Original Article

The role of serum IL-6 in colorectal cancer patients and it's relationship with serum CEA level

Batool H. Al-Ghurabi* **BSc, PhD**
Luma G. Al-Saady** **BSc, MSc**
Ahmed A. Al-Hassan*** **VM, PhD**

J Fac Med Baghdad
Vol. 51, No.4, 2009
Received: Feb., 2009
Accepted: May, 2009

Summary :

Background: The role of cytokines in cancer immunity and carcinogenesis in general has been well established, which play an important role in pathogenesis of many solid cancer. This study aimed to shed light on the possible role of IL-6 in pathogenesis of CRC and its relationship with serum CEA level.

Patients and methods*:* This study covered 50subjects. It comprised of 30 patients with CRC, compared with 20 healthy normal controls. Serum IL-6 and CEA analysis were performed by ELISA.

Results: This study revealed a significant elevation in serum IL-6 level among CRC patients (16.2 pg/ml) in comparison to that of healthy control (4.8 pg/ml) ($p<0.001$). As well as an interesting significant increase of mean serum CEA level in CRC patients (7.5± 6.62 ng/ml) as compared to healthy control (2.4±0.90 ng/ml). On the other hand there was strong linear correlation between serum CEA level and serum IL-6 level $p<0.001$.

Conclusion: There are a significant correlation between the elevation of the serum IL-6 and CEA levels and the progression of this cancer. Moreover, positive association was found between IL-6 and CEA and this may help us to understanding the pathogenesis of this disease and ultimately may be use in the development of a new therapeutic technique.

Key words*:* Colorectal Cancer, Interleukin -6, Carcinoembryonic antigen

Introduction:

Cytokines are potential new serum markers, especially desirable for malignancies with poor prognosis.Secretion of IL-6 has been reported from a variety of carcinomas (1) many studies observed that the effect of IL-6 on the growth of carcinoma cells is stimulatory one (2).In colorectal cancer (CRC) the biological effects of IL-6 remain ill- defined. It has been reported that specific binding of IL-6 to two CRC cell lines which resulted in the enhanced expression of several acute phase proteins (3). On the other hand, other reports have indicated a stimulatory effect of IL-6 on the expression of surface antigens such as CEA and HLA class I molecules (4). IL-6 proved to be a potent stimulator of growth of primary and metastatic CRC cells in vivo under certain conditions, and this stimulation appears to be occur through a paracrine mechanisms (5). Although CEA was first identified in colon cancer it also present in a variety of bengin and non neoplastic disease like UC, FAP, liver cirrhosis and other cancer like cancer of lung, ovary, pancreas, prostate and hepatoma (6). It was found that CEA is not a screening test for CRC; recently the CEA has a routine clinical application in the prognosis and follow-up of patients during postoperative period (7). Ishizuka et al., (8) have evaluated the clinical significant of preoperative CEA and carbohydrate antigen 19-9 (CA19-9) in patients with CRC, and they found that the CEA level is closely associated with the extent of liver metastasis, while the CA19-9 level may reflect multiplicity of hepatic deposits. So they suggested that measurement of both markers appears to be having some prognostic value. Moreover, Allende and colleagues similarly noted that preoperative serum level of CEA may be useful to predict tumoral extension, and also for the prognosis regarding stage C CRC patients (9). Recently it has been proposed that CEA may function as a metastatic potentiator by several different pathways, e.g., modulation of immune responses, facilition of intercellular adhesion and cellular migration. Thus, CEA is a molecular reactant that confronts neighboring barriers to effect invasiveness of CRC (10). This study was established to shed light on the possible role of IL-6 in pathogenesis of CRC and its relationship with serum CEA level.

Patients and methods:

Patients

The present study included 30 Iraqi CRC patients (12females and 18 males; mean age of 51.4± 17.1 years, ranged between 21-81 years). Duke's classification and degree of differentiation are

**Dept. Basic science, College of dentistry/ University of Baghdad.*
*** Dept. of biology, College of Science/ Al-Mustansyria University.*
**** Dept. Of microbiology, Medical College/ Al-Nahrain University*

presented in Table-1, compared with 20 apearantely healthy individuals considered as a controls.

Mtehods

Estimation of IL-6 and CEA

IL-6 and CEA were determined in serum using commercially available ELISA and performed as recommended in leaflet with kit.

Statistical analysis

It was assessed using P(Kruskull-Wallis-test) and P(Mann-Whitney-test), as well as P(ANOVA-test) and P(Bonferroni-test).

Table 1: Degree of differentiation and stage classification (Duke's A-D) of the tumor.

	Well Differe N=5	*Moderately Differe N=17*	*Poorly Differe N=8*
Duke's A	1	5	0
Duke's B	1	9	4
Duke's C	1	2	1
Duke's D	2	1	3

Results:

Serum IL-6 and CEA were estimated in 30 patients with primary untreated CRC, compared 20 healthy controls.Table (2) revealed a significant elevation in serum IL-6 level among CRC patients (16.2 pg/ml) in comparison to that of healthy control (4.8 pg/ml) ($p<0.001$).An anticipated, the current study revealed positive linear correlation between serum IL-6 level and the progression of the disease $P<0.001$. Since table (3) showed that the median serum level of this cytokine in CRC patients increased with stage A, B, C, and D (5.; 10.2; 40.7 and 102 pg/ml).

Table 2: The difference in median levels of baseline IL-6 (pg/ml) between the two studied groups.

	Colorectal cancer cases	Healthy control	P(Mann-Whitney)
Baseline serum IL6			
Minimum	2.9	1.9	
Maximum	150	8.2	
Median	16.2	4.8	<0.001
NO.	30	20	

Table 3: The difference in median serum IL-6 (pg/ml) level by stage of CRC.

Duke's classification system					
Values	*A*	*B*	*C*	*D*	*P(Kurskull-wallis)*
Minimum	2.9	5.7	11.1	15.4	
Maximum	11.4	57.3	90.3	150	
Median	5.8	10.2	40.7	102	<0.001
NO.	3	8	10	9	

The results of the mean serum level of CEA are clearly shown in table (4). An interesting significant increase of mean serum CEA level in CRC patients (7.5± 6.62 ng/ml) as compared to healthy control (2.4±0.90 ng/ml). Concerning the correlation of serum CEA level with Duke's classification of tumor, table (5) revealed that higher concentration of this antigen was observed in patients with stages C and D (9.6 ± 13.32 and 16.1 ± 6.47 ng/ml respectively), $p<0.001$ when compared to stages A and B (3.0 ± 1.84 and 5.4 ± 3.42 ng/ml respectively). On the other hand Fig (1) shows graphically that there was strong linear correlation between serum CEA level and serum IL-6 level $p<0.001$.

Table 4: The difference in mean baseline serum CEA (ng/ml) levels among the two studied groups.

	Colorectal cancer case	Healthy control	P (Bonferroni t-test)
Serum CEA			
Minimum	1.5	1	
Maximum	25	4	
Mean	7.5	2.4	<0.001
Median	5	2.5	
SD*	6.62	0.9	
SE**	1.05	0.28	
No.	30	20	

SD*: Standard deviation

SE**: Standard error

Table 5: The difference in mean serum CEA (ng/ml) level by stage of CRC.

Duke's classification system					
Values	*A*	*B*	*C*	*D*	*P (ANOVA)*
Minimum	1.5	1.6	6.0	7	
Maximum	4.0	18	15	25	
Mean	3.0	5.4	9.6	16.0	<0.001
Median	3.5	3.3	8.3	16.5	
SD	1.84	3.42	3.20	6.47	
SE	0.39	0.70	1.31	2.29	
NO.	1	18	6	5	

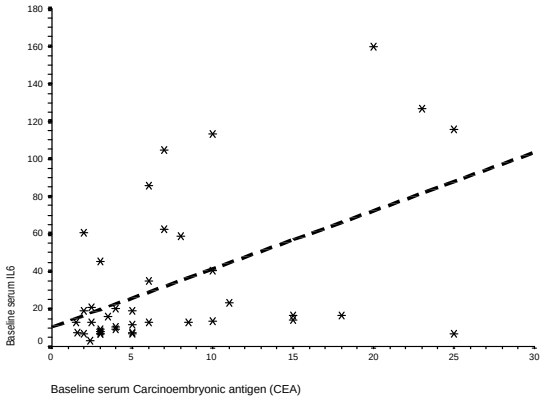

Fig. 1Linear correlation between serum levels of CEA and IL-6.

Discussion:

Colorectal carcinoma is regarded as one of the common malignant tumors of GIT that occurs frequently among relatively old individuals and it's incidence increased in frequency in the last few

years (11). The results obtained from the present study were similar to that reported by Rohini and associates, who found that a high levels of IL-6 were frequently observed in more advanced stages of CRC (12). Similarly Kaminska et al., (13), also reported a significant elevation in serum IL-6 levels in advanced tumor stage prior to surgery in comparison to healthy controls, and on the 10^{th} day following surgery, the levels were significantly reduced. Moreover, Bataille et al., (14) and Tsukamoto et al., (15) interestingly pointed out that concentrations of IL-6 in the tumor tissue were significantly higher than that in normal mucosa and were strongly correlated with serum IL-6 concentrations. Thus the authors concluded that serum concentrations of IL-6 reflect the tumor tissue concentration of IL-6 and indicate the proliferation activity of tumor. The elevation of IL-6 levels in sera of patients with CRC could be attributed to the following possibilities: It has been shown that CEA can trigger the release of several cytokines by Kupffer cells in the liver, including IL-6, which in turn may stimulate tumor cell growth at metastatic sites (16) and another source for IL-6 might be the infiltrating immune cells. The presence of IL-6 transcripts in colorectal tumor tissue has been reported, using RT-PCR analysis. However; this cytokin might be the product of macrophages, in agreement with previous results which also reinforce the monocytic origin of inflammatory cytokines in colorectal tumors (17).

It seems that cytokines secreted by tumor cells works as autocrine or paracrine growth factor to provide a better environment for cancer growth (2).

Serum CEA level is the most widely used marker for both prognostic and post treatment monitory of patients with CRC (18). The results obtained from the present study were similar to that reported by many workers (8 and 19) who showed that CEA levels correlate positively with extent of CRC and Duke's staging. Similarly Chapman and colleagues mentioned that a raised preoperative serum CEA is likely to be associated with advanced tumor stage and poor-term survival, compared with patients with normal value (20). Furthermore, Groblewsk and associates observed that serum IL-6 and CEA were significantly higher in cancer patients when compared to adenoma patients and healthy subjects (21).

The possible explanation for the higher levels of serum CEA may be due to released IL-6 by liver cells which might increase CEA expression on the surface of colorectal cells (22). On the other hand up regulation of CEA could in turn cause further increase the IL-6 release by Kupffer cells creating a situation in which metastatic neoplastic cells use bystander cells to gain growth advantage (23). Interestingly, this supports the result of the present study in Fig. (1) regarding the presence of positive linear correlation between serum CEA and serum IL-6 levels. In conclusion there are a significant correlation between the elevation of the serum IL-6 and CEA levels and the progression of this cancer. Moreover, positive association was found between IL-6 and CEA and this may help us to understanding the pathogenesis of this disease and ultimately may be use in the development of a new therapeutic technique.

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