sciendo
ПРИЛОЗИ. Одд. за мед. науки, XLIII 1, 2022 МАНУ
CONTRIBUTIONS. Sec. of Med. Sci., XLIII 1, 2022 MASA

10.2478/prilozi-2022-0006 ISSN 1857-9345

INFLAMMATORY BOWEL DISEASES IN RENAL TRANSPLANTAT RECIPIENTS: A CASE SERIES AND REVIEW OF THE LITERATURE

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ABSTRACT

Inflammatory bowel diseases are autoimmune disorders affecting the gastrointestinal tract and producing a wide variety of extraintestinal manifestations. Kidneys are a rare target organ of their extraintestinal activity, but if affected, renal function could deteriorate to end-stage kidney disease, which is curable only by organ transplantation. Renal calculi are the most common pathological kidney manifestation in IBD patients, followed by tubulointerstitial nephritis, glomerulonephritis, and other kidney pathologies.

The liver is the most commonly transplanted organ in IBD patients (primary sclerosing cholangitis and autoimmune hepatitis), and a scarcity of literature on kidney recipients is present to date regarding the incidence of renal insufficiency, kidney transplantations, post-transplant IBD course and further complications such as graft rejection or infections in this specific group of patients. De novo IBD is a paradoxical entity in the setting of rigorous post-transplant immunosuppression.

In this case series, we present three patients who underwent kidney transplantation with a history of an IBD and one patient who developed de novo Crohn's disease after the deceased donor organ transplant was performed.

Keywords: inflammatory bowel disease, end-stage kidney disease, 5-aminosalicylate toxicity, tubulointerstitial nephritis, kidney transplantation, de novo IBD

INTRODUCTION

Inflammatory bowel diseases (IBD) are systemic autoimmune disorders with increasing prevalence [1]. Two entities of IBD are Crohn's disease (CD) and ulcerous colitis (UC). CD is manifested with an extensive transmural granulomatous inflammation, primarily beginning in the ileum and spreading across the gastrointestinal tract with skip lesions, but also penetrating the intestinal wall and forming fistulous canals and abscesses. Ulcerous colitis is well known for its pathognomonic occurrence in the rectum, with the tendency to spread proximally but not across the Bauchin's valve. Its inflammation is strictly located in the mucosal and submucosal layers [2, 3].

Both diseases have an abundance of extraintestinal manifestations. Therefore, it is not always clear whether a concomitant solid organ disease is an extraintestinal manifestation of the

same underlying pathological process, secondary complication due to electrolyte and volume disturbances, circulating proinflammatory cytokines and endotoxins, malnutrition, medication toxicity, or whether it represents the individuals susceptibility to autoimmune diseases [2, 3].

Kidneys are rarely the site of significant organ damage in IBD patients, even less so severe damage that it requires patients to undergo kidney transplantation [4]. That is why this case study and the following discussion could be of some value to clinicians who regularly have patients with IBD.

CASE REPORTS

Patient 1 is a 56-year-old male who was diagnosed with CD in 1992. In December of 1992 the patient was operated on, and 16 cm of the terminal ileum were resected together with right hemicolectomy. In January 1998 he was hospitalized for abscess evacuation and reanastomosis but postoperatively developed an acute kidney injury which required three dialysis procedures. By then, his pharmacological treatment included glucocorticoids and aminosalicylates. In June 2012 he was readmitted for drainage of abdominal wall abscess, and a small intestine passage was done, which verified 10 cm stenosis in the region of ileotransversoanastomosis. Because of elevated liver enzymes, an MRCP was done with the suspicion of primary sclerosing cholangitis, but no biliary ducts dilatation was found. The patient was again operated on two months later and had 20 cm of his ileum and 8 cm of his transversal colon resected. Since then, he has been on mesalazine and azathioprine therapy (azathioprine removed in February 2019). He was started on hemodialysis in July 2019 because of the progression of renal insufficiency, which was pathohistologically (PHD) diagnosed as tubulointerstitial nephritis. The patient received a deceased donor kidney transplant in August 2021. Standard basiliximab induction therapy was combined with tacrolimus, mTOR inhibitors, and prednisone. Because of urine retention after urine catheter removal, the patient had to undergo TURP. The PHD showed a well-differentiated adenocarcinoma with Gleason score 3+3=6 and a prognostic grade of group 1, according to WHO/ISUP classification. One week later he experienced worsening of the allograft function. Renal allograft biopsy showed borderline acute cellular rejection (Banff ACR borderline) and acute tubular damage with negative C4d and moderate vascular changes. He received steroid pulses (3x500 mg of 6-methylprednisolone) to improve and stabilize the allograft function.

Patient 2 is a 33-year-old female who has been diagnosed with UC (pancolitis) since 2009. She was treated with azathioprine, mesalazine, and corticosteroids. Aminosalicylates, with which she was treated, caused progressive kidney dysfunction. A kidney biopsy revealed tubulointerstitial nephritis. She was started on peritoneal dialysis in January 2016. In October 2017 she received a deceased donor allograft. Immunosuppressive protocol included tacrolimus, everolimus, and corticosteroids, with a basiliximab induction. In January 2018, everolimus was switched to mycophenolate-sodium because of severe leg oedema. Eight months later, she was hospitalized because of subfebrility and acute enterocolitis. Cytomegalovirus infection was proven (CMV DNA PCR 2170 copies/ml). With a reduction in MMF therapy and intravenous antiviral therapy, diarrhea stopped. She has a stable renal allograft function.

Patient 3 is a 56-year-old male with a history of polycystic liver and kidney disease since 1997. He had started with hemodialysis in July 2013 and received a deceased donor renal allograft in August 2014. At the beginning of 2019, he developed severe diarrhea and was suspected to have a CMV colitis. However, after a thorough evaluation he was diagnosed with Crohn's disease. He was treated with sulfasalazine and increased doses of steroids with good response, and a stable renal allograft function.

Patient 4 is a 39-year-old female who has been diagnosed with UC since 2002. In May 2017 she had started with peritoneal dialysis, but a kidney biopsy was never performed (tubulointerstitial nephritis was diagnosed ex anamnesis). She also developed hypertension in 2017. In December 2018, she received a renal allograft from a deceased donor. Immunosuppressive therapy following kidney transplantation included basiliximab induction, followed by tacrolimus, everolimus, and glucocorticoid maintenance.

Table 1. *Patients' characteristics. CD - Crohn's colitis, UC – ulcerous colitis, 5-ASA – 5-aminosalicylates, SOT – solid organ transplantation, NSTEMI – non-ST elevated myocardial infarction*

	Patient 1	Patient 2	Patient 3	Patient 4
Age/sex	56 y/o male	33 y/o female	56 y/o male	39 y/o female
Year of IBD diagnoses (a)	1992, CD	2009, UC	2019, CD	2002, UC
Year of transplantation (b)	2021	2017	2014	2018
IBD duration	29 years	8 years	-5 years	16 years
IBD medication	Corticosteroids, 5-ASA, azathioprine	Azathioprine, mesalazine, corticosteroids	Tacrolimus, corticosteroids, mycophenolate mofetil (SOT)	Sulfasalazine, corticosteroids
Kidney biopsy	Tubulointerstitial nephritis	Tubulointerstitial nephritis		
Post-operative complications	Uroinfection, borderline acute cellular rejection	Acute enterocolitis, uroinfection	De novo IBD	
Other comorbidities	Hypertension, nephroangiosclerosis, bilateral renal cysts	Anemia	Polycystic liver and kidney disease, NSTEMI	Anemia

DISCUSSION

Renal and lower genitourinary tract involvement in IBD patients has a prevalence of 4-23% [5, 6]. However, no study so far has focused solely on renal insufficiency. The significant prevalence differences in "renal" involvement may be misleading because authors combine renal and genitourinary tract involvement.

The most common renal pathology in IBD patients are renal calculi at 12-28%. Some of the rarer kidney manifestations are tubulointerstitial nephritis, glomerulonephritis and renal amyloidosis. All renal pathology in IBD patients shows a strong correlation with the intensity of intestinal inflammation [6]. Ambruzs et al. have proven that the most common PHD of the renal biopsy specimen is IgA nephropathy (which is also the most common cause of glomerulonephritis) [7].

IBD patients' risk of developing urolithiasis is 10 to 100 times higher than in general hospital patients [5]. Although none of our patients were diagnosed with renal calculi, it is essential to note that patients who underwent surgical procedures, especially total colectomy, distal ileum resection, or formation of an intestinal bypass, are at a higher risk (patient A) [8]. Furthermore, the extent of the inflammation is a significant risk factor for renal calculi formation, such that the inflammatory process located in the ileum and colon presents a higher risk factor than when the inflammation is located only in the ileum [9]. Renal calculi in IBD patients are urate stones and oxalate stones. The predisposing factors for urine oversaturation with uric acid include low pH (bicarbonate loss by stool), hypermetabolism of the critically ill (hyperuricemia), and water loss via feces excretion. Oxalate stones are formed because of elevated oxalate absorption, higher mucosal permeability and lower oxalate metabolism in the gut [10].

In many cases, it is difficult to differentiate if tubulointerstitial nephritis is induced by medication (5-aminosalicylates being the most important in IBD patients) or a sign of extraintestinal IBD progression. Tubulotoxicity of 5-ASA has been shown in dogs and rats, but the doses far exceeded those used in human treatment protocols [11]. Single cases of nephrotoxicity in humans were also reported [12, 13]. A study from 1997 connected 5-ASA treatment with tubular proteinuria, however, higher 5-ASA doses correlated with more severe intestinal inflammation. They stated that their results might

indicate either a drug-induced, dose-dependent, or an inflammation-induced, time-dependent process capable of impacting kidney function in the long term, but no distinction between the influence of medication and the disease itself could be made [14]. Herrlinger et al. investigated the prevalence, origin and likely cause of proteinuria in IBD patients. They found a high proportion of patients (52%) with pathological proteinuria, and apart from very few patients, the origin of the detected proteinuria was tubular. In further reading, it is marked that the analysis of variance did not show any influence of 5-ASA on proteinuria. They concluded that proteinuria in patients with active disease, being higher than in patients with inactive disease, even in the absence of 5-ASA, makes a strong influence of 5-ASA doubtful [15]. In 2004 a British cohort study concluded that the incidence rate of renal dysfunction in patients treated with 5-ASA was low and unrelated to dosage [16]. A literature review from Gisbert and al. found that the incidence of nephrotoxicity in patients treated with 5-ASA was lower than 0.5% and that only 10% of patients who develop 5-ASA tubulointerstitial nephritis will also develop end-stage kidney disease. They also concluded that the kidney damage associated with 5-ASA use is an idiosyncratic reaction rather than dose related [17]. There is no statistically relevant difference in nephrotoxicity induced by mesalazine or sulfasalazine [10]. It is possible that aminosalicylate therapy in our patients with tubulointerstitial nephritis and end-stage renal disease is not related to them in a causal effect or may have played only a minor role in their development.

Few studies have focused exclusively on chronic renal failure and/or end-stage renal disease in IBD patients. A case-control study from 2013 found that out of a sample of 775 patients with IBD, 11 patients had chronic renal failure, all of which had Crohn's disease. Only two patients required hemodialysis. It was estimated that the extent of bowel resection and recurrent urolithiasis were two major risk factors for chronic renal failure, but also the duration of IBD, which was associated with a higher frequency of renal insufficiency [18]. Lewis et al. conducted a case-control study on both CD and UC patients (total of 251) and estimated the frequency of renal insufficiency to be 15.9%. Possible risk factors were older age at admission and a longer median duration of IBD. For every 5-year increase in age at the time of admission, the likelihood of having renal insufficiency increased by 30% [19].

A meta-analysis set out to assess the incidence of and complications from IBD in adult kidney transplant recipients. All studies included subjects undergoing kidney transplantation regardless of the previous history of IBD. The pooled incidence of recurrent IBD was 27.6%, the pooled incidence of de novo IBD was 18.8%, the pooled incidence of post-transplant infection was 4.7%, the pooled incidence of graft rejection was 31.4%, and the pooled incidence of re-transplantation was 30.4% [20]. For comparison, a retrospective study of 91 liver transplant patients (the most frequently solid organ transplanted in IBD patients) showed that up to 65% IBD recurred post-transplant and 19% had de novo IBD [21]. In theory, it could be possible that the recurrence rate of IBD in kidney transplant patients is less than in liver transplant patients. This could be explained by the immunosuppressive regimen used in kidney recipients, consisting of corticosteroids and calcineurin inhibitors, which are used to dampen the autoimmune response in IBD. However, the scarcity of studies leaves this theoretical assumption unsubstantiated [20]. Tacrolimus is superior to cyclosporine in improving graft survival and preventing graft rejection after kidney transplantation [22]. Switching from tacrolimus to cyclosporine to prevent IBD relapses cannot be recommended due to a lack of substantiated evidence. Anti-TNF therapy was effective in patients with refractory IBD [23], and the role of TNF molecules was pinpointed in allograft rejection [24]. Hence anti-TNF therapy could be a promising alternative treatment in patients with acute rejection and active IBD.

As for low infection incidence, the authors of the meta-analysis are cautious, implying that the low percentage of infections could be due to a reporting bias because infections were not the primary outcome measured in most studies. If measured, only serious infections were most likely documented, leaving out the mild infections. One retrospective study reported that up to 25% of kidney transplant patients had at least one episode of nosocomial infection and that patients with mTOR inhibitors showed a significantly higher rate of infections than those receiving calcineurin inhibitors [25] (patient A). Another study showed that approximately 80% of transplant recipients (in general) develop an infection after transplantation [26]. A progressive reduc-

tion in graft rejection has led to increased infectious diseases, particularly those associated with latent viruses such as CMV. CMV is the virus that most commonly infects patients undergoing solid organ transplantation. The gastrointestinal tract is most commonly affected during CMV tissue-invasive disease, resulting in esophagitis, gastritis, enteritis, or colitis [27] (patient B). Another reason for kidney transplant recipients developing watery diarrhea could be mycophenolate side effects, reaching an incidence of 36% and persisting even after the drug withdrawal [28, 29] (patient B).

The incidence of IBD after solid organ transplantation is approximately ten times higher than that observed in the general population. Most de novo cases of IBD occur after liver transplantation, with only 5% occurring in kidney recipients [30] (patient C). Several hypotheses have been suggested to explain the paradoxical development of de novo IBD in kidney recipients. Immunosuppressive therapy may provoke dysregulation of the intestinal immune environment (suppression of IL-2 dependent regulatory T-cells proliferation could lead to less activation-induced cell death (AICD) of T-cells [20]). Additionally, it could damage the intestinal mucosa's epithelial barrier, leading to prolonged exposure to luminal antigens, and finally, the dysbiosis of the gut microbiota may also play a role in post-transplant IBD development [30].

CONCLUSION

Renal manifestations in patients with IBD are rare, but close monitoring of renal function is essential, especially in older patients with longer disease duration, more intense intestinal inflammation, and patients who underwent bowel resection. These individuals are at a 10-100 times higher risk of developing renal calculi (urate and oxalate stones) than general hospital patients. Most up-to-date studies suggest that 5-ASA nephrotoxicity in IBD patients does not present a significant cause of kidney damage. The assumption of dose-dependent worsening of the renal function may be overestimated and unnecessary (indications are it could be an idiosyncratic reaction). Tubulointerstitial nephritis and proteinuria related to nephrotoxic medication could have a different origin in this group of patients, primarily depending on the concentrations of circulating cytokines. The liver is the most frequently transplanted organ in IBD patients, and post-transplant IBD recurrence rates are higher in liver recipients than in kidney recipients, which could be due to different immunosuppressive regimens, but that still needs to be scientifically proven. Also, post-transplant de novo IBD incidence is higher in liver recipients. As for other post-transplant complications, infections are significantly higher in patients receiving mTOR inhibitors than calcineurin inhibitors, with latent CMV infection being the most common viral infection in solid organ recipients. Another reason for watery diarrhea other than infection might be mycophenolate use.

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Резиме

ВОСПАЛИТЕЛНИ БОЛЕСТИ НА ЦРЕВАТА КАЈ РЕЦИПИЕНТИ НА РЕНАЛЕН ТРАНСПЛАНТАТ: СЕРИЈА СЛУЧАИ И ПРЕГЛЕД НА ЛИТЕРАТУРАТА

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Воспалителните болести на цревата се автоимуни нарушувања што влијаат на гастроинтестиналниот тракт и предизвикуваат широк спектар на екстраинтестинални манифестации. Бубрезите се редок целен орган на нивната екстраинтестинална активност, но доколку се засегнати, бубрежната функција може да се влоши до крајна фаза на бубрежна болест, која може да се излечи само со трансплантација на органи. Бубрежните калкули се најчеста патолошка бубрежна манифестација кај пациентите со воспалителни болести на цревата, проследена со тубулоинтерстицијален нефритис, гломерулонефритис и други бубрежни патологии.

Црниот дроб е најчесто трансплантираниот орган кај пациенти со воспалителни болести на цревата (примарен склерозирачки холангитис и автоимун хепатитис), а недостигот на литература за примателите на бубрези е присутен до денес во врска со инциденцата на бубрежна инсуфициенција, трансплантацијата на бубрези, посттрансплантацискиот тек на воспалителните болести на цревата и дополнителни компликации како што се отфрлање на графтот или инфекции кај оваа специфична група пациенти. De novo, воспалителните болести на цревата е парадоксален ентитет во услови на ригорозна имуносупресија по трансплантацијата.

Во оваа серија случаи, презентираме тројца пациенти кои биле подложени на трансплантација на бубрег со историја на воспалителни болести на цревата и еден пациент кој развил де ново Кронова болест по извршената трансплантација на органи од починат донор.

Клучни зборови: воспалителна болест на цревата, крајна фаза на бубрежна болест, 5-аминосалицилатна токсичност, тубулоинтерстицијален нефритис, трансплантација на бубрег, de novo воспалителни болести на цревата