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A novel point in association between Crohn's disease duration and colorectal carcinoma development

Crohn's hastalığı süresi ile kolorektal karsinom gelişimi ilişkisinde aktüel bir nokta

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ÖZET: *Crohn's hastalığında (CH) kolorektal karsinom (KRK) riskinin 10 yıllık hastalık süresinden sonra başladığına inanılmaktadır. CH süresi ile KRK gelişimi arasındaki ilişkiyi araştırmak amacıyla 23 KRK saptanan 21 CH'lıklı vakanın klinik özellikleri gözden geçirildi. CH ve KRK tanılarına enstütümüzde 1956-1991 yılları arasında histopatolojik yöntemle ulaşılmıştır. CH başlanıcı ile KRK teşhisi arasındaki ortalama süre 17.3±13.5 yıldı. 8 hastada 40 yaştan sonra CH başlama öyküsü mevcuttu ve bu grupta KRK teşhisine kadarki ortalama süre 4.4±4.1 yıldı. Buna zıt olarak 40 yaş veya altında CH başlamış KRK'li 15 hastada bu süre 24.2±11.7 yıl idi (p<0.05). 40 yaştan sonra CH'lığı başlamış hastaların %87.5'inde (7/8) KRK CH ile birlikte yahut ilk 10 yıllık hastalık döneminde teşhis edilmişti. Halbuki 40 yaş veya altında CH başlamış vakaların sadece %7'sinde (1/15) KRK CH ile birlikte yahut ilk 10 yıllık hastalık döneminde teşhis edilmişti (p<0.05). Enteresan olarak CH ile birlikte yahut ilk 10 yılda teşhis edilen KRK'lerin %87.5'i (7/8) 40 yaştan sonra CH başlayan vakalarda gelişmişti. Oysaki, 10 yıllık hastalık süresinden sonra teşhis edilen KRK'lerin sadece %7'si (1/15) 40 yaştan sonra CH başlayan vakalarda gelişmişti (p<0.05).*

	CH BAŞLANGICI-KRK ARASINDAKİ SÜRE		
	CH ve KRK'in birlikte teşhis i	≤ 10 yıl	>10 yıl
CH Başlangıç yaşı >40 yıl olan hastalar	4	3	1
CH Başlangıç yaşı ≤40 yıl olan hastalar	1	0	14

P<0.05

Bulgularımız şu sonuçlara işaret etmiştir: 1. CH süresi ile KRK gelişimi arasındaki ilişki üniform değildir. 2. KRK CH 40 yaştan sonra başlayanlarda 40 yaş ve altında başlayanlara göre daha kısa sürede (p<0.05) gelişmektedir. 3. KRK riski CH 40 yaş ve altında başlayanlarda 10 yıllık bir hastalık süresinden sonra ortaya çıkmasına rağmen, bu risk 40 yaştan sonra CH başlayan vakalarda ilk 10 yıllık hastalık süresinde de gözönünde tutulmalıdır.

Anahtar Kelimeler: **Crohn's hastalığı, ülseratif kolit, kolerektal kanser**

SUMMARY: *It is believed that colorectal carcinoma (CRC) risk in Crohn's disease (CD) begins after 10 yrs. disease duration. To evaluate the association between duration of CD and CRC occurrence; we reviewed the clinical characteristics of 21 CD patient (pts) with 23 CRC. The diagnosis (dx) of CD and CRC were made at our institution between 1956-1991 by histopathological review. The mean duration from onset of CD to CRC dx was 17.3±13.5 yrs. 8 pts had a history of CD onset after age 40 and the mean time till CRC dx was 4.4±4.1 yrs. in this group. In contrast, in 15 CRC pts with CD onset ≤40 yrs. of age; the mean time from CD onset to CRC dx was 24.2±11.7 yrs. (p<0.05). In 87.5% (7/8) of pts with CD onset after age 40 yrs., CRC were diagnosed concomitantly with CD or in the first 10 yrs. CD duration. Conversely, in only 7%(1/15) of pts with an age of CD onset ≤40 yrs., CRC was diagnosed concomitantly with CD (p<0.05). Interestingly; 87.5% (7/8) of CRC diagnosed concomitantly with CD or in the first 10 yrs. CD duration developed in pts with CD onset after age 40. Whereas, only 7% (1/15) of CRC diagnosed after 10 yrs. CD duration developed in pts with CD onset after age 40 (p<0.05).*

	CD DURATION FROM CD ONSET TO CRC DX (YRS.)		
	Concomitant dx of CD and CRC	≤ 10 yrs.	>10 yrs.
Pts with age of CD onset>40 yrs.	4	3	1
Pts with age of CD onset ≤40 yrs.	1	0	14

P<0.05

Our results suggest that: 1. The association between CD duration and CRC occurence is not uniform. 2. The time from CD onset to CRC dx was statistically significantly shorter in pts with CD onset after age 40 than in pts with an age of CD onset≤40 yrs. 3 While CRC risk starts after 10 yrs. of CD duration in pts with an age of CD onset≤40yrs., this risk should be considered even in the first 10 yrs. CD duration in pts with CD onset after age 40.

Key words: **Crohn's disease, ulcerative colitis, colorectal carcinoma**

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Table 1. *IBD duration from IBD onset to CRC diagnosis*

	Concomitant dx. with IBD	≤10 yrs.	>10 yrs.
CD related CRC (n)	5 (21.8%)	3 (13%)	15 (65.2%)
UC related CRC (n)	0	5 (12.8%)	34 (87.2%)

p< 0.01

LONG-standing Crohn's disease (CD) predisposes to cancer (1-3). It is a widely held view that colorectal cancer (CRC) risk in CD is much less than that in ulcerative colitis (UC) (4,5), but time will probably prove this view to be mistaken. Evidence is rapidly mounting to indicate that given the same total duration and anotomic extent of colonic disease the cancer risk in CD is at least as great as in UC (6,7). The risk for colorectal carcinoma (CRC) in patients with CD or ileocolitis has been reported to be 4 to 20 times that in the general population (7-9).

Studies (10) suggesting a rising incidence of CD in the general population places a great number of patients at increased risk of developing carcinoma. Therefore, an understanding of this problem is becoming critical. Association between duration of UC and CRC is well known but this association however has not been studied carefully in CD patients. To understand this association better, we analyzed the clinical characteristics of 21 CD patients with 23 CRC and compared this group to 38 UC patients with 39 CRC.

MATERIALS and METHODS

The records of patients having the simultaneous diagnoses of CD and CRC or UC and CRC from 1956 to 1991 were reviewed. Cases were identified by searching the Johns Hopkins Inflammatory Bowel Disease Registry, surgical pathology files and the Oncology Center Cancer Registry. The diagnoses of CD and UC were confirmed by standart clinical, roentgenographic, endoscopic, and histological criteria for these 59 patients. The onset of inflammatory bowel disease (IBD) was defined as the time when the patient first experienced symptoms consistent with UC or CD. Each patient's medical records were evaluated and telephone contact with the individual or surviving family members was made if historical data was not current. Follow-up was 100%. Chi-square and Mann-Whitney U tests were used for statistical evaluation and $p<0.05$ was accepted as statistically significant.

RESULTS

In CD and UC patients the mean age of CRC diagnosis was 50.4±13.8 yrs. vs. 47.8±14.3 yrs. ($p>0.05$) and the mean time from onset of inflammatory bowel disease to CRC diagnosis was 17.3±13.5 yrs. vs. 20.8±9.4 yrs. ($p>0.05$) respectively. The number of CRC diagnosed concomitantly with IBD diagnosis or in the first 10 yrs. IBD duration was significantly greater in CD patients than that found in UC patients (Table 1).

When CD and UC patients were classified with respect to age of onset of IBD, a significantly greater proportion of CRC appeared in CD patients with an onset of IBD after age 40 (8/23;34.8%) than that observed in UC patients with an onset of IBD after age 40(4/39;10.3%) ($p<0.02$). The mean of IBD duration from IBD onset to CRC diagnosis with respect to age of IBD onset in CD and UC patients showed the data seen in Table 2.

Lastly we analyzed the distribution of CRCs according to IBD duration from IBD onset to CRC diagnosis and age of onset of IBD for CD and UC patients separetely (Table 3, Table 4).

Table 2. *Mean duration from IBD onset to CRC diagnosis*

	Age of IBD Onset		
	≤40 yrs.	>40 yrs.	
CD related CRC	24.2 yrs.	4.4 yrs.	p<0.05
UC related CRC	21.2 yrs.	17 yrs.	p>0.05
	p>0.05	p< 0.05	

Table 3. *Distribution of CRCs Complicating CD*

	CRCs diagnosed concomit. with CD or in CD duration of ≤ 10 yrs.	CRCs diagnosed in CD duration of > 10 yrs.
CD patients with IBD onset ≤ 40 yrs.	1	14
CD patients with IBD onset >40 yrs.	7	1

p< 0.05

DISCUSSION

Although it is believed that CRC risk in CD begins after 10 years disease duration; some reports demonstrated that substantially greater number of CRCs were diagnosed concomitantly with CD diagnosis (9,11-13) or in the first 10 years IBD duration (13-16). Previously, we reported that CD patients with an IBD onset after age 40 might require special attention (17). In our current study we analyzed the clinical characteristics of 21 CD patients with 23 CRC and compared this group to 38 UC patients with 39 CRC.

Our results showed that CRC complicating CD and UC develops at younger ages than that observed in general population. In addition; the mean duration of CD and UC from IBD onset to CRC diagnosis showed that CRC develops in long-standing CD and UC in general. These findings are compatible with the literature reports. Importantly, the number of CRC diagnosed concomitantly with IBD diagnosis or in the first 10 yrs. IBD duration was significantly greater in CD patients than that found in UC patients. This was the reason of shorter mean duration from IBD onset to CRC diagnosis in CD patients with respect to UC patients. It seems that IBD duration pattern of CD related CRC is different than that found for UC related CRC. In fact limited number of previous literature reports showed that 20 to 50% of CRC complicating CD were diagnosed concomitantly with CD diagnosis (9,11,12) and 25 to 37% of CD related CRC developed in the first 10 yrs IBD duration (13,15,16). Our results also revaled that; if IBD starts after age 40, CRC develops significantly earlier in CD patients but not in UC patients with respect to IBD patients with an age of IBD onset ≤40 yrs (Table 2).

In patients with CD, 87.5% of those who developed CRC within the first 10 yrs. of IBD were older than 40 years of age when CD started, compared with 7% of those with IBD duration of greater than 10yrs. ($p<0.05$). In comparison, 25% of patients with UC who developed cancer within the first 10 yrs. of IBD were older than 40 yrs of age when UC started, compared with 8.8% of those with UC duration of greater than 10 yrs. ($p>0.05$).

Our findings show that some clinicopathological features of carcinoma complicating CD and UC are strikingly similar. Similarities include typical long duration of disease before the diagnosis of cancer. relatively young age at diagnosis of cancer compared with sporadic CRC, frequent multpl tumours at presentation.

Some dissimilarities were seen as well. Ages at onset of disease and cancer diagnosis were older for patients with CD compared with patients with UC. Although the duration of disease to cancer diagnosis was typically long for both diseases, it was shorter for patients with CD. In fact, a significantly greater proportion of patients with CD had their cancer diagnosed within the first 10 yrs. of the onset of disease, a tendency previously noted (13-16). Paradoxically, the age at cancer di-

Tablo 4. *Distribution of CRCs Complicating UC*

	CRCs diagnosed concomit. with UC or in UC duration of ≤10 yrs.	CRCs diagnosed in UC duration of > 10 yrs.
UC patients with IBD onset ≤40 yrs.	4	31
UC patients with IBD onset >40 yrs.	1	3

p> 0.05

agnosis of patients with CD of shorter duration was older than that of the patients with a longer duration of disease.

Although these findings may be explained by sampling and referral biases, a review of the published reports showed identical findings. Of 67 analysable patients in 73 reported cases (11-15,18-22), CRC developed in 21(31.1%) within the first 10 yrs. of CD including 5 CRC diagnosed concomitantly with CD diagnosis. A substantial proportion of these patients (76.2%) were older than 40 years at CD onset compared with only 19.6% of the remaining 46 patients with a duration of disease longer than 10 yrs. ($p<0.05$). Thus, it is unlikely that a chance occurrence of sporadic CRC related to age may explain the shorter duration of disease before the diagnosis of CRC in these older patients. It is possible that these patients had, in fact subclinical CD.

Our results suggest that: 1. The association between CD duration and CRC occurence is not uniform 2. The time from CD onset to CRC diagnosis was statistically significantly shorter in patients with CD onset after age 40 than in patients with an age of CD onset <40 yrs. 3. While CRC risk starts after 10 yrs. of CD duration in patients with an age of CD onset ≤40 yrs., this risk should be considered even in the first 10 yrs. disease duration of CD patients who had IBD onset after age 40.

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