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Case Report Open Access

Celiac Disease Secondary to Tacrolimus after Human Renal Transplantation: A Case Report

Narjes Ben Aicha*, Sahtout Wissal, Azzabi Awatef, M'rabet Sanda, Toumi Salma, Guedri Yosra, Zallema Dorsaf and Achour Abdellatif

Department of Medicine, University of Sousse, France

***Corresponding author:** Narjes Ben Aicha, Department of Medicine, University of Sousse, France, Tel: 21698277304; E-mail: narjesbenaicha@hotmail.fr

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Abstract

Celiac disease is an autoimmune disorder affecting primarily the small intestine. Although rare celiac disease is a possible cause of diarrhea after renal transplantation. Our case is the first to report that tacrolimus could be cause of celiac disease after renal transplantation. A woman aged 34 years old, with a renal transplantation from a cadaveric donor. For maintenance therapy, she underwent tri-therapy with Tacrolimus. She was complaining from chronic diarrhea with weight loss unimproved at 16 months after the TR and despite the switch from Mycophenolate mofetil to Azathioprine. She had an anemia and signs of malabsorption with a congestive duodenitis in the gastroscopy and villous atrophy in moderate area in the biopsy. Celiac serology was positive. The patient underwent gluten-free diet during 6 months without improvement. Tacrolimus was stopped and switched to Cyclosporine A. After this attitude the diarrhea disappeared and we note a weight gain and improvement of biological parameters. Control of antibodies after conversion to cyclosporine A was negative. Celiac disease is rare in the transplant recipient and never confirmed with immunogical test. There was no case in the literature that reported tacrolimus as cause of celiac disease. Our case is the first witch reported celiac disease after transplantation and confirmed with an immunological test and it was caused by tacrolimus.

Keywords: Celiac disease; Renal transplantation; Tacrolimus; Calcineurin inhibitor

Introduction

Celiac disease is an autoimmune disorder affecting primarily the small intestine that occurs in people who are genetically predisposed. It is caused by a reaction to gluten, which are various proteins found in wheat and in other grains such as barley. Upon exposure to gluten, an abnormal immune response may lead to the production of several different autoantibodies that can affect a number of different organs. In the small-bowel this causes an inflammatory reaction and may produce shortening of the villi lining the small intestine (villous atrophy). This affects the absorption of nutrients. Celiac disease appears to be multifactorial, both in that more than one genetic factor can cause the disease and in that more than one factor is necessary for the disease to manifest in a person. Drug induced such as tacrolimus was rarely reported.

Tacrolimus (FK506) is a macrolide molecule that potently inhibits the expression of interleukin 2 by T lymphocytes. It represents a potential major advance in the management of rejection following renal transplantation. The introduction of tacrolimus, a calcineurin inhibitor (CNI), in human kidney transplantation revolutionized transplantation medicine, and made it a preferable therapeutic intervention for end-stage renal diseases. Currently, 94% of kidney transplant recipients are discharged after transplantation with a CNI-based immunosuppressive regimen [1]. Benefits of treatment with tacrolimus have included a reduction in steroid dose [2,3] a decreased need for antihypertensive drugs [2] and a lower serum cholesterol concentration [2]. However, because this drug has narrow therapeutic window, it is associated with many side-effects, such as nephrotoxicity, metabolic disorders (diabetes), neurotoxicity, haematological disorders and promoting of de novo cancers. Gastrointestinal symptoms such as diarrhea are rare and mostly related after transplantation to mycophenolate mofetil (MMF). The main problem is that the nature of diarrhea in organ transplant is largely unknown, mainly because the pathophysiology of diarrhea is complex and is characterized by several interacting mechanisms, such as motility disorders, inflammatory agents and mediators, and the number of abnormal cell function. Although rare celiac disease is a possible cause of diarrhea and it may be due to the use of tacrolimus in kidney recipients.

Materials and Methods

To the best of our knowledge, few cases of celiac disease after renal transplant have been reported in the literature. In our case, celiac disease was the cause of diarrhea and weight loss and it was due to tacrolimus.

Case Presentation

A woman aged 34 years old with the history of chronic renal failure of unknown etiology; she was on Hemodialysis since 2006 until the date of her transplantation on the 26th of May 2010 from a cadaveric donor with 3 HLA mismatches (Figure 1).

She had as an induction therapy with polyclonal antibodies, Solumedrol and for maintenance she underwent tri-therapy with oral corticosteroids, Tacrolimus and Mycophenolate Mofetil (MMF). She was released after 15 days of transplantation with a creatinine level of 96 µmol/l.

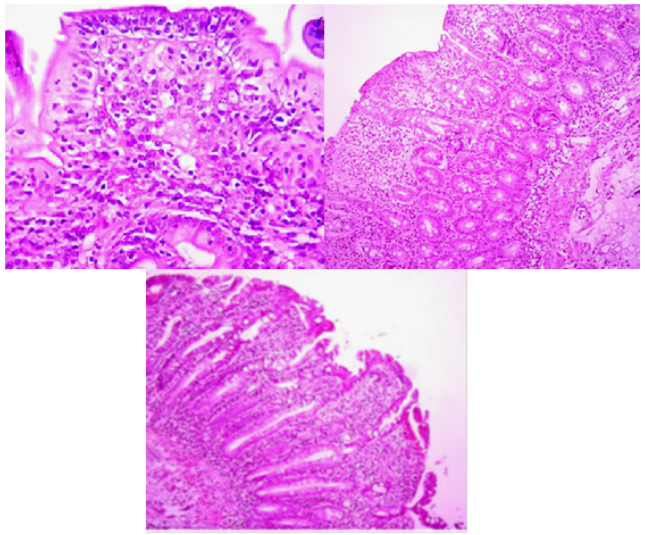

Figure 1: Duodenal biopsy.

Several complications had occurred after transplantation: graft pyelonephritis at day 7 of surgery, hypertension at day 5 of graft. She was complaining from chronic diarrhea with weight loss unimproved from September 2011(16 months after the TR) and despite the switch from MMF to Azathioprine. She had many explorations including:

1. Biology analysis: normal graft function (urea=5.9 mmol/l; creatinine=76 µmo/l), and signs of malabsorption with anemia (hemoglobin=9.2 g/dl; GVM=90); low serum iron=4 mmol/l; low ferritin=6.9 mmol/l, hypocholesterolemia (total cholesterol=2.3 mmol/l), hypotriglyceredemia (TG=0.5 mmol/l), hopocalcemia (calcium=2.1 mmol/l), hypophosphoremia (p=0.5 mmol/l), prealbumin= 133 mg/l, vitamin D= 6.5, B12 vitamin=208, folate=3.7.
2. All microbiologic stool examination including rotavirus, adenivirus and parasites such as Giardia Lamblia, cryptosporidium, isospora and bacteria was negative.
3. There was not also replication of neither CMV nor EBV.
4. Abdominal ultrasound showed fluid distension of small bowel loops without visible parietal anomalies and a retroparietale lymphadenopathy of benign inflammatory pace.
5. Gastroscopy and colonoscopy were normal. Bowel scanner showed no small bowel wall thickening or tumor process with a mesenteric lymphadenopathy. We decide to repeat gastroscopy because of the importance of the weight loss and we found in this time a congestive duodenitis with villous atrophy in moderate area in the biopsy.
6. Bowel IRM made and showed an abnormality of mucosal folding jejunal and ileal loops with expansion and hypotonia which may be in favor of celiac disease; that's why we complete with celiac serology which shows positive antibodies against Gliadin (IgG and IgA) Endomysium (IgA) with negative anti tranglutaminase.

The level of vasoactive intestinal peptide (VIP) was also high (121 for normal value between 23 and 63).

The diagnosis of celiac disease was made after approximately two years from beginning of diarrhea.

The patient underwent gluten-free diet from October 2013 to April 2014 without improvement of symptoms: the diarrhea and the biological malabsorption syndrome persist.

In April 15th, 2014, Tacrolimus was stopped and switched to Cyclosporine A.

After this attitude the diarrhea disappeared and we note a weight gain and improvement of biological parameters.

In September 2014 (Hb=12 g/l, total cholesterol=4.2 mmol/l, tryglicerdemia=1.7 mmol/l, calcium=2.4 mmol/l, phosphorus=1.1 mmol/l and always a normal graft function.

Control of antibodies after conversion to cyclosporine A was negative.

Discussion

Diarrhea is a common complication following transplantation, it not only leads to weight loss, dehydration, increase serum creatinine, and inconsistent levels of immunosuppressant drugs, but it also increases the risk of graft loss and patient death [4-6]. The incidence is above 12% [7]. The etiology of diarrhea can be found in 80% of cases. The infection is the most common cause (41.5%) followed by immunosuppressive drugs (34%) [7,8]. The most common etiologic agents of infectious are bacteria (*Enterotoxigenic Escherichia coli*, *Salmonella spp., Campylobacter jejuni* , *Shigella, Clostridium difficile*), parasites (Giardia, Amoebiasis, Cryptosporidium, Isospora, Microsporidiosis) and virus (cytomegalovirus CMV, adenovirus and Rotavirus). Maes et al. [9] reported that 108 renal transplant patients in Belgium with diarrhea for more than 7 days, 17 were diagnosed with bacterial infection (11 *Campylobacter jejuni*, 2 *Salmonella spp.*, 2 *Clostridium difficile*, 2 other), 4 with parasitic infections, 8 with CMV infection, and 1 other viral infection.

Diarrhea is the most frequently reported adverse event in patients treated with Mycophenolate Mofetil. It can rarely complicate calcineurin inhibitors (tacrolimus and cyclosporine A).

A number of possible mechanisms for MMF-associated diarrhea have been proposed, such as inhibition of colonic crypt cell division possibly due to immune-mediated mechanism as well as loss of normal villous structure in the duodenum [10].

Following oral administration, tacrolimus is rapidly absorbed in the duodenum and jejunum, but with a low oral bioavailability and highly variable pharmacokinetics, largely as a result of metabolism in the intestine. Tacrolimus is a substrate for cytochrome P450 (CYP) 3A4 and A5 isoforms, and for P-glycoprotein (Pgp), a multi-drug efflux pump. Both CYP3A isoform enzymes and P-gp exist at high levels in the liver as well as the enterocytes respectively [11].

Altered bioavailability of orally administered calcineurin inhibitors during episodes of diarrhea noted in a few cases may have multiple causes [12,13]. This may be due to changes in intestinal absorption due to changes in the solubilization or intestinal permeability of drugs, and changes in the liver or mucosal drug metabolism. However, we observed a marked discrepancy between FK506 and CsA that needs further exploration: there was increase in FK506 trough levels, while CsA trough levels decrease. In the gastrointestinal mucosa, CYP3A4 is mainly located at the apex of the villus enterocytes of the proximal small intestine, while P-glycoprotein is maximally expressed in the colon. Whether there is a different affinity for P-glycoprotein than for

CYP3A4, or whether gut metabolism is more important for FK506 compared with cyclosporine is unknown at present [14].

Celiac disease (CD) is an uncommon cause of diarrhea after transplantation and there are few case reports of CD developing *de novo* after kidney transplantation. Celiac disease (CD) is an immune-mediated enteropathy caused by exposure to gluten, which is found mainly in wheat, rye, barley, and that affects genetically susceptible people. Celiac disease is characterized by villous atrophy, intraepithelial lymphocytosis and crypt hyperplasia [15]. To the gastrointestinal mucosa, CYP3A4 is primarily on top of the villus enterocytes of the proximal small intestine.

Clinical manifestations of CD in adults are highly variable, including intestinal and extra-intestinal symptoms. In a retrospective analysis of adult CD, weight loss was the clinical presentation in 22% of the patients [16]. In another study, weight loss was present in 69% [17].

Only one case of celiac disease management has been reported as a cause of weight loss after renal transplantation recipients [18] and the diagnosis of CD was confirmed with moderate-to-severe mucosal changes in the intestinal mucosa and positivity of the genetic test, HLA-DQ8. However, serologic markers of CD were negative perhaps because of immunosuppressive treatment which may have impaired the ability to produce antibodies and when the patient was put on a gluten-free diet, she gained weight. In our case, the main symptoms were diarrhea and weight loss, serologic markers of CD were positive despite immunosuppressive treatment. The symptomatology (diarrhea and weight loss) was not stopped after gluten-free diet but only when tacrolimus was converted to cyclosporine A the diarrhea disappeared and we note an increasing of the weight.

Further study Farina et al. [19] is the first to report 18 cases of celiac disease after transplantation. These patients responded to gluten-free diet. Although tests for tissue transglutaminase antibody and deamidated gliadin peptide antibody were not conducted before transplant, all of the study patients were asymptomatic. Our case is the first to report that tacrolimus could be cause of celiac disease after renal transplantation.

Through our observation, we can suggest that in case of unexplained diarrhea in a renal transplant, a celiac disease should be evoked and specific antibodies applied; these antibodies could be induced by Tacrolimus.

It is obviously necessary to begin by eliminating the usual and specific microbiological causes of the transplant, seeking toxicity of mycophenolic acid and a chronic inflammatory bowel disease.

Conclusion

There is thus a need to optimize and standardize the management of post-transplant diarrhea with consistent diagnostic and therapeutic strategies. Diarrhea may be caused by pathogen microorganisms or immunosuppressive agents. Mycophenolate mofetil has long been implicated in post-transplant diarrhea. Although less commonly implicated as a cause of post-transplant diarrhea, tacrolimus is associated with an increased risk of diarrhea in numerous studies. However, inflammatory bowel disease such as celiac disease is rare in the transplant recipient. There was no case in the literature that reported tacrolimus as cause of celiac disease. Through our case we concluded that we must think for celiac disease to a chronic non-infectious diarrhea and it may be due to tacrolimus.

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