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REVIEW

Gastrointestinal complications in renal transplant recipients

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Summary

Gastrointestinal complications are frequent in renal transplant recipients and can include oral lesions, esophagitis, peptic ulcer, diarrhea, colon disorders and malignancy. Oral lesions may be caused by drugs such as cyclosporine and sirolimus, by virus or fungal infections. Leukoplakia may develop in patients with Epstein–Barr virus (EBV) infection. The commonest esophageal disorder is represented by fungal esophagitis usually caused by candida. A number of patients may suffer from nausea, vomiting and gastric discomfort. These disorders are more frequent in patients treated with mycophenolate mofetil (MMF). Peptic ulcer is more rare than in the past. Patients with a history of peptic ulcer are particularly prone to this complication. Other gastroduodenal disorders are caused by cytomegalovirus (CMV) and herpes simplex infection. Diarrhea is a frequent disorder which may be caused by pathogen microorganisms or by immunosuppressive agents. The differential diagnosis may be difficult. Colon disorders mainly consist of hemorrhage, usually sustained by CMV infection, or perforation which may be caused by diverticulitis or intestinal ischemia. Colon cancer, anal carcinoma, and EBV-associated lymphoproliferative disorders are particularly frequent in transplant recipients. A particular gastric lymphoma called mucosa-associated lymphoid tissue (MALT) lymphoma may develop in renal transplant patients. It usually responds to the eradication of *Helicobacter pylori*.

Introduction

The incidence of gastrointestinal complications in renal transplantation is relatively high, ranging around 20% [1]. These complications may be severe in about 10% of patients [2] and may lead to graft loss and even patient death. The most frequent gastrointestinal complications in renal transplant recipients include oral lesions, esophagitis, peptic ulcer, diarrhea, colon hemorrhage or perforation. These disorders may be related to medications, infections and/or exacerbation of pre-existing gastrointestinal pathology.

Oral lesions

Cyclosporine-induced gingival hyperplasia is a well known complication in renal transplant patients, which can be worsened by the concomitant use of calcium channel blockers [3,4]. Prevention with appropriate oral hygiene is important in controlling the inflammatory component and decreasing the severity of overgrowth. A 5-day treatment with azithromycin can improve the subjective symptoms and the clinical picture in some patients [5]. In others, orthodontic therapy may be necessary.

Aphtous ulcers are frequent and often recur in the same patient. They are usually caused by cytomegalovirus (CMV). Aphtous ulcers present as well defined circles and may be single or multiple. Ulcers can be found on all areas of the oral mucosa, except the hard palate, gingiva, and vermilion border. Biopsy specimen obtained from ulcer beds usually shows intranuclear inclusions resembling an owl eye [6]. Mouth ulcers can also be caused by drugs. In a study [7] they occurred in about one-fourth of kidney transplant recipients treated with sirolimus and

mycophenolate mofetil (MMF) without steroids. It was unclear whether ulcers were caused by overimmunosuppression, by lack of steroids, or were rather attributable to the use of oral emulsion of sirolimus instead of pills.

Herpes simplex may cause cold sores or a gingivostomatitis often accompanied by fever, malaise and lymphadenopathy. Mucosal vesicles may also be caused by Varicella–Zoster virus.

Leukoplakia, characterized by white plaques, and histologically by benign hyperkeratosis, may occur in any area of the mouth. It is still unclear whether leukoplakia arises from activation of endogenous Epstein–Barr virus (EBV) or by exogenous EBV infection. In some transplant patients this lesion may rapidly progress to squamous cell carcinoma [8]. Oral warts are more frequent than in the normal population. Kaposi's sarcoma may present as a red, purple, brown or bluish macule or nodule, usually located on the palate or the oropharynx. A number of other premalignant and malignant lesions of the oral mucosa and of the tongue have also been reported in transplant recipients.

Oral candidiasis is frequent in renal transplant recipients. It can be the result of the immunosuppression or may develop after vigorous antibiotic treatment. It may cause irregular or widespread erythema, erosive changes, or a typical creamy surface. Nystatin swish and shallow every 6 h or clotrimazole may be effective in preventing oral and esophageal fungal infections. Plaque-like lesions of the oral mucosa may also be associated with bacterial overgrowth and should be treated with antibiotics and antiseptics.

Esophageal disorders

The commonest esophageal disorder in renal transplant recipients is represented by candidal esophagitis. This usually occurs within 6 months after transplantation and is particularly frequent in leukopenic or overimmunosuppressed patients as well as in diabetic patients and in patients debilitated from infection or other complications. Usually esophagitis is associated with candidal stomatitis and epiglottitis. Occasionally, esophagitis may be complicated by fungemia. Milder cases may be treated with local nystatin. Most patients respond to a treatment of intravenous amphotericin B for 2–6 days [9]. Other causes of esophagitis include CMV or herpes simplex infection. The typical appearance of herpetic esophagitis, which occurs more frequently during periods of intensive immunosuppression, is represented by multiple vesicular lesions with or without ulcers along the entire esophagus. However, as the endoscopic manifestation of herpetic esophagitis may be variable, the diagnosis should be confirmed by cytology, tissue studies and viral cultures. The infection responds to acyclovir, which should be started as soon as the diagnosis is confirmed as untreated herpetic ulcers can progress to hemorrhage, which may even be fatal, or to esophageal perforation [10].

The esophagus may be involved by Kaposi's sarcoma. On endoscopy the lesions appears as multiple grayish-purple plaques. Although most lesions are asymptomatic, a digestive hemorrhage may be the first sign of the disease.

Stomach and duodenum disorders

A number of transplant patients may suffer from nausea, vomiting, abdominal pain, or gastric discomfort. These symptoms may be caused by the numerous pills some patients have to take every day, by trivial infections favored by the immunosuppressive therapy, or by specific gastric toxicity of calcineurin inhibitors, corticosteroids or MMF. Nausea, vomiting, dyspepsia, and anorexia are particularly frequent in patients given MMF [1], and are related to the doses of the drug and to the peak concentration in the blood [11]. These gastric adverse effects are irritative in nature and are often reversible. However, in a number of patients they may require a dose change, which may increase the risk of acute rejection [12] and decrease the graft survival [1,13]. Recently, an enteric-coated mycophenolate sodium has been produced which proved to be therapeutically equivalent to MMF in de novo renal transplant patients [14]. The safety profile and incidence of gastrointestinal adverse events were similar for both groups [15].

Peptic ulcer was a frequent cause of mortality until a few years ago, accounting for about 4% of deaths after transplantation [16]. More recently, however, the prognosis has improved and mortality or graft losses because of peptic ulcer have become exceptional. Several factors may contribute to the development of post-transplant peptic ulcer disease. An important risk factor is a history of peptic ulcer disease [17,18]. In this regard, it must be remembered that although the prevalence of peptic ulcer is not increased in dialysis patients, almost 50% of them suffer from dyspepsia and show an elevated gastric acid secretion [19]. Moreover, about 30% of renal transplant recipients have *Helicobacter pylori* colonization of the stomach [20]. MMF displays a similar side-effect profile to nonsteroidal anti-inflammatory drugs with 3–8% cases of ulcer perforation or bleeding within 6 months [21]. The role of corticosteroids is still controversial [22] but it is likely that the high doses of corticosteroids used for treating rejection may have an ulcerogenic effect as several cases of hemorrhagic ulcers in transplant patients occurred during or immediately after the administration of intravenous high-dose methylprednisolone pulses. As

a matter of fact, a strong association between intravenous high-dose methylprednisolone pulses and development of peptic ulcer has been found in a series [18]. The emotional stress caused by the operation and by possible complications may also play an important role, although the mechanisms by which stress contributes to ulcer disease are still uncertain. Finally, cigarette smoking may also lead to ulceration by reducing the pyloric sphincter pressure by decreasing pancreatic bicarbonate secretion, and by impairing the gastric microcirculation [23,24].

At present the incidence of peptic ulcer has declined substantially. This is mainly because of the fact that transplant candidates are actively screened for evidence of peptic ulcer before transplantation. Patients with pre-existing ulcer are usually treated with H_2-receptor antagonists or proton-pump inhibitors without substantial differences between omeprazole and ranitidine [25]. Appropriate antibiotic therapy directed to eradicate *H. pylori* further contributes to a complete healing of ulcer. Moreover, the doses of corticosteroids have been considerably reduced in comparison with the past. The incidence of rejection and other complications is also reduced. Today, many transplant groups use prophylactic H_2-receptor antagonists, proton-pump inhibitors or sucralfate after operation. The utility of this routine prophylaxis may be challenged but it is a common experience that the mortality because of gastroduodenal perforation or hemorrhage fell to almost zero after the constant use of preventive antiulcer therapy. At any rate, there are no doubts that patients with a history of a previous ulcer should be given gastric protection for the first few months after transplantation. Considering the excellent results of nonoperative ulcer therapy in transplant patients, surgery should be limited to exceptional, complicated cases. Rare cases of massive gastrointestinal hemorrhage because of visceral Kaposi's sarcoma have also been described [26]. In many of these cases minimization of immunosuppressive therapy and anti-*H. pylori* therapy results in disease regression [27].

The development of hyperplastic and multiple gastric polyps in organ transplant has been firstly reported recently [28]. The cause is unknown. About 10% of post-transplant lymphoproliferative disorders (PTLD) present with gastrointestinal symptoms [29]. Most cases are associated with EBV infection. However, gastric lymphoma can also develop in carriers of *H. pylori*. This microorganism is often associated with a particular case of mucosa-associated lymphoid tissue lymphoma, called MALT lymphoma. Mucosa-associated lymphoid tissue (MALT) lymphoma has been described in a number of renal transplant patients, is less aggressive than other lymphomas, and may be cured by the eradication of *H. pylori* [30].

Other causes of gastroduodenal disorders include CMV and herpes simplex infection. CMV infection is a frequent cause of nausea, vomiting, gastroparesis or bleeding. In a study, of 54 liver transplant recipients with upper gastrointestinal symptoms, 37 (69%) had CMV positive cells at gastric or duodenal mucosa biopsy [31]. In a Hungarian study 40% of organ transplant recipients with upper gastrointestinal symptoms showed a polymerase chain reaction positive for CMV at biopsy [32].

Small bowel disorders

An increased incidence of ischemia and obstruction of small bowel has been reported in patients with polycystic kidney disease, possibly as a consequence of circulating active secretagogues produced by extrarenal cysts [33].

Ulcers of the small intestine represent a rare but dreadful complication of renal transplantation, development of which may be favored by corticosteroids, intestinal ischemia, and even more often by CMV infection [34,35]. The clinical picture consists of periumbilical colicky pain, nausea and vomiting. Frequently the patient presents with small bowel obstruction, bleeding, or perforation. The diagnosis is difficult. Plain films of the abdomen may show signs of obstruction or perforation. Endoscopy may reveal ulcers in the high jejunum. A new noninvasive technique, the wireless capsule endoscopy, allows visualization of the entire small intestine and represents a major improvement in the diagnosis. If the involved segment is perforated, stenotic or bleeding, it should be resected.

Diarrhea

Diarrhea may be defined as more than three bowel movements per day with a daily stool bulk exceeding 150 ml. Diarrhea is frequent in renal transplant recipients. The main causes of diarrhea after transplantation are: infections, immunosuppressive drugs, antibiotics and other drugs.

A number of microorganisms may be responsible for diarrhea, bacteria, viruses, parasites (Table 1). The most

Table 1. Main microorganisms responsible for diarrhea in renal transplant patients.

Bacteria	*Clostrydium difficile* (oral vancomycin), *Salmonella* species (fluoroquinolones), *Campylobacter jeujuni*, *Listeria monocytogenes* (ampicillin-sulbactam), other enteric pathogens (*Shigella*, *Yersinia*, *Escherichia coli*)
Viruses	CMV, Herpes simplex, Adenovirus, Coxachiae, Rotavirus
Parasites	*Criptosporidium*, *Microsporidium*, *Isopsora belli*, *Strongyloides stercoralis*, *Giardia lamblia* (Quinacrine, Metronidazole)

frequent cases of acute diarrhea are of viral etiology and typically last for a period of 1–3 days. Approximately 50% of transplant patients receiving antibiotics for any reason develop *Clostridium difficile*-associated diarrhea [36]. Symptoms may begin at any time during the course of antimicrobial treatment or even after antimicrobial agents have been stopped. Pseudomembranous colitis is the result of a toxin-mediated enteric disease while there is no microbial invasion of the intestinal mucosa. The most common symptom is diarrhea, often associated with fever. Dehydration, hypoalbuminemia, electrolyte disturbances and colonic perforation, because of necrotizing colitis with gangrene, are the most frequent complications. Colonoscopy, showing a typical pseudomembranous colitis, and the identification of *C. difficile* or its toxin in the stool may confirm the diagnosis. Recurrent disease may develop in about 20% of cases [37]. Other enteric bacteria responsible for diarrhea are *Shigella*, *Salmonella typhi*, *Salmonella typhimurium* and *Campylobacter*.

Cytomegalovirus infection with gastrointestinal involvement is another cause of diarrhea. In CMV enterocolitis, with or without fever, gastrointestinal bleeding, perforation and toxic megacolon are possible complications. Diarrhea because of gastrointestinal protozoal infection is not reported frequently in transplant patients, although T-cell associated immunity plays an important role against protection from these agents.

Drug-induced diarrhea is also frequent. Immunosuppressive agents may cause diarrhea [38]. In a study diarrhea incidence was significantly higher with MMF, 3 g/day, than with azathioprine at 1 and 3 years. Diarrhea on MMF at 2 g/day was significantly higher than for azathioprine within 6 months [39]. It has been hypothesized that the potent inhibition of the purine salvage pathway cannot keep up with the growing need of guanine nucleotides needed by the rapidly dividing nature of the gastrointestinal tract [40]. Rapamycin may also cause diarrhea. Antibiotics are a well-recognized cause of diarrhea, by altering the gut flora. Other agents that may cause diarrhea are colchicine and misoprostol.

Differentiating between infectious disease and drug-caused diarrhea in transplant recipients is as important as difficult. Drug history should be the initial step of the diagnostic approach.

As a rule in any case of diarrhea stools should be examined for bacteria and parasites, including coccidians and microsporidia. In cases of negative work-up, endoscopic assessment should be carried out in search of diagnosis. Of note, while blood levels of cyclosporine under diarrhea maintain stable the blood levels of tacrolimus show a significant increase. Thus, the blood levels of tacrolimus should be carefully monitored, especially when MMF is withdrawn [41].

Nonspecific treatment of diarrhea includes rest and large fluid intake, preferably with sugar and electrolytes. In the most severe cases intravenous infusion of fluid and electrolytes is needed. Opioids should be avoided at the beginning as diarrhea can eliminate toxins and microorganisms. However, they may be of relief in case of persisting diarrhea. Specific treatment depends on the etiology. In the case of diarrhea caused by an immunosuppressive agent, the removal of the offending drug is usually sufficient to reverse the symptoms. Anti-bacterial (fluoroquinolones, ampicillin) or anti-parasitic agents (metronidazole) may be given waiting for the results of the stool cultures. Treatment of *Clostridium difficile* consists of vancomycin given orally, 125–500 mg four times daily for 7–14 days. The addition of the probiotic agent *Saccharomyces boulardii* can reduce the risk of recurrence [42]. Cholestyramine, 1 g three times daily for 5 days, may bind the toxin and may be used in milder cases.

Colon disorders

There is an increased risk of colonic complications in renal transplant recipients, particularly in aged subjects and in patients with polycystic kidney disease [43]. Cecum or ascending colon hemorrhage can occur in association with severe CMV infection. Colon perforation may complicate a diverticular disease or be a consequence of intestinal ischemia. Abdominal pain, fever, tenderness and leukocytosis are the most frequent signs, but the clinical presentation may be atypical with vague abdominal symptoms in immunosuppressed patients. In this regard, it should be noted that about half of renal transplant recipients presenting with lower abdominal symptoms may show abnormalities at colonoscopy [44]. Pneumoperitoneum may occur in about one-third of cases. Plain abdominal X-ray films, CT scan and/or colonoscopy are helpful for a correct diagnosis. Intestinal ischemia is an important cause of morbidity and mortality. Its diagnosis should be considered in patients who develop abdominal symptoms during the early post-transplant period. It is more frequent in patients older than 40 years and in patients receiving long-term hemodialysis. The prognosis is particularly severe, with a mortality rate ranging around 55% [45]. Aggressive diagnostic evaluation and treatment may improve the prognosis [46]. Treatment should consist of early surgery under a broad spectrum of antibiotics and reduction of immunosuppressive therapy. An increasing number of life-threatening ischemic colitis caused by CMV is being reported in organ transplant recipients [47–49]. In patients with fever and abdominal pain early viral detection by CMV polymerase chain reaction can be life saving [49].

Pseudo-obstruction is a potentially dangerous condition with symptoms, signs, and radiologic appearance of an acute, large bowel obstruction, but without any identifiable cause. The treatment is conservative with nasogastric decompression and neostigmine [50].

A series of 14 transplant patients who developed inflammatory bowel disease in spite of immunosuppression has been reported. Of them nine developed ulcerative colitis and five Crohn's disease. Seven patients with ulcerative colitis remained in remission, but two patients required colectomy. Patients with Crohn's disease continued to have flares despite treatment [51].

In a transplant patients with abdominal pain, digestive bleeding, weight loss, and unexplained fever, the possibility of intestinal tuberculosis should be considered. The vague character of symptoms and the radiographic presentation of this disease which frequently mimics many other conditions may lead to great difficulties in its diagnosis. All levels of the gastrointestinal tract may be involved. The endoscopic findings most characteristic of intestinal tuberculosis are circular ulcers, small diverticula and sessile firm polyps. The suspected diagnosis must be confirmed by the presence of caseating granulomas and/or acid fast bacilli. Polymerase chain reaction is currently recommended for assessing the presence of tubercle bacilli in tissue specimens obtained by endoscopic biopsy.

Gastrointestinal malignancy

While the risk of gastric cancer is not increased in transplant patients and that of rectal cancer is significantly reduced, the risk of colon cancer is higher than in the general population [52]. Particularly elevated is the risk of anal carcinoma which is around 100 times more frequent than in general population [53].

Lymphoproliferative disorders can involve gastrointestinal tract in up to 10% of transplant recipients. The diagnosis is usually difficult. The disease is often heralded by hemorrhage or by acute abdomen from perforation or obstruction [10]. As pointed out above, a particular form of lymphoma is MALT lymphoma which is associated with *H. pylori* infection in the gastric location and to *Campylobacter jejuni* in the small intestine. MALT lymphoma may respond in milder cases to reduction of immunosuppression and/or to specific antibiotics against *H. pylori* [28,54,55].

Most PTLD are B cell lymphomas associated with EBV. The risk of PTLD is particularly elevated for transplant patients without anti-EBV antibodies and for those treated with anti-lymphocyte antibodies [56]. In the normal subjects acute EBV infection is kept under control by natural killer cells and by specific cytotoxic cells. In organ transplant recipients the immunosuppressive therapy may impair the surveillance mechanisms. As a consequence B lymphocytes can harbor EBV DNA and become immortalized. Infected B cells express only a limited number of genes. This restricted gene expression is a mechanism through which the virus evades host responses [57]. The EBV proteins may mimic the actions of growth factors, transcription factors, and anti-apoptotic factors that interfere with control of the cellular pathways, so favoring the development of malignancy [58]. However, the causal relation with malignancy is still unclear. EBV might actually serve as a tumor cofactor or might modify the phenotype of a tumor, contributing to tumor progression rather than causing the tumor [59]. Treatment of EBV infection is difficult. The role of antiviral agents is still under discussion. However a combination of reducing immunosuppression, antiviral agents and anti-CMV immunoglobulins could obtain a significant reduction of EBV DNA levels in a consistent number of organ transplant recipients [60]. Increased virus-specific immune response and reduced viral load can be obtained with infusion of autologous EBV-specific cytotoxic T lymphocytes prepared from peripheral blood mononuclear cells recovered at the time of virus reactivation [61]. Recent experimental studies showed that the mTOR inhibitors sirolimus [62] and everolimus [63] can inhibit the replication of EBV, suggesting a possible role of these drugs for preventing and treating EBV infection and related disorders. Treatment of EBV-associated lymphoproliferative disorders may consist in different steps. Reduction or withdrawal of immunosuppression may give good results in low-risk patients [64]. Rituximab, a monoclonal antibody directed against CD20 antigen of B cells, can obtain response in two-third of PTLD [65]. However resistance may occur either because of the variable expression of CD20 by neoplastic cells or by elevated apoptotic threshold [66]. In these cases treatment may be more effective when combined with chemotherapy [67]. Adoptive immunotherapy with EBV-specific cytotoxic T cells (CTL) may also be used in patients with EBV-associated malignancy. However, the efficacy of immunotherapy may be reduced by the immune evasion strategies by tumor cells. Targeting CTL to subdominant EBV antigens and genetically modifying CTL to increase their potency are promising approaches to overcome evasion strategies [68].

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Conflict of interest

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