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Refractory Giardiasis in a kidney transplant recipient

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ABSTRACT:

Giardiasis is a relatively rare parasitic infection causing gastrointestinal disease in patients after a solid organ transplant. In the background of immunosuppression, the infection is often missed and hence can lead to complications. Here, we present a case of a patient who received a living donor kidney transplant and later presented with persistent diarrhoea and acute allograft dysfunction. The patient was investigated for potential causes of diarrhoea in the post-transplant setting. As the patient continued to have symptoms, an endoscopic biopsy from the duodenum was done, which clinched the diagnosis.

Keywords: Diarrhoea, Renal transplant, Immunosuppression, Giardiasis.

Key messages: Giardiasis is a potential cause of refractory diarrhoea in patients after a solid organ transplant.

- The infection if untreated, can indirectly lead to allograft dysfunction.
- Non-infectious causes such as immunosuppressant related toxicity need to be ruled out in all cases of diarrhoea in the post-transplant setting.
- Endoscopy is a worthwhile diagnostic tool, when routine investigations such as stool examination do not reveal the cause.

INTRODUCTION

Diarrhoea in a kidney transplant recipient can have several atypical presentations and the causes range from infections and immunosuppressant related gastro-intestinal adverse reactions, to rarer entities such as post-transplant lymphoproliferative disorder[1]. Persistent diarrhoea can lead to post-transplant morbidity and renal allograft dysfunction, and hence, identifying the cause of this symptom is of paramount significance. We report a case of a living donor kidney transplant recipient in whom giardiasis was the cause for persistent diarrhoea in the post- transplant period.

CASE REPORT

A kidney transplant recipient, with mother as the donor, was admitted with history of persistent loose watery stools two months following kidney transplantation. The 29-year-old male did not have fever, abdominal pain, hematochezia or dysentery. His native kidney disease was reflux nephropathy, secondary to a posterior urethral valve. He had received an induction regimen of steroids, anti-thymocyte globulin and tacrolimus prior to transplant, and had stable graft function with a baseline serum creatinine value of 1.1 mg/dl. He was on mainte-

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nance immunosuppression with steroids, tacrolimus, and mycophenolate mofetil. On physical examination, no abnormalities were found. Blood cell counts and serum C-reactive protein (CRP) level were normal. Serum creatinine had risen to 1.6 mg/dl on initial presentation. Stool examination did not reveal pus cells, ova, cyst or parasites. Stool cultures were negative. Tacrolimus drug assay revealed elevated trough levels (24 ng/ml), and hence tacrolimus drug dose was reduced. Despite these measures, symptoms ceased to abate. A nitro-imidazole regimen (Tinidazole) was hence initiated. Mycophenolate mofetil was replaced with the enteric coated formulation of mycophenolate sodium to address potential gastrointestinal adverse events[2]. As his symptoms did not subside, Mycophenolate sodium was replaced with azathioprine, with continuation of steroids and tacrolimus. His allograft dysfunction persisted. Serum creatinine reached a peak level of 2.5 mg/dl, and tacrolimus trough levels were fluctuating possibly because of diarrhoea[3]. Owing to persistent diarrhea despite the aforementioned measures, he was started on a combination of nitro-imidazole-quinolone (Ornidazole-ofloxacin) with an anti-helminthic (Ivermectin), and anti-protozoal agent (Nitazoxanide); the latter was continued for four weeks. Renal doppler studies were done and no abnormality was found. Imaging of the abdomen revealed diffuse wall thickening of the small bowel loops. On colonoscopy normal mucosa was seen up to the ileum. In view of refractory diarrhea, an upper gastro-intestinal endoscopy was performed, and duodenal biopsy was taken. Biopsy revealed trophozoites of Giardia intestinalis attached to the duodenal mucosa, with inflammation of the lamina propria which was infiltrated with plasma cells, lymphocytes and a few eosinophils. (Figures 1-3). Thus, the diagnosis of intestinal giardiasis was confirmed. The patient was continued on Nitazoxanide for an extended period following which symptoms resolved. Allograft function also returned to normal.

DISCUSSION

Diarrhoea is a common complaint among patients who have undergone renal transplantation. Refractory diarrhea during the post transplantation period is often a difficult entity to treat as a myriad of uncommon conditions including infections can cause diarrhoea in a transplant recipient. Among the spectrum of infections that cause diarrhoea in the post-transplant setting, common bacterial causes include Clostridium difficile, Campylobacter spp., Salmonella, Escherichia coli, or bacterial overgrowth. Viruses such as cytomegalovirus, norovirus, rotavirus, and adenovirus are common intestinal pathogens. Among parasites, giardia, cryptosporidium, isospora, cyclospora, microsporidium and entamoeba are the causative agents of diarrhoea[1]. In comparison to bacterial and viral causes of infections parasitic infestations are relatively rare, in solid organ transplant recipients; they account for only 5 percent of the infections[4]. Among drugs, mycophenolate mofetil (MMF) is the most commonly implicated in causing diarrhoea. Remission of diarrhoea has been noted following dose

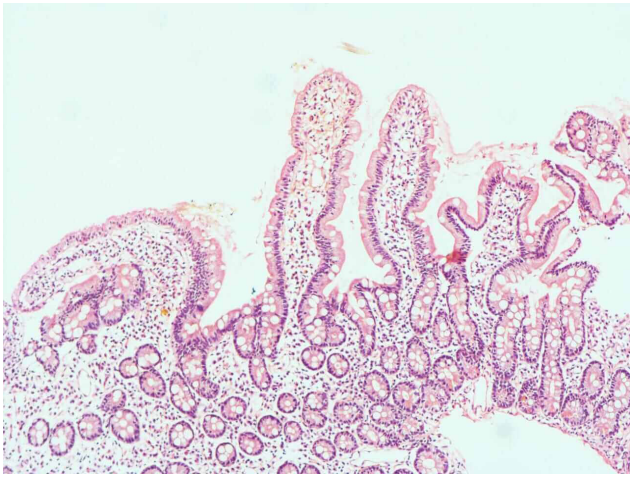

Figure 1. Photomicrograph (Haematoxylin-eosin stain with 10 X magnification) of the duodenal biopsy; showing preserved duodenal mucosal villi with trophozoites of Giardia.

adjustments of tacrolimus, cyclosporine and steroids, albeit to a lesser extent[5]. Although the mechanisms underlying causation of diarrhoea by mycophenolate are not fully clear, duodenal villous atrophy due to the drug is considered to be a factor[6]. Patients with Mycophenolate mofetil-induced colitis presenting as diarrhoea have also been reported. Mycophenolate mofetil is a pro-drug which is metabolized in the liver into the active compound mycophenolic acid (MPA). MPA is degraded by the liver to acyl gluconoride which triggers mononuclear cells to release TNF-α. TNF-α-mediated inflammatory damage combined with reduced intestinal regeneration is implicated in MMF-induced colitis[7].

In a study that followed up kidney transplant recipients for four years, 50% cases of diarrhea were attributed to infection than to immunosuppressants. Comparison of a group of patients in whom diarrhea occurred within one year after transplant with another group in whom diarrhoea occurred later, revealed the incidence of an infective cause as 37% and 30%, respectively. In this study, change in dosage or formulation for immunosuppressant therapy led to cessation of diarrhoea in 27% of patients in

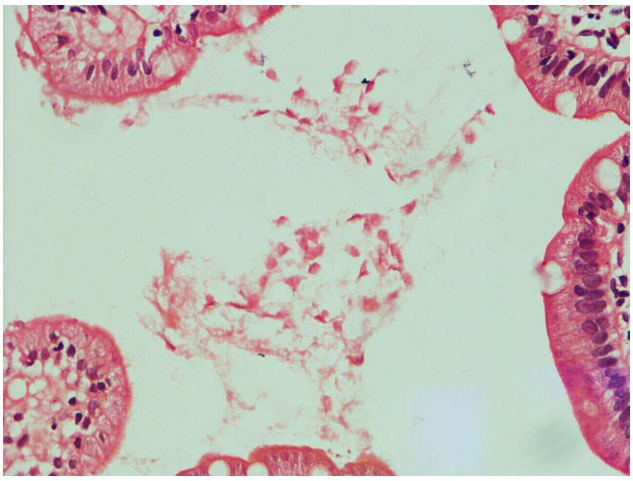

Figure 2. Photomicrograph – H & E stain with 40 X magnification demonstrating Giardia duodenalis trophozoites.

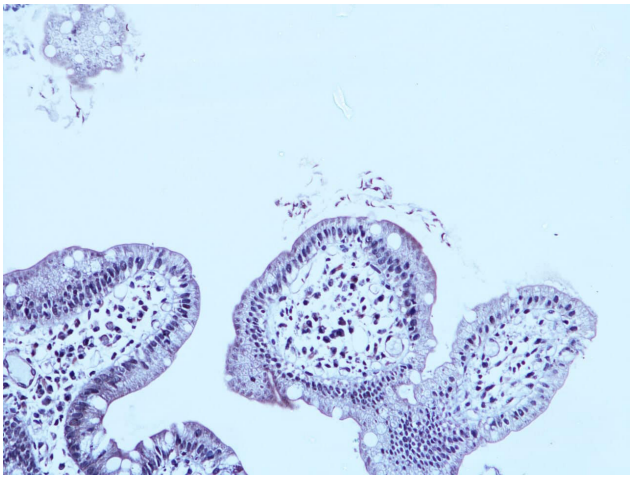

Figure 3. Masson's trichrome stained section of duodenal mucosa revealing trophozoites of Giardia.

whom diarrhoea occurred in the first-year post transplantation and in 26% of patients in whom diarrhoeal symptoms started one year after renal transplantation[5].

The relative prevalence of parasitic infestation in transplant recipients is rare compared to bacterial and viral infections. Studies during the past one decade however reveal a rising trend in prevalence of parasitosis in recipients of solid organ transplant. The reasons attributed for the rise in prevalence are the increasing number of patients who undergo transplantation and hence on immunosuppression, population shift owing to travel to endemic areas for parasitic infestations and the greater emphasis on notification of such cases. In patients with solid organ transplants, parasitic infestation may be acquired by transmission from transplanted organ or a blood product, through recrudescence of a latent infection in a previously infected recipient, or *de novo* by natural infection[8].

In our patient, following the failure in detecting a cause on stool examination, in view of refractory diarrhoea, endoscopic studies were performed. Duodenal biopsy revealed trophozoites of Giardia intestinalis anchored to the duodenal mucosa and thus to a definitive diagnosis of Giardiasis. Giardia lamblia (also known as Giardia intestinalis or Giardia duodenalis) is a flagellated protozoan parasite, with trophozoite and cystic forms. The mode of transmission is predominantly feco-oral or through indirect ingestion of infected cysts. The symptoms of giardiasis include watery diarrhoea, epigastric pain, and weight loss in patients with chronic diarrhoea[9]. In suspected cases, stool microscopy may reveal trophozoites or cysts. Intermittent excretion of giardia cysts necessitate examination of up to three stool samples before ruling out a diagnosis of Giardiasis. Other diagnostic tests include antigen detection assays employing direct fluorescent antibody (DFA) and enzyme linked immunosorbent assay (ELISA) techniques[10] and nucleic acid amplification assays (NAAT) to detect giardia in stool samples[11]. In patients in whom all such investigations are inconclusive as in our patient, endoscopy guided duodenal biopsy is the key in making a final diagnosis. Duodenal biopsy findings may be non-specific and can depend on whether parasitic colonization is light, intermediate or heavy. Villous architecture comprising grade I villous flattening, increased number of intra-epithelial lymphocytes, and presence of lymphoid follicles may be seen in biopsy specimens, but they are not entirely specific to giardiasis. Isolation of Giardia lamblia trophozoites with a characteristic tear drop shape, a binucleate ventral disc and four pairs of flagella is confirmatory[12].

Persistent refractory diarrhoea in patients who are poorly treated for giardiasis is a disabling entity with deleterious impact on the quality of life of a transplant recipient. The long-term complications following sub-optimal treatment, include post infectious irritable bowel syndrome, stunting of growth and failure to thrive owing to malnutrition, hypokalemic myopathy, and reactive arthritis. Rare complications are also known to occur in chronic untreated patients; they are ocular diseases such as iridocyclitis and choroiditis, and cutaneous allergic manifestations[13].

There is neither a consensus nor guidelines for treatment of refractory giardiasis. 5-nitroimidazoles and benzimidazole derivatives, nitazoxanide, paromomycin, quinacrine, and furazolidone are the main drugs for treating giardiasis. Our patient had an initial regimen of nitro-imidazole (Tinidazole). Following failed monotherapy with a nitro-imidazole regimen, in our patient we resorted to a combination therapy with nitro-imidazole-quinolone combination (Ornidazole-Ofloxacin) and finally Nitazoxanide which curbed the diarrhoea. Drug resistance, host related factors such as immunodeficiency states or immunosuppressant therapy as in our patient could lead to treatment refractoriness. Gut microbiota associated factors such as intestinal flora dysbiosis or drug non-compliance and variations in pharmacokinetics have also been implicated as other factors. In treatment of refractory giardiasis, a combination therapy could often be effective in comparison to higher doses of the drug or extended periods of therapy with a failed monotherapy. Efforts are on for the synthesis of chimeric compounds which have the features of two active molecules with different structures and mechanisms of action, for treatment of giardiasis. Repurposed drugs and drugs such as Auranofin, Fumagillin, Disulfiram are also under evaluation[14].

Our experience in managing a transplant patient with refractory diarrhoea from giardiasis indicates: (i) the usefulness of a protocol endoscopy and duodenal biopsy in detecting a rare cause and (ii) the utility of a combination regimen in treatment.

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Data sharing is not applicable to this article as no data sets were generated or analyzed during the current study. We only used information contained in the patient's clinical record.

Author's contributions:
FY wrote the initial manuscript. PM and SB guided, corrected and revised the paper. MS, AB, LD provided clinical assistance to the case. All authors read and approved the final manuscript.

Conflict of Interest:
The authors declare that they have no conflict of interests.

Informed Consent:
The informed consent was obtained by the patient before the study.

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