Terminal ileitis after kidney transplantation : Crohn's disease or other? Case reports and literature review

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Abstract

The finding of a terminal ileitis after kidney transplantation can cause a diagnostic challenge. Because the development of Crohn's disease under immunosuppressive therapy is unlikely, this diagnosis should only be considered after exclusion of infectious disease and drug-related intestinal toxicity. Defining the underlying cause of terminal ileitis is often hampered by a shortage of specific diagnostic tests or their lack of sensitivity. We present three patients with terminal ileitis after kidney transplantation resulting from different etiologies. Subsequently, we describe the characteristics that can help to make the differential diagnosis. (Acta gastroenterol. belg., **2019**, 82, **63-66**).

Key words : terminal ileitis, kidney transplantation, immunosuppression, Crohn's disease.

Introduction

Terminal ileitis is occasionally encountered in the workup for diarrhea or abdominal pain. Although typically associated with Crohns disease, it can be caused by a wide variety of diseases (Table 1) (1-2). In kidney transplant recipients the diagnosis of Crohn's disease seems paradoxical since these patients are treated with immunosuppressants which makes an infectious or drug-related cause much more likely.

Drugs like mycophenolate mofetyl (MMF) or non-steroidal anti-inflammatory drugs and infections with various pathogens like Yersinia, Mycobacterium Tuberculosis (TBC), and Cytomegalovirus (CMV) can cause terminal ileitis. Because of the high densities of lymphoid aggregates and physiologic stasis the ileocecal region is more prone to infections. (2)

Defining the underlying etiology of terminal ileitis is crucial because misdiagnosis may result in errors and delays in patient management. However, because of a shortage of specific and sensitive diagnostic tests the diagnosis is often made on an empirical basis.

For Crohn's disease no gold standard diagnostic test is currently available. Diagnosis relies on a combination of diagnostic tools including clinical and endoscopic evaluation as well as histologic and radiologic assessment. Much effort has been invested in the development of sensitive and specific non-invasive biomarkers, and with the recent advances in metabolomics, genetics and proteomics, more tools become available. However so far, no biomarker is reliable enough to make a confident diagnosis of Crohn's disease. (3)

Table 1. — **Overview of different causes of terminal ileitis**

Infectious	Yersinia
	Salmonella
	Clostridium
	Mycobacterium tuberculosis and avium
	Cytomegalovirus
	Actimomycosis
	Anisakiasis
	Histoplasmosis
	Norovirus
	Typhlitis
Drug-related	NSAID
	Mycophenolate mofetil
Vasculitides	Systemic lupus erythematosus
	Polyarteritis Nodosa
	Henöch-Schönlein purpura
Ischemia	
Small bowel neoplasms	Adenocarcinoma
	Lymphoma
	Carcinoid tumor
Infiltrative	Eosinophilic enteritis
	Sarcoidosis
	Amyloidosis
Other	Backwash ileitis due to ulcerative colitis
	Radiation enteritis
	Cryptogenic Multifocal Ulcerating Stenosing Enteritis (CMUSE)

Cases and Discussion

Case 1

A 64 year-old Caucasian male, who received a kidney transplant 3 months earlier for end stage renal disease (ESRD) due to IgA nephropathy, consulted because of peri-umbilical crampoid pain and low-grade fever since 2 weeks, without change in bowel movements. His immunosuppressive regimen consisted of methylprednisolone (8 mg q.d.), cyclosporine (150 mg b.i.d.), mycophenolate mofetil (1 g b.i.d.) and prophylactic valgancyclovir (450 mg b.i.d.) because of CMV-incompatibility with the donor (Donor D+,

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Submission date : 09/10/2018
Acceptance date : 18/10/2018

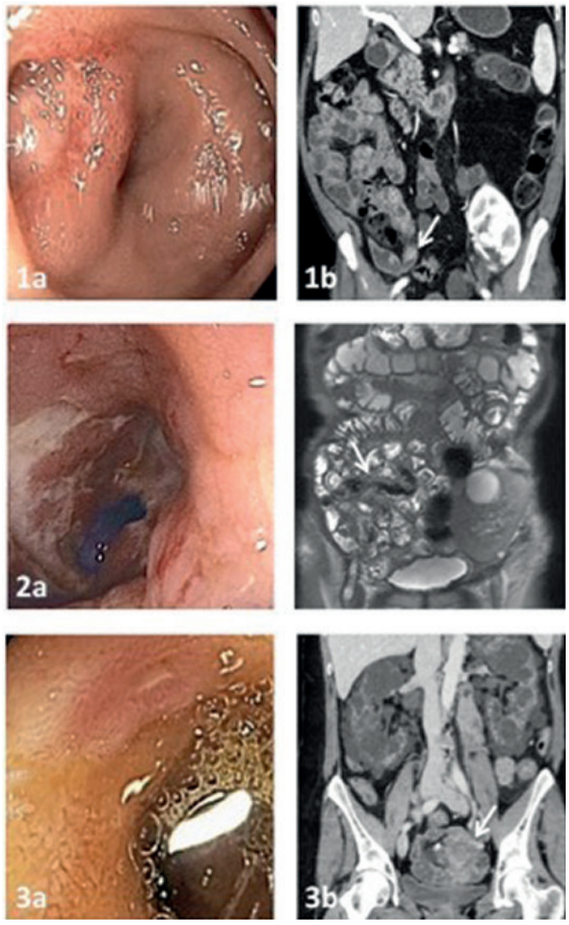

Fig. 1. — Endoscopic (a) and radiologic (b) findings for cases 1-3.
Case 1 : Endoscopic aspect of the terminal ileum (1a) with small oval ulcerations and radiographic image (1b-CT enterography) which shows thickening and hypervascular aspect (arrow) of the terminal ileum.
Case 2 : Endoscopic aspect of the terminal ileum (2a) with serpinginous ulcerations and radiographic image (2b-MR enterography) which shows thickening and hypervascular aspect of the terminal and preterminal ileum. (arrow)
Case 3 : Endoscopic aspect of the terminal ileum (3a) with small isolated ulcus and radiographic image (3b-CT abdomen) which shows thickening of the sigmoid (arrow).

Recipient R-). Blood analysis showed an elevated C-reactive protein (CRP) level and leukopenia. CMV plasma polymerase chain reaction (PCR) was negative. Because of leukopenia the dosage of valgancyclovir was reduced (450 mg q.d.) and MMF was replaced by azathioprine (75 mg q.d.). Two weeks later the patient was hospitalised because of increasing abdominal pain, weight loss and fever. CT enterography revealed enteritis, predominantly in the terminal ileum (ex. Fig 1-1b). Ileocolonoscopy confirmed terminal ileitis with a few small oval ulcerations (ex. Fig 1-1a) and a normal colon. Histopathology demonstrated an acute inflammation with infiltration of granulocytes and eosinophils, suggestive of an infectious cause. No granulomas or viral inclusions were found. CMV-immunohistochemistry and acid-fast staining for mycobacteria was negative.

CMV plasma PCR remained undetectable. Anti-saccharomyces cerevisiae antibodies (ASCA) were negative. Further anamnesis revealed a sibling with Crohn's disease.

Because an infectious cause was suspected, an empiric treatment with ciprofloxacin and metronidazole was initiated, with a marked clinical improvement and normalisation of the CRP-level. However, a new CT-enterography 2 months later revealed persistent inflammation of the ileocecal transition. Around that time valgancyclovir was stopped because of expiration of the standardized 6-months CMV -prophylaxis post-transplantation.

A few weeks later the patient presented again with fever, flu-like symptoms and abdominal pain. CMV plasma PCR demonstrated a high viral load (1129 copies/ml). Azathioprin was temporarily discontinued and valgancyclovir (900 mg q.d) was re-initiated resulting in a rapid clinical response.

Ileocolonoscopy 6 months later showed significant improvement: the terminal ileum was normal except for 2 scars; no active inflammation was found on histopathology. MRI- enterography demonstrated a fibrotic transformation of the terminal ileum. The patient remained asymptomatic until now, 2 years later.

Discussion

The diagnosis of **CMV enteritis** was presumed based on the subacute presentation of gastrointestinal symptoms in the presence of fever and leucopenia, with typical exacerbation of the disease after reduction and cessation of CMV-prophylaxis, and the healing after CMV-treatment.

Symptomatic CMV-infections occur in approximately 8 to 32% of kidney transplant recipients, with decreasing incidence since the implementation of CMV-prophylaxis in high-risk (D+, R-) patients after transplantation. (4)

Gastrointestinal CMV disease typically causes esophageal ulcers and colitis, whereas small bowel involvement occurs in only 4% of cases. (5)

Clinical manifestations include diarrhea, abdominal pain, vomiting and gastrointestinal bleeding. Endoscopy typically shows punched-out ulcerations but also erosions, mucosal haemorrhage and mass lesions can occur, mimicking many diseases, such as C. difficile colitis, ischemia, cancer and inflammatory bowel disease (IBD). (6)

Confirming the diagnosis of gastrointestinal CMV disease can be difficult: since plasma CMV DNA can be negative (sensitivity of ±85%), the gold standard is the identification of viral inclusions or positive CMV-specific immunohistochemistry staining on tissue biopsy. However, the infection can be patchy which results in low sensitivity of histopathologic diagnosis (±79%), implying that multiple biopsies may be needed to confirm the diagnosis. The sensitivity can be improved by performing qPCR for CMV on biopsy specimens. (7)

Case 2

A 68 year-old North-African male, who received a CMV-compatible (D+, R+) kidney transplant 2 years earlier for ESRD due to Autosomal Dominant Polycystic Kidney Disease (ADPKD), presented with bloody diarrhea since several months and weight loss. His immunosuppressive therapy consisted of methylprednisolone 4 mg q.d., tacrolimus 2 mg b.i.d. and MMF 500 mg b.i.d. Blood analysis showed an elevated CRP-level and iron-deficient anemia. CMV plasma PCR was undetectable and stool cultures were normal. An ileocolonoscopy demonstrated a right-sided erosive colitis and a terminal ileitis with multiple serpinginous ulcers (ex. Fig 1-2a), suggestive of Crohn's disease.

Histopathology revealed a severe chronic inflammation with cryptitis and crypt destruction; no granulomas were found. These results were compatible with Crohn's disease but not specific. Immunohistochemistry for CMV and herpes, as well as the acid-fast staining for mycobacteria, were negative. MRI-enterography showed active inflammation of the terminal ileum over 20 cm (ex. Fig 1-2b). ASCA were elevated (IgA 11, IgG 18 U/ml). To exclude a MMF-associated enterocolitis, MMF was replaced by azathioprine 75 mg q.d. However, episodes of diarrhea persisted and CRP and fecal calprotectin levels remained elevated. A follow-up ileocolonoscopy after 2 years demonstrated a distorted ileocaecal valve, stenosis of the terminal ileum and persisting ulcers. Recent revision of his medical history uncovered a record of Crohn's disease 30 years ago in another hospital, which the patient had forgotten about since he was asymptomatic without treatment for decades. Pre-transplant colonoscopy was normal but the ileum was not intubated.

Discussion

Because of the typical endoscopic aspect with compatible histopathology, the chronic character and medical history of the patient, the diagnosis of **Crohn's disease** was made.

In patients with pre-existing IBD before transplantation, ±30% develop worsening of IBD-activity despite immunosuppressive treatment. (8) Hypothesized risk factors are active IBD at the time of transplantation, discontinuation of 5-aminosalicyclic acid (5-ASA) or azathioprin and use of tacrolimus. (9-10) The development of de novo Crohn's disease during an immunosuppressive treatment is possible but rather rare. However, it is reported that the incidence of IBD after solid organ transplantation is ten times higher than in the general population. The exact mechanism is unclear but hypothesized risk factors are the use of tacrolimus and CMV infection. (11-12) De novo IBD is more frequently seen after liver transplantation than after kidney transplantation. This can be explained because of the strong association between primary sclerosing cholangitis (PSC) and ulcerative colitis (UC) (13), but also cases of new onset Crohn's disease after kidney or liver transplantation have been reported. (14-17) Treatment of Crohn's disease is similar as in non-transplanted patients but it is suggested to replace tacrolimus by azathioprin that seems to have a protective effect. (18) Anti-TNFalfa could be effective and safe in refractory IBD in patients with concomitant anti-rejection therapy but experience is still very limited. Careful surveillance is indicated regarding infections, autoimmune diseases and neoplasms. (9)

Case 3

A 46 year-old patient who received a CMV-compatible (D+, R+) kidney transplant 3 years earlier for ESRD due to ADPKD, consulted because of episodes of diarrhea since a few months. Her immunosuppressive regimen consisted of tacrolimus 7 mg q.d. and MMF 500 mg b.i.d. Blood sample demonstrated an elevated CRP-level, normal ASCA and an undetectable viral load for CMV. Fecal cultures were normal. CT abdomen confirmed a left-sided colitis (Fig 1-3b). An ileocolonoscopy showed a left sided colitis with small ulcerations, a spared rectum and a small isolated ulcer in the terminal ileum (Fig 1-3a). Histopathology showed fibrosis and glandular atrophy, suggestive of ischemia, which can be primary or secondary as caused by infection (CMV) or medication (NSAIDs, MMF). Acid-fast staining and immunohistochemistry for CMV was negative.

Since the patient had no cardiovascular risk factors and an intra-arterial digital subtraction angiography (IA-DSA) displayed no arguments for macrovascular ischemia it was assumed that an ischemic colitis was less probable. To exclude an MMF-associated enterocolitis, MMF was replaced by azathioprine 75 mg q.d., which led to a fast improvement of the symptoms.

Control ileocolonoscopy 6 months later showed an absence of inflammatory lesions, with normal histopathology. The patient remained asymptomatic until today, 2 years later.

Discussion

The tentative diagnosis of **MMF-associated enterocolitis** was made because of the compatible histopathologic findings and the rapid recovery after discontinuation of MMF. MMF is part of standard maintenance immunosuppressive protocols in many kidney transplant centers across the world. The most common adverse effect is watery afebrile diarrhea in 20-40% of patients. (19, 20) The endoscopic findings of MMF-associated enterocolitis range from no macroscopic abnormalities to erythema, erosions and ulcers. (21) Typically, the right colon is most severely affected, with a downstream attenuation of mucosal changes along the left colon. The terminal ileum and rectum seem to be less frequently affected. (22) The most common histological

finding is a Crohn's disease-like pattern in association with increased epithelial apoptosis and crypt distortion and loss. (23, 24) The diagnosis is difficult because there are no specific hallmarks for the disease: it requires a combination of typical endoscopic and histological findings and the exclusion of other mimicking conditions like infections (particularly CMV and Norovirus), graft versus host disease (in bone marrow allografts) and Crohn's disease. (21) The diagnosis is usually confirmed by the resolution of symptoms after interruption of MMF, although this effect might also be attributable to a spontaneous resolution of infectious diarrhea after reduction of immunosuppression.

Conclusions

Terminal ileitis in kidney transplant recipients can be caused by a wide variety of diseases. Although paradoxical, the incidence of IBD after solid organ transplantation is ten times higher than in the general population.

Differential diagnosis with infectious or drug-induced ileitis can be difficult due to the lack of sensitive and specific diagnostic tests, as shown in our case reports. A correct diagnosis requires a thorough examination with focus on medical history, physical examination, fecal cultures, serologic markers, radiology and endoscopy with extensive biopsies for histopathology and PCR. In many cases, a clear-cut diagnosis cannot be made from the start. The tentative diagnosis is based on the clinical disease course, the clinical findings, and is confirmed by the response to empirical therapy. The three cases we presented illustrate the challenges encountered in diagnosing terminal ileitis in kidney transplant recipients, and the need for more accurate diagnostic tools in order to optimize the management of these vulnerable patients.

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