Colorectal Neoplasia in Patients with Ulcerative Colitis and Primary Şclerosing Cholangitis

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Özet: *ÜLSERATİF KOLİT VE PRİMER SKLEROZAN KOLANJİTLİ HASTALARDA KOLOREKTAL NEOPLAZİ*

Primer Sklerozan kolanjitli hastaların çoğuda ülseratuf kollitte mevcuttur. Bu hastalarda kolorektal kanser ve displazi gelişimi iyi araştırılmamış olmakla beraber bazı çalışmacılar primer sklerozan kolanjitle birlikte seyreden ülseratif kolit vakalarındaki kolorektal neoplazinin pür ülseratif kolitli vakalardakinden daha sık olduğuna inanmaktadır. Biz retrospektif bir çalışma ile 1979 ve 1991 yılları arasında Johs Hopkins hastanesinde primer sklerozan kolanjit ve ülseratif kolit tanılarıyla izlenen 35 hastayı kolorektal neoplazi hususu ön planda olmak üzere klinikopatolojik özellikleri açısından inceledik.

Sonuç: Primer sklerozan kolanjitle birlikte seyreden ülseratif kolit vakalarındaki kolorektal neoplazi sıklığı pür ülseratif kolitlilerde umulan orana benzerlik göstermektedir. Kolitin sinsi ve sessiz seyri bu grup vakalarda ülseratif kolit teşhisini sıklıkla geciktirmektedir. Bu nedenle, primer sklerozan kolanjit ve ülseratif kolitli vakalardaki kolorektal kanser surveyansı muhtemelen ülseratif kolit teşhisi konduğu anda başlatılmalı, yahut daha yoğun bir biçimde uygulanmalıdır.

Anahtar kelimeler: Sklerozan kolanjit, kolorektal kanser.

Summary: *Most patients with primary sclerosing cholangitis also have ulcerative colitis. The occurence of colorectal cancer and dysplasia in these patients has not been well studied, but some investigators suggest that colorectal neoplasia is more frequent in this patient group than those with ulcerative colitis alone. In a retrospective stduy, we evaluated the clinicopathological characteristics with emphasis on presence of colorectal neoplasia of 35 consecutive patients with primary sclerosing cholangitis and ulcerative colitis seen at the Johns Hopkins Hospital between 1979 and 1991.*

Conclusion: Ulcerative colitis patients with primary sclerosing cholangitis appear to have a similar frequency of colorectal neoplasia as is expected in patients with ulcerative colitis alone. Because of the subtle nature of the colitis, the diagnosis of ulcerative colitis is often delayed. Therefore, colorectal cancer surveillance in patients with primary sclerosing cholangitis and ulcerative colitis should probably start or be intensified at the time of ulcerative colitis diagnosis.

Key words: Sclerosing cholangitis, colorectal cancer.

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

This association between PSC and inflammatory bowel disease (IBD) is well known. However,

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none of the current standard text books describe the association of PSC with colorectal cancer in patients with UC. Despite this lack of attention, a recent report implies that the presence of PSC increases the risk of developing dysplasia and colorectal carcinoma in UC patients (10). Other studies have also suggested that the risk of colorectal neoplasia development might be increased by the coexistence of PSC (2,11). Unfortunately, frequency studies have not been done.

Risk factors for having PSC in ulcerative colitis patients are male gender (2-4) and pancolitis (2,4,12). Despite pancolitis, some patients with PSC have mild symptoms without rectal bleeding (3,4,7,12) ad many have asymptomatic disease for prolonged periods of time (2). Forty-five percent of patients with ulcerative colitis and PSC in one series had initial disease activity followed by a long quiescent period (2). At follow up endoscopy, macroscopically inactive disease was found in 76% of these patients with UC and PSC. Only 5% showed severe inflammatory changes (2). Despite the high prevalence of pancolitis, few patients required colectomy (4,13) because of the relatively mild disease activity, thus leaving them at risk for colorectal cancer development. Whether the hepatobiliary tract disease of PSC enhances this cancer risk is not known.

To obtain further information on the occurrence of colorectal neoplasia in ulcerative colitis patients with PSC, we investigated the association of ulcerative colitis complicated by PSC and colorectal neoplasia in a consecutive series of 35 patients with UC and PSC seen between 1979 to 1991. We describe the clinicopathological features of this group and determine the cumulative incidence of colerectal neoplasia.

METHODS

A search for patients with primary sclerosing cholangitis and ulcerative colitis was performed in our institutional record room, the Johs Hopkins Inflammatory Bowel Disease Registry, the computerized surgical pathology files, and the Oncology Center Cancer Registry in the period of 1979 through 1991. A total of 36 patients with UC and PSC were identified. One patients with ulcerative colitis and sclerosing cholangitis was excluded from the study because the liver disease was thought secondary to intraarterial chemotherapy for hepatocellular carcinoma. The diagnosis of ulcerative colitis and sclerosing cholangitis was verified in 35 patients by the clinical and pathological records. The diagnosis of ulcerative colitis had been made on the basis of the usal clinical, radiographic, and pathologic criteria (14).

The diagnosis of PSC was verified in the presence of abnormal liver function tests by cholangiography in 25 patients [endoscopic retrograde cholangiopancreatography (ERCP) in 22 and percutaneous transhepatic cholangiography in 3], liver biopsy in 4 patients, and both ERCP and liver biopsy in 6 patients.

The presence of dysplasia was assessed using the standard accepted (15) criteria. Colorectal cancer stage was determined by histopathologic examination and clinical observation at the time of surgery and post operatively. Colorectal cancer was staged according to the TNM system of the American Joint Committee on Cancer (16) as follows:

I= Invasion of submucosa or muscularis propria.

II= Invasion through muscularis propria into subserosa or nonperitonealized pericolic or perirectal tissues or perforates visceral peritoneum or directly invades other organs or structures.

III= Metastasis to pericolic or perirectal lymph nodes.

IV= Distant metastasis.

Stages I, II, and III are equivalent to stages A,B, C, under the original Dukes' classification.

Our findings were also compared with literature reports by literature search from 1966 to 1992 performed through MEDLINE, accessed via the BRS Colleague Search Service.

RESULTS

The study group consisted of 24 men and 11

Table I

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 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)	n.a.	PAN	TNM 3
5	M	17	18	88 (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	n.a.	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.
CRC = colorectal carcinoma
CRD = colorectal dysplasia
PAN = pancolitis

women with ulcerative colitis complicated by primary sclerosing cholangitis. The male to female ratio was 2.2. The mean age of onset of ulcerative colitis symptoms was 23.8±11.2 (SD) (range 7 to 47 years); the mean age at ulcerative colitis diagnosis was 29.7±16.0 years (range 7 to 74 years); resulting in a delay of UC diagnosis from onset of symptoms of 5.9±8.1 years (range 0-31 yeras). In 14 of 32 patient (40.6%) the delay of diagnosis form onset of UC symptoms was 4 or more years.

Data was available concerning the clinical course of ulcerative colitis in 27 patients. Prolonged remission occurred in 22 of these 27 patients (81.4%). The colitis was quiescent for a mean period 14.3±9.4 years (range 6 to 25 years) in these 22 patients. Only 3 patients were on sulfasalazine. The extent of iflammatory bowel disease was available in 27 patients and 26 had pancolitis (96%).

The mean age of PSC diagnosis was 39.6±12.7 years. The mean time from onset of UC symptoms to PSC diagnosis was 15.8±9.7 years. In 28 patients ulcerative colitis was diagnosed before PSC. The PSC was diagnosed first in two others. Both diagnoses were made concurrently in 4 patients. Cholangiocarcinoma developed in 4 patients at a mean age of 45±17.2 years (range 23-61) with a mean duration after PSC diagnosis of 3.3±4.6 year (range 0-10). Four patients underwent liver transplantation at a mean age of 43.3±7.3 years (range 36 to 50 years)with a mean duration after PSC diagnosis of 7.5±2.4 years (range 6 to 11 years).

In this cohort of 35 patients, colorectal neoplasia was detected in 13 patients (5 colorectal cancer and 8 dysplasia). The cilinical characteristics of the patients with colorectal neoplasia are shown

in Table I. Fourteen additional patients were followed by colonoscopic biopsy surveillance for a mean of 22.2±9.1 years (range 10-45 years). No colorectal neoplasia has been detected in these 14 patients. In 8 additional patients, surveillance was not done either because the patients had ulcerative colitis duration of less than 8 years (1 patient), were lost to follow-up (5 patients), or died form liver disease before 8 years of IBD (2 patients). In the 27 patients udergoing surveillance, the cumulative incidence at 28 years of colerectal cancer and colorectal neoplasia (cancer and dysplasia) was 18.5% and 48.1% respectively (Figure 1).

In the patients with neoplasia, the mean age at colorectal cancer or dysplasia diagnosis was 51.4±16.2 years and 39.8±6.4 years respectively. In this neoplasia group, the mean time from onset of UC to diagnosis of neoplasia was 19.9±4.9 years. However, the mean time from 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%) developed neoplasia in less than 8 years from the time of actual diagnosis of UC. The mean duration of diagnosed disease in this small group of 5 patients was of 2.4±1.8 years.

In the entire 35 person study group, 8 patients have died, 7 from liver disease and 1 from colorectal cancer.

DISCUSSION

Although the association between PSC and inflammatory bowel disease is well known, this paper focuses attention on the coexistence of colorectal neoplasia with UC in patients with PSC.

Nearly one half (13 of 27; 48.2%) of the patients who underwent colonoscopic examination had colorectal neoplasia. Importantly, because of the subtle or quiescent nature of the UC, most were primarily cared for by hepatologists. None of these idividuals had been referred to our institution for the management of colorectal neoplasia.

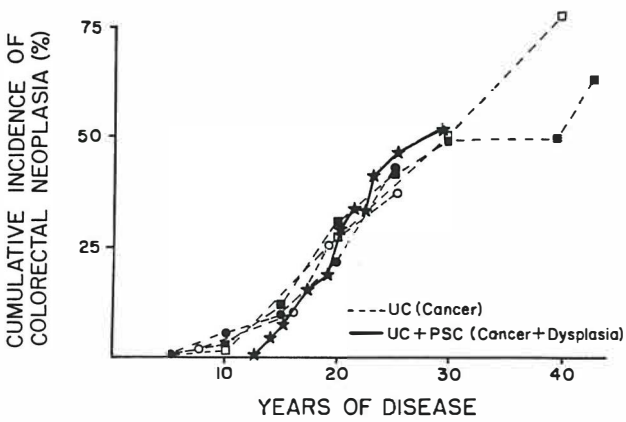

Figure 1

The cumulative incidence of colorectal neoplasia (carcinoma and dysplasia) over time in ulcerative colitis patients with primary sclerosing cholangitis (solid line with stars) compared with the cumulative incidence of cancer over time in ulcerative colitis patients alone as reported in 4 separate studies (ref 17–20). (Figure adapted from Devroede, G: In Colorectal Cancer: Prevention, Epidemiology, and Screening. Edited by S. Winawer, D. Schottenfeld, and P. Sherlock. Raven Press, New York, 1980).

Rather, colorectal neoplasia was found as the result of routine colorectal surveillance (77%) or as the result of work up of cancer related symptoms. Also, the clinical characteristics of our cohort were similar to that of typical UC patients with PSC, being predominately male and all having extensive colitis.

A high frequency of colorectal neoplasia in UC patients with PSC, has been suspected by others (2,10,11). In a series of 107 patients with a variety of hepatobiliary liver disease seen at the Mayo Clinic (11), 10% had colorectal cancer. However, those with primary sclerosing cholangitis were not differentiated from the other patients. Also, in a series of 27 PSC patients with both UC and Crohn's disease seen in Oslo, Norway (2), colorectal carcinoma and colorectal dysplasia occurred in 3.7% and 22.2% of patients respectively. This report did not separete those with UC from Crohn's disease. These studies failed to mention follow-up time or the presence or absence of a surveillance program. A recent study of UC patients with colorectal cancer, dys-

plasia, or aneuploidy suggested that more of these patients also had PSC than expected from the historical reports of the incidence of PSC (10).

The risk of colorectal cancer with duration of panulcerative colitis has been studied in several referral centers (17-20). In these studies, about 2% of patients develop cancer during the first 10 years of ulcerative colitis, after which the risk increases to 10 to 20% per decade. Estimates are based on progressively fewer patients and but the risk may approach 30% after 25 years of disease and 50% by the fourth decade. In our study group, the cumulative incidence of both colorectal cancer and dysplasia reached 50% at 28 years (Figure 1). Thus, although the cumulative frequency of cancer and dysplasia is high, it is probably not different than that seen in patients with pancolitis alone.

The 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. The subtle nature of the colitis not only delayed the diagosis of UC, but probably accounted for the low rate of colectomy for colitis in our patient group. Actually, none of the 35 patients had colectomy for colitis which is less than the usual 10% expected in a series of pancolitis patients. Also, our patients had a long duration of ulcerative colitis at the time of PSC diagnosis (15.8 years from onset of UC symptoms).

As a point that could confuse plans for a surveillance program, there was a delay in the diagnosis of ulcerative colitis after the onset of colonic symptoms. In our cohort the undiagnosed portion averaged 5.9±8.1 years and was even longer in those who developed colorectal neoplasia (7.8±9.0 years). The delay in UC diagnosis resulted in an apparently shorter time than expected from UC diagnosis to colorectal neoplasia diagnosis. The 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. Alterations in bile salts secondary to the biliary-hepatic disease might aso result in more potent carcinogens being released into the already damaged colon. This could produce another factor contributing to neoplastic degeneration.

The ideal investigation to determine risk of colorectal cancer in patients with UC with PSC would be a prospective cohort study matched with comparable patients with UC alone. Although we care for over 400 patients with ulcerative colitis who have either colorectal dysplasia or cancer or are in a surveillance program, our statistical consultants did not feel that it was justified to select those patients as controls because some had been referred because of our interest in UC and dysplasia and others had a childhood onset of UC. This was not true in the UC-PSC group. Also, it would have been difficult to match the prolonged subtle nonspecific symptoms that occurred in the UC-PSC patients.

Surveillace strategies for the general UC patient, which include commencement of colonoscopic surveillance after 7 to 10 years of known disease (15,21) appear inappropriate for patient with PSC. Consideration should be given to beginning surveillance 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 surveillance should be initiated at that time.

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