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Evaluation of preoperative elevation of serum c-reactive protein as an indicator for prognosis of colorectal cancer

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Abstract

Background: Cancer has not been elucidated in colerectal site. 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 was evaluated using CRP as a predictive indicator for the malignant potential and prognosis.

Methods: Forty consecutive patient with colorectal cancer whose local lesions were resected in our department, plus forty healthy volunteers, were selected. Any patient with inflammatory diseases such as infection or collagen disease was excluded from the current study. The preoperative serum CRP level and the control group were measured. 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 the colorectal cancer patients in comparison to the control group (55% versus 2.5%). Furthermores 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 the colorectal cancer patients without a preoperative elevation of the serum CRP proved to be significantly more favorable than that of the colorectal cancer patients with such an elevation (94.4% versus 59.1% ; $P<0.001$).

Conclusion: A preoperative serum elevation of CRP was thus found to be an indicator of the malignant potential of the tumor as well as prognostic factor for patients with colorectal cancer.

Keywords: C-reactive protein,colorectal cancer.

Introduction

The colorectal cancer is the second most prevalent cancer and the third leading cause of cancer deaths world-wide [5,21] and is often diagnosed at a late stage [5].

Accurate prediction of prognosis is important in the management of colorectal cancer as it may assist in determining the type, timing, and appropriateness of therapy. Inflammatory status are a relatively new prognostic factor that appear to be worth investigating in colorectal cancer patients [5,22].

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The acute phase reaction occures in response to damage to the body tissues due to inflammation, trauma, and malignant disease [47, 13, 5, 22, 35]. It is characterized by the alteration in production and secretion of more than 30 different plasma proteins19,29,38. These proteins are termed the acute phase proteins19,29,38. The functions of these different proteins are variable, such as modulation of the immune response and mediation of the inflammatory response [38,43,53]. C-reactive protein (CRP) is an acute phase protein and a sensitive marker of inflammation19,29,38,43,53. It is synthesized in the hepatocytes and up-regulated by cytokines such as interleukin-1, interleukin-6 and tumor necrosis factor-a (TNF-a) [38,6,15,5,19, 29]. Preoperative CRP levels have been found to be prognostic test for various cancer [5,12,13,22, 29]. In this study we want to assess the value of CRP level in colorectal cancer patients in comparison to healthy persons, and the value of increased CRP level in prognosis of colorectal cancer patients due to clinicopathological finding, were assessed.

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 centers) from January 1998 to January 2001 were selected and compared with forty volunteer healthy person (20 men, 20 women; age range 20-80 years). Patients with inflammatory disease, including infections and collagen diseases, as well as primary cancers in other organs were excluded from the study.

All the patients were followed up until 5 years or death.The study was performed through an analytical method. The serum CRP value was measured by latex agglutination test. Five milliliters of blood samples were withdrawn from all the patients preoperatively and also from the control group by peripheral venupuncture and after centrifuging blood samples, the serums were mixed with a drop of latex agglutination test. After completion of the test, presence or absence of percipitation, grossly and microscopically. The chi-squared test, Fisher's exact test, and t-student test were used to compare the clinicopathological data of the patients and control group, with or without elevation of serum CRP levels. A 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 to control group (55% versus 2.5%). In colorectal cancer patients, the primary lesions were located in the cecum and ascending colon 6(15%), the transverse colon 1(2.5%), the descending colon 4(10%), the sigmoid colon 5(12.5%), and the rectum 25(60%). In 5(12.5%) patients, liver metastases were detected preoperatively by both abdominal computed tomography and ultrasonography. The preoperative elevation of the serum CRP value in colorectal cancer group was recognized in 22(55%) patients (group A), whereas this elevation was recognized in 18(45%) patients (group B). The clinicopathological factors are shown in the Table 1. No significant differences was observed regarding age or gender between groups A and B. The maximal size of the tumor in group A (5.8±2.1 cm) was significantly larger than those 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 those 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 the proportion of histopathologically detected lymph node metastases in group A and B (54.5%; 12 of 22, versus 16.7%; 3 of 18; $P<0.05$).

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

Table 1. The clinicopathological factors and elevated serum CRP level.

The ratio of stage D cases by Dukes' classification, for which the surgical treatment was an absolute noncurative resection for either liver metastase or peritoneal dissemination, was significantly higher in group A than in group B (31.8% versus 11.1%).

The 5 year survival rate in group A were 59.1%; and significantly more unfavorable than those in group B which were 94.4% (P<0.01). Also poorly differentiated tumors were higher in group A than in group B (31.8% versus 22.2%).

Discussion

In patients with chronic malignant disease, changes in protein metabolism will result in muscle wasting, oedema, cachexia, or the production of acute-phase proteins, such as CRP [19,44,51]. The acute phase synthesis of CRP is upregulated by such proinflammatory cytokines as interleukin-1, interleukin-6, and tumor necrosis factor [29,46], which act as autocrine growth factors for neoplasms [29,45, 47]. It has also been reported that following tumor recurrence and progression, a proportion of patients will develop an acute-phase protein response [29,54]. 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 is proved to be valid.

In 3 case-control studies reported that serum

CRP level in patients with colorectal cancer was higher than those in controls [11,17,25,34].

Shumin [11] reported that there were no significant positive associations between CRP levels and stage of colorectal cancer. Some previous studies have noted independently the apparent association between CRP and poor prognosis [29,19,39,44]. Our results indicate that increased CRP in cancer patients is significantly higher than the control groups, and generally associated with the larger tumor size, lymph node or liver metastases, peritoneal carcinomatosis, and advanced Dukes' stage. Also the CRP expression correlated inversely 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 that of patients with such an elevation. These results indicated that the serum CRP level may be used as a prognostic factor in colorectal cancer, and therefore can also provide valuable information when determining the treatment strategies for such patients.

In order to elucidate relationship between the serum CRP and alterations in the oncogens concerned with 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 the malignant potential in the tumor as well as an appropriate prognostic factor for patients with colorectal cancer.

References

1. Crozier JE, et al. Preoperative but not postoperative systemic inflammatory response correlates with survival in colorectal cancer. Br J Surg. 2007 Apr 16; [Epub ahead of print].

2. Wong VK, et al. C-reactive protein as a predictor of prognosis following curative resection for colorectal liver metastases. Br J Cancer. 2007 Jun 29; 96(2): 222-5. Epub 2007 Jun 9.

3. Dymicka-Piekarska V, et al. Relationship between soluble P-selectin and inflammatory factors (interleukin-6 and C-reactive protein) in colorectal cancer. Thromb Res. 2006 Dec 11.

4. Gunter MJ, et al. A prospective study of serum C-reactive protein and colorectal cancer risk in men. Cancer Res. 2006 Feb 15; 66(4): 2483-7.

5. Read JA, et al. Evaluation of nutritional and inflammatory status of advanced colorectal cancer patients and its correlation with survival. Nutr Cancer. 2006; 55(1): 78-85.

6. Helzlsouer KJ, et al. C-reactive protein levels and subsequent cancer outcomes: results from a prospective cohort study. Eur J Cancer. 2006 Apr; 42(6): 704-7. Epub 2006 Mar 2.

7. Ilyasova D, et al. Circulating levels of inflammatory markers and cancer risk in the health aging and body composition cohort. Cancer Epidemiol Biomarkers Prev. 2005 Oct; 14(10): 2413-8.

8. Nikiteas NI, et al. Serum IL-6, TNFalpha and CRP levels in Greek colorectal cancer patients: prognostic implications. World J Gastroenterol. 2005 Mar 21; 11(11): 1639-43.

9. Ito Y, et al. Colorectal cancer and serum C-reactive protein levels: a case-control study nested in the JACC Study. J Epidemiol. 2005 Jun; 15 Suppl 2: S185-9.

10. Vermeire S, et al. The role of C-reactive protein as an inflammatory marker in gastrointestinal diseases. Nat Clin Pract Gastroenterol Hepatol. 2005 Dec; 2(12): 580-6.

11. Shumin M, et al. C-reactive protein levels are not associated with increased risk for colorectal cancer in women. Ann Intern Med. 2005 Mar 15; 142(6): 425-32.

12. Guillem P, et al. Elevated serum levels of C-reactive protein are indicative of a poor prognosis in patients with esophageal cancer. Dis Esophagus. 2005; 18: 146-150.

13. Hashimoto K, et al. The impact of preoperative serum C-reactive protein on the prognosis of patients with hepatocellular carcinoma. Cancer. 2005; 103: 1856-1864.

14. De Jong KP, et al. Portal and systemic serum growth factor and acute-phase response after laparotomy or partial hepatectomy in patients with colorectal liver metastases: a prognostic role for C-reactive protein and hepatocyte growth factor. Scand J Gastroenterol. 2004 Nov; 39(11): 1141-8.

15. Miki C, et al. C-reactive protein as a prognostic variable that reflects uncontrolled up-regulation of the IL-1, IL-6 network system in colorectal carcinoma. Dig

Dis Sci. 2004 Jun; 49(6): 970-6.

16. Erlinger TP, et al. C-reactive protein and the risk of incident colorectal cancer. JAMA. 2004 Feb 4; 291(5): 585-90.

17. Chung YC, et al. Serum interleukin-6 levels reflect the disease status of colorectal cancer. J Surg Oncol. 2003; 83: 222-6.

18. McMillan DC, et al. Systemic inflammatory response predicts survival following curative resection of colorectal cancer. Br J Surg. 2003 Feb. 90(2): 215-9.

19. Chung YC, et al. Serum c-reactive protein correlates with survival in colorectal cancer patients but is not an independent prognostic indicator. Eur J Gastroenterol Hepatol. 2003 Apr; 15(4): 369-73.

20. Eaden JA, et al. The risk of colorectal cancer in ulcerative colitis: a meta-analysis. Gut. 2001; 48: 526-35.

21. Parkin DM. Global cancer statistics in the year 2000. lancet Oncol. 2001; 2: 533-543.

22-Nozoe T, et al. Significance of preoperative elevation of serum C-reactive protein as an indicator of prognosis in esophageal carcinoma. Am J Surg. 2001; 182: 197-201

23. Nozoe T, et al. Preoperative elevation of serum C-reactive protein in related to impaired immunity in patients with colorectal cancer. Am J Clin Oncol. 2000 Jun; 23(3): 263-6.

24. Kaminska J, et al. CRP, TNF-alpha, IL-1, IL-6, IL-8 and IL-10 in blood serum of colorectal cancer patients. Pathol Oncol Res. 2000; 6(1): 38-41.

25. Kinoshita T, et al. Serum interleukin-6 level reflects the tumor proliferative activity in patients with colorectal carcinoma. Cancer. 1999; 85: 2526-31.

26. Higaki S, et al. Metaplastic polyp of the colon develops in response to inflammation. J Gastroenterol Hepatol. 1999; 14: 709-14.

27. Visser M, et al. Elevated C-reactive protein levels in overweight and obese adults. JAMA. 1999; 282: 2131-5.

28. Ridker PM, et al. Long-term effects of pravasatatin on plasma concentration of C-reactive protein. The Cholesterol and Recurrent Events (CARE) Investigators. Circulation. 1999; 100: 230-5.

29. Nozoe T, et al. Significance of preoperative elevation of serum C-reactive protein as an indicator for prognosis in colorectal cancer. Am J Surg. 1998 Oct; 176(4): 335-8.

30. IARC working group. IARC hand book of cancer prevention, volume 1: non-steroidal anti-inflammatory drugs. Lyon (france): IARC-WHO; 1997.

31-Jackson JR, et al. The codependence of angiogenesis and chronic inflammation. FASEB J. 1997; 11: 457-65.

32. Tracy RP, t al. Life time smoking exposure effects the association of c-reactive protein witch cardiovascular disease risk factors and subclinical disease in healthy elderly subjects. Arterioscler Thromb Vasc Biol. 1997; 17: 2167-76.

33. Witting BM, et al. Elevated serum E-selectin in patients with liver metastases of colorectal cancer. Eur J Cancer. 1996; 32A: 1215-1218.

34. Yuceyar S, et al. The role of acute-phase reactant proteins, carcinoembryonic antigen and CA 19-9 as a marker in the preoperative staging of colorectal cancer: a prospective clinical study. Int Surg. 1996 Apr-Jun; 81(2): 136-9.

35. Riche E, et al. Levels of portal and systemic blood cytokines after colectomy in patients with carcinoma or Crohn's disease. J Am Coll Surg. 1995 Jun: 180(6): 718-24.

36. Gurleyik E, et al. Accuracy of serum C-reactive protein measurments in diagnosis of acute appendicitis compared with surgeons clinical impression. Dis Colon Rectum. 1995; 38: 1270-1274.

37. McMillan DC, et al. A prospective study of tumor recurrence and actue phase response after apparently curative colorectal cancer surgery. Am J Surg. 1995; 170: 319-322.

38. Simpson WG, et al. Acute phase proteins and recombinant Il-2 therapy: prediction of response and survival in patients with colorectal cancer. Clin Exp Immunol. 1995 Feb; 99(2): 143-7.

39. Falconer JS, et al. Acute phase protein response and survival in pancreatic cancer. Cancer 1995; 75: 2077-2082.

40. McMillan DC, et al. Interleukin-6, neutrophilia and the acute phase protein response in colorectal cancer patients. Eur J Surg Oncol. 1994; 20: 151-154.

41. Shimono R,et al. Immunohistochemical expression of carbohydrate antigen 19-9 in colorectal carcinoma. Am J Gastroenterol. 1994; 89: 101-105.

42. Fillela X, et al. Prognostic value of CA19-9 levels in colorectal cancer. Ann Surg. 1992; 216: 55-59.

43. Ballou SP, et al. C-reactive protein and the acute phase response. Adv Intern Med. 1992; 37: 313-36.

44. Stamatiadis AP, et al. Combination of serum carcinoembryonic antigen and C-reactive protein a useful test in preoperative staging of colorectal cancer. Eur J Surg Oncol. 1992; 18: 41-43.

45. Gelin J, et al. Role of endogenous tumor necrosis factor alpha and interleukin-1 for exprimental tumor growth and the development of cancer cachexia. Cancer Res, 1991; 51: 415-421.

46. Castell JV, et al. Acute phase response of human hepatocytes: regulation of acute phase protein synthesis by interleukin-6. Hepatology. 1990; 12: 1179-1186.

47. Miki S,et al.Interleukin-6 functions as an autocrine growth factor in renal cell carcinoma. FEBS Lett. 1989; 250: 607-610.

48. Chang AE,et al.Determinants of survival in patients with unresectable colorectal liver metastases. J Surg Oncol. 1989; 40: 245-251.

49. Allen-Mersh TG,et al.Significance of a fall in serum CEA concentration in patients treated with cytotoxic chemotherapy for disseminated colorectal cancer. Gut. 1987; 28: 1625-1629.

50. Wolmark N,et al.The prognostic significance of preoperative carcinoembryonic antigen levels in colorectal cancer. Ann Surg. 1984; 199: 375-381.

51. Weinstein PS, et al. Acute phase proteins or tumor markers: the role of SAA, SAP, CRP and CEA as indicators of metastasis in a broad spectrum of neoplastic disease. Scand J Immunol. 1984; 19: 193-198.

52. Kushner I. The phenomenon of the acute phase response. Ann NY Acad Sci. 1982; 389: 39-48.

53. Gewarz HC, et al. C-reactive protein and the acute phase response. Adv Intern Med. 1982; 27: 345-72.

54. Cooper EH, et al. Acute phase reactant proteins in cancer. In: klein G, Weinhouse S, eds. Advances in Cancer Research. 30th ed. New York: Academic Press; 1979: 1-44.