Inflammatory Intestinal Diseases

Research Article

Inflamm Intest Dis 2024;9:96–102
DOI: 10.1159/000538334

Received: November 20, 2023
Accepted: March 8, 2024
Published online: March 18, 2024

De novo Inflammatory Bowel Disease in Kidney Transplant Recipients: A Single-Center Case Series Study

Masatomo Ogata[a] Masaki Kato[b] Takamasa Miyauchi[a]
Marie Murata-Hasegawa[a] Yuko Sakurai[c] Kazunobu Shinoda[d]
Hajime Yamazaki[e] Yugo Shibagaki[a] Masahiko Yazawa[a]

[a]Division of Nephrology and Hypertension, Department of Internal Medicine, St. Marianna University School of Medicine, Kawasaki, Japan; [b]Division of Gastroenterology and Hepatology, Department of Internal Medicine, St. Marianna University School of Medicine, Kawasaki, Japan; [c]Division of Pharmacy, St. Marianna University School of Medicine, Kawasaki, Japan; [d]Department of Urology, St. Marianna University School of Medicine, Kawasaki, Japan; [e]Section of Clinical Epidemiology, Department of Community Medicine, Graduate School of Medicine, Kyoto University, Kyoto, Japan

Keywords
Inflammatory bowel disease · Kidney transplantation · Ulcerative colitis · Crohn's disease

Abstract
Introduction: Gastrointestinal complications are common after solid organ transplantation. New-onset inflammatory bowel disease (IBD) after transplantation (de novo) is a major differential diagnosis of diarrhea after liver transplantation (LT) because of its high incidence in the field. However, the incidence of IBD after kidney transplantation (KT) remains unknown. ***Methods:*** This case series comprised six de novo IBD patients who had undergone KT at our hospital from April 1998 to December 2020. In this period, 232 KT recipients were identified. Participants were analyzed based on their colonoscopy diagnoses. Detailed clinical information regarding both KT- and IBD-related symptoms or outcomes was obtained, and we calculated the incidence of de novo IBD from the date of KT. ***Results:*** Of the 232 recipients in the median observation period of 6.1 (interquartile range: 2.6, 10.8) years, six recipients (one with Crohn's disease and five with ulcerative colitis) were diagnosed with de novo IBD. The incidence of de novo IBD after KT was 355.8/100,000 person-years (95% confidence interval, 159.8–791.9 per 100,000 person-years). Bloody stools and diarrhea did not always occur, with bloody stools occurring in three and diarrhea in 2 patients at the time of diagnosis. No recipient developed graft failure or extra-intestinal complications (e.g., IBD-related nephritis or arthritis). ***Conclusion:*** Despite a small sample size, this study's results indicate that the incidence of de novo IBD after KT may be similar to that after LT and higher than that in the general population. Larger studies are required to validate these preliminary findings.

Introduction

Gastrointestinal complications, including immunosuppressive medication (IM)-induced diarrhea, ischemic colitis, malignancy, posttransplant lymphoproliferative

karger@karger.com
www.karger.com/iid

Correspondence to:
Masahiko Yazawa, masahikoyazawa@gmail.com

disorder, ulcers, and infections (such as *Clostridioides difficile* colitis, intestinal tuberculosis, and cytomegalovirus [CMV] colitis), are common after solid organ transplantation (SOT) [1, 2]. Recently, new-onset inflammatory bowel disease (i.e., de novo IBD) was identified as another gastrointestinal complication of SOT, with several reviews reporting its high incidence in association with liver transplantation (LT) [2, 3]. LT recipients have a de novo IBD incidence 10 times higher than that in the general population because LT is often performed in patients with primary sclerosing cholangitis who are susceptible to IBD [2, 3]. Moreover, another pathogenesis of de novo IBD could be related to the IM prescribed, especially steroids and calcineurin inhibitors (CNI), even though they are used for the treatment of IBD [4]. Nevertheless, to our knowledge, no data specific to the incidence of de novo IBD in kidney transplant (KT) recipients are currently available, and some reports have opposing descriptions of its incidence [2, 4]. Several case reports and case series have reported nonspecific characteristics and only prevalence, especially in those who underwent colonoscopy or were IBD recipients, regarding de novo IBD recipients [4–6].

We hypothesize that KT recipients also have a high incidence of de novo IBD since all KT recipients take CNI, one of the risk factors for developing IBD in LT [7, 8]. Furthermore, as colonoscopy is needed to diagnose IBD, occurrence of IBD might be unrecognized for some time (i.e., underdiagnosed). Fortunately, we could evaluate whether the recipient had de novo IBD (i.e., new-onset IBD posttransplant) or prevalent IBD (i.e., IBD existed before transplant) since almost all KT recipients in our institute underwent colonoscopy before KT. We were able to capture the actual incidence rate of de novo IBD after KT with detailed clinical information. To investigate the abovementioned questions, we performed a preliminary investigation on the incidence and clinical course of de novo IBD in post-KT patients.

Methods

Study Design and Population

This case series comprised 6 patients with de novo IBD. We first reviewed the electronic medical records of all first KT recipients from April 1998 to December 2020 at St. Marianna University Hospital ($N = 232$) and enrolled those diagnosed with de novo IBD by colonoscopy, including patients with ulcerative colitis (UC) or Crohn's disease (CD). The diagnosis of de novo IBD was based on clinical, endoscopic, and pathological assessments performed by gastroenterologists. The criteria for colonoscopy were based on patient symptoms. Colonoscopy was not routinely performed in any KT recipients after transplantation. The only exclusion criterion was diagnosis of IBD prior to KT. This study was approved by our Institutional Review Board (IRB) (IRB No. 5293). According to the Ethical Guidelines for Medical and Health Research Involving Human Subjects established by the Ministry of Health, Labour and Welfare (Japan) and the IRB of the St. Marianna University School of Medicine, the need for written informed consent was waived for all participants.

Clinical Parameters and Data Source

We retrospectively extracted clinical information from paper-based and electronic medical records, including age, sex, cause of end-stage kidney disease, donor source (living or deceased), and human leukocyte antigen (HLA) typing. Furthermore, IBD-related information included the type of IBD (UC or CD), timeline of IBD onset (from KT to diagnosis), laboratory data (e.g., serum creatinine, C-reactive protein, and erythrocyte sedimentation rate), symptoms of IBD diagnosis, features of clinical symptoms, clinical severity (Lichtiger index or International Organization for the Study of Inflammatory Bowel Disease [IOIBD]), endoscopic findings, endoscopic severity (Mayo endoscopic subscore [MES] or simple endoscopic score for CD [SES-CD]), histological features, treatment, effects of IBD, transplant-related information such as rejection history or CMV infection, CMV immunoglobulin G (IgG) serological status, IM regimen at IBD diagnosis, and graft and patient survival. All participants were followed up at our hospital by transplant physicians and gastroenterologists; thus, consequences such as recipient and graft survival and IBD status were completely captured. A gastroenterologist determined remission based on the recipient's clinical symptoms and colonoscopy findings.

Statistical Analysis

Data were expressed as means ± standard deviations or as medians (interquartile ranges or ranges) for continuous variables and frequency (%) for categorical variables. We evaluated the time from KT to IBD diagnosis to analyze the incidence of de novo IBD. We censored events such as the date of loss to follow-up, death, graft loss, or end of the follow-up period (March 31, 2021) in the survival analysis. We calculated the incidence rate using a cumulative incidence plot and estimated the number using a 95% confidence interval [CI] (incidence/person-years). All analyses were performed using the Stata version 16 software (Stata LLC, College Station, TX, USA).

Results

Baseline Characteristics

Of the 232 recipients who underwent KT between 1998 and 2020, six were diagnosed with de novo IBD. The baseline characteristics of the six recipients are shown in Table 1. All patients had undergone KT from a living donor and had no history of rejection before being diagnosed with de novo IBD. Furthermore, all patients received tacrolimus, and only one had a history of CMV infection (colitis and fatigue). Some of the data on CMV IgG serological status could not be captured. Thus, 3 out

Table 1. Baseline characteristics (transplant-related information) in participants

	Case No.					
	1	2	3	4	5	6
Age at KT, years	42	40	36	44	13	29
Sex	Male	Female	Male	Male	Female	Male
Cause of ESKD	DKD	IgAN	Unknown	IgAN	Nephrotic syndrome	IgAN
Donor type	Living	Living	Living	Living	Living	Living
ABO blood type against donor	Compatible	Compatible	Incompatible	Compatible	Compatible	Compatible
Induction therapy	Basiliximab	Basiliximab	Basiliximab, rituximab	Basiliximab	Basiliximab	Basiliximab
Maintenance IM	Tac, MMF, steroid	Tac, MMF, steroid	Tac, MZ, steroid	Tac, MMF, steroid	Tac, MMF, steroid	Tac, MZ, steroid
History of allograft rejection	None	None	None	None	None	None
History of CMV infection	None	None	None	None	Yes	None
CMV IgG serological status (donor/recipient)	(+/+)	unknown	(+/+)	unknown	unknown	(+/−)
HLA typing	A: 26,24 B: 35,52 DR: 9,15	A: 2,11 B: 62,39 DR: 8,15	A: 24,31 B: 61 DR: 4,9	A: 2,33 B: 61,44 DR: 4,13	A: 11,2 B: 39,51 DR: 8,2	A: 24,26 B: 39,61 DR: 4

KT, kidney transplantation; ESKD, end-stage kidney disease; DKD, diabetic kidney disease; IgAN, IgA nephropathy; Tac, tacrolimus; MMF, mycophenolate mofetil; MZ, mizoribine; CMV, cytomegalovirus; HLA, human leukocyte antigen.

of 6 patients had to be listed as unknown. The CMV IgG mismatch (CMV IgG in donor +/CMV IgG in recipient −) was identified in 1 of 6 cases.

Clinical Characteristics at the Diagnosis of IBD

Table 2 shows the clinical characteristics of patients at the time of IBD diagnosis. The mean duration from KT to diagnosis of de novo IBD was 6.7 ± 3.8 years (range, 2.1–12.1). The patient who was diagnosed with CD underwent upper gastrointestinal endoscopy, which revealed no inflammation characteristic of CD. One recipient required a colonoscopy to diagnose IBD at another hospital; therefore, symptoms, laboratory results, endoscopic findings, and histological features were not obtained. Bloody stools, diarrhea, and inflammatory symptoms (e.g., fever or abdominal pain) did not develop during IBD diagnosis in our series. Additionally, two participants who were diagnosed with CD and pancolitis-type UC had increased levels of inflammatory markers. Furthermore, three participants with UC had phenotypic frequencies of HLA-B52, -DR2, and -DR15, which may be associated with UC. Endoscopic findings for 5 of the 6 de novo IBD patients diagnosed at our hospital are attached in the Appendix (online suppl. Fig. 1; for all online suppl. material, see https://doi.org/10.1159/000538334).

Treatment and Consequences of de novo IBD

All participants diagnosed with UC received 5-aminosalicylic acid as their initial therapy, and recipients diagnosed with CD received infliximab. At the discretion of the gastroenterologists, other treatments were administered to achieve remission. However, the recipient diagnosed with pancolitis-type UC eventually underwent total colectomy. No recipient developed graft failure or extraintestinal complications (e.g., IBD-related nephritis or arthritis) by the end of the study period (Table 2). Most of the participants achieved complete clinical remission.

Incidence Rate of de novo IBD

The incidence rate of de novo IBD from KT was 355.8 per 100,000 person-years (95% CI, 159.8–791.9 per 100,000), with a median observation period of 6.1 years (interquartile range, 2.6, 10.8). Cumulative incidence plots are shown in Figure 1.

Table 2. IBD-related information in participants

Case No.	1	2	3	4	5	6
Types of IBD	UC (rectum-limited)	UC	CD (colon type; A3L2B1p by Montreal Classification)	UC (left-sided colitis)	UC (left-sided colitis)	UC (pancolitis)
Age at onset of IBD	45	48	40	53	25	34
Duration from KT to IBD, years	2.1	8.4	3.7	9.3	12.1	4.5
Mean±SD			6.7±3.8			
Median (IQR)			6.4 (3.7, 9.3)			
Symptom						
Bloody stool	Yes	Unknown	None	Yes	Yes	None
Diarrhea	None	Unknown	Yes	None	None	Yes
Inflammation (fever or pain)	None	Unknown	Yes	None	None	Yes
Clinical severity (Lichtiger index/ IOIBD)	6	Unknown	4	8	11	16
Laboratory data						
CRP, mg/dL	0.24	N/A	3.53	0.07	0.32	6.38
Mean±SD			2.1±2.8			
Median (IQR)			0.32 (0.24, 3.53)			
ESR, mm/h	27	N/A	71	9	26	81
Mean±SD			42.8±31.3			
Median (IQR)			27 (26, 71)			
sCr, mg/dL	1.50	1.36	1.82	0.94	1.15	1.57
Mean±SD			1.39±0.31			
Median (IQR)			1.43 (1.20. 1.55)			
Endoscopic severity (MES/SES-CD)	2	Unknown	16	2	2	3
Histological findings	Lymphocytic infiltration in mucosa, with erosions and goblet cells decreased	Unknown	Highly infiltrated lymphocytes and neutrophils in mucosa, with erosions and crypt abscesses	Highly infiltrated lymphocytes in mucosa, with decreased goblet cells and crypts	Highly infiltrated lymphocytes in mucosa, with crypt abscess and decreased goblet cells	Highly infiltrated lymphocytes in mucosa, with erosions, cryptitis, and decreased goblet cells
Treatment for IBD	5-ASA	5-ASA	Infliximab	5-ASA	5-ASA, Salazosulfasalazine	5-ASA, steroid pulse, infliximab, vedolizumab
Consequences						
Survival	Yes	Yes	Yes	Yes	Yes	Yes
Graft survival	Yes	Yes	Yes	Yes	Yes	Yes
IBD	Remission (concurrent use of 5-ASA)	Remission (concurrent use of 5-ASA)	Remission (concurrent use of infliximab)	Remission (concurrent use of 5-ASA)	Remission (concurrent use of 5-ASA)	Total colectomy
Extraintestinal complications (nephritis or arthritis)	None	None	None	None	None	None

IBD, inflammatory bowel disease; UC, ulcerative colitis; CD, Crohn's disease; IOIBD, International Organization for the Study of Inflammatory Bowel Disease; MES, Mayo endoscopic subscore; SES-CD, simple endoscopic score for Crohn's disease; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; sCr, serum creatinine; IQR, interquartile range; ASA, aminosalicylic acid.

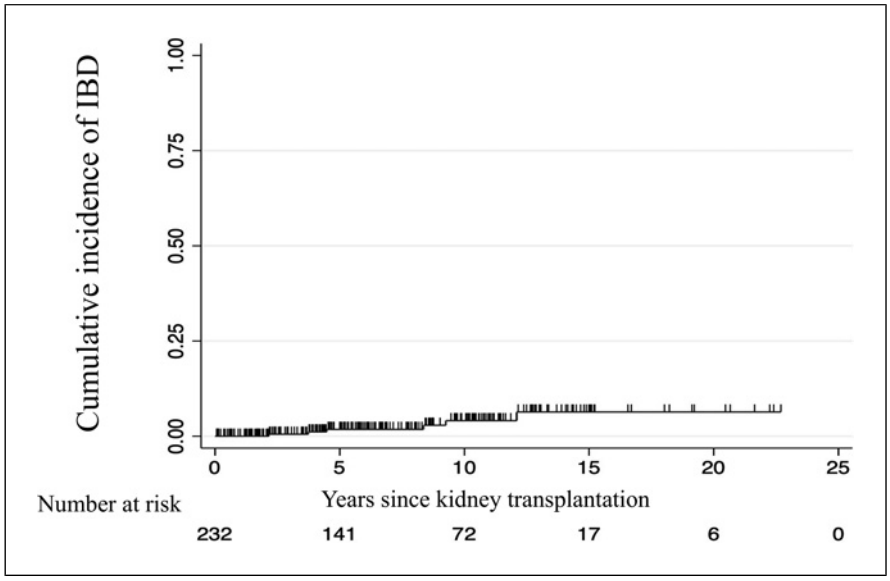

Fig. 1. Time-to-event curve for de novo IBD following KT.

Discussion

This case series revealed the detailed clinical course of patients diagnosed with de novo IBD after KT. Not all patients initially presented with bloody stools, diarrhea, or inflammatory symptoms at diagnosis. We observed a substantial incidence of de novo IBD after KT of 355.8/100,000 person-years despite receiving immunosuppressive treatment with steroids and CNI. To our knowledge, except for a few small studies, our data are the first to describe the exact incidence of de novo IBD in KT recipients during the era of modern IMs.

Gastrointestinal complications such as diarrhea are common after SOT [2]. The differential diagnosis and diagnostic strategy for posttransplant diarrhea is to change the dose of mycophenolate mofetil (MMF) or stop MMF for IM-related diarrhea, obtain a stool examination for *C. difficile* colitis and tuberculosis, and perform CMV polymerase chain reaction for CMV colitis. Although inflammation is a well-known symptom of IBD, our results showed relatively few inflammatory symptoms in patients with UC, which might have been related to the anti-inflammatory effects of IM [9]. Furthermore, not all recipients with de novo IBD present with diarrhea. In this regard, colonoscopy may be required if symptoms persist after the abovementioned strategy or if bloody stools develop. Because of the variable causes of abdominal symptoms after SOT, histological diagnosis needs to be made carefully and may require specific stains to differentiate other causes.

The incidence of IBD after SOT, reported mainly in LT recipients, is higher than that in the general population (206 vs. 20 per 100,000 person-years) [10]. In contrast, de novo IBD after KT is uncommon [2]. A meta-analysis integrated several articles on de novo IBD in KT and concluded that the pooled incidence of de novo IBD was 18.8% [4]. However, these included a case-control study and an observational study which only included patients with IBD. The lack of inclusion of all KT recipients made it difficult to calculate the "true" incidence proportion and rate. However, two reports integrated in the meta-analysis could be used to calculate the incidence of de novo IBD post-KT, which was 0.7% in Poland and 0.6% in the USA [5, 6]. Our cohort had an incidence proportion of 2.6% (6/232) for de novo IBD, which seemed relatively high in comparison. Furthermore, despite the large 95% CI due to the small number of patients, we calculated the incidence rate of de novo IBD post-KT to be 355.8/100,000 person-years. This incidence rate would be significantly higher than that of general population in Asia from a systematic review (the incident rate of UC in Asia was 0.1 to 6.3 per 100,000 person-years) [11]. The high incidence rate could possibly be explained by easier access to colonoscopy in Japan, despite the nonroutine colonoscopy in this study. Moreover, our institute had a smaller number of recipients, higher quality public health insurance, and a higher intensity of health maintenance compared to those observed in Western countries. Furthermore, our study is the first to investigate the incidence rate in an entire cohort from a single center.

Although this study could not detect or identify the risk factors for incident de novo IBD in KT recipients, some IM and non-IM transplant-related factors warrant further

discussion. In terms of IM transplant-related factors, tacrolimus is a causative or exacerbating factor for de novo IBD and preexisting IBD, respectively, in LT recipients, despite being used for the treatment of IBD in the general population [7, 8]. IBD is caused by the functional disruption of the intestinal barrier, exposure of luminal components to immune cells, and an overactive immune response [12]. Tacrolimus increases the permeability of the intestinal barrier, thereby increasing exposure to endogenous antigens and stimulating the intestinal immune system [12]. Dual treatment with CNI and MMF was associated with an increased incidence of IBD after LT [13]. CNI suppresses interleukin-2 (IL-2) production, decreases IL-2-dependent regulatory T-cell production, destabilizes intestinal immune system homeostasis, and increases T-cell apoptosis resistance [14, 15]. Since these observations were made in the LT field, especially in patients with primary sclerosing cholangitis, the exact association between CNI and de novo IBD in the KT field remains unknown. However, it is hypothesized that de novo IBD post-KT may be developed due to these IM transplant-related factors. Rituximab is an important preoperative desensitizer for ABO-incompatible KT, and an association between rituximab and the development of IBD has also been reported in the literature of patients with lymphoma and nephrotic syndrome [16, 17]. On the other hand, there are no reports of an association between basiliximab, which is used in most KT recipients as a desensitizer, and the development of IBD. However, we could not conclude it from our small cohort since posttransplant de novo IBD has occurred mostly in ABO-compatible KT recipients who were not administrated rituximab.

In terms of non-IM transplant-related factors in Japanese patients with phenotypic frequencies of IBD, HLA-B52, -DR2, and -DR15 are associated with the development of UC. Contrariwise, HLA-DR4 and -DQ4 have been associated with the development of CD [18, 19]. Although some patients in this study harbored these HLAs, the exact association between incident de novo IBD and HLA was unclear because of the small sample size. As HLA typing is examined before KT, transplant physicians should check for HLA typing related to the development of IBD in each country and consider this when a patient presents with abdominal symptoms. IgA nephropathy (IgAN) is common in renal disease associated with IBD [20]. In our study, 3 of 6 patients underwent KT from IgAN and 1 patient was treated for recurrent IgAN prior to the onset of de novo IBD. We could not completely conclude the clear association between de novo IBD and IgAN as a cause of end-stage kidney disease or a recurrent disease from our small cohort. However, IgAN can be associated with the development of IBD even in low activity of IgAN in non-KT patients, such as the absence of hematuria/proteinuria [21]. Thus, this association might extrapolate to transplant recipients.

This preliminary study had some limitations. First, this was a case series with a small sample size; therefore, the incidence rate of de novo IBD may have been imprecise, with a wide 95% CI. Second, we did not compare patients without de novo IBD; thus, we could not identify risk factors for the development of de novo IBD. Third, the incidence of de novo IBD was calculated from the date of KT, making it difficult to compare the incidence of IBD in the general population. However, 355.8/100,000 person-years was logically higher in our cohort than in the general population.

In conclusion, we reported the clinical characteristics and substantial incidence rate of de novo IBD after KT, which may be similar to that after LT and higher than that in the general population. De novo IBD should be considered in the differential diagnosis of bloody stools or diarrhea after KT despite low or mildly elevated inflammatory markers. A larger multicenter study is warranted to assess the incidence of de novo IBD after KT.

Statement of Ethics

All procedures were performed in accordance with the ethical standards of the Institutional Research Committee of the St. Marianna University School of Medicine (IRB No. 5293) and the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This retrospective observational study included fewer than 10 patients who had not undergone any new interventions or invasive procedures. According to the Ethical Guidelines for Medical and Health Research Involving Human Subjects established by the Ministry of Health, Labour and Welfare (Japan) and the Institutional Review Board of the St. Marianna University School of Medicine, the requirement for written informed consent was waived for all participants. An opt-out method was used to obtain consent for this study.

Conflict of Interest Statement

H.Y. received lecture fees from Janssen Pharmaceutical K.K., Mitsubishi Tanabe Pharma, Kowa Co. Ltd., AstraZeneka K.K., Kyorin Pharmaceutical Co. Ltd., and Takeda Pharmaceutical Co. Ltd. outside the submitted work. Fees for consultation for H.Y. were paid to Kyoto University by Magmitt Pharmaceutical Co. and Takeda Pharmaceutical Co. Ltd. outside the submitted work. The other authors declare no conflicts of interest.

Funding Sources

This study was not supported by any sponsor or funder.

Author Contributions

Conceptualization: Masatomo Ogata, Takamasa Miyauchi, Marie Murata-Hasegawa, Yuko Sakurai, Masahiko Yazawa. Methodology: Masatomo Ogata, Takamasa Miyauchi, Marie Murata-Hasegawa, Yuko Sakurai, and Masahiko Yazawa. Data curation: Masatomo Ogata, Yuko Sakurai, and Masahiko Yazawa. Formal analysis and writing – original draft: Masatomo Ogata and Masahiko Yazawa. Project administration: Kazunobu Shinoda, Yugo Shibagaki, and Masahiko Yazawa. Visualization: Masatomo Ogata, Masaki Kato, Hajime Yamazaki, and Masahiko Yazawa. Supervision: Masaki Kato and Hajime Yamazaki. Writing – review and editing: Masatomo Ogata, Takamasa Miyauchi, Kazunobu Shinoda, Masaki Kato, Hajime Yamazaki, Yugo Shibagaki, and Masahiko Yazawa. Approval of the final manuscript: all the authors.

Data Availability Statement

All clinical data were available from the electronic medical records at St. Marianna University Hospital. The data supporting the findings of this study are available from the corresponding author upon reasonable request.

References

1 Kurnatowska I, Banasiak M, Daniel P, Wagrowska-Danilewicz M, Nowicki M. Two cases of severe de novo colitis in kidney transplant recipients after conversion to prolonged-release tacrolimus. Transpl Int. 2010;23(5):553–8. doi: 10.1111/j.1432-2277.2009.01009.x.
2 Gioco R, Corona D, Ekser B, Puzzo L, Inserra G, Pinto F, et al. Gastrointestinal complications after kidney transplantation. World J Gastroenterol. 2020;26(38):5797–811. doi: 10.3748/wjg.v26.i38.5797.
3 Indriolo A, Ravelli P. Clinical management of inflammatory bowel disease in the organ recipient. World J Gastroenterol. 2014;20(13):3525–33. doi: 10.3748/wjg.v20.i13.3525.
4 Hansrivijit P, Puthenpura MM, Thongprayoon C, Brar HS, Bathini T, Kovvuru K, et al. Incidence and impacts of inflammatory bowel diseases among kidney transplant recipients: a meta-analysis. Med Sci. 2020;8(3):39. doi: 10.3390/medsci8030039.
5 Dobies A, Renke M, Wołyniec W, Palenicek L, Januszczyk J, Król E, et al. Gastrointestinal pathologies in patients after successful renal transplantation-A pilot study. Transplant Proc. 2016;48(5):1566–9. doi: 10.1016/j.transproceed.2016.02.060.
6 Pittman ME, Jessurun J, Yantiss RK. Differentiating posttransplant inflammatory bowel disease and other colitides in renal transplant patients. Am J Surg Pathol. 2017;41(12):1666–74. doi: 10.1097/PAS.0000000000000921.
7 Haagsma EB, Van Den Berg AP, Kleibeuker JH, Slooff MJ, Dijkstra G. Inflammatory bowel disease after liver transplantation: the effect of different immunosuppressive regimens. Aliment Pharmacol Ther. 2003;18(1):33–44. doi: 10.1046/j.1365-2036.2003.01613.x.
8 Verdonk RC, Dijkstra G, Haagsma EB, Shostrom VK, Van den Berg AP, Kleibeuker JH, et al. Inflammatory bowel disease after liver transplantation: risk factors for recurrence and de novo disease. Am J Transplant. 2006;6(6):1422–9. doi: 10.1111/j.1600-6143.2006.01333.x.
9 Silverberg MS, Satsangi J, Ahmad T, Arnott ID, Bernstein CN, Brant SR, et al. Toward an integrated clinical, molecular and serological classification of inflammatory bowel disease: report of a Working Party of the 2005 Montreal World Congress of Gastroenterology. Can J Gastroenterol. 2005;19(Suppl A):5a–36a. doi: 10.1155/2005/269076.
10 Riley TR, Schoen RE, Lee RG, Rakela J. A case series of transplant recipients who despite immunosuppression developed inflammatory bowel disease. Am J Gastroenterol. 1997;92(2):279–82.
11 Molodecky NA, Soon IS, Rabi DM, Ghali WA, Ferris M, Chernoff G, et al. Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. Gastroenterology. 2012;142(1):46–e30 e42; quiz e30. doi: 10.1053/j.gastro.2011.10.001.
12 Groschwitz KR, Hogan SP. Intestinal barrier function: molecular regulation and disease pathogenesis. J Allergy Clin Immunol. 2009;124(1):3–22 quiz 21-2. doi: 10.1016/j.jaci.2009.05.038.
13 Jørgensen KK, Lindström L, Cvancarova M, Karlsen TH, Castedal M, Friman S, et al. Immunosuppression after liver transplantation for primary sclerosing cholangitis influences activity of inflammatory bowel disease. Clin Gastroenterol Hepatol. 2013;11(5):517–23. doi: 10.1016/j.cgh.2012.12.027.
14 Strauss G, Osen W, Debatin KM. Induction of apoptosis and modulation of activation and effector function in T cells by immunosuppressive drugs. Clin Exp Immunol. 2002;128(2):255–66. doi: 10.1046/j.1365-2249.2002.01777.x.
15 Peppelenbosch MP, van Deventer SJ. T cell apoptosis and inflammatory bowel disease. Gut. 2004;53(11):1556–8. doi: 10.1136/gut.2004.040824.
16 Morita K, Shibano T, Maekawa K, Hattori M, Hida N, Nakamura S, et al. Crohn's disease following rituximab treatment in a patient with refractory nephrotic syndrome. CEN Case Rep. 2019;8(1):55–60. doi: 10.1007/s13730-018-0364-8.
17 Kristjánsson VB, Lund SH, Gröndal G, Sveinsdóttir SV, Agnarsson HR, Jónasson JG, et al. Increased risk of inflammatory bowel disease among patients treated with rituximab in Iceland from 2001 to 2018. Scand J Gastroenterol. 2021;56(1):46–52. doi: 10.1080/00365521.2020.1854847.
18 Asakura H, Tsuchiya M, Aiso S, Watanabe M, Kobayashi K, Hibi T, et al. Association of the human lymphocyte-DR2 antigen with Japanese ulcerative colitis. Gastroenterology. 1982;82(3):413–8. doi: 10.1016/s0016-5085(82)80387-9.
19 Matake H, Okabe N, Naito S, Yao T. An HLA study on 149 Japanese patients with Crohn's disease. Gastroenterol Jpn. 1992;27(4):496–501. doi: 10.1007/BF02777785.
20 Ambruzs JM, Walker PD, Larsen CP. The histopathologic spectrum of kidney biopsies in patients with inflammatory bowel disease. Clin J Am Soc Nephrol. 2014;9(2):265–70. doi: 10.2215/CJN.04660513.
21 Hayashi R, Ueno Y, Tanaka S, Onishi K, Takasago T, Wakai M, et al. Clinical characteristics of inflammatory bowel disease patients with immunoglobulin A nephropathy. Intest Res. 2021;19(4):430–7. doi: 10.5217/ir.2020.00067.