De novo Crohn's Disease Following Orthotopic Liver Transplantation: A Case Report and Literature Review

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Abstract

The development of de novo Crohn's disease (CD) after orthotopic liver transplantation (OLT) is rare, possibly due to the continuous use of immunosuppressive treatment. Although several cases of CD following OLT have been reported worldwide, there are currently so such cases in Japan. We herein report the case of a patient who newly developed CD after undergoing OLT for congenital biliary atresia. The patient subsequently underwent ileocecal resection and has since maintained clinical remission. This is the first report of this condition in Japan. We also review the literature concerning cases of de novo inflammatory bowel disease (IBD) developing after OLT, and discuss the causes of and role of immunosuppressive agents in treating IBD.

Key words: Crohn's disease, de novo Crohn's disease, orthotopic liver transplantation, immunosuppressive agents

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Introduction

Inflammatory bowel disease (IBD) is a T-cell driven form of inflammation in the gut that is thought to be the result of the inappropriate and ongoing activation of the mucosal immune system (1, 2). Therefore, treatment regimens for IBD include immunosuppressive agents, and the immunosuppressive drugs used to manage moderate to severe IBD, such as cyclosporine, azathioprine and corticosteroids, are also employed in the management of post-transplant patients. Nevertheless, 69 cases of de novo ulcerative colitis (UC) have been reported to have developed after orthotopic liver transplantation (OLT), regardless of the use of immunosuppressive agents (Table). A total of 0.25% of UC patients have accompanying primary sclerosing cholangitis (PSC), and 55-70% of PSC patients also have UC (3, 4). The relationship between UC and PSC may be associated with the development of UC after OLT. However, there have been very few reports of the development of de novo Crohn's disease (CD) after OLT (5-8). In this article, we report the case of a pa-

tient who newly developed CD (de novo) after undergoing OLT for congenital biliary atresia. We also review the literature of de novo IBD following OLT and discuss both the causes of this type of IBD and the role of immunosuppressive agents in treating IBD patients.

Case Report

A 23-year-old Japanese woman experienced repeated episodes of diarrhea and fever in June 2011. She had no past history of IBD, although she had received a liver transplant from her mother for congenital biliary atresia in 2003. After undergoing OLT, she had received treatment with cyclosporine at a dose of 100 mg/day. Although cytomegalovirus (CMV) antigenemia became positive one month after the OLT procedure, the patient exhibited no symptoms, and the antigenemia turned negative within one week without any specific treatment. No other major complications occurred; however, she was admitted to our hospital and diagnosed with acute enterocolitis in June 2011. Her symptoms subsequently improved with the administration of antibiotics, al-

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Table. Development of De novo IBD after Orthotopic Liver Transplantation in the Literature

Reference	Underlying cause of liver transplant	No. of de novo IBD patients	No. of de novo UC patients	No. of de novo CD patients	Other	Treatment for de novo IBD	No. of patients who achieved remission	No. of patients who failed remission
3	3/PSC	3	3			CS	2	1
5	2/PSC,4AIH,8/Others	14	9	5		5ASA,CS	7	7
6	2/HCV,1/AIH,1/ALD	4	3	1		CS	NA	NA
7	3/PSC,3/AIH	6	3	1	2(IC)	5ASA,CS	6	
8	1/PBC,1/HBV	2		2		5ASA,CS	2	
9	3PSC/5AIH	8	7		1(IC)	5ASA,CS, AZA	6	2
13	1/AIH,1/PSC,1/PBC	3	2	1		5ASA,CS	3	
29	2/AIH,1/Wilson 1/HBV,1/cryptogenic	5	5			5ASA,CS	5	
30	3/PSC	3	3			NA	NA	NA
31	1/HBV	1	1			NA	NA	NA
32	1/PSC	1	1			5ASA,CS	1	
33	2/PSC	2	2			NA	NA	NA
34	1/PSC,2/AIH	3	3			5ASA,CS	3	
35	2/PSC	2	2			NA	NA	NA
36	2/AIH	2	2			CS	NA	NA
37	1/PSC	1	1			NA	NA	NA
38	1/HCV	1		1		NS	NA	NA
39	1/PSC	1	1			CS	NA	NA
40	5/PSC	5			NA	NA	NA	NA
41	3/PSC	3	3			NA	2	1
42	1/cryptogenic LC	1	1			CS,5ASA	1	
43	1/fluminant hepatitis	1	1			5ASA	1	
44	PSC	11	10	1		NA	NA	NA
45	1/PSC,1/AIH,1/BA	3		2	1(IC)	3IFX,1ADA	2	1
46	6/PSC	6	6			5ASA,CS,AZA	6	
total		92	69	14	9		47	12

PSC: primary sclerosing cholangitis, AIH: autoimmune hepatitis, HBV: hepatitis B virus, HCV: hepatitis C virus, Wilson: Wilson's disease, ALD: alcoholic liver disease, BA: biliary atresia, IC: indeterminate colitis, NA: not available, CS: corticosteroid, 5ASA: 5 aminosalicylic acid, AZA: azathioprine, IFX: infliximab, ADA: adalimuma

Figure 1. Computed tomography demonstrated wall thickening in the ileum and an increased density of circumintestinal fat tissue (circle).

Figure 2. Small bowel follow-through showed mucosal irregularities and narrowing of the terminal ileum (arrowheads).

though, at the end of November, she again developed diarrhea and fever and was readmitted to our hospital in December.

No pathogenic bacteria, such as *Salmonella*, *Shigella*, *Yersinia*, *Campylobacter*, etc., were detected in a stool culture, and *Clostridium difficile* toxin A and B were not detected in stool samples. However, computed tomography revealed wall thickening in the ileum and an increase in the density of the circumintestinal fat tissue (Fig. 1). Small

bowel follow-through (SBFT) showed mucosal irregularities and narrowing of the terminal ileum (Fig. 2). Although, there were no findings in the colon on colonoscopy, except for several small polyps, both ulcers and mucosal edema were noted in the terminal ileum (Fig. 3). Meanwhile, histopathology of the biopsy specimens disclosed mucosal inflammation and non-caseating granuloma, with no malignant findings, and the possibility of CMV infection was excluded histopathologically and serologically using an immunohisto-

Figure 3. Colonoscopy performed in December 2011 revealed ulcers and mucosal edema in the terminal ileum.

Figure 4. Colonoscopy performed in September 2012 showed ulcers and mucosal edema in the terminal ileum. The oral side of the lesions could not be visualized due to the crooked shape of the intestinal tract.

Figure 5. The resected specimen exhibited longitudinal ulcers and a cobblestone appearance. A diagnosis of Crohn's disease was made based on these findings.

chemical analysis and the CMV antigenemia method, respectively. Since the differential diagnoses of infectious enterocolitis and lymphoproliferative diseases were also excluded, the patient was suspected to have CD and given

2,250 mg/day of 5-aminosalicylic acid (5-ASA). Her condition was stable after discharge; however, she again developed diarrhea and fever in August 2012 and was readmitted to our hospital in late September.

Consequently, colonoscopy showed ulcers and mucosal edema in the terminal ileum (Fig. 4), and SBFT revealed narrowing of the terminal ileum. In contrast, upper gastrointestinal endoscopy showed none of the characteristic features frequently observed in CD patients, such as a bamboo joint-like appearance. Based on these findings, the patient underwent ileocecal resection in October. The resected specimen was found to have longitudinal ulcers and a cobblestone-like appearance (Fig. 5), and the histopathological analysis revealed transmural inflammation with a large number of non-caseating granulomas (Fig. 6). The patient was therefore given a definitive diagnosis of ileitis-type CD. Since January 2013, she has received treatment with infliximab (IFX, 5 mg/kg) every eight weeks and subsequently maintained a status of clinical remission.

Figure 6. The histopathological analysis revealed transmural inflammation and a large number of non-caseating (epithelioid cells) granulomas (arrows) [A: Hematoxylin and Eosin (H&E) staining $\times 2$, B: H&E staining $\times 10$].

Discussion

In the past, it was thought that IBD does not recur after OLT due to the continuous administration of immunosuppressive agents. However, several reports have shown that IBD can recur or newly develop (de novo) after OLT. The cumulative risk of recurrent IBD and de novo IBD 10 years after OLT is estimated to be as high as 70% and 30%, respectively, and the median time between OLT and recurrence/incidence is 1.3/5.2 years (9). In addition, the incidence of de novo IBD after OLT has been shown to be higher than that observed in the general population (206 vs. 20 per 100,000 cases annually) (2, 10). There are 92 previous cases of de novo IBD reported in the literature, with the majority of patients having UC (69 UC, 14 CD and others) (Table). This phenomenon may be associated with the fact that most patients with PSC, a common indication for liver transplantation, also have UC (2). However, the development of de novo CD after OLT is rare, and the current article is the first report of such a case in Japan.

Risk factors for and the prognosis of de novo and recurrent IBD have been reported. For example, the use of tacrolimus and presence of CMV infection after OLT have been identified to be risk factors for the onset of de novo and recurrent IBD (2, 7, 9, 11-13). As for tacrolimus, Haagsma et al. reported six patients who developed de novo IBD; five of whom had been treated with tacrolimus (7). Another study reported that the use of tacrolimus increases the risk of de novo IBD, although not significantly (9). Tacrolimus, a calcineurin inhibitor, strongly inhibits the production of interleukin-2 (IL-2) (7). IL-2 is required for the development of regulatory T cells (Tregs), which are crucial for maintaining immunological homeostasis in the intestines (14, 15). In fact, IL-2-deficient mice spontaneously develop colitis with a normal gut flora (16, 17). Therefore, a too strong degree of inhibition of IL-2 by tacrolimus may cause a decrease in

the Treg concentration, which may result in the development of UC and/or CD. On the other hand, the efficacy of tacrolimus in UC and CD patients has been reported in several studies (18-20); there are currently no published reports explaining this discrepancy. Cyclosporin A (CyA), which was used in the present case, is also a calcineurin inhibitor. Although the pharmacokinetics of CyA resemble those of tacrolimus, the IL-2 suppressant effects of CyA are weaker than those of tacrolimus, and no previous reports have indicated that CyA is a potential risk factor for de novo IBD (21). In contrast to tacrolimus, the administration of azathioprine after OLT has been reported to reduce the risk of both recurrent and de novo IBD (7, 12). Hence, it may be better to use immunosuppressive regimens that include azathioprine, not tacrolimus, in patients with known IBD.

With respect to CMV infection, Verdonk et al. reported that, in their series, all patients who developed de novo IBD after OLT had a history of CMV infection, and no patients who had not experienced CMV infection developed de novo IBD (22). Increased intestinal permeability and endothelialitis may explain the subsequent increased risk for IBD in patients with CMV infection. For example, increased intestinal permeability has been shown to occur during CMV infection in both humans and mouse models (23, 24). This defect in the barrier function facilitates the exposure of the mucosal immune system to antigens from the luminal flora (23). In addition, the expression of vascular cell adhesion molecule-1 is induced in endothelial cells under conditions of CMV infection (25-27), which subsequently facilitates the adhesion of leukocytes to the endothelial lining and may play a role in the pathogenesis of endothelialitis. Consequently, endothelialitis may induce damage to the microcirculation of the intestines, thus leading to the development of ulceration and/or erosion seen in cases of IBD. The present patient did not receive tacrolimus, although she experienced an episode of positive CMV antigenemia after the OLT procedure in 2003. Furthermore, she displayed no symptoms, including enteri-

tis. However, increased intestinal permeability may occur in cases of asymptomatic CMV infection (25). By the same mechanism, the positive CMV antigenemia noted in this case may have been associated with the onset of de novo CD.

There are various reports regarding the disease course and prognosis of recurrent IBD after OLT. For example, Gavalier et al. reported that 15/17 (82.4%) patients with symptomatic UC before OLT experienced an improvement in symptoms after undergoing OLT (28). On the other hand, Verdonk et al. reported that 32/49 (65%) patients previously diagnosed with IBD developed recurrence of IBD, and 19/32 (59%) patients required either dose escalation of medications or colectomy after OLT (9). As to the course and prognosis of de novo IBD, it has been reported that most such cases respond favorably to medical treatment and do not require surgery. According to the literature, 37/49 individuals with de novo IBD achieved remission (Table). The present patient did require surgery; however, remission has been maintained with IFX.

In summary, we herein reported a case of de novo CD after OLT for congenital biliary atresia despite the continuous use of CyA. To our knowledge, this is the first case report of this condition in Japan. The number of OLT cases in Japan is one-tenth of that observed in Western countries (500/year vs. 5,000/year). If the number of OLT procedures increases due to the use of organs from brain-dead donors, the incidence of de novo IBD after OLT may increase. The details of the present case suggest that it is important to consider the possibility of de novo IBD in patients who develop refractory diarrhea after OLT, especially those with a history of tacrolimus treatment or CMV infection.

The authors state that they have no Conflict of Interest (COI).

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