dx: 2 Symptoms: Diarrhea	

¹Transplant: All patients (except ID 4) received immunosuppression with corticosteroids, tacrolimus, and mycophenolate mofetil (MMF) following transplant

²(Trough): Refers to mean Tacrolimus trough for the year prior to IBD diagnosis

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Radiology studies: SBFT (Small Bowel Follow Through), MRI (Magnetic Resonance Imaging of Abdomen), MRE (Magnetic Resonance Enterography), CT (Computerized tomography of Abdomen)

³ Patient on cyclosporine instead of tacrolimus for immunosuppression immediately following transplant

Table 2

Macroscopic & Microscopic Findings of IBD at Diagnosis

ID	Upper Gastrointestinal Tract		Ileum & Colon	
	Macroscopic Findings	Microscopic Findings	Macroscopic Findings	Microscopic Findings
1 ¹	Esophagus: Normal Stomach: Normal Duodenum: Normal	E: No significant pathologic finding ³ S: Chronic gastritis D: NSPA	Ileum: Not assessed Colon: Friable mucosa	I: Not Assessed C: Active colitis; Non-necrotizing granuloma in sigmoid colon and rectum
2	E: Normal S: Ulcers and erythema D: Normal	E: NSPA S: NSPA D: NSPA	I: Normal C: Ulcers	I: NSPA C: Focal inflammation in left /sigmoid colon, and rectum
3	E: Nodular S: Normal D: Normal	E: NSPA S: Mild chronic gastritis. D: Focal inflammation	I: Normal C: Friable mucosa	I: NSPA C: Active colitis in cecum/ascending colon. Active colitis (Paneth cells metaplasia, histiocyte aggregate) in transverse and descending colon.
4	E: Normal S: Ulcers D: Normal	E: NSPA S: Inflammation, reactive changes and focal intestinal metaplasia in the antrum. D: NSPA	I: Normal C: Normal	I: Active ileitis with prominent eosinophils C: Prominent eosinophils
5	No concurrent endoscopy	No concurrent endoscopy	I: Normal appearance C: Ulcers in ascending and transverse colon	I: NSPA C: Architectural distortion and increased eosinophils in right colon
6	E: Normal S: Nodular D: Normal	E: NSPA S: Chronic active gastritis D: Focal active duodenitis	I: Nodular Ileum C: Areas of nodularity	I: NSPA C: Prominent eosinophils within the lamina propria.
7	E: Normal S: Normal D: Inflammation	E: Increased intraepithelial eosinophils S: Focal reactive lymphocyte aggregates. D: NSPA	I: Nodular C: Nodular right colon	I: Intramucosal reactive lymphocyte aggregates. C: Intramucosal reactive lymphocyte aggregates.
8 ²	E: Normal S: Normal D: Normal	E: Increased intraepithelial eosinophils S: Chronic Gastritis D: Prominent intraepithelial lymphocytes	I: Normal C: Normal	I: NSPA C: Chronic active colitis in transverse, left, and rectosigmoid colon.
9	E: Nodular S: Normal D: Normal	E: Increased intraepithelial eosinophils S: Mild chronic gastritis D: NSPA	I: Normal C: Normal	I: NSPA C: Granuloma in cecum. Histiocyte aggregate in transverse colon

¹ Exam limited to the sigmoid at approximately 40cm for patient safety

² Exam limited to the hepatic flexure due to technical limitations

³ NSPA: No significant pathologic abnormality