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Alterations of Humoral Immunity in Patients with Gastric Cancer

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SUMMARY **For better understanding of the alterations of humoral immunity in gastric cancer patients, IgG, IgA, IgM, complement C_3, C_4, CH_{50}, natural antibody (isohemagglutinin-IgM class), ESR, CRP, albumin and globulin were quantitated in sera taken preoperatively from 81 patients with gastric cancer and from 29 control patients with hernia. The results from patients with gastric cancer were grouped according to pTNM staging (including stage I + II, III, and IV). Serum globulin and IgG levels in all stages of cancer patients were significantly lower than that of the controls ($p < 0.05$). The CRP and ESR levels in stage III and IV cancer patients were significantly higher ($p < 0.05$). There was no difference between cancer and hernia patient groups in IgA, IgM, isohemagglutinin-IgM class, C_3, C_4, CH_{50}, albumin, WBC and total lymphocyte counts. In conclusion, the significant changes in humoral immunity in patients with gastric cancer include: (1) decrease in serum IgG and globulin levels, and (2) increased levels of acute phase reactants (ESR, CRP). These results imply that patients with gastric cancer have lower acquired humoral immunity and have acute phase reactions.**

Serum concentrations of immunoglobulins (IgS) in various cancer patients showed conflicting results in previous reports. It was described to be increased,[1,2] normal,[3] or decreased.[4] The discrepancy may be due to differences in patients selected, disease staging and sera collected. But fluctuations in patients' serum Ig levels can be due to infections or malnutrition which predispose them to advanced diseases. A decreased antibody response may be related to these underlying complications rather than to the cancer itself. Therefore, in this study, the underlying complications were taken into consideration.

Besides the serum complement (C) components, complement activity CH_{50}, is often used for the measurement of host responses to tumor.[5,6] The erythrocyte sedimentation rate (ESR) and C-reactive proteins (CRP) are acute phase reactants in inflammation. Their roles in malignant diseases are frequently discussed.[7-10]

The purpose of this study is to determine the level of IgG, IgA, IgM, C_3, C_4, CH_{50}, ESR, CRP, isohemagglutinin-IgM class in patients with gastric cancer, by which, the humoral immunity status of gastric cancer patients can be evaluated.

MATERIALS AND METHODS

Patients

Patients with newly detected gastric cancer were selected for this study. They were admitted to the Department of Surgery in Veterans General Hospital, Taipei, Taiwan, in the period between Aug 1985 - Feb 1986. Patients excluded from this study included those with additional tumors, or other diseases (diabetis mellitus, tuberculosis, chronic renal failure), or any obvious infection (fever, leukocytosis) at the time of diagnosis. They were divided into stages I-IV according to the TNM post-surgical histopathological classification.[11] Because of the limited cases of stage I cancer patients ($n = 2$), both stages I & II were grouped together. There were 17

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male and 5 female patients with a mean age of 62 years in this group. In the stage III group, there were 35 male and 3 female patients with a mean age of 62 years, while the stage IV group had 19 male and 2 female patients with a mean age of 64 years. There was no significant disparity in age or sex between the groups of various disease extents (Table 1).

Controls

Twenty-nine patients admitted in the same period for inguinal hernia, were served as controls. Their ages were between 24 and 82 years old with a mean of 61 years. Ten percent of the patients were women. Those with additional diseases were excluded from this study.

Laboratory examinations

After clinical assessment, serum samples of the patients were examined for electrolytes, albumin, globulin, alkaline phosphatase, SGOT, SGPT, and bilirubin. Besides these, blood urea determination and complete blood count were also performed.

Those serum parameters including IgG, IgA, IgM, C_3, C_4 and CRP, were measured by light intensity rate nephelometry [12] (Immunochemistry Analyzer II, Beckman, Fullerton, CA, USA). Serum hemolytic complement (CH_{50}) was estimated by the method described by Mayer [13] and ESR was estimated by the Wintrobe method. [14]

Natural antibody

Isohemagglutinin-IgM class antibody titre was estimated according to the method commonly used in hematology laboratories. [15]

Statistics

The mean values of each parameter obtained from the cancer and control groups were compared by a Student-Newman-Keuls multiple range test, preceded by ANOVA. If the variance was not equal (for CRP value), multiple comparisons were carried out,preceded by Kruskal-Wallis test.

RESULTS

Serum protein

The mean serum globulin level in each group of the gastric cancer patients was significantly decreased as compared to the controls ($p < 0.05$). No difference in serum albumin level was observed between gastric cancer patients and the controls (Table 1).

Serum immunoglobulin, complement component and activity

The serum concentrations of immunoglobulins, complement components, and the activties of complement are presented in Table 2.

In the entire series the concentration of IgG in gastric cancer patients was significantly lower than in the controls ($p < 0.05$) for every stage of the disease. The concentrations of IgA and IgM were not different from those of the controls, and the same was true for the concentration of C_3, C_4 and complement activities (CH_{50}).

There was no significant correlation between immunoglobulins and complement components ($p > 0.05$). However C_3 was significantly correlated with C_4 in stage I + II and stage III, but not in

Table 1. Patient profile (Aug 1985 – Feb 1986, VGH, Taipei)

Stage	n	M/F	Age (yrs)	Albumin (mg/ml)	Globulin (mg/ml)
Gastric cancer					
I+II	22	17/5	62±7	3.93±0.48	2.59±0.34*
III	38	35/3	62±10	3.71±0.61	2.63±0.54*
IV	21	19/2	64±6	3.88±1.12	2.68±0.40*
Total	81	71/10	63±9 (23–83)		
Controls (Hernia)					
	29	26/3	61±12 (24–82)	3.65±0.81	3.40±0.66

* $p < 0.05$ comparing to the controls.
Mean values±SEM expressed.

Table 2. Serum immunoglobulin, complement component & activity

Stage	IgG (mg/ml)	IgA (mg/ml)	IgM (mg/ml)	C_3 (mg/ml)	C_4 (mg/ml)	CH_{50} (units/ml)
I+II	1051.82* ±225.92	249.78 ±103.53	102.46 ±53.98	98.58 ±23.16	27.71 ±10.29	24.50 ±10.17
III	1163.03* ±322.98	241.26 ±98.66	103.22 ±39.70	107.19 ±23.72	26.86 ±8.52	26.39 ±10.82
IV	1149.45* ±316.02	212.97 ±76.91	97.26 ±55.07	98.05 ±30.89	29.17 ±10.11	24.14 ±10.62
Controls	1417.59 ±315.87	237.24 ±75.42	120.68 ±53.09	105.80 ±28.75	30.08 ±9.39	20.00 ±10.62

* $p < 0.05$ comparing to the controls.
Mean values±SEM were expressed.

Table 3. Correlation coefficients between immunoglobulins and complement components in gastric cancer patients

	IgG	IgA	IgM	C_3	C_4
Stage I+II (n=22)					
IgA	0.311				
IgM	0.049	0.285			
C3	0.376	0.118	−0.044		
C4	0.054	−0.105	−0.010	0.504*	
CH50	−0.152	0.026	−0.143	−0.186	0.377
Stage III (n=38)					
IgA	0.409				
IgM	0.152	−0.053			
C3	0.257	0.307	−0.108		
C4	0.152	0.086	−0.153	0.494*	
CH50	0.074	0.302	−0.127	0.619*	0.380*
Stage IV (n=21)					
IgA	0.471*				
IgM	0.188	−0.085			
C3	0.069	0.251	−0.126		
C4	−0.032	−0.018	0.002	0.407	
CH50	−0.127	0.260	0.113	0.279	0.095

* $p < 0.05$

Table 4. Isohemagglutinin–IgM, ESR, CRP, WBC and Lymphocyte values

Stage	Isohemagglutinin–IgM (titre)	ESR (mm/hr)	CRP (mg/dl)	WBC/μl	Lymphocyte/μl
I+II	229.27 ±315.08	13.06 ± 7.86	1.21 ±1.49	7580.00 ±2227.96	2203.35 ±863.85
III	229.84 ±382.05	18.00* ±10.93	3.26* ±4.93	7562.86 ±2795.59	2291.15 ±1191.57
IV	137.90 ±225.17	17.82* ±8.01	4.22* ±5.29	7838.89 ±2901.35	1956.39 ±1221.44
Controls	421.93 ±654.74	11.17 ±10.45	1.16 ±2.41	7150.00 ±2500.61	2228.56 ±807.06

ESR : Only data of male patients are presented.
* : $p < 0.05$ compared to controls.
Mean values ± SEM expressed.

stage IV. C_3 was also correlated with CH_{50} only in stage III (Table 3).

Natural antibody (isohemagglutinin IgM class)

There was no significant difference either between groups of gastric cancer patients or between the cancer patients and the controls (Table 4).

Acute phase reactants

Because of limited female cases, only the ESR value of male patients were compared. In patients with advanced gastric cancer (stage III and IV), the ESR and CRP levels were significantly higher than those of the controls ($p < 0.05$).

DISCUSSION

The purpose of the present study was to evaluate the humoral immunity status of gastric cancer patients. All patients included in this study were carefully evaluated for signs of concurrent infection, or any additional tumors at the time of presentation. As can be seen in Table 4, there was no difference in leukocyte counts between gastric cancer patients and the controls.

All gastric cancer patients in this study showed a decrease in serum IgG level, with normal IgA and IgM levels (Table 2). Most tumor tissues have been reported to contain high levels of IgG.[16,17] Therefore, the low level of serum IgG found in the present study could be partly the consequence of preferential binding of IgG to gastric tumor tissues.[18] There was no consistent correlation between complement components and no relationship between the various immunoglobulin classes and complement components. The humoral immunodeficiency in gastric cancer patients may imply that these patients have a lower acquired immunity, because natural immunity as assessed by the level of isohemagglutinin-IgM class (natural antibody) appears to be normal (Table 4).

In comparison to the controls, all patients with gastric cancer, regardless of stages, had a normal serum albumin level, but a lower serum globulin level ($p < 0.05$) (Table 1). This suggests that the humoral immunodeficiency in patients with gastric cancer may not be secondary to malnutrition.

The ESR level is elevated in patients with acute illness, as well as in some patients with cancer.[19] Peyman in 1962 reported a high frequency of elevated ESR in cancer patients with skeletal, pulmonary and hepatic metastases.[7] Janssen *et al* had shown that in patients with gastric cancer the ESR levels increased with advancing extent of disease.[20] This was supported by our data that gastric cancer patients in advanced stages (stages III & IV) has significantly higher ESR than that of controls ($p < 0.05$).

Traditionally, CRP has been regarded as an acute-phase reactant. Its serum concentration rises dra-

matically in response to most forms of tissue damage, infection, and inflammation. In malignant diseases, CRP has been shown to be able to inhibit cancer cell growth and distant metastasis in tissue culture and animal studies.[21-23] Clinically, in those cancer patients with metastases, there is a high incidence of elevated CRP levels. In a study of 501 patients with carcinoma of the breast, ovary, uterus, or colon, the CRP level closely reflected tumor mass[24]. Rashid *et al* disclosed that in gastric cancer patients, a high CRP level carries a high probability of poor prognosis.[9] Our data revealed an elevated CRP level in advanced gastric cancer patients ($p < 0.05$).

In this report, gastric cancer patients had decreased IgG and globulin, and had unchanged natural antibody and serum complement. The acute phase reactions (increased ESR and CRP levels) were observed in these patients. The result imply that patients with gastric cancer have lower acquired immunity and have an acute phase reaction.

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