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Proctocolectomy for Colon Cancer Associated with Ulcerative Colitis a Few Months After Living Donor Liver Transplantation for Primary Sclerosing Cholangitis: Report of a Case

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Abstract
Colorectal cancer (CRC) frequently develops in patients with ulcerative colitis (UC). We report a case of CRC treated successfully by proctocolectomy 8 months after living donor liver transplantation (LDLT) for primary sclerosing cholangitis (PSC). The lesion was detected early, probably as a result of colonoscopic surveillance after LDLT. Thus, patients with a long history of UC, who undergo LDLT for PSC, should be followed up with regular surveillance colonoscopy. Moreover, surgery, such as radical resection of the colon and rectum should be performed without delay, even shortly after LDLT. To our knowledge, this is the first report of a patient undergoing proctocolectomy after LDLT.

Key words Primary sclerosing cholangitis · Ulcerative colitis · Liver transplantation

Introduction

Primary sclerosing cholangitis (PSC) is a chronic cholestatic liver disease characterized by chronic inflammation and obliterative fibrosis of the hepatic biliary tree. It often leads to bile stasis, hepatic fibrosis, and ultimately, end-stage liver disease. Although a disorder of the autoimmune system might predispose to the development of PSC, its etiology is still unknown. Palliative therapy such as internal ursodeoxycholic acid is frequently given; however, orthotopic liver transplantation (OLT) is the only potentially curative treatment for PSC.[1] At major transplant centers, the 5-year survival rate after OLT for PSC has been reported to exceed 70% and has even reached 90%.[2,3]

Primary sclerosing cholangitis is frequently associated with ulcerative colitis (UC), retroperitoneal fibrosis, and cholangiocellular carcinoma. In fact, PSC develops in 2%–5% of patients with UC.[4] In Northern Europe and the United States 70%–80% of patients with PSC have UC,[4,5] whereas in Japan 20% of patients with PSC have UC, but this percentage is steadily increasing.[6] On the other hand, UC is one of the most common inflammatory bowel diseases, characterized by episodes of inflammatory exacerbation and remission. Ulcerative colitis is considered to be an autoimmune disease and its multiple complications include pancreatitis, pyoderma gangrenosum, uveitis, and ankylosing spondylitis. Colorectal cancer (CRC) is one of the most serious complications of UC. The risk of CRC increases by 0.5%–1.0% per year after 8–10 years of disease in patients with extensive UC; thus, the risk of colitis-associated CRC increases from 1%–3% 10 years after diagnosis to 10% 20 years after diagnosis, and to 25% 35 years after diagnosis in patients with pancolitis.[7] The greater the extent of colitis, the longer the duration of UC, the earlier the age of onset, and backwash ileitis all appear to increase the risk of CRC.[8] Recent epidemiological studies have implicated PSC as an additional risk factor for malignant transformation in UC.[9,10]

Several groups have reported dysplasia and cancer occurring within months of OLT despite normal colonoscopy results preoperatively;[11] however, it remains unclear if the immunosuppression given to prevent organ rejection after transplantation might trigger neoplastic transformation in UC patients. We report a case of CRC treated successfully by proctocolectomy in a patient with UC, 8 months after he underwent living donor liver transplantation (LDLT) for PSC.

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Case Report

A 49-year-old man was admitted to our hospital to undergo surgery for colon cancer associated with pancolitis-type UC, which had been diagnosed 9 years earlier. He had been treated with steroids and aminosalicylates to maintain disease remission during this time. Surveillance colonoscopy, performed every year, had not revealed a neoplastic lesion.

Liver dysfunction developed about 6 years after he began to suffer from UC and PSC was diagnosed from a liver biopsy 2 years later. The PSC ultimately caused end-stage liver disease (Child–Pugh score 10) about 1 year later and he underwent LDLT. Steroids, tacrolimus, and mycophenolate mofetil were used for immunosuppression and there was no sign of organ rejection.

About 6 months after LDLT, surveillance colonoscopy (Fig. 1) revealed flat erosions in the ascending colon and cecum. Severe dysplasia and moderately differentiated adenocarcinoma were diagnosed from the biopsy findings. We decided that the patient was well enough to undergo a proctocolectomy, although he had splenomegaly and persistent thrombocytopenia.

To preserve his anal function, we performed a proctocolectomy with ileoanal-canal anastomosis for colon cancer 8 months after LDLT. The dense collateral vessels related to the hypersplenism made it difficult to control intraoperative bleeding. The intestine from the terminal ileum to the anal canal was resected, and a J-type ileac pouch was made and anastomosed to the anal canal using a double stapling technique (Fig. 2). Pathological examination of the section revealed moderately to poorly differentiated adenocarcinoma with marked mucin production massively invading the muscularis propria, but no lymph node metastasis was observed. Degrees of epithelial dysplasia were observed in the transverse colon (Fig. 3).

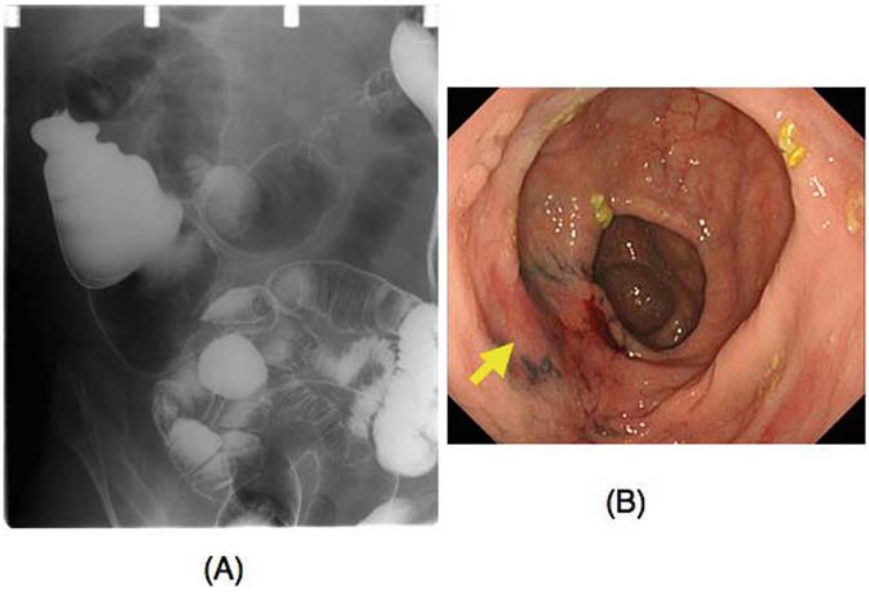

Fig. 1. A Barium enema showed mild dilatation but no cancerous lesion. **B** Surveillance colonoscopy revealed a flat erosion in the cecum, which was diagnosed as moderately differentiated adenocarcinoma from the biopsy findings

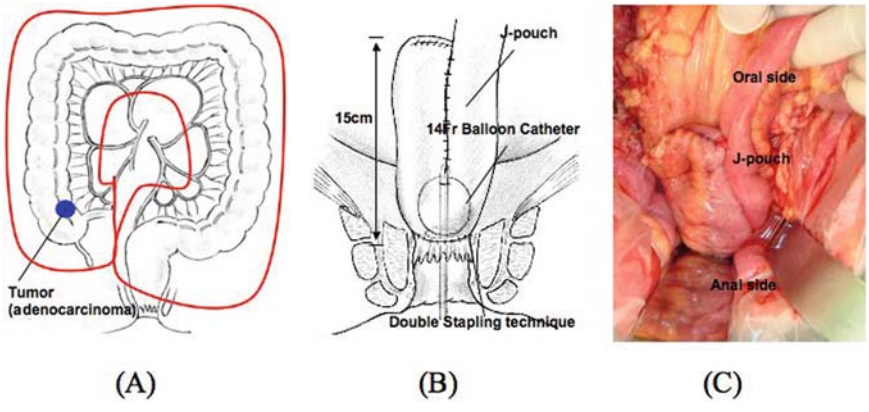

Fig. 2. A Schematic drawing of colectomy for colon cancer. We resected from the terminal ileum to the rectum with lymph node dissection. **B, C** Schematic drawing and photograph of the anastomosis between the iliac J-type pouch and anal canal. A 14-F balloon catheter was inserted into the ileum and fixed above the anastomosis

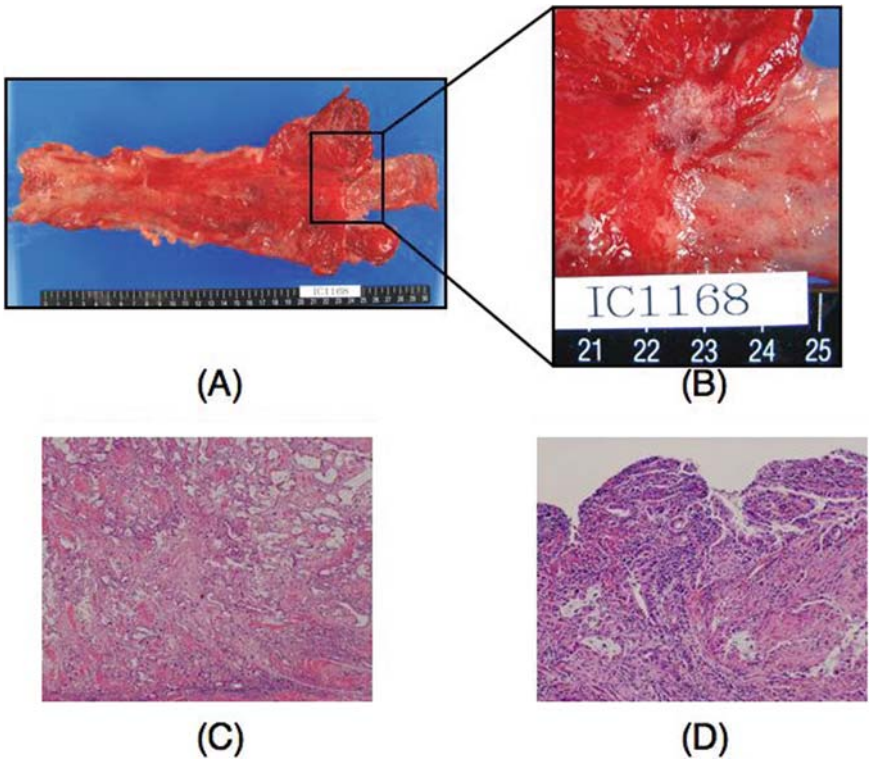

Fig. 3. A, B Macroscopic findings of the lesion. A tumor with ulceration, 1.5 × 1.2 cm in size, was detected in the cecum. **C** Histological examination of the tumor revealed moderately to poorly differentiated adenocarcinoma with marked mucin production and massive invasion of the muscularis propria (H&E stain, × 100). **D** Severe inflammation was observed in the colonic mucosa, with carcinoma cells diffusely distributed in the submucosal layer (H&E stain, × 200)

The patient had an uneventful postoperative course and was discharged on postoperative day 13. He is being followed up with regular surveillance endoscopy of the remnant rectal mucosa.

Discussion

Patients with UC have an increased risk of CRC.[8] In patients with extensive UC, the risk is thought to increase by 0.5%–1.0% per year, after 8–10 years of disease; therefore, the risk of colitis-associated CRC increases from 1%–3% 10 years after the diagnosis to 10% 20 years after the diagnosis, and to 25% 35 years after the diagnosis in patients with pancolitis.[7]

Well-differentiated adenocarcinoma is the predominant histology of CRC in patients without UC and usually develops in solitary form. In contrast, the predominant histology of CRC associated with UC tends to be poorly differentiated carcinoma that develops in multiple forms and is accompanied by dysplasia.[12,13] The definite risk factors for CRC in patients with UC have been reported as the duration and extent of colonic involvement and the severity of inflammation.[14]

Follow-up guidelines recommend surveillance colonoscopy every 1–2 years from 8 years after the onset of the disease in patients with pancolitis or from 15 years after the onset of the disease in those with left-side colitis.[15] However, surveillance colonoscopy should be performed for every patient, starting from 8–10 years after the onset of the disease, to accurately assess the extent of the disease.[16] Dye-spraying endoscopy and magnified endoscopy have also been reported as effective methods of detecting small lesions. The standard therapy for patients with CRC associated with UC is proctocolectomy.[17,18] However, the indications for prophylactic colectomy in patients with multiple risk factors remain controversial.[8]

Primary sclerosing cholangitis is a progressive disease, for which OLT is the only potentially curative treatment available. To our knowledge, there is no other report of CRC developing after LDLT in any of the 97 Japanese patients who have undergone this operation for PSC (as of 2006). The association between UC and PSC is well known. In fact, UC is found in 70%–80% of patients with PSC in Northern Europe and the United States. In general, CRC associated with UC tends to develop in the rectum or sigmoid colon. However, there is a significantly increased risk of proximal colic malignancies in UC patients with PSC, suggesting the influence of carcinogenic bile acids in this group.[10] The reasons why PSC predisposes UC patients to colon cancer, especially proximal malignancies, are unclear. One group of investigators reported the possible involvement of antitropomyosin antibody in the etiology of both UC and PSC.[19] Several studies have found that PSC is associated

with an increased risk of dysplasia and CRC; thus, the risk of colorectal neoplasia development might also be increased by the coexistence of PSC.[4,20,21]

It is possible that liver transplantation and immunosuppressive therapy trigger the development of CRC in patients with PSC and UC. Loftus et al.[22] reported that the risk of carcinoma after liver transplantation appeared to be four times higher than in pre-transplant patients, although this difference was not significant. Vera et al.[23] analyzed the factors that could influence the development of CRC in a patient with UC who undergoes liver transplantation for PSC. They found that colonic dysplasia after LT in patients with more than a 10-year history of colitis or pancolitis was a risk factor for colon cancer. Dvorchik et al.[24] investigated the influence of liver transplantation and immunosuppression on the course and progression of inflammatory bowel disease and concluded that they both accelerated the progression of inflammatory bowel disease but did not affect the incidence of CRC. The incidence of CRC in patients who undergo LDLT for PSC and who suffer UC has been reported to range from 1% to 2% per year.[23,25] However, multiple factors such as the duration of disease influence these data.

The liver regeneration process during the early post-transplant period is possibly related to the growth of malignancy. Some studies have shown that prostimulatory factors, such as hepatocyte growth factor, affect the proliferation of hepatocellular carcinoma.[26] Man et al.[27] reported that hepatic ischemia–reperfusion injury of a small liver remnant exacerbated liver tumor growth by activating cell adhesion, invasion, and the angiogenesis pathways. However the effects of hepatectomy and liver transplantation on the tumor growth of CRC have not been reported.

These findings suggest that patients who undergo liver transplantation for long-standing PSC who also have extensive colitis should be followed up with intensive surveillance colonoscopy. Since proctocolectomy can be performed safely in patients who have undergone liver transplantation for PSC, surgery is the treatment of choice, even shortly after LDLT.

References

1. Marsh JW, Jr, Iwatsuki S, Makowka L, Esquivel CO, Gordon RD, Todo S, et al. Orthotopic liver transplantation for primary sclerosing cholangitis. Ann Surg 1988;207:21–5.
2. Graziadei IW, Wiesner RH, Marotta PJ, Porayko MK, Hay JE, Charlton MR, et al. Long-term results of patients undergoing liver transplantation for primary sclerosing cholangitis. Hepatology 1999;30:1121–7.
3. Narumi S, Roberts JP, Emond JC, Lake J, Ascher NL. Liver transplantation for sclerosing cholangitis. Hepatology 1995;22: 451–7.
4. Olsson R, Danielsson A, Jarnerot G, Lindstrom E, Loof L, Rolny P, et al. Prevalence of primary sclerosing cholangitis in patients with ulcerative colitis. Gastroenterology 1991;100:1319–23.
5. Wiesner RH, Grambsch PM, Dickson ER, Ludwig J, MacCarty RL, Hunter EB, et al. Primary sclerosing cholangitis: natural history, prognostic factors and survival analysis. Hepatology 1989; 10:430–6.
6. Takikawa H, Manabe T. Primary sclerosing cholangitis in Japan — analysis of 192 cases. J Gastroenterol 1997;32:134–7.
7. Bruewer M, Krieglstein CF, Utech M, Bode M, Rijcken E, Anthoni C, et al. Is colonoscopy alone sufficient to screen for ulcerative colitis-associated colorectal carcinoma? World J Surg 2003;27:611–5.
8. Ekbom A, Helmick C, Zack M, Adami HO. Ulcerative colitis and colorectal cancer. a population-based study. N Engl J Med 1990;323:1228–33.
9. Brentnall TA, Haggitt RC, Rabinovitch PS, Kimmey MB, Bronner MP, Levine DS, et al. Risk and natural history of colonic neoplasia in patients with primary sclerosing cholangitis and ulcerative colitis. Gastroenterology 1996;110:331–8.
10. Marchesa P, Lashner BA, Lavery IC, Milsom J, Hul TL, Strong SA, et al. The risk of cancer and dysplasia among ulcerative colitis patients with primary sclerosing cholangitis. Am J Gastroenterol 1997;92:1285–8.
11. Higashi H, Yanaga K, Marsh JW, Tzakis A, Kakizoe S, Starzl TE. Development of colon cancer after liver transplantation for primary sclerosing cholangitis associated with ulcerative colitis. Hepatology 1990;11:477–80.
12. Harpaz N, Talbot IC. Colorectal cancer in idiopathic inflammatory bowel disease. Semin Diagn Pathol 1996;13:339–57.
13. Sugita A, Greenstein AJ, Ribeiro MB, Sachar DB, Bodian C, Aditiya K, et al. Survival with colorectal cancer in ulcerative colitis. A study of 102 cases. Ann Surg 1993;218:189–95.
14. Sugita A, Sachar DB, Bodian C, Ribeiro MB, Aufses AH Jr, Greenstein AJ. Colorectal cancer in ulcerative colitis. Influence of anatomical extent and age at onset on colitis-cancer interval. Gut 1991;32:167–9.
15. Winawer SJ, Fletcher RH, Miller L, Godlee F, Stolar MH, Mulrow CD, et al. Colorectal cancer screening: clinical guidelines and rationale. Gastroenterology 1997;112:594–642.
16. Winawer S, Fletcher R, Rex D, Bond J, Burt R, Ferrucci J, et al. Colorectal cancer screening and surveillance: clinical guidelines and rationale-Update based on new evidence. Gastroenterology 2003;124:544–60.
17. Larson DW, Pemberton JH. Current concepts and controversies in surgery for IBD. Gastroenterology 2004;126:1611–9.
18. Fu CG, Muto T, Masaki T. Results of the double stapling procedure in colorectal cancer. Surg Today 1997;27(8):706–9.
19. Sakamaki S, Takayanagi N, Yoshizaki N, Hayashi S, Takayama T, Kato J, et al. Autoantibodies against the specific epitope of human tropomyosin(s) detected by a peptide based enzyme immunoassay in sera of patients with ulcerative colitis show antibody dependent cell mediated cytotoxicity against HLA-DPw9 transfected L cells. Gut 2000;47:236–41.
20. Broome U, Lindberg G, Lofberg R. Primary sclerosing cholangitis in ulcerative colitis — a risk factor for the development of dysplasia and DNA aneuploidy? Gastroenterology 1992;102: 1877–80.
21. Shetty K, Rybicki L, Brzezinski A, Carey WD, Lashner BA. The risk for cancer or dysplasia in ulcerative colitis patients with primary sclerosing cholangitis. Am J Gastroenterol 1999;94: 1643–9.
22. Loftus EV Jr, Aguilar HI, Sandborn WJ, Tremaine WJ, Krom RA, Zinsmeister AR, et al. Risk of colorectal neoplasia in patients with primary sclerosing cholangitis and ulcerative colitis following orthotopic liver transplantation. Hepatology 1998;27: 685–90.
23. Vera A, Gunson BK, Ussatoff V, Nightingale P, Candinas D, Radley S, et al. Colorectal cancer in patients with inflammatory

bowel disease after liver transplantation for primary sclerosing cholangitis. Transplantation 2003;75:1983–8.
24. Dvorchik I, Subotin M, Demetris AJ, Fung JJ, Starzl TE, Wieand S, et al. Effect of liver transplantation on inflammatory bowel disease in patients with primary sclerosing cholangitis. Hepatology 2002;35:380–4.
25. Oo YH, Gunson BK, Lancashire RJ, Cheng KK, Neuberger JM. Incidence of cancers following orthotopic liver transplantation in a single center: comparison with national cancer incidence rates for England and Wales. Transplantation 2005;80:759–64.
26. Efimova EA, Glanemann M, Liu L, Schumacher G, Settmacher U, Jonas S, et al. Effects of human hepatocyte growth factor on the proliferation of human hepatocytes and hepatocellular carcinoma cell lines. Eur Surg Res 2004;36:300–7.
27. Man K, Kevin T, Lo CM, Ho JW, Sun BS, Sun CK, et al. Ischemia–reperfusion of small liver remnant promotes liver tumor growth and metastases activation of cell invasion and migration pathways. Liver Transpl 2007;13:1669–77.