Colorectal Neoplasia in Patients with Ulcerative Colitis and Primary Sclerosing Cholangitis

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PURPOSE: Most patients with primary sclerosing cholangitis also have ulcerative colitis. It has been suggested that in the presence of primary sclerosing cholangitis the risk of colorectal dysplasia and carcinoma is greater than in patients with ulcerative colitis alone. METHODS: In a retrospective study, we evaluated the possibility of colorectal cancer or dysplasia in 35 consecutive patients with primary sclerosing cholangitis and ulcerative colitis seen at The Johns Hopkins Hospital between 1979 and 1991. RESULTS: Thirteen of the 35 patients (37 percent) with ulcerative colitis and primary sclerosing cholangitis had colorectal neoplasia (5 with adenocarcinoma and 8 with dysplasia). In the 27 patients undergoing colonoscopic biopsy surveillance, the cumulative incidence at 28 years of colorectal cancer was 18.5 percent and for colorectal dysplasia it was 29.6 percent. The high incidence of colorectal cancer was less than the rate of colorectal cancer in patients with extensive colitis of childhood onset without primary sclerosing cholangitis (35 percent), but the rate of colorectal cancer and dysplasia (48.1 percent) is similar to the highest rates of cancer noted in the comparison group. Because patients had subtle, quiescent colitis, a short time from diagnosis of ulcerative colitis to diagnosis of colorectal neoplasia was noted (mean, 12.2 ± 9 years; less than 8 years in 5/13 (38.5 percent) patients). CONCLUSION: Ulcerative colitis patients with primary sclerosing cholangitis appear to have a high frequency of colorectal cancer but a rate lower than expected in patients with extensive quiescent ulcerative colitis of childhood onset alone. However, exact conclusions are complicated by the high incidence of colorectal dysplasia found, which portends malignant transformation. Because of the subtle nature of colitis, the diagnosis of ulcerative colitis is often delayed, and surveillance programs should start as soon as ulcerative colitis is diagnosed. [Key words: Primary sclerosing cholangitis; Ulcerative colitis; Dysplasia; Colorectal Cancer; Colorectal neoplasia]

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Primary sclerosing cholangitis (PSC) is a chronic cholestatic liver disease characterized by fibrosing inflammation of segments of the intrahepatic and extrahepatic bile ducts.[1] Although PSC patients can have several associated diseases, inflammatory bowel disease (IBD), predominately ulcerative colitis (UC), is found in 50 to 82 percent of individuals with PSC.[2–6] Conversely, PSC occurs in 3 to 7 percent of UC patients.[7–9]

This association between PSC and IBD is well known. However, none of the current standard text books describe the association of PSC with colorectal cancer in patients with UC. Nevertheless, a recent report hypothesizes that the presence of PSC increases the risk of developing dysplasia and colorectal carcinoma in UC patients.[10] Other recent studies have also suggested that the risk of colorectal neoplasia development might be increased by the coexistence of PSC,[2, 11–13] perhaps by altered bile acids acting on colorectal mucosa. Whether the hepatobiliary tract disease of PSC enhances this cancer risk is not known.

We investigated the association of ulcerative colitis complicated by PSC and colorectal neoplasia (cancer and dysplasia) in a consecutive series of 35 patients with UC and PSC seen between 1979 and 1991. These results are compared with the cumulative incidence of colorectal cancer in patients with extensive, long-duration, ulcerative colitis alone.

METHODS

Thirty-six patients with ulcerative colitis and primary sclerosing cholangitis were identified at The Johns Hopkins Medical Institutions for the period of 1979 through 1991. One patient with UC and PSC was

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excluded from the study because the liver disease was thought secondary to intra-arterial chemotherapy for hepatocellular carcinoma. The study group consisted of 24 men and 11 women (male:female ratio, 2.2:1).

Diagnosis of ulcerative colitis had been made in 35 patients on the basis of usual clinical, radiographic, and pathologic criteria.[14] Diagnosis of PSC was verified in the presence of abnormal liver function tests by cholangiography in 25 patients (endoscopic retrograde cholangiopancreatography in 22 and percutaneous transhepatic cholangiography in 3), liver biopsy in 4 patients, and both endoscopic retrograde cholangiopancreatography and liver biopsy in 6 patients.

Presence of dysplasia was assessed using the standard accepted criteria.[15] Colorectal cancer stage was determined by histopathologic examination and clinical observation at the time of surgery and postoperatively. Colorectal cancer was staged according to the tumor, nodes, metastasis (TNM) system of the American Joint Committee on Cancer.[16] Information from tertiary medical centers on the incidence of colorectal cancer in patients with extensive, long-duration, ulcerative colitis was obtained from previous experience in the literature.[17–20]

RESULTS

The mean age of onset of ulcerative colitis symptoms was 23.8 ± 11.2 (standard deviation) (range, 7–47) years. The mean age of PSC diagnosis was 39.6 ± 12.7 years. The average time from onset of ulcerative colitis symptoms to PSC diagnosis was 15.8 ± 9.7 years. In 29 patients, UC was diagnosed before PSC, and the patients were under care for inflammatory bowel disease. The PSC was diagnosed first in two others. Both diagnoses were made concurrently in four patients. These latter six patients all came to medical attention because of hepatobiliary disease rather than colonic disease. In the entire 35-person study group, 8 patients have died, 7 from liver disease and 1 from colorectal cancer.

The extent of inflammatory bowel disease and data on the clinical course were available in 27 of 35 patients. Twenty-six of 27 patients had pancolitis (96 percent). Prolonged remission occurred in 22 of these 27 patients (81.4 percent). Extensive colitis was quiescent for a mean period of 14.3 ± 9.4 (range, 6–25) years in these 22 patients. Only 3 patients were on sulfasalazine, and only 1 patient of 35 (3 percent) underwent colectomy for unresponsive UC. Because of the subclinical nature of colitis, there was a delay between the onset of symptoms and actual diagnosis of ulcerative colitis of 5.9 ± 8.1 (range, 0–31 years).

Mean age at colorectal cancer or dysplasia diagnosis was 51.4 ± 16.2 years and 39.8 ± 6.4 years, respectively. Mean time from actual diagnosis of UC to diagnosis of neoplasia was 12.2 ± 18.9 years because of a delay of 7.8 ± 9.0 years between onset of UC symptoms and diagnosis of UC. All colorectal neoplasia developed in patients with a disease duration (from onset of symptoms) of at least 11 years, but 5 of 13 (38.5 percent) developed neoplasia in less than 8 years from the time of actual diagnosis of UC. Mean duration of diagnosed disease in this small group of five patients was of 2.4 ± 1.8 years.

Colorectal neoplasia was detected in 13 of 35 patients (5 colorectal cancer and 8 dysplasia) (Table 1). No colorectal cancer or dysplasia has been detected in 14 additional patients followed by colonoscopic biopsy surveillance for a mean of 22.2 ± 9.1 (range, 10–45) years. Surveillance was not done in the remaining eight additional patients either because ulcerative colitis duration was less than eight years (one patient), the patients were lost to follow-up (five patients), or death from liver disease occurred before eight years of IBD (two patients).

In the 27 patients whose colon neoplasia status was known, cumulative incidence at 28 years of colorectal cancer and dysplasia was 18.5 percent and 29.6 percent, respectively. Cumulative incidence of colorectal cancer/dysplasia was 48.1 percent (Fig. 1). In comparison, cumulative incidence of colorectal cancer (average of four published studies) in patients with panulcerative colitis without PSC at 28 years was 35 percent. Risk of cancer and dysplasia in ulcerative colitis patients with PSC (48.1 percent) is similar to the highest published risk of colorectal cancer in ulcerative colitis patients without PSC (Fig. 1).

DISCUSSION

The concept that PSC increases risk of colorectal neoplasia development in patients with ulcerative colitis has recently been proposed by Broome *et al.*[10] In a study of 17 patients with ulcerative colitis found to have dysplasia, carcinoma, and/or DNA aneuploidy, they noted 5 patients (28 percent) had PSC.[10] These authors concluded that UC-PSC patients seem to run

Table 1.
Characteristics of UC-PSC Patients with Colorectal Cancer and Dysplasia

Pt. No.	Sex	Age of Onset of UC Symptoms	Age of Diagnosis of UC	Age of Diagnosis of Neoplasia	Age of Diagnosis of PSC	Extent of Colitis	Neoplasia Stage or Grade
1	M	16	16	39 (CRC)	39	PAN	TNM 1
2	M	54	74	74.3 (CRC)	74.3	PAN	TNM 3
3	F	23	39	43 (CRC)	42	PAN	TNM 1
4	M	33	62	62.5 (CRC)	NA	PAN	TNM 3
5	M	17	18	38 (CRC)	39	PAN	TNM 3
6	M	22	22	48 (CRD)	42	PAN	High grade
7	M	25	30	48 (CRD)	30	PAN	Low grade
8	M	19	21	37 (CRD)	35	PAN	High grade
9	M	30	40	44 (CRD)	58	PAN	High grade
10	F	12	20	31 (CRD)	38	PAN	Low grade
11	F	14	16	33 (CRD)	34	NA	Low grade
12	F	23	23	39 (CRD)	39	PAN	High grade
13	M	27	35	38 (CRD)	33	Left-sided	Low grade

All colorectal dysplasia patients underwent total proctocolectomy. M = male; F = female; CRC = colorectal carcinoma; CRD = colorectal dysplasia; PAN = pancolitis; NA = not available.

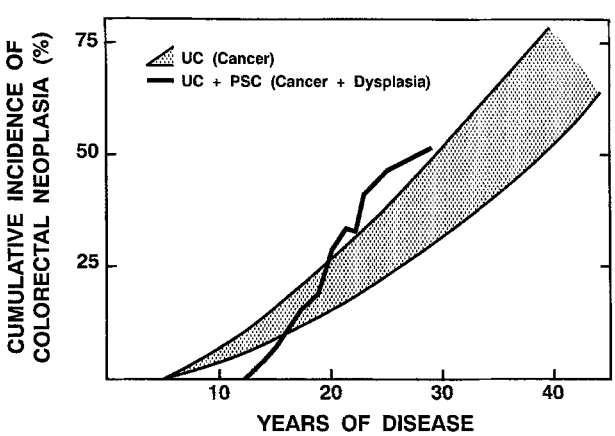

Figure 1. Cumulative incidence of colorectal neoplasia (carcinoma and dysplasia) over time in ulcerative colitis patients with primary sclerosing cholangitis (*solid line*) compared with the range of cumulative incidence of cancer over time in ulcerative colitis patients alone, as reported in four separate studies (*hatched area*).[17–20] (Figure adapted from Devroede G. Colorectal cancer. In: Winawer S, Schottenfeld D, Sherlock P, eds. Prevention, epidemiology, and screening. New York: Raven Press, 1980).

an increased risk of developing colorectal neoplasia when compared with historic data. Two recent abstracts also support this concept.[21, 22]

A high frequency of colorectal neoplasia in ulcerative colitis patients with primary sclerosing cholangitis has been suspected[2, 10, 11] from literature surveys. Of 107 patients with a variety of hepatobiliary liver disease seen at the Mayo Clinic, 10 percent had colorectal cancer.[11] However, those with primary sclerosing cholangitis were not differentiated from other patients with hepatobiliary disease. Also, in a series of 27 PSC patients with both UC and Crohn's disease seen in Oslo, Norway, colorectal carcinoma and colorectal dysplasia occurred in 3.7 percent and 22.2 percent of patients, respectively.[2] These studies failed to mention duration of disease and follow-up time or the presence or absence of a surveillance program for dysplasia/carcinoma, which could influence the frequency of neoplasia detection.

In our study, patients with PSC and UC had a cumulative incidence at 28 years of colorectal cancer and dysplasia of 18.5 and 29.6 percent, respectively. Hence, risk of colorectal neoplasia (cancer and dysplasia) approaches 50 percent at 28 years (Fig. 1). In comparison, we used the risk *vs.* time of colorectal cancer in a group of patients with panulcerative colitis without PSC studied in four referral centers.[17–20] About 2 percent of patients with extensive UC develop invasive cancer during the first ten years of colitis, after which the risk increases to 10 to 20 percent per decade. Risk estimates approach 30 percent after 25 years of disease, 35 percent at 28 years of disease, and 50 percent by the fourth decade. Thus, although the cumulative frequency of cancer in our UC-PSC population is high (18.5 percent), it appears lower than that seen in patients with long-duration pancolitis alone (35 percent). However, the issue is complex because the rate of colorectal cancer and

dysplasia (48.1 percent) is similar to the highest rates of cancer noted in the comparison group with ulcerative colitis without PSC (Fig. 1). Moreover, our experience is consistent with that of Choi *et al.*,[23] who reported that the risk of colorectal neoplasia in patients with long-standing UC was not significantly influenced by the presence of PSC.

One reason for a high frequency of colorectal neoplasia in UC patients with PSC probably relates to the high percentage of pancolitis found in patients with PSC. Also, the subtle nature of colitis not only delayed diagnosis of UC but probably accounted for the low rate of colectomy for colitis in our patient group. In fact, none of the 35 patients had colectomy for colitis, which is less than the usual 20 percent expected in a series of pancolitis patients. In addition, our patients had a long duration of ulcerative colitis at the time of PSC diagnosis (average, 15.8 years from onset of UC symptoms).

One aspect of this subject could confuse plans for a surveillance program; because of the often subtle nature of colitis, there was a delay in diagnosis of ulcerative colitis after onset of colonic symptoms. In our group, the undiagnosed (subclinical) portion of UC averaged 5.9 ± 8.1 years and was even longer in those who developed colorectal neoplasia (7.8 ± 9.0 years). Delay in UC diagnosis resulted in an apparently shorter time than expected from UC diagnosis to colorectal neoplasia diagnosis. Delay in diagnosis of UC in the PSC group was probably explained by the subtlety of colitic symptoms and the subclinical nature of colitis. This trend is also noted in literature reports of patients with PSC without colorectal neoplasia.

CONCLUSION

Surveillance strategies for the general UC patient, which include commencement of colonoscopic surveillance after seven to ten years of known disease,[15, 24] appear inappropriate for patients with PSC. Consideration should be given to beginning an early detection strategy at the time of diagnosis of UC in association with PSC. Also, in the same context, newly diagnosed patients with PSC should undergo colonoscopy rather than sigmoidoscopy to search for UC, and if present total colonoscopic biopsy examination should be initiated at that time.

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