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Brief communication

An enigmatic case of undiagnosed severe diarrhoea post living donor liver transplant

Amey Sonavane, Sanjiv Saigal*

Medanta Institute of Liver Transplantation and Regenerative Medicine, Medanta-the Medicity, Gurugram, India

ABSTRACT

Graft versus Host Disease (GVHD) after orthotopic liver transplant (OLT), although rare, carries > 80% mortality. Early diagnosis, prompt treatment, and aggressive supportive care are imperative to potentially reverse this otherwise fatal ailment. We describe a case of severe diarrhoea post living donor OLT who was diagnosed with acute GVHD. Addition of oral budesonide therapy to systemic corticosteroid therapy controlled the symptoms of diarrhoea.

1. Brief communication

A 56 year old woman underwent (swap) living donor liver transplantation in June 2016 for Hepatitis C related chronic liver disease. She was treated with directly acting antiviral therapy in 2015 and had achieved a sustained virological response. Her decompensation included gastrointestinal bleeding, jaundice and multifocal hepatocellular carcinoma. The Child–Pugh score was 8 and the Model End-stage Liver Disease score was 16. Her transplant surgery was uneventful with graft weight of 528 g, cold ischemia time of 128 min and warm ischemia time of 40 min. Donor was a healthy 33 year old woman and the transplant was ABO-compatible. Donor was cytomegalovirus IgG seropositive. Post-operative course was complicated with air embolism which was managed conservatively. She was discharged on the 12th day post-surgery. Initial immunosuppression consisted of tacrolimus (trough levels were maintained between 6 and 10 ng/mL), mycophenolate mofetil and prednisolone. At ten weeks post-transplantation, sirolimus was introduced and tacrolimus tapered off. Prednisolone was tapered and stopped at 30 weeks post-transplant. She had developed steroid induced diabetes and was started on insulin therapy. At 78 and 84 weeks post-transplantation she suffered from two episodes of acute cellular rejection that were treated with pulse intravenous methylprednisolone therapy (500 mg for four consecutive days followed by tapering doses of oral wysolone) on both occasions (Fig. 1).

She developed profuse watery painless diarrhoea with significant nocturnal symptoms at 90 weeks post-transplantation. She was admitted to the hospital on three occasions over 4 months due to severe diarrhoea, nausea, vomiting and transaminitis. She also complained of loss of appetite. On examination she was afebrile, had tachycardia and features of dehydration. Per abdominal examination was normal and the post-operative scar was healthy. She was treated with intravenous fluid replacement and antibiotics during all admissions.

With respect to diarrhoea, she was worked up extensively. Microscopic examination of the stool was bland (no pus cells, red blood cells, mucus, ova and cysts) on multiple occasions. Furthermore, it did not reveal any acid fast structure morphologically resembling cryptosporidium. Clostridium difficile toxin A, B and GDH antigen were negative. There was no Cytomegalovirus viremia. Laboratory parameters revealed mild anemia, normal total leucocyte and differential counts and thrombocytopenia. Liver function tests revealed hypoalbuminemia (serum albumin 2.8 g/dL) and transaminitis (alanine and aspartate transaminase – 108 IU/mL and 76 IU/mL respectively) with normal serum bilirubin levels (serum total bilirubin 1.1 mg/dL). Thyroid and renal function tests were normal. Celiac disease serology was negative. She had an elevated C-reactive protein level (45.6 ng/mL). Erythrocyte sedimentation rate (6 mm/h), fecal calprotectin level (ELISA) (18 μg/mg), alpha-feto protein level (2.1 ng/mL) and sirolimus level (4.39 μg/L) were normal. She had vitamin D deficiency (9.8 ng/mL) which was corrected with therapeutic doses of oral vitamin D. Ultrasound and Doppler examination of the abdomen was normal. Glycosylated haemoglobin was 6.4% and she was treated empirically without benefit with oral rifaximin therapy for likelihood of small intestinal bacterial overgrowth. Mycophenolate mofetil was stopped.

Each time her symptoms used to settle briefly with intravenous fluids and antibiotics, only to recur within few days. Transaminase levels followed diarrhoeal symptoms. She underwent an upper gastrointestinal endoscopy which was normal. Duodenal biopsy was without any diagnostic abnormality. Ileocolonoscopic examination was also normal (Fig. 2). Random terminal ileum and colonic biopsies revealed mild active GVHD. Lamina propria showed mild chronic inflammatory cell infiltrate along with lymphoid aggregates. Each high power field showed few crypts that demonstrated apoptotic bodies on both luminal

* Corresponding author at: 14th Floor, Medanta-the Medicity, Sector 38, Gurugram, India.
E-mail address: sanjivsaigal@hotmail.com (S. Saigal).

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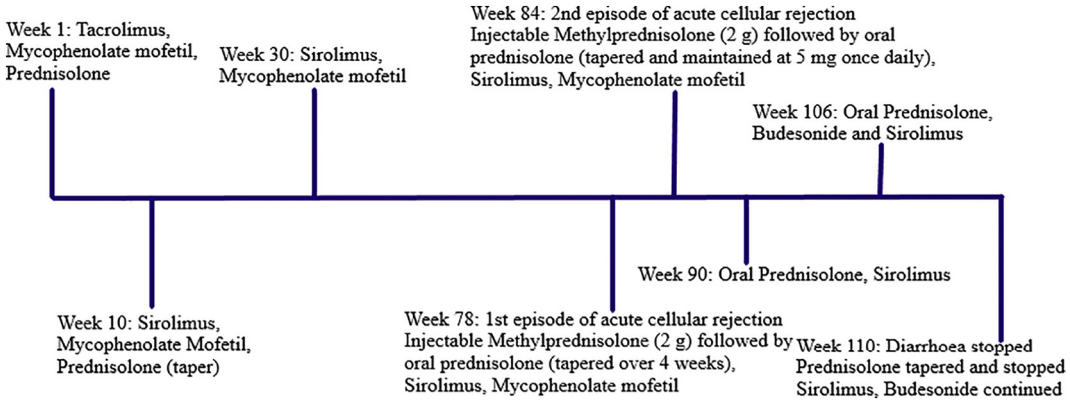

Fig. 1. Time-line of immunosuppressive medications administered to the patient.

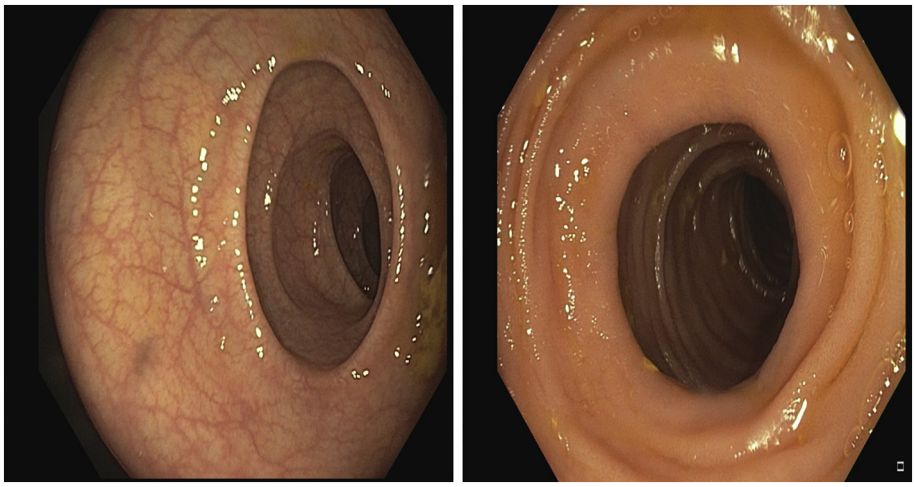

Fig. 2. Colonoscopy findings: Normal gross appearance of the colon.

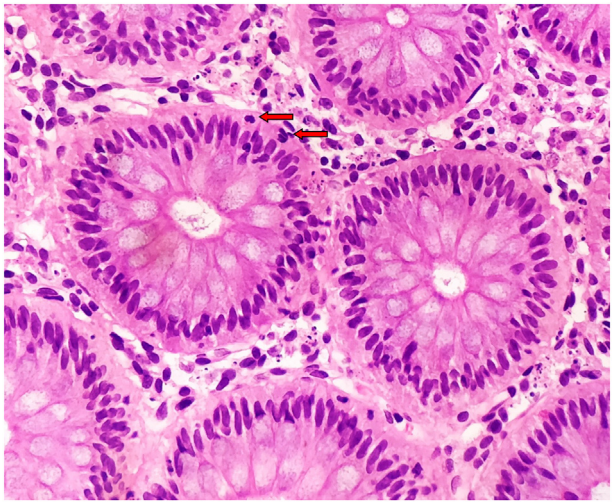

Fig. 3. H&E sections show large intestinal mucosa with maintained crypt architecture. Crypt shows apoptotic bodies on its luminal as well as basal side (red arrows). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

and basal side (Fig. 3). There were no crypt dropouts (GVHD grade I). There was no evidence of cryptitis or crypt abscesses. Chimerism studies were not performed. She was started on oral budesonide therapy (3 mg TID) (Fig. 1). Her symptoms responded briskly and diarrhoea subsided. At nine months follow-up, she was completely asymptomatic with normal liver function tests.

2. Discussion

Acute graft versus host disease (GVHD), a frequent complication following hematopoietic cell transplantation (HCT), occurs uncommonly after solid organ transplantation [1]. Any procedure that transmits viable allogenic lymphocytes from a donor (graft) into a non-identical recipient (host) carries the potential danger of inducing GVHD. The donor lymphocytes colonize the recipient, identify the host tissue antigens as foreign and react against the host tissue. It was first described by Billingham in 1966. After orthotopic liver transplant (OLT), incidence of GVHD is estimated between 0.1 and 2%. However, the mortality rate is 80–100% [2]. Risk factors for the development of acute GVHD in liver transplantation include a close degree of HLA match, recipient age (typically > 65 years), immunocompromised recipient and difference in donor and recipient age of > 40 years [3].

Acute GVHD after OLT usually occurs 2–8 weeks postoperatively and presents with bone marrow aplasia, maculopapular skin rash, persistent nausea and/or vomiting, crampy diarrhoea and rising serum bilirubin levels. Chronic GVHD presents with skin involvement resembling lichen planus or scleroderma; dry oral mucosa with ulcerations and sclerosis of the gastrointestinal tract; and a rising serum bilirubin concentration. In the post HCT scenario, GVHD is classified as acute (< 100 days, clinical features of acute GVHD), late onset acute (> 100 days, clinical features of acute GVHD), chronic (any time post HCT, features of chronic GVHD) and overlap syndrome (any time post HCT, features of both acute and chronic GVHD).

Diarrhoeal symptoms occur in 54% of patients with GVHD post OLT. Acute GVHD often involves both the upper and lower gastrointestinal tract. Diagnosis is confirmed by histopathologic evaluation of tissue biopsies obtained via upper gastrointestinal or ileocolonoscopic endoscopy. The degree of gastrointestinal involvement is graded as per the severity of diarrhoea. Diarrhoea occurs secondary to malabsorption, but can also be secretory in nature (diarrhoea despite fasting). Loose stools may occasionally become mixed with blood, necessitating not just fluid replacement but also blood transfusions to maintain a stable haematocrit. Severe ileus (dilated lumen with small bowel wall thickening on radiograph) may develop in association with acute GVHD or secondary to opioid use. Endoscopic features of lower gastrointestinal involvement in acute GVHD include aphthous ulcers, denuded mucosa and patchy erythema. However, a normal gastrointestinal tract mucosa on endoscopy does not rule out pathologic involvement [4]. On histopathological examination, acute GVHD shows increased crypt epithelial apoptosis with accumulation of degenerative material in dead crypts, crypt loss and neutrophilic infiltration. Apoptosis of epithelial cells is induced by activated donor cytotoxic T-lymphocytes. With severe disease, whole areas may be denuded with total loss of the epithelium, a finding similar to that observed in the skin [5]. The differential diagnosis of gastrointestinal tract involvement in GVHD include infectious causes (eg, cytomegalovirus infection, clostridium difficile infection, bacterial toxins), disordered motility (diabetes mellitus), endocrinopathies, inflammatory diarrhoea, bile acid malabsorption, medication and toxin effects including chemoradiation toxicity, neoplasms and vasculitis.

In patients having gastrointestinal involvement with GVHD, decrease/cessation/increase or replacement of the immunosuppressive medications may help. Supplemental nutrition may also be required. Severe protein-calorie malnutrition as a result of malabsorption and protein loss requires robust protein intake upto 1.5 g/kg/day. Additionally, vitamin, micronutrient and essential trace elements (including magnesium and zinc) should be supplemented. Octreotide may reduce the amount of diarrhoea but can potentially cause ileus. For patients with glucocorticoid-resistant acute GVHD (non-response by day 7), second-line therapy may be necessary. These include mycophenolate mofetil, anti-thymocyte globulin, sirolimus, rituximab, infliximab, etanercept, photopheresis, mesenchymal stromal cells and pentostatin [6].

Occasionally, patients can have both GVHD and viral colitis as part of post transplantation associated diarrhoea. A decision to increase immunosuppression to ameliorate GVHD must be weighed carefully against the potential risk of flaring up the infection.

Acute GVHD with isolated gastrointestinal manifestations following OLT has rarely been described. GVHD carries a rather poor prognosis with high mortality rates. Early detection and institution of prompt treatment is necessary to salvage the patient.

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