

Teaching Point (Section Editor: A. Meyrier)

A day at the pool

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Introduction

Gastrointestinal side effects affect ~20% of renal transplant recipients [1]. Among such side effects, diarrhoea is common [2] but under-recognized [3]. Diarrhoea may relate to immunosuppressive drugs or infectious complications. The latter may be caused by one of the usual microbial pathogens that also cause gastroenteritis in immunocompetent patients, such as campylobacter, salmonella or viruses. Cytomegalovirus (CMV) colitis, for example, is seen as a cause of diarrhoea, usually within the first one or two post-transplant years. Once these usual suspects have been excluded, the clinician is left with a long differential diagnosis of other causes of diarrhoea in the immunosuppressed host. We describe the interesting case of a 49-year-old renal transplant recipient who presented with an unusual cause of diarrhoea 2.5 years after transplantation.

Case

A 49-year-old renal transplant recipient presented, on 1 November 2010, with new-onset diarrhoea.

His primary renal disease was polycystic kidney disease and he had received a first renal transplant in 2008. His current immunosuppression comprised of enteric-coated mycophenolic acid (EC-MPA) 360 mg three times daily, prednisolone 7.5 mg daily and tacrolimus 2 mg twice daily. He was also on aspirin, atorvastatin, lansoprazole, doxazosin, lercanidipine and furosemide. For the past 12 months, he had been doing extremely well, with stable transplant function [serum creatinine 150 µmol/L, estimated glomerular filtration rate 43 mL/min].

The patient now reported a 1-week history of diarrhoea, nausea and lassitude. On examination, there were two large polycystic kidneys and an unremarkable renal transplant in the iliac fossa but no other pertinent findings. He was normotensive and afebrile. Laboratory results showed C-reactive protein 6.3 mg/L (normal 0–5), normal full blood count and serum creatinine 182 µmol/L. CMV polymerase chain reaction (PCR) was negative. A stool sample was neg-

ative for *Salmonella*, *Shigella*, *Campylobacter* and *Escherichia coli* 157. Enzyme-linked immunosorbent assay (EIA) for *Giardia* was also negative, as was an assay for clostridium difficile toxin. EIA for norovirus, enterovirus and adenovirus was also negative. Another stool sample was submitted, which, surprisingly, revealed the presence of *Cryptosporidium* by enzyme immunoassay which was confirmed by microscopy (Figure 1). This was later speciated as *Cryptosporidium hominis* by the reference laboratory, PCR being used.

Oral nitazoxanide was begun on 3 November 2010. An attempt was made, in conjunction with local public health authorities, to identify the source of infection. The patient denied any recent travel. There were no cases of diarrhoea in his family or among colleagues. He had not eaten any unusual foods. However, he had been to a public swimming pool a week prior to the onset of symptoms and could not exclude having swallowed pool water. Two weeks later, the patient was no better and also reported weight loss, continued diarrhoea as well as fever and chills. Blood and urine cultures remained sterile and another CMV PCR remained negative. The dose of tacrolimus was reduced. Another stool sample was still positive for *Cryptosporidium* spp. Oral paromomycin 750 mg t.d.s. was added and nitazoxanide was continued. By 6 December 2010, the symptoms were still no better. EC-MPA was stopped. Prednisolone was increased to 10 mg daily. The tacrolimus dose was reduced yet again. On 17 December 2010, the patient reported significant improvement and was essentially asymptomatic. The tacrolimus level had come down to 10.4 and serum creatinine was 154 µmol/L.

When seen on 14 January 2011, he was essentially well. Laboratory results were essentially unchanged, except for the new finding of elevated liver function tests [γ -glutamyltransferase (γ -GT) 292 U/L (normal, 1–71 U/L)]. Serum transaminases and bilirubin were normal. Hepatitis B and C serology were negative. Atorvastatin was stopped. A repeat stool EIA was negative for *Cryptosporidium*. Another CMV PCR was negative. A side effect of either paromomycin or nitazoxanide was considered. Ultrasound showed multiple cysts within the liver but a normal calibre common bile duct. When seen in February 2011, the patient reported that in the meantime, he had not taken paromomycin or

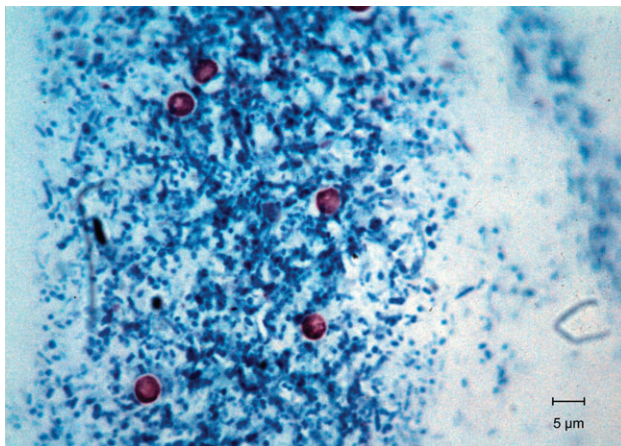


Fig. 1. *Cryptosporidium* in stool sample (modified acid-fast stain).

nitazoxanide for a week and that diarrhoea had returned. Another stool sample was negative for *Cryptosporidium*. Nonetheless, it was felt that, given the almost instantaneous recurrence of diarrhoea after stopping nitazoxanide and paromomycin, a relapse of *Cryptosporidium* infection was the most likely diagnosis. Both drugs were restarted and diarrhoea settled. When seen in March 2011, he was essentially well although liver function tests had increased further (γ -GT 457 U/L). Magnetic resonance cholangiopancreatography showed a normal biliary system. When seen in April 2011, he was still well but had now developed a maculopapular rash over both legs. Liver function tests were largely unchanged (γ -GT 511 U/L). Nitazoxanide was reduced to 250 mg twice daily and paromomycin was continued unchanged. When seen in May 2011, the rash had resolved and liver function tests had improved (γ -GT 379 U/L). When last seen in December 2011, he was entirely well, without diarrhoea or any other complaints, back to work full time and with stable transplant function. Figure 2 provides an overview of symptoms, anti-cryptosporidial treatment and immunosuppression.

Discussion

Diarrhoea is a common gastrointestinal problem in renal transplant recipients and may have a considerable impact on the quality of life [2]. An association between post-transplant diarrhoea and decreased graft and patient survival has been reported as well [4]. Diarrhoea is often caused by bacterial and viral pathogens that are also seen in immunocompetent hosts, whereas some pathogens only occur in the context of immunosuppression (Table 1). It is worthwhile to note that some of these infections, such as CMV, occur in both HIV and transplantation, while others, such as *Mycobacterium avium intracellulare* or *Microsporidia* are almost exclusively seen in HIV [5]. CMV colitis is indeed a well-recognised cause of diarrhoea in renal transplant patients. It is sometimes difficult to diagnose and CMV DNA PCR as well as endoscopy with biopsies and immunohistochemistry for CMV antigens may be required to make a diagnosis. In our case, CMV PCR was repeatedly negative, although CMV colitis may occur in the absence of CMV DNA and antigen in peripheral blood. Other viral, bacterial and fungal infections that affect transplant patients are reviewed in detail elsewhere [5].

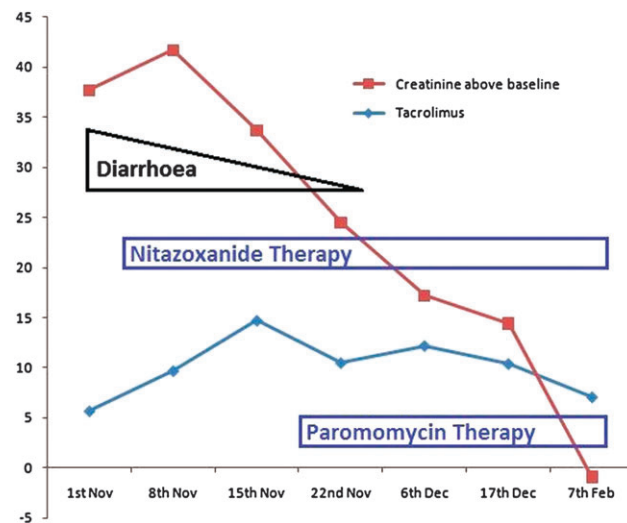


Fig. 2. Time course of symptoms, immunosuppressive regime and antimicrobial treatment.

Table 1. Unusual causes of diarrhoea seen in immunocompromised patients (selection) [4, 5]

Infectious agent	Risk factors and comments
Viruses	
CMV	Common in all solid organ and bone marrow transplant recipients; may occur in the absence of CMV antigenemia in peripheral blood
Astrovirus	Some reports in bone marrow transplant recipients
Adenovirus	Well described in bone marrow transplantation but rare in solid organ transplant; adenovirus inclusion bodies on intestinal histology
Parasites	
<i>Blastocystis hominis</i>	Contact with infected patients, contaminated water or food, occasional cases in transplant patients
<i>Cyclospora</i> spp.	More common in HIV than in transplant patients
<i>Cryptosporidium</i> spp.	See text
<i>Entamoeba histolytica</i>	Colitis and liver abscess; occasional reports in transplant patients, chiefly from Asia or acquired during travel
<i>Enterocytozoon</i> spp.	Microsporidiosis, well described in HIV (encephalitis, shortness of breath, sinusitis, keratitis and diarrhoea with wasting), occasional reports in transplant patients
Helminths	
<i>Strongyloides stercoralis</i>	Contact with infected patients may cause fulminant infection in immunosuppressed patients. Can cause bowel obstruction

Parasitic infections are often considered rare in recipients of solid organ transplants in Western countries. However, this preconception may represent under-diagnosis and bias in diagnostic testing. A contemporary French study in paediatric renal transplant recipients found *Cryptosporidium* responsible for 18% of cases of infectious diarrhoea [6]. Robust data from large studies in adult renal transplant recipients are lacking and what little we know is based on anecdotal reports and case series [4, 5]. Of note, reactivation of dormant infection (as in strongyloidiasis)

must be distinguished from new infection. It is also unknown whether and if so to what degree parasitic infections contribute to mortality in solid organ recipients worldwide. The topic is well reviewed in great detail by Barsoum *et al.* [6].

Cryptosporidium is an intracellular protozoan parasite that is associated with gastrointestinal disease. Amphibians, reptiles, birds and mammals serve as hosts for >22 species of *Cryptosporidium*. However, most human infections are due to *Cryptosporidium hominis* or *Cryptosporidium parvum*. The former is adapted to humans and largely reflects human-to-human transmission, while the latter has a natural reservoir in animals with ruminants implicated as the main sources in the UK. Along with *Giardia*, it is among the most common parasitic enteric pathogens in humans. The organism infects and reproduces in the epithelial cells of the digestive tract, whereas infection of the respiratory tract is much less common. Infection is predominantly associated with diarrhoea and occasionally biliary tract disease. The disease can be transmitted from person to person or from infected animals or via contaminated food and water. The incubation period is variable, ranging from 3 to 12 days. A major source of infection is contaminated drinking or swimming water and outbreaks have been reported [7]. The largest such outbreak to date affected 400 000 inhabitants of Milwaukee in the USA in 1995 [8]. Contaminated swimming pools are a well-described cause of outbreaks [9, 10]. A late summer and early autumn peak of cryptosporidiosis are frequently observed in annual reports although reasons for this observation are not entirely clear [10]. *Cryptosporidium* oocysts are present in 65–97% of surface waters, are difficult to eradicate and can survive in the environment for months. As a result, oocysts can be intermittently detected in tap water. Swimming pools and other recreational water sources are significant sources of infection, mostly due to contamination from bathers. In our case, the patient reported a day at the pool just prior to the onset of symptoms. In the absence of any other plausible route of infection, and because it was speciated as *C. hominis* indicating a human source, we regard this as the most likely way in which he acquired the disease.

The typical clinical manifestation in the immunocompetent host is watery and/or mucoid diarrhoea with or without abdominal pain lasting up to 4 weeks. *Cryptosporidium* infection causes sporadic cases of water-related outbreaks consisting of self-limited diarrhoea in immunocompetent hosts. In contrast, it may cause chronic and even life-threatening illness in immunocompromised patients, particularly those with the HIV infection. A further scenario is diarrhoea and malnutrition in young children in developing countries. Even in the immunocompetent host, *Cryptosporidium* may follow different patterns of disease, ranging from asymptomatic infection to mild diarrhoeal illness or severe gastroenteritis, with or without biliary tract involvement. Along with diarrhoea, people tend to experience malaise, nausea and anorexia, abdominal pain and low-grade pyrexia. The diarrhoea can follow an acute or a chronic pattern. In healthy individuals, spontaneous recovery is usually seen within 10–14 days for most cases. However, up to 30% of patients complain of fatigue and some irritable bowel-type symptoms for several months post-resolution.

The diagnosis depends on the detection of *Cryptosporidium* in the stool. It is possible that *Cryptosporidium* infection is under-diagnosed if specific testing is not requested although many laboratories now routinely test for *Cryptosporidium* in all stool samples of patients with diarrhoea rather than restricting testing to specific request or to those with recognized risk factors. *Cryptosporidium* infection is not

truly rare when looked for with appropriate assays. Microscopy of stained faecal smears using auramine phenol or modified acid-fast stains is most widely used as per the UK standards for microbiological investigations. A range of alternative stains, such as hot safranin, haematoxylin and eosin and Giemsa, are not commonly used today. Specialized tests, such as EIA, offer improved sensitivity. Histopathology of biopsy specimens can be useful when stools are negative but as infection is not homogeneous, biopsy specimens are probably less sensitive than stool cultures. In the case under discussion, endoscopy was not performed as the patient was not keen on invasive testing. EIA have a role and the test is now used routinely in some laboratories, despite higher cost, as they require less-skilled staff and are more reliable when large batches of stools are being processed. PCR is highly sensitive and has the advantage of showing which *Cryptosporidium* genotype is involved, which is useful in epidemiological investigations, but not as yet for front-line diagnosis. Lastly, evidence of previous *Cryptosporidium* infection can be detected by serology.

No treatment is necessary for *Cryptosporidium* in immunocompetent individuals and fluid and electrolyte replenishment suffice in such patients. The presentation, and response to treatment, may be entirely different in immunosuppressed hosts [11]. The infection is best characterized in patients infected with human immunodeficiency virus (HIV), while the situation in other immunosuppressed patients is less well defined [11]. However, others have previously reported cases of *Cryptosporidium* in kidney [12, 13] and kidney-pancreas transplant recipients [14]. Cases have also been noted in recipients of allogeneic haematopoietic stem cell transplants [15]. There is limited evidence to guide the treatment of *Cryptosporidium* in the immunosuppressed host, particularly in HIV-negative patients. Nitazoxanide, a nitrothiazole benzamide [16], has been used with good success in HIV although randomized trials failed to show any effect compared to placebo [17]. Nonetheless, current recommendations suggest using nitazoxanide in severe cryptosporidiasis in immunosuppressed patients due to the seriousness of the infection and the lack of good alternatives [17]. Paromomycin is a non-absorbable aminoglycoside which is recommended for amoebiasis but it has not been specifically approved for cryptosporidiosis. It is probably fair to say that the lack of robust evidence for the use of this drug is essentially comparable to the situation for nitazoxanide [18]. In our case, we tried nitazoxanide first with no tangible improvement and then added paromomycin, again with little effect. Next, we reduced the immunosuppression drastically, which led to rapid recovery with resolution of diarrhoea and malaise. This approach was essentially based on the experience in HIV patients, in that the success of *Cryptosporidium* treatment depends on antiretroviral treatment, rather than specific anti-parasitic drugs, and that clinical improvement often parallels the restoration of the immune response. In hindsight, we have to admit that we were quite slow in appreciating that *Cryptosporidium* infection in a renal transplant patient is a major, significant and difficult to treat, complication, rather than a temporary episode of diarrhoea with an unusual pathogen. Our case also underscores, again, that diarrhoea in transplant patients requires vigilance as to the possibility of unusual pathogens. It is also possible that our patient had other unidentified pathogens. We were keen to exclude sclerosing cholangitis in our patient when he presented with elevated liver function tests. However, imaging excluded this and the liver function improved, together with the rash, after dose

reduction of nitazoxanide. Rash and mild hepatotoxicity are occasionally reported in conjunction with nitazoxanide use although these cases usually feature elevated serum transaminases [19]. We cannot be sure what caused the elevated γ -GT in our case. Slowly improving biliary *Cryptosporidium* infection is conceivable, as is a side effect of the anti-parasitic drugs.

Finally, we considered whether strategies for prevention were required due to the significant morbidity that cryptosporidiosis can cause in the context of immunosuppression. Personal hygiene and hand washing should be maintained in transplant patients, and boiling water may reduce the risk of infection. A previous UK guideline recommended that patients with compromised T-cell immunity should boil their drinking water. However, whether this blanket advice is still appropriate remains unclear [20]. Others have previously suggested that immunosuppressed patients should be advised to avoid swimming pools and similar facilities [9].

Teaching points

(i) Diarrhoea is a common problem in renal transplant recipients. The differential diagnosis includes a broad variety of drug-induced syndromes as well as a multitude of infectious causes.

(ii) *Cryptosporidium* is a recognized cause of diarrhoea in immunosuppressed patients. Much of the evidence regarding treatment stems from HIV infection.

(iii) *Cryptosporidium* should always be part of the differential diagnosis of diarrhoea, particularly if symptoms persist and initial stool cultures remain negative. Where *Cryptosporidium* is suspected it should be specified on the request form to ensure that appropriate testing is carried out.

(iv) Nitazoxanide and paromomycin have activity against *Cryptosporidium* but there is little evidence to guide treatment in a given patient.

(v) Reduction of the immunosuppression, rather than specific treatment, seems to be crucial for the management of *Cryptosporidium* infection in the immunosuppressed host.

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Conflict of interest statement. None declared.

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