Evaluation of Preoperative Elevation of Serum C-Reactive Protein as an Indicator for Prognosis in Colorectal Cancer

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Abstract

Background: The C-reactive protein (CRP) is a product synthesized in hepatocytes and has been reported to be up-regulated by such proinflammatory cytokines as interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor (TNF).

The significance of a preoperative serum elevation in CRP as a predictive indicator for the malignant potential and prognosis in colorectal cancer has not been elucidated.

Method: Forty consecutive patients with colorectal cancer, whose local lesions were resected in our department, plus forty volunteer healthy persons, were selected. Any patient with inflammatory diseases such as infection or collagen disease was excluded from the current study. Then preoperative serum CRP level were measured, and also from the control group. The relationships between the serum elevation of CRP and both the clinicopathologic factors and prognosis of the patients was investigated.

Results: The rate of patients with elevated serum CRP level was significantly higher in colorectal cancer patients in comparison with the control group (55% versus 2. 5%). Furthermore the incidence of liver metastasis, peritoneal carcinomatosis, histopathologic lymph nodes metastasis, and tumor invasion in colorectal cancer patients with a preoperatively elevated serum CRP level were significantly more frequent than in those with a negative serum CRP level. The survival rates of colorectal cancer patients without a preoperative elevation of serum CRP proved to be significantly more favourable than what in colorectal cancer patients with such an elevation (94. 4% versus 59. 1%; P<0. 001).

Conclusions: A preoperative serum elevation of CRP was thus found to be an indicator of malignant potential of the tumor as well as a predictor for the prognosis of patients with colorectal cancer.

Keywords: c - reactive protein, colorectal cancer

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Introduction

The colorectal cancer is the second most prevalent cancer and the third leading cause of cancer deaths world wide(1,2). It is often diagnosed at a late stage(1)

Accurate prediction of prognosis is important for management of colorectal cancer as it may assist in determining type, timing, and appropriateness of therapy. Inflammatory status is a relatively new prognostic factor that appears to be worth in colorectal cancer patients (1,3).

The acute phase response occurs in response to damage of body tissues as a result of inflammation, trauma, and malignant disease (3,4,5,6,7). It is characterized by alteration in production and secretion of more than 30 different plasma proteins (8,9,10). These proteins are termed as the acute phase proteins(8,9,10). The functions of these different proteins are variable, such as modulation of immune response and mediation of inflammatory response (10,11,12). The C-reactive protein (CRP) is an acute phase protein and a sensitive marker of inflammation(8,9,10,11,12,13). It is synthesized in hepatocytes and up-regulated by the cytokines such as interleukin-1, interleukin-6 and tumor necrosis factor-α (TNF-α)(1,8,9,10,13,14). Preoperative CRP levels have been found to be prognostic in various cancer(1,3,5,9,15). In this study we want to assess the value of CRP level in colorectal cancer patients

comparison with healthy persons, and also the value of increased CRP level in prognosis of colorectal cancer patients due to clinicopathological finding.

Methods

In this investigation, 80 cases were studied. Forty consecutive patients (21 men, 19 women; age range 21-80 years) who underwent resection for colorectal cancer in our department (four university medical centres) from January 1998 to January 2001 were selected and compared with forty volunteer healthy persons (20 men, 20 women; age range 20-80 years). The patients with inflammatory disease, including infections and collagen diseases, as well as primary cancers in other organs were excluded from the current study.

All the patients were followed up until 5 years or death. The study was performed in an analytical method. The serum CRP value was measured by latex agglutination test. Five ml of blood were withdrawn from all the patients preoperatively and also from the control group by peripheral venupuncture and after centrifuging, the serum was mixed with a drop of latex agglutination test. After some steps, it was investigated for the presence or absence of precipitation, grossly and microscopically. Chi-squared test, Fisher's exact test, and t-student test were used to compare the clinicopathological data of patients and control group, with or without elevation of serum CRP levels. P value of less than 0.05 was regarded as significant.

Results

The rate of patients with elevated serum CRP level was significantly higher in colorectal cancer patients in comparison with control group (55% versus 2. 5%). In colorectal cancer patients, the primary lesions were located in cecum and ascending colon in 6 (15%) patients, transverse colon in 1 (2. 5%) patient, descending colon in 4 (10%) patients, the sigmoid

Table 1. Clincopathologic factors

Clinicopathologic Backgrounds (Serum elevation of CRP)			
P Value	Negative n=18	Positive n=22	Clinicopathologic factors
NS	11/7	14/8	***Male/female***
NS	51.7 (29-71	51.5 (21-80)	***Age, years (Range)***
			Location of tumors
<0.01	3	2	Cecum and ascending colon
	1	-	Transverse colon
	1	3	Descending colon
	4	1	Sigmoid colon
	9	16	Rectum
<0.01	4.1±1.5	5.8±2.1	***Maximal size of tumor (cm)***
			Differentiation
<0.05	13	12	Well
	1	3	Moderately
	4	7	Poorly
			Liver metastases
<0.01	1	4	Positive
	17	18	Negative
			Lymph node metastases
<0.01	3	12	Positive
	15	10	Negative
			Peritoneal carcinomatosis
<0.01	1	5	Positive
	17	17	Negative
			Stage (dukes classification)
<0.05	5	1	A
	4	5	B
	7	9	C
	2	7	D

colon in 5 (12. 5%) patients, and rectum in 25 (60%) patients. In 5 (12. 5%) patients, liver metastases were detected preoperatively by both abdominal computed tomography and ultrasonography. The preoperative elevation of serum CRP value in colorectal cancer group was recognized in 22 (55%) patients (group A), whereas no such elevation was recognized in 18 (45%) patients (group B). The clinicopathological factors are shown in the Table 1. No significant difference was observed regarding to age or gender between groups A and B. The maximal size of tumour in group A (5. 8 ± 2. 1 cm) was significantly larger than what in group B (4. 1 ± 1. 5 cm; P<0. 01). The incidence of peritoneal dissemination in group A (22. 7%; 5 of 22) was significantly higher than what in group B (5. 5%; 1 of 18; P<0. 05), and the incidence of liver metastases in group A (18. 2%; 4 of 22) was also significantly more frequent than that in group B (5. 5%; 1 of 18; P<0. 05). Moreover, a significant difference was seen between proportion of histopathologically detected lymph node metastases in group A and B (54. 5%; 12 of 22, versus 16. 7%; 3 of 18; P<0. 05).

The ratio of stage D cases by Dukes' classification, for which the surgical treatment was an absolute noncurative resection for either liver metastasis or peritoneal dissemination, was significantly higher in group A compared to in group B (31. 8% versus 11. 1%).

The 5 year survival rate in group A was 59. 1%; and significantly more unfavourable than those in group B which were 94. 4% (P<0. 01). Also poorly differentiated tumours were higher in group A compared to in group B (31. 8% versus 22. 2%).

Discussion

In patients with chronic malignant disease, changes in protein metabolism will result in muscle wasting, edema, cachexia, or the production of acute-phase proteins, such as CRP(8,16,17). The acute phase synthesis of CRP is up-regulated by such proinflammatory cytokines as interleukin-1, interleukin-6, and tumour necrosis factor(9,19), which act as autocrine growth factors for neoplasms (4,9,20). It has also been reported that following the tumour recurrence and progression, a proportion of patients will develop an acute-phase protein response (9,21). Moreover, the serum CRP can be measured more easily and promptly compared with other oncogenic markers. Thus the hypothesis that the serum concentration of CRP may be an indicator of the malignant potential of the colorectal cancers appears to be valid.

In 3 case-control studies, it is reported that serum CRP level in the patients with colorectal cancer was higher than what in control groups (22,23,24,25).

Shumin reported that there was no significant positive association between the CRP levels and stage of colorectal cancer11. Some previous studies have noted independently the apparent association between the CRP and poor prognosis (8,9,16,18). Our results indicate that the increased CRP in cancerous patients is significantly higher than what in control groups, and generally associated with larger tumor size, lymph node or liver metastases, peritoneal carcinomatosis, and advanced Dukes' stage. Also the CRP expression is inversely correlated with overall survival. These results suggested that the serum CRP level could thus be an indicator of the malignant potential and a marker of metastases in colorectal cancer.

The prognosis of patients without a preoperative elevation of serum CRP level proved to be significantly better than what in those patients with such an elevation. These results indicated that the serum CRP level may thus be a predictive indicator for the prognosis of patients with colorectal cancer, and therefore can also provide valuable information when determining the treatment strategies for such patients.

In order to elucidate the relationship between the serum CRP and alterations in the oncogens related to metastases in colorectal cancer, further investigations are thus required.

In conclusion, an elevation in the serum CRP level is considered to be an indicator of malignant potential in tumour as well as an appropriate predictor of prognosis for the patients with colorectal cancer.

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