Increased Risk of Early Colorectal Neoplasms After Hepatic Transplant in Patients with Inflammatory Bowel Disease

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Inflammatory bowel disease (IBD) is associated with an increase in colon and rectal carcinoma. Immunosuppression after transplantation increases the incidence of certain types of tumors. PURPOSE: We reviewed the postoperative course of IBD patients who had undergone hepatic transplantation for primary sclerosing cholangitis to see whether there was an increase in the rate of colorectal neoplasms. METHODS: The charts of 44 patients from two institutions who had undergone a hepatic transplant for primary sclerosing cholangitis were reviewed. Of these 44 patients, 33 had IBD (32 chronic ulcerative colitis, 1 Crohn's). Of these 33 patients, 2 had previously undergone total colectomy/proctectomy and 4 died in the perioperative period. The remaining 27 patients had all undergone colonoscopic evaluation just prior to transplant. Postoperatively all patients were given prednisone, cyclosporine, and azathioprine. Minimum follow-up was 12 months; mean follow-up was 39 months. RESULTS: Three of the 27 patients (11.1 percent) developed early colorectal neoplasms (2 cancers, 1 large villous adenoma with severe dysplasia) at 9, 12, and 13 months post-transplant. All three patients were successfully treated with a total colectomy/proctectomy or resection of any remaining colon. These 3 patients had a mean 19-year history of IBD (range, 9–27 years), while the 24 patients without tumors had a mean 18-year history of IBD (range, 6–39 years). CONCLUSION: There is a subset of transplant patients with primary sclerosing cholangitis and IBD who rapidly develop colorectal neoplasms. Frequent surveillance is recommended for IBD patients in the post-transplant period. [Key words: Hepatic transplant; Colitis; Neoplasms]

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Ulcerative colitis and Crohn's disease are uncommon diseases of the colon and rectum, with the incidence ranging from two to four people per 100,000 within North America.[1] A small percentage of patients with inflammatory bowel disease (IBD) will also manifest chronic inflammatory changes in the intrahepatic and extrahepatic bile ducts. This biliary disease, known as primary sclerosing cholangitis (PSC), will sometimes lead to liver failure. Some patients will then need to undergo an orthotopic liver transplant (OLT) in order to cure the liver failure that may complicate PSC. Hepatic transplantation requires significant immunosuppression to prevent rejection of the transplanted graft. This immunosuppression has been associated with an increase in certain types of malignancies, such as carcinoma of the skin, lips, perineum, and vulva, along with certain types of lymphomas and Kaposi's sarcoma.[2] The incidence of colorectal malignancies has not been shown to increase when looking at the total transplant population.[2, 3] Patients with inflammatory bowel disease, especially ulcerative colitis, however, have been shown to have an increased incidence of colorectal cancer.[4–7] When a patient with inflammatory bowel disease who had undergone an OLT presented to our clinic with a colorectal malignancy 13 months post-transplant, we asked the question is there an increased incidence of colon and rectal cancer in the subset of patients who have ulcerative colitis and who have undergone a hepatic transplant for severe primary sclerosing cholangitis, and as such are maintained on chronic immunosuppression to prevent rejection? To analyze this question, we reviewed the records

of all patients who underwent orthotopic liver transplantation for primary sclerosing cholangitis at the University of Minnesota Hospital, Minneapolis, Minnesota, or the New England Deaconess Hospital, Boston, Massachusetts, to see if those patients with associated IBD had an increased risk of developing colorectal cancer in the post-transplant period while on chronic immunosuppression.

MATERIALS AND METHODS

Charts of all patients who underwent orthotopic liver transplantation for primary sclerosing cholangitis at either the University of Minnesota Hospital, Minneapolis, Minnesota, or the New England Deaconess Hospital, Boston, Massachusetts from November 30, 1984 to July 15, 1990 or from September 15, 1985 to March 12, 1991, respectively, were reviewed. Patients with inflammatory bowel disease (chronic ulcerative colitis or Crohn's disease) were selected from this population and the preoperative, perioperative, and postoperative clinical course including the investigation and follow-up of the colon and rectum were studied. Recent follow-up was obtained on surviving patients by outpatient review, direct contact with the primary surgeon, or telephone contact with the primary physician or gastroenterologist. Clinical events noted included: the preoperative endoscopic findings of the colon and/or rectum, the postoperative endoscopic findings, and the postoperative clinical course including changes in symptoms attributable to the colon and rectum.

Hepatic transplantation was performed using cyclosporine, azathioprine, and steroids for the acute and chronic immunosuppression. OKT3, a mouse monoclonal antibody directed against an antigen on human lymphocytes, was used for rejection episodes in several patients. Patients were eligible for the study if they were at least six months out from their hepatic transplant.

We calculated the number of tumors per person per year at risk for colorectal cancer beginning with the time of OLT. The expected number of gastrointestinal cancers for the general population was computed using Surveillance Epidemiology and End Results (SEER) mortality tables[8] and compared with the study population of 27 patients who underwent liver transplant for primary sclerosing cholangitis with inflammatory bowel disease. Historic controls for the expected number of colon and rectal cancers in patients with ulcerative colitis were obtained from the literature[6] and also compared with the study population. For patients in the study population, the expected number of cancers was computed using the time interval beginning with the liver transplant. A chi-squared test was used to compare the observed *vs.* the expected number of gastrointestinal cancers. Of note, for the SEER comparison gastrointestinal cancers included cancers of the esophagus, stomach, liver, biliary tract, pancreas, small intestine, colon, rectum, and anus; colon cancers comprised 45 percent of the gastrointestinal cancers in the age-sex incidence tables. For the study population, Student's *t*-test was used to compare variables in the patients who had cancer with the patients who did not develop cancer.

RESULTS

A total of 44 patients with PSC underwent OLT in the two institutions during the study period. Of the 44 liver transplant recipients, IBD was diagnosed in 33 patients (32 with chronic ulcerative colitis and 1 with Crohn's colitis). Six of the 33 patients who had PSC associated with IBD were excluded from the study because 2 patients had undergone proctocolectomy prior to OLT and 4 patients died in their perioperative period (Fig. 1). As seen in Table 1, the ages at the time of OLT of the 27 patients who were available for review ranged from 22 to 67 years (mean = 46 years). Eighteen (66.7 percent) were men. Age of IBD

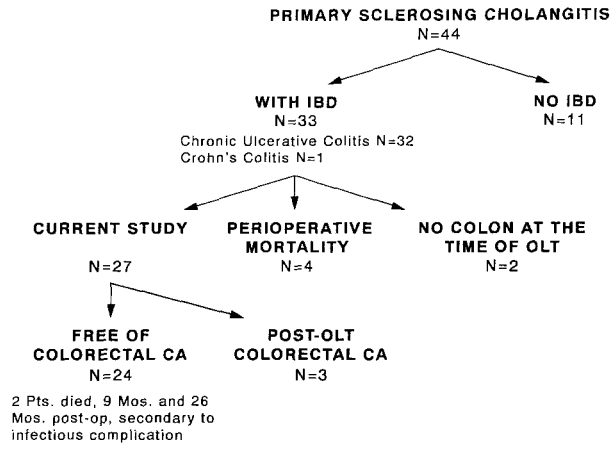

Figure 1. Patient population reviewed included patients with IBD who were post-OLT for PSC. Those who died in the perioperative period from infectious causes or who had previously undergone a total proctocolectomy were excluded.

Table 1.
Incidence of Colorectal Cancer Post-OLT

	No. of Patients	Age of Transplant (yr)	Age Onset of IBD (yr)	Duration of IBD (yr)	Follow-Up (mo)
Patients free of CRC post-OLT	24	46 ± 11	27 ± 11	18 ± 11	40 ± 19
Patients with CRC Post-OLT	3	43 ± 6	24 ± 6	19 ± 9	36 ± 10
Total	27	46 ± 11	27 ± 11	18 ± 10	39 ± 18

CRC = colorectal cancer.

onset was 15 to 51 years (mean = 27 years). Duration of IBD prior to OLT was 1 to 39 years (mean = 18 years).

Of the 27 patients reviewed, 5 patients had undergone subtotal colectomy prior to OLT, thereby having only rectum remaining at the time of transplant. All patients had undergone a colonoscopic evaluation of their colon within several weeks prior to transplantation. Two patients died 9 and 26 months after OLT secondary to infectious complications from chronic immunosuppression. Postmortem examination of these two patients revealed no evidence of colorectal cancer. The mean follow-up in the 27 patients, including the 2 who died, was 39 months (range, 6–69 months).

Three of the 27 patients (11.1 percent) developed colorectal cancer or a villous tumor with severe dysplasia (Table 2). Possible associated risk factors such as the mean age of transplant, the mean age of chronic ulcerative colitis onset, and the mean duration of chronic ulcerative colitis between the 24 patients (15 males and 8 females) who were free of colon tumors post-OLT and the 3 patients (2 males and 1 female) who developed colon tumors were not statistically significantly different (Table 1). The intervals between OLT and the development of colorectal cancer or severe dysplasia were only 9, 12, and 13 months, respectively. Two of the three patients developed Dukes stage B adenocarcinoma, one at the hepatic flexure and the other at the rectosigmoid junction. The third patient, who previously had a subtotal colectomy with ileorectal anastomosis, developed a 6-cm villous tumor with severe dysplasia in the rectal remnant. As mentioned, all three of these patients had undergone extensive colon surveillance prior to OLT.

The incidence of malignant transformation in our study was 1 tumor per 28 patient years (1/28) and this is relatively high compared with historic controls of 1 tumor per 137 patient years (1/137) after 10 years of pancolitis and 1 tumor per 103 patient years (1/103) after 20 years of pancolitis.[6] Chi-squared analysis of our data with these historic controls shows that this difference is significant ($P < 0.0001$). Furthermore, using SEER mortality tables for the general population,[8] only 0.3 cases of malignant transformation would be expected in a study group of our size *vs.* the 3 cases seen ($P < 10^{-9}$).

All three patients who were diagnosed with colorectal cancer or a dysplastic villous tumor underwent either a total colectomy-proctectomy with end ileostomy or a completion proctectomy with end ileostomy without significant complication.

DISCUSSION

Patients with inflammatory bowel disease, particularly ulcerative colitis, have an increased risk of developing colorectal cancer, especially with long-

Table 2.
Patients with Colorectal Tumors Post-OLT

Sex	Age at OLT (yr)	Age Onset of IBD (yr)	Duration of IBD (yr)	Previous Colorectal Surgery	Interval between OLT and CRC (mo)	Pathology
F	39	30	9	None	9	Adenocarcinoma at hepatic flexure; Dukes B
M	40	18	22	Subtotal with ileorectal	12	6-cm villous tumor with severe dysplasia
M	50	23	27	None	13	Mucinous cancer at rectosigmoid junction; Dukes B

CRC = colorectal cancer.

standing disease (Table 3).[4-7, 9-17] Carcinomas developing in ulcerative colitis patients have been shown to be associated with a severe mucosal dysplasia in quiescent mucosa.[17-19] This severe dysplasia is considered to be a marker of potential malignant transformation.[6, 9, 10, 17-19] Riddell *et al.*[20] described these changes and attempted to standardize the histologic classification. Recent studies, particularly by Nugent *et al.*,[9] have shown that biopsies from the colon or rectum in patients with ulcerative colitis with no or only mild dysplasia are rarely associated with a colorectal malignancy, *vs.* those patients who have persistent, severe dysplasia. In the study by Nugent *et al.*[9], they found that only 2 of 175 patients with low-grade dysplasia developed colorectal cancer at 34 and 38 months, and these 2 patients both had deferred follow-up until symptomatic from their colorectal cancer and, therefore, were not a failure of surveillance. Thus, patients with persistent, severe dysplasia should have a total colectomy-proctectomy and patients with no dysplasia or only low-grade dysplasia appear to have a relatively small risk of harboring colorectal cancer and can be followed.

In this study the data show that there is a statistically significant increased incidence of developing colorectal tumors in patients with inflammatory bowel disease in the post-transplant period when compared with historic controls (1/28 per patient year *vs.* 1/137 per patient year) and compared with the general population (SEER data). A potentially disturbing finding is that the patients who developed these tumors had no predisposing histologic marker such as severe dysplasia or a distinguishing clinical feature such as a complicated postoperative course to be able to predict the development of malignant transformation. This phenomenon of rapidly developing colorectal tumors after liver transplantation for primary sclerosing cholangitis in patients with inflammatory bowel disease has also been described by the Pittsburgh transplant group.[13] During follow-up on their patients with primary sclerosing cholangitis and IBD, 2 of 31 patients who were eligible for review developed colorectal cancers at 11 and 21 months post-transplant. These two patients also did not have any severe dysplasia in the colorectal mucosa on the pretransplant colonoscopies 3 and 9 months prior to their surgery. Although this retrospective study and that of the Pittsburgh group alerts us to the potential for early colorectal carcinomas in PSC patients post-transplant, a prospective evaluation with concurrent controls will be needed to definitively conclude that there is an increased risk of colorectal cancer in this subset of patients.

The patients who developed colorectal cancer in our study and in the Pittsburgh study appeared to do so in the immediate post-transplant period. This phenomenon may reflect a sampling error with the pretransplant colonoscopic biopsies or difficulty in identifying an early cancer on pretransplant endoscopy because of the flat morphology seen with tumors that develop in IBD patients. However, recently a retrospective study showed a significantly higher incidence of dysplasia and colorectal cancer in IBD patients with PSC *vs.* IBD patients without PSC.[21] Therefore, IBD patients with PSC may be a select subset of IBD patients more prone to colorectal cancer. Some factor or factors associated with organ transplantation may also promote carcinogenesis in this sensitive "premalignant" colorectal epithelium. We suspect that, should this increased risk of colorectal cancer in post-transplant PSC patients be reaffirmed in a prospective

Table 3.
Incidence of Colorectal Cancer in Patients with Chronic Ulcerative Colitis

Study	No. of Patients	Patients with Cancer	Length of Study (yr)	Mean Duration of CUC (yr)	Cancer (%)
Leideniuse *et al.*,[10] Helsinki, Finland	66	0	13	15	0
Nugent *et al.*,[9] Burlington, MA	175	2	15	14	1.1
Lofberg *et al.*,[11] Stockholm, Sweden	72	1	15	20	1.4
Rosenstock *et al.*,[12] Cleveland, OH	248	7	11	12	2.8
Ekbom *et al.*,[15] Uppsala, Sweden	3117	91	62		2.9
Lennard-Jones *et al.*,[18] London, England	401	22	22		5.5
Higashi *et al.*,[13] Pittsburgh, PA	31	2	4 (s/p liver transplant)	14	6.5
Current study	27	3	4 (s/p liver transplant)	18	11.1

study, the etiology of this phenomenon would be related to both the inherent biology of the colorectal mucosa in this group of patients and to some factor or factors involved with chronic post-transplant immunosuppression. With respect to this last point, with the increasing use of more powerful immunosuppressive agents for the treatment of flares of ulcerative or Crohn's colitis, frequent surveillance and biopsy of the colorectal mucosa needs to be strongly considered until more long-term data on the potential side effects of these drugs are obtained and analyzed.

The treatment of a colorectal cancer that develops in an IBD patient after OLT should be a total proctocolectomy with end ileostomy. No high-risk mucosa should be left behind. For a patient with dysplasia an ileal pouch-anal anastomosis with mucosal stripping can be considered; however, the potential complications from long suture lines and an anastomosis needs to be considered in this subset of patients that are to remain chronically immunosuppressed. Furthermore, rectal cancers can and have developed from residual mucosal cells after mucosal stripping beneath an ileal pouch anal anastomosis[22, 23] and, therefore, long-term follow-up would be needed.

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