Original Article

Spectrum of Pathological Lesions Observed in Post-Transplant Gastrointestinal Mucosal Biopsies

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Abstract

Background: Gastrointestinal mucosal biopsies in post-transplant patients reveal diverse pathologies, including infections and post-transplant inflammatory bowel disease (IBD). Immunosuppressants, crucial for preventing rejection, pose risks such as nausea, diarrhea, peptic ulcers, infections, and cancers. Diagnosing post-transplant colitis is challenging due to similar clinical and histological features. Pathologies include drug-induced colitis, infection-related colitis, graft-versus-host disease (GVHD), de novo IBD, neoplasms, post-transplant lymphoproliferative diseases (PTLD), and non-specific colitis. Each requires specific treatments, highlighting the need for a multidisciplinary approach. This study evaluates these lesions in our tertiary care center.

Methods: A retrospective study analyzed 46 post-renal and liver transplant patients who underwent GI endoscopy/colonoscopy biopsies at VPS Lakeshore, Kochi, between January 2017 and December 2022. Variables such as patient age, gender, presenting complaint, time from transplantation to symptoms, and histopathological diagnosis were analyzed using SPSS software.

Results: From 2017 to 2022, 46 out of 985 transplant recipients underwent GI biopsies (39 kidney, 7 liver). The cohort was predominantly male (93.5%) with a mean age of 54.93 years. Diarrhea was the primary symptom (45.7%), followed by dyspepsia and anemia, occurring on average 23 months post-transplant. Pathological findings included infection-related colitis (26.1%), drug-induced colitis (8.7%), de novo IBD (2.2%), neoplasms (2.2%), post-transplant lymphoproliferative diseases (2.2%), non-specific colitis (32.6%), and no significant pathology (26.1%).

Conclusion: Post-transplant gastrointestinal diseases are complex, impacting the health and quality of life of recipients. Timely diagnosis and personalized management are crucial. A multidisciplinary approach is essential for effective care, and continued research and clinical efforts are vital for improving outcomes.

Keywords:

solid organ transplantation; colitis; transplant recipients; gastrointestinal tract; kidney transplantation; cytomegalovirus.

Introduction

Gastrointestinal mucosal biopsies in post-transplant patients exhibit diverse pathologies, ranging from infections to post-transplant inflammatory bowel disease (IBD) [1][2]. Immunosuppressant therapy is crucial for preventing acute rejection in post-transplant

patients, but it does come with significant risks. Long-term use of these medications can lead to various complications, including nausea and diarrhea to more severe problems like peptic ulcers, infections, and even gastrointestinal cancers. It's a delicate balance between managing the risk of rejection and minimizing the side effects of the medication [1].

Gastrointestinal diseases in post-transplant patients are mostly colitis. Differentiating between the various forms of post-transplant colitis is the most challenging part since most have similar clinical and histological features. Histologically, they may look alike, making it tough to identify the specific cause [3].

A variety of pathological lesions have been described, namely drug-induced colitis (mainly MMF-related colitis), infection-related gastrointestinal colitis (mainly CMV-derived colitis), graft-versus-host disease (GVHD), de novo inflammatory bowel disease, neoplasms, post-transplant lymphoproliferative diseases (PTLD), and non-specific colitis. Each type has unique characteristics and requires specific treatments. For instance, drug-induced colitis often improves with medication adjustments, while infection-related colitis needs targeted antimicrobial therapy. GVHD and de novo IBD can be particularly tricky, as they might need specialized immunosuppressive treatments. Neoplasms and PTLD require oncological approaches. With such varied causes, it's essential to have a multidisciplinary team to address these complications effectively [4].

The clinical and histological characteristics of gastrointestinal complications in post-transplant recipients are not frequently reported. In this study, we evaluated the spectrum of pathological lesions observed in post-transplant gastrointestinal mucosal biopsies in our tertiary care centre.

Materials and Methods

Study Design: Ours was a retrospective observational descriptive-type study. The collected data comprised all post-renal and liver transplant patients who underwent GI endoscopic mucosal biopsies over a 6-year period from January 2017 to December 2022, obtained at the Department of Pathology at VPS Lakeshore Hospital, Ernakulam, Kerala.

Selection Criteria: Both upper and lower gastrointestinal endoscopic mucosal biopsies were included. Only mucosal biopsies were included; surgical resection specimens were excluded.

Sample Size: 46 cases. During the study period, among the 985 kidney/liver transplant recipients, 46 patients underwent endoscopic mucosal biopsies from various sites of the alimentary tract.

Data Collection and Analysis: Hematoxylin and eosin slides of these 46 cases were reviewed. The details of the clinical history of each of these patients were collected from medical case records. All data thus collected were entered into Microsoft Excel to prepare a master chart and subjected to statistical analysis using SPSS software. For all cases, variables such as patient age, gender, presenting complaint, post-transplant endoscopic mucosal findings, and the average time from transplantation to presenting complaint were analyzed. All the results were presented in appropriate tables.

We defined the following categories for the spectrum of pathological lesions observed in post-transplant gastrointestinal mucosal biopsies: (a) Infection-related gastrointestinal colitis, (b) Drug-induced colitis, (c) De novo IBD, (d) Neoplasms, (e) Post-transplant lymphoproliferative diseases, (f) Non-specific causes, (g) No significant mucosal pathology

Results

Over the period spanning January 2017 to December 2022, a total of 985 cases underwent kidney/liver transplants. Within the

duration of this six-year study, 46 cases underwent endoscopy/colonoscopy biopsies at our hospital for various indications, with 39 cases being post-kidney transplant patients and 7 being liver transplant patients.

Our investigation revealed a significant male predominance (93.5%) among the studied cohort, with the majority falling within the 5th to 6th decade of life, exhibiting a mean age of 54.93 years. The most prevalent presenting symptom was diarrhea (45.7%), followed by dyspepsia and anemia.

The mean duration from transplantation to the onset of presenting complaints was 23 months, with a standard deviation of 21.9 months. A diverse array of pathological lesions was identified in post-transplant gastrointestinal mucosal biopsies, encompassing various categories (Refer to Table 1): Infection-related gastrointestinal colitis (26.1%), Drug-induced colitis (8.7%), De novo inflammatory bowel disease (IBD) (2.2%), Neoplasms (2.2%), Post-transplant lymphoproliferative diseases (2.2%), Non-specific causes (32.6%), Mucosal biopsies showing no significant pathology (26.1%).

Table 1: post-transplant gastrointestinal mucosal biopsies, encompassing various categories

Catergories	Frequency	Percent
Neoplasms	1	2.2%
Drug induced colitis	4	8.7%
Ibd	1	2.2%
Infection related gastrointestinal colitis	12	26.1%
PTLD	1	2.2%
Non specific causes	15	32.6%
No significant mucosal pathology	12	26.1%
Total	46	100.0

Within the subset of infection-related gastrointestinal colitis cases (26.1%), the most frequently identified pathogens were cytomegalovirus (CMV) (6/12), followed by Cryptosporidium (1/12), Herpes simplex virus (2/12), and Tuberculosis (1/12). In two instances, the infective etiology remained undetermined. Non-specific colitis cases (32.6%) comprised mucosal biopsies demonstrating erosions, ulcerations, active colitis, and mild gastritis.

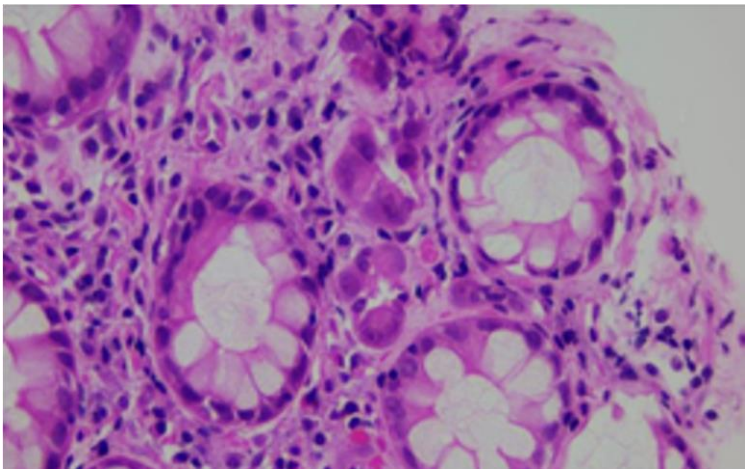

Figure 1: CMV colitis (H&E, 10X)

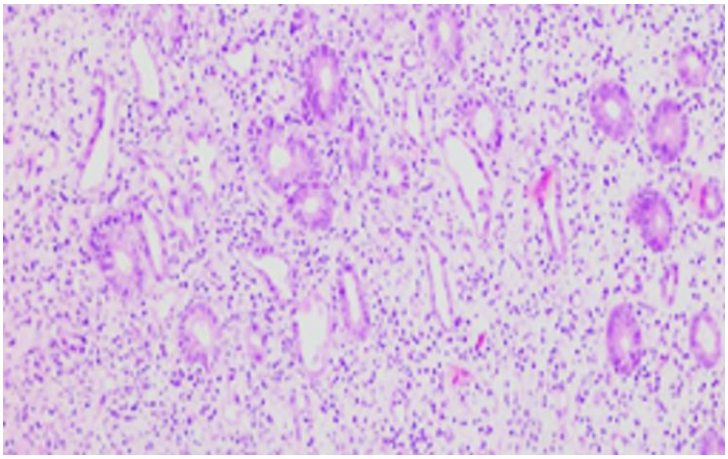

Figure 2: Drug-induced colitis (H&E, 10X)

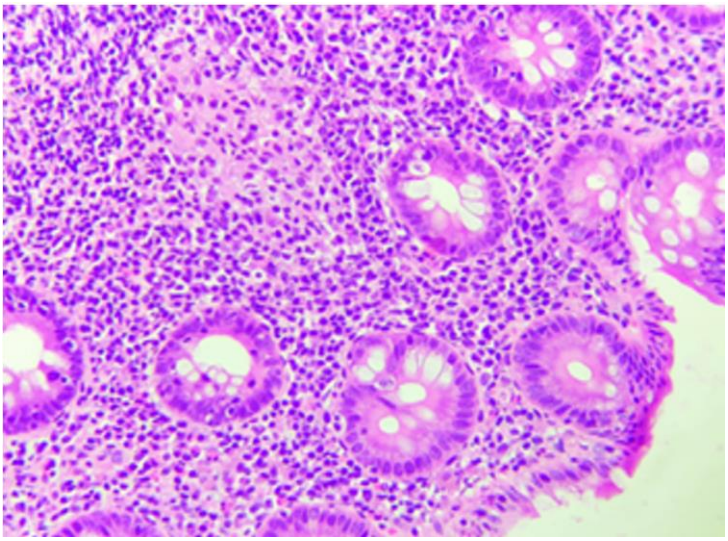

Figure 3: Post-transplant IBD (Crohn's disease) (H&E, 40X)

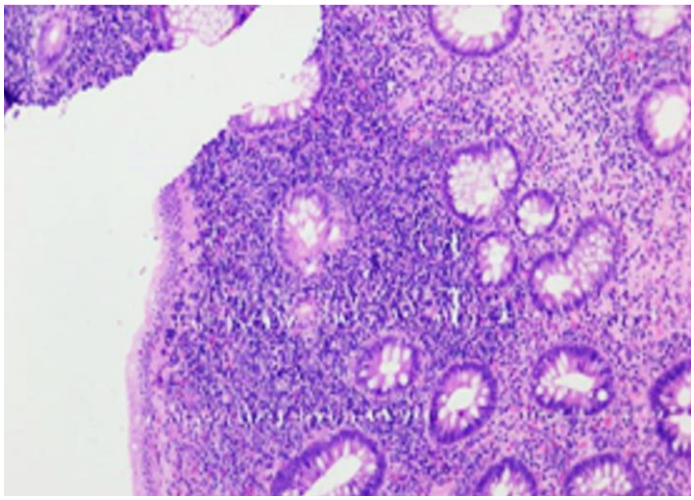

Figure 4: Multifocal monomorphic PTLD favoring extranodal marginal zone lymphoma (H&E, 40X)

Discussion

Gastrointestinal (GI) diseases in post-transplant patients encompass a spectrum of conditions that can affect various parts of the digestive tract following solid organ transplantation. Differentiating between various gastrointestinal complications can indeed be challenging due to several factors, including overlapping symptoms, the effects of immunosuppressive therapy, and the presence of multiple potential etiologies.

In the study of 46 cases, there were predominantly male patients, with 43 males and 3 females. The mean age of the patients in this study was 54.93 ± 11.53 years. Comparing these findings with similar studies, Gioco et al. reported a mean patient age of 55 ± 10 years, while Bamias et al. observed a mean age of 51.4 years. These results suggest consistency in the predominance of male patients across the studies, although there may be slight variations in mean age. Factors contributing to these age differences could include variations in study populations, geographic locations, and underlying medical conditions of the transplant recipients [5][6].

In the study, diarrhea was the most common presenting complaint, accounting for 45.7% of cases requiring endoscopy or colonoscopy. This finding is consistent with a similar study conducted by Bamias et al., which also identified diarrhea as a predominant indication for endoscopic evaluation in post-transplant patients. Following diarrhea, dyspepsia (indigestion or upper abdominal discomfort) and anemia were the next most common indications for endoscopy/colonoscopy in the study. These findings underscore the importance of gastrointestinal symptoms as key indicators of potential post-transplant complications [5].

The mean time from transplantation to the presenting complaint was found to be 23 ± 21.9 months. According to a study by Gioco et al., the mean time from transplantation to colonoscopy was reported to be 9.8 ± 9.6 years. Another study by Bamias et al. indicated a mean time from transplantation to colonoscopy of 62.3 ± 53.2 months. These findings suggest that post-transplant GI complications may manifest at varying intervals following transplantation, ranging from months to several years. The wide range of time intervals reflects the diverse nature of GI issues encountered by transplant recipients, which can arise due to factors such as immunosuppressive therapy, alterations in gut microbiota, infections, and underlying medical conditions. Understanding the timing of GI complications following transplantation is important for clinical management and surveillance strategies [3][5].

The various pathological lesions observed in 46 cases of post-transplant gastrointestinal mucosal biopsies were: infection-related gastrointestinal colitis 12 (26.1%), drug-induced colitis 4 (8.7%), de novo IBD 1 (2.2%), neoplasms 1 (2.2%), post-transplant lymphoproliferative diseases 1 (2.2%), non-specific causes 15 (32.6%), and mucosal biopsies with no significant pathology 12 (26.1%).

Among the cases studied, the most common infective etiology identified was cytomegalovirus (CMV), accounting for 6 out of 12 cases. This finding is consistent with a study conducted by Lin et al., which also reported CMV as a prevalent cause of infective colitis in post-transplant patients [7]. In addition to CMV, other identified causes of infective colitis included cryptosporidium, herpes simplex virus (HSV), and tuberculosis. These pathogens can cause gastrointestinal infections in immunocompromised individuals, including transplant recipients, and may present with symptoms such as diarrhea, abdominal pain, and fever.

In two cases, no specific infective etiology could be determined, leading to a diagnosis of "infective colitis" without a specific microbial cause identified. This highlights the challenge of diagnosing infectious colitis in transplant recipients, as multiple pathogens may be responsible, and diagnostic testing may yield inconclusive results in some cases. Overall, the identification of CMV as the most common infective etiology in post-transplant colitis underscores the importance of screening for this opportunistic infection and implementing preventive strategies, such as antiviral prophylaxis or preemptive therapy, in at-risk

transplant recipients.

In our study, 4 cases (8.7%) of drug-induced colitis were identified, predominantly associated with mycophenolate mofetil (MMF) immunosuppressant use. This finding aligns with previous research by Calmet et al. and de Andrade et al., which reported similar trends in MMF-induced histologic changes, including acute colitis-like features, inflammatory bowel disease (IBD)-like characteristics, ischemia-like findings, graft-versus-host disease (GVHD)-like features, nonspecific colitis, and normal/near normal colitis [2][8].

In our study, 15 cases (32.6%) were categorized as non-specific causes, and 12 cases (26.1%) showed no significant mucosal changes. These non-specific changes encompassed erosion, ulceration, ischemic colitis, active colitis, and mild gastritis. Several of these mucosal biopsies could not be definitively categorized as MMF-related colitis or drug-related colitis due to the absence of key histopathological features. These features, including crypt architectural distortion, dilated damaged and degenerated crypts, atrophic crypts, or increased crypt apoptosis, are typically indicative of drug-induced colitis. However, their absence in the histopathological examination posed challenges in establishing a conclusive diagnosis of MMF-related colitis or drug-induced colitis in these cases. Hence, a few of the cases of non-specific causes in our study may be attributed to drug-induced/MMF-related colitis. As a consequence, patients on MMF immunosuppressants may require colonoscopy biopsy on a timely basis.

In our study, we reported one patient with de novo IBD-Crohn's disease 1 (2.2%). Despite typically responding to immunosuppressive therapy, inflammatory bowel disease (IBD) can emerge post-transplantation, even with immunosuppression in place. This paradox suggests complexities in immune modulation and gastrointestinal inflammation. Factors such as damage or pathogen-associated molecular pattern molecules (DAMPs/PAMPs) may contribute. DAMPs released during transplantation or tissue injury in the transplanted organ, along with gut microbiota changes, can foster intestinal inflammation. Understanding these mechanisms is crucial for developing targeted therapies to mitigate post-transplant IBD-like conditions [9].

Patients with a history of solid organ transplantation or hematopoietic stem cell transplantation are at an increased risk of developing post-transplant lymphoproliferative disorder (PTLD). The gastrointestinal tract is commonly affected as it has an abundance of B and T cells. Like other lymphomas, PTLD is aggressive and mortality rates improve with early treatment. Prognosis and treatment are dependent on the time of disease presentation, morphological subtype of PTLD, and concomitant systemic disease. In our spectrum of post-transplant cases, one such patient with PTLD (multifocal monomorphic PTLD favoring extra nodal marginal zone lymphoma) was diagnosed in our study [1].

One patient with malignancy (moderately differentiated adenocarcinoma colon) was also reported in our study. The Israel Penn International Transplant Tumor Registry showed that the stage-specific survival for cancer of the colon, lung, breast, prostate, and bladder, was lower in patients after solid organ transplant compared with those without it. The 1-year adjusted survival of recipients with colorectal, prostate, and non-small-cell lung cancer were 10%, 40%, and 20%, respectively, compared with 40%, 80%, and 30% in the general population [4].

Limitations of the Study: The study is constrained by a few limitations which include a relatively small sample size, a restricted time duration of data collection, and the restriction of the study to a single center.

Conclusion

Post-transplant gastrointestinal diseases represent a multifaceted challenge for solid organ transplant recipients, affecting their health and quality of life. Timely recognition, precise diagnosis, and personalized management are critical for improving outcomes

and mitigating complications in this vulnerable population. A collaborative approach involving gastroenterologists, transplant surgeons, infectious disease specialists, and other healthcare professionals is often indispensable to deliver holistic care to affected individuals. Through ongoing research efforts and dedicated clinical care, strides can be made toward achieving better management strategies and ultimately improving the lives of transplant recipients worldwide.

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