De Novo Inflammatory Bowel Disease After Pediatric Orthotopic Liver Transplant: A Case Report

Seyed Mohsen Dehghani,[1,2] Ahad Eshraghian,[2] Ali Bahador,[1] Farzad Kakaei,[1] Bita Geramizadeh,[1] Seyed Ali Malek-Hosseini[1]

Abstract

Objectives: **The improvement of pre-existing inflammatory bowel disease after orthotopic liver transplant might be anticipated. However, both the exacerbation of inflammatory bowel disease and de novo inflammatory bowel disease after orthotopic liver transplant (despite sufficient allograft immunosuppressive therapy) have been described.**

Materials and Methods: **We present a case of ulcerative colitis in a pediatric liver transplant recipient.**

Results: **A 13-year-old boy with cryptogenic liver cirrhosis received an orthotopic liver transplant from a deceased donor. Five months later, he presented with watery diarrhea and abdominal distention. He was treated with the immunosuppressive agents tacrolimus (0.15 mg/kg/d) and mycophenolate mofetil (20 mg/kg/d). A general physical examination revealed a boy with stable vital signs and without fever. The only positive finding was enlargement of the abdomen without tenderness. Many pus cells and a few red blood cells were detected in the patient's stool, but the results of a stool culture for bacteria were negative. Because of his chronic diarrhea, this patient underwent colonoscopy, which revealed diffuse erythematous mucosa, multiple ulcers, exudate, and pseudo-polyps with a diffuse loss of vascularity. Those findings are indicators of colitis. The results of histopathologic examination of the colonic mucosa suggested ulcerative colitis. The patient was treated with mesalamine and prednisolone, and a repeat colonoscopy revealed an improvement in his bowel disease.**

Conclusions: **De novo inflammatory bowel disease should be considered in patients in whom chronic diarrhea develops after an orthotopic liver transplant. We suggest that colonoscopy and biopsy should always be performed if other causes of diarrhea have been excluded.**

Key words: *Ulcerative colitis, Liver transplant, Children*

Inflammatory bowel disease is an idiopathic condition with a likely autoimmune cause (1). Most patients with inflammatory bowel disease after liver transplant have known bowel disease before they undergo their transplant procedure, and most cases of inflammatory bowel disease are associated with primary sclerosing cholangitis (2). Controversy about the degree of inflammatory bowel disease that develops after orthotopic liver transplant exists. Because immunosuppressive therapy is the treatment of choice for severe inflammatory bowel disease, it may expected that pre-existing inflammatory bowel disease would improve after orthotopic liver transplant. However, in patients who have received an orthotopic liver transplant, there are reports of unchanged inflammatory bowel disease (3), an improvement in the symptoms caused by that disorder (4), the exacerbation of inflammatory bowel disease (5), and de novo inflammatory bowel disease. There are few reports of de novo ulcerative colitis after a liver transplant in pediatric patients; most cases of that condition occur in patients who

From the [1]Shiraz Transplant Research Center, Nemazee Hospital, Shiraz University of Medical Sciences, Shiraz, Iran, [2]Gastroenterohepatology Research Center, Nemazee Hospital, Shiraz University of Medical Sciences, Shiraz, Iran

Address reprint requests to: *Seyed Mohsen Dehghani, MD, Assistant Professor of Pediatric Gastroenterology, Shiraz Transplant Research Center, Gastroenterohepatology Research Center, Nemazee Hospital, Shiraz University of Medical Sciences, Shiraz, 71937-11351, Iran.*

Phone: *+98 711 626 1775* ***Fax:*** *+98 711 647 4298* ***E-mail:*** *dehghanism@sums.ac.ir*

Experimental and Clinical Transplantation (2009) 3: 145-148

received an orthotopic liver transplant to treat primary sclerosing cholangitis (6, 7). In this report, we describe de novo ulcerative colitis in a pediatric patient who had received an orthotopic liver transplant to treat cryptogenic liver cirrhosis.

Case report

The patient was a 13-year-old boy with cryptogenic liver cirrhosis who received a liver transplant from a deceased donor. His diagnosis of liver disease was based on the lack of autoantibodies (antinuclear, antimitochondrial, antismooth muscle, and anti-liver–kidney microsomal antibodies) and on a negative test result for viral hepatitis. The results of tests for alpha1-antitrypsin deficiency, Wilson disease (serum ceruloplasmin, 24-hour urine copper concentration), and hemochromatosis (serum ferritin, specific mutation) were within the normal range. His immunosuppressive medications included tacrolimus 0.15 mg/kg/d and mycophenolate mofetil 20 mg/kg/d. Five months after he received his liver transplant, this patient presented with watery diarrhea and abdominal distention. A general physical examination revealed a boy with stable vital signs and without fever. The only positive finding was enlargement of the abdomen without tenderness. Stool examination showed many pus cells, a few red blood cells, and no parasites. The results of a stool culture were negative. Stool exam for *Clostridium* difficile toxin was negative, as were the results of polymerase chain reaction for *Cytomegalovirus*. His level of tacrolimus was 9.7 ng/mL. To establish the cause of his chronic diarrhea, this patient underwent colonoscopy, which revealed diffuse erythematous mucosa, multiple superficial ulcers from the anal verge to the cecum, diffuse exudate, and pseudopolyps with a diffuse loss of vascularity, all of which are indicators of colitis. Histopathologic examination of the colonic mucosa show complete distortion of architecture, goblet cell depletion, crypt abscess and severe lymphoplasma cell infiltration in the lamina propria that suggested ulcerative colitis (Figure 1). The patient received mesalamine 50 mg/kg/d and prednisolone 0.5 mg/kg/d. That treatment led to a rapid clinical improvement that was confirmed 5 weeks later by colonoscopy, which showed a nearly normal mucosa with only slight signs of inflammation on biopsy.

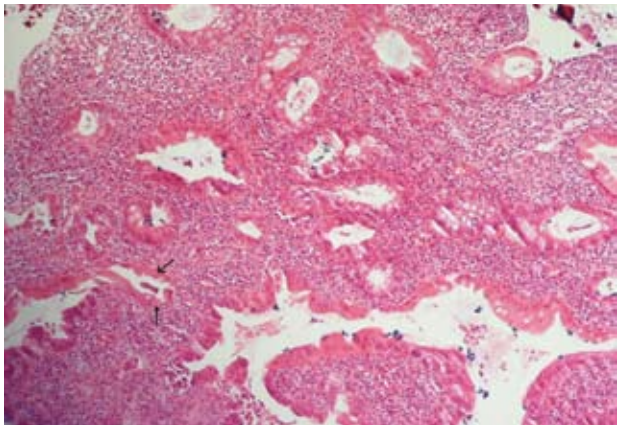

Figure 1. Section from colon shows complete distortion of architecture, goblet cell depletion, crypt abscess and severe lymphoplasma cell infiltration in the lamina propria (H&E×250)

Discussion

Our patient presented with watery diarrhea and abdominal distension. The frequency of diarrhea after organ transplant is high (the reported incidence is as high as 72%) (8, 9). The most common causes of diarrhea after liver transplant are infections and medication-associated adverse effects caused by immunosuppressive agents and broad-spectrum antibiotics. However, the cause of diarrhea remains unidentified in one-third of such patients (10). Those treated with an immunosuppressive agent are prone to the development of enterocolitis caused by a wide variety of infectious agents such as C difficile and *Cytomegalovirus*. Infection with those pathogens was carefully ruled out in our patient. Diarrhea is a common adverse effect (with an unknown pathophysiology) of calcineurin inhibitors such as tacrolimus and cyclosporine. The treatment for that type of diarrhea is conservative and usually consists of substitution with other immunosuppressive drugs or dose reduction (11). Drug-associated diarrhea is diagnosed by the exclusion of other causes. Peripheral leukocytosis, inflammatory cells in the stool, the absence of fever, and abnormalities revealed via endoscopy or computed tomography differentiate drug-associated diarrhea from diarrhea caused by an infection (11).

De novo inflammatory bowel disease or a flare-up of pre-existing inflammatory bowel disease should be considered after the exclusion of other causes of posttransplant diarrhea. The incidence of de novo inflammatory bowel disease after solid

organ transplant is much higher than the incidence of inflammatory bowel disease in the normal population worldwide (206 vs 20 per 100 000 cases annually) (7). It is surprising that immunosuppressive drugs such as cyclosporine and tacrolimus are ineffective in preventing de novo inflammatory bowel disease because they do prevent allograft rejection. Some authors have suggested that immunosuppressive medications may mask a more definitive histologic diagnosis of inflammatory bowel disease in patients who experience diarrhea after orthotopic liver transplant (12).

We reviewed the literature on de novo inflammatory bowel disease after liver transplant (13-21) (Table). Primary sclerosing cholangitis was the most common underlying liver disease in such patients, and de novo ulcerative colitis was more common than Crohn disease after liver transplant. One patient in a case series by Wörns and colleagues had cryptogenic cirrhosis as an underlying disease (20).

Table. De novo inflammatory bowel disease after liver transplant: results of a literature search.

Authors (reference No.) No. disease cases/type of de novo IBD	No. cases of de novo IBD/ underlying
van de Vrie, et al. (13) 1/UC	1/PSC
Shaked, et al. (3) 3/UC	3/PSC
Papatheodoridis, et al. (5) 3/UC	3/PSC
Chalasani and Smallwood (14) 2/UC	2/PSC
Befeler, et al. (15) 1/UC	1/PSC
Haagsma, et al. (16) 3/UC, 1/CD, 2/IC	3/PSC, 3/AIH
Khan, et al. (17) 3/UC	1/PSC, 2/AIH
Ramji, et al. (18) 2/CD	1/PBC, 1/HBV
Cuoco, et al. (6) 1/UC	1/HBV
Papadakis, et al. (19) 1/CD	1/HCV
Riley, et al. (7) 9/UC, 5/CD	6/PSC, 4/AIH, 8/other
Wörns, et al. (20) 4/UC, 1/IC	2/AIH, 1/Wilson disease, 1/HBV, 1/cryptogenic cirrhosis
Vu, et al. (21) 3/UC, 1/CD	2/HCV, 1/AIH, 1/alcoholic cirrhosis

Abbreviations: AIH, autoimmune hepatitis; CD, Crohn disease; HBV, hepatitis B virus; HCV, hepatitis C virus; IBD, inflammatory bowel disease; IC, indifferent colitis; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis; UC, ulcerative colitis.

Conclusion

De novo inflammatory bowel disease should be considered in patients who experience chronic diarrhea after orthotopic liver transplant, and colonoscopy and biopsy should always be performed after other causes of diarrhea have been excluded.

References

1. MacDonald TT, Murch SH. Aetiology and pathogenesis of chronic inflammatory bowel disease. Baillieres Clin Gastroenterol. 1994;8(1):1-34.
2. LaRusso NF, Wiesner RH, Ludwig J, MacCarty RL. Current concepts. Primary sclerosing cholangitis. N Engl J Med. 1984;310(14):899-903.
3. Shaked A, Colonna JO, Goldstein L, Busuttil RW. The interrelation between sclerosing cholangitis and ulcerative colitis in patients undergoing liver transplantation. Ann Surg. 1992;215(6):598-603; discussion 604-605.
4. Stephens J, Goldstein R, Crippin J, et al. Effects of orthotopic liver transplantation and immunosuppression on inflammatory bowel disease in primary sclerosing cholangitis patients. Transplant Proc. 1993;25(1 Pt 2):1122-1123.
5. Papatheodoridis GV, Hamilton M, Mistry PK, Davidson B, Rolles K, Burroughs AK. Ulcerative colitis has an aggressive course after orthotopic liver transplantation for primary sclerosing cholangitis. Gut. 1998;43(5):639-644.
6. Cuoco L, Tursi A, Cammarota G, Papa A, Fedeli G, Gasbarrini G. Onset of ulcerative colitis during immunosuppressive therapy for liver transplantation. Am J Gastroenterol. 1997;92(11):2134-2135.
7. Riley TR, Schoen RE, Lee RG, Rakela J. A case series of transplant recipients who despite immunosuppression developed inflammatory bowel disease. Am J Gastroenterol. 1997;92(2):279-282.
8. Altiparmak MR, Trablus S, Pamuk ON, et al. Diarrhoea following renal transplantation. Clin Transplant. 2002;16(3):212-216.
9. Helderman JH. Prophylaxis and treatment of gastrointestinal complications following transplantation. Clin Transplant. 2001;15(suppl 4):29-35.
10. Ginsburg PM, Thuluvath PJ. Diarrhea in liver transplant recipients: etiology and management. Liver Transpl. 2005 Aug;11(8):881-890.
11. Rubin RH. Gastrointestinal infectious disease complications following transplantation and their differentiation from immunosuppressant-induced gastrointestinal toxicities. Clin Transplant. 2001;15(suppl 4):11-22.
12. Wahbeh G, Hupertz V, Hallowell S, Patel R, Chrisant MR. Idiopathic colitis following cardiac transplantation: three pediatric cases. Pediatr Transplant. 2003;7(6):464-468.
13. van de Vrie W, de Man RA, van Buuren HR, Schouten WR, Tilanus HW, Metselaar HJ. Inflammatory bowel disease and liver transplantation for primary sclerosing cholangitis. Eur J Gastroenterol Hepatol. 2003;15(6):657-663.
14. Chalasani N, Smallwood G. Idiopathic ulcerative colitis in patients with primary sclerosing colitis undergoing orthotopic liver transplantation (OLT). Am J Gastroenterol. 1998;93(3):481-482.
15. Befeler AS, Lissoos TW, Schiano TD, et al. Clinical course and management of inflammatory bowel disease after liver transplantation. Transplantation. 1998;65(3):393-396.
16. Haagsma EB, Van Den Berg AP, Kleibeuker JH, Slooff MJ, Dijkstra G. Inflammatory bowel disease after liver transplantation: the effect of different immunosuppressive regimens. Aliment Pharmacol Ther. 2003;18(1):33-44.

17. Khan S, Lichtman SN, Reyes J, Di Lorenzo C. Ulcerative colitis after liver transplant and immunosuppression. J Pediatr Gastroenterol Nutr. 1999;28(2):206-209.
18. Ramji A, Owen DA, Erb SR, Scudamore CH, Yoshida EM. Post-liver transplant Crohn's disease: graft tolerance but not self-tolerance? Dig Dis Sci. 2002;47(3):522-527.
19. Papadakis KA, Matuk R, Abreu MT, et al. Crohn's ileitis after liver transplantation from a living related donor with Crohn's disease. Gut. 2004;53(9):1389-1390.
20. Wörns MA, Lohse AW, Neurath MF, et al. Five cases of de novo inflammatory bowel disease after orthotopic liver transplantation. Am J Gastroenterol. 2006;101(8):1931-1937.
21. Vu F, Maillard M, Pascual M, Michetti P, Felley C. De novo inflammatory bowel diseases after liver transplantation: description of four new cases and a review of the literature [in French]. Gastroenterol Clin Biol. 2006;30(8-9):1096-1101.