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Research Article

Qi and Blood Deficiency Contributes to Peripheral T-Cell Dysfunction and Reduced Natural Killer Cell Activity in Gastric Cancer

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ABSTRACT

Gastric Cancer (GC), a major cause of cancer-related mortality, is susceptible to invasion and metastasis, which triggers dismal prognosis. Traditional Chinese medicine (TCM) exerts a pivotal role in various cancers, including GC. Correct syndrome differentiation is the most important principle guiding the treatment strategy. Here in, the present study aims to explore the relationship of different TCM syndrome types of GC patients and the cellular immune function, which was evaluated by observing peripheral T-cell subsets and activity of Natural Killer (NK) cells. GC patients and healthy controls were enrolled in this study, with venous blood during fasting collected. Patients with deficiency syndromes exhibited decreased number of CD4+ T-cells, ratio of CD4+/CD8+ T-cells and the activity of NK cells as compared with those with sufficiency syndromes. Then, the relationship between TCM syndrome types and TNM classification was analyzed, which revealed that TCM syndrome types were associated with TNM classification. Finally, we evaluated the number of T-cell subsets and NK cell activity in peripheral blood by means of flow cytometry and Lactate Dehydrogenase (LDH) release assay. GC patients with qi and blood deficiency showed reduced CD4+ T-cells, CD4+/CD8+ T-cells and NK cell activity and increased CD8+ T-cells when compared with other syndrome types, which indicated significantly impaired cellular immune function. Taken together, we concluded that peripheral T-cell subsets and NK cell activity, representing the cellular immune function, were associated with different TCM syndrome types of GC. Notably, qi and blood deficiency led to the most severe cellular immune dysfunction of the GC patients.

Keywords: Traditional chinese medicine syndrome type; Gastric cancer; Peripheral blood; T-cell subsets; Natural killer cell activity; Flow cytometry

INTRODUCTION

Gastric cancer (GC) is a major cause of mortality in relation to cancer in the world due to its high occurrence and poor prognosis [1,2]. Despite the improved treatment strategies emerged in recent years, invasion and metastasis significantly impeded the treatment outcomes [3]. Recently, studies have suggested that Traditional Chinese Medicine (TCM) functions as potential treatment options for GC [4,5]. However, most of these studies focus on the effect of TCM on GC cell behaviors. Here in this study, TCM syndrome types of GC patients at different stages were analyzed. TCM syndrome differentiation, also known as syndrome differentiation or Zheng differentiation, is the basic and core content of TCM theory on diagnosis and treatment of human diseases [6]. Commonly, TCM syndrome is classified into sufficiency syndrome and deficiency syndrome [7]. TCM syndrome plays an important role in the guidance to TCM treatments for its identification of human body patterns and its function on reflection of the nature of the pathological changes at different stages [8].

Accumulating evidence suggests that interaction of multiple immune cell types, implicated in the immune response to GC, exerts a critical function on the disease progression [9]. The low immune function in GC patients results in the progression of tumor and prevents patients' recovery [10]. While T-cells, the main group of tumor infiltrating immune cells, play an important role in suppressing the growth and development of tumor [11]. Interestingly, TCM have been reported to exert function on various types of immune diseases by regulating T cells [12,13]. The determinants of T-cell subsets in GC are relevant to the assessment of the status of patients, among which CD4+ and CD8+ T-cells are treated as a significant determiner for what kind of treatment the patient needs to receive [14]. In addition, a previous study pointed out that Natural Killer (NK) cells, effector lymphocytes of the

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innate immune system, are capable of reacting to various types of tumors and microbial infections [15]. Decreased NK cell activity is found in GC patients, which could be an independent prognostic indicator for GC patients as well as NK cells, plays a potential role in the inhibition of GC progression [16]. Besides, another study reported that NK cells, accounting for 10% to 15% in total blood lymphoid cells, show a decreased level in the carcinoma tissues and peripheral blood, consequently leading to reduced NK cell function in the tissue and peripheral blood in patients with GC [17]. In this study, the number of T-cell subsets and NK cell activity in peripheral blood of patients with various TCM syndromes were detected by flow cytometry and Lactate Dehydrogenase (LDH) release assay. We aim to explore the association of the T-cell subsets and NK cell activity in the peripheral blood with different TCM syndrome types in GC in the hope of identifying new treatment methods for patients with GC.

MATERIALS AND METHODS

Ethics statement

The study was conducted with the approval of the Ethics Committee of Huzhou Central Hospital. All participating patients signed informed written consents prior to experiments.

Study subjects

A total of 103 patients who underwent surgical resection and were subsequently pathologically confirmed as GC in Huzhou Central Hospital from October 2014 to October 2016 were recruited, including 68 males and 35 females aged 31-74 years (mean age 53.66 ± 9.10 years). None of the patients had received any anticancer or immunotherapy before admission. Inclusion criteria were as follows: (i) patients were diagnosed as GC by gastroscopic and pathological examinations; (ii) patients could cooperate with examination without examination contraindication; (iii) patients signed informed consents. Exclusion criteria were as follows: (i) patients had active bleeding or took anticoagulant drugs during treatment; (ii) patients had perforation; (iii) patients would not cooperate with gastroscopic examination; (iv) patient with unclear pathological diagnosis; (v) patients could not receive surgical treatment due to severe underlying diseases. Thirty healthy volunteers (Huzhou Central Hospital) were set as the control group, consisting of 18 males and 12 females who aged 31-74 years.

Observation of TCM syndrome types and Tumor-Node-Metastasis (TNM) classification

The clinical indicators such as TCM syndrome type, general information, maximum tumor diameter, depth of infiltration, degree of differentiation, and distant metastasis of lymph nodes were determined. According to TCM syndrome types recorded in the "Guidelines for diagnosis and treatment of gastric cancer in traditional Chinese medicine (Draft)", GC was classified as liver qi invading the stomach type, qi stagnation and blood stasis type, phlegm-dampness accumulation type, yin deficiency due to stomach heat type, qi and blood deficiency type and deficiency-cold of the spleen and stomach type. The former 3 types were sufficiency syndrome types, and the latter 3 types belong to deficiency syndrome types. TNM classification was also defined as primary tumor classification, which was in line with the 7th Edition of the Union for International Cancer Control-American Joint Committee on Cancer (UICC-AJCC) TNM staging system 2010 for GC. Next, 5 mL of the morning fasting venous blood of patients of stage III and stage IV were obtained with aseptic technology, anticoagulated by Ethylene Diamine Tetra Acetic Acid (EDTA) and diluted at a ratio of 2:1 with Hanks solution for subsequent experiments.

Flow cytometry

Lymphocytes were isolated by lymphocyte separation medium, followed by centrifugation for 15 min at 1700 r/min. Then, lymphocytes were added with 5 μL of CD3-TC/CD4-PE/CD8-FITC labeled antibodies (Beckman Coulter, Fullerton, CA, USA). After incubation for 15 min at room temperature in the darkroom, red blood cells were lysed by CAL-LYSE solution lysate (Caltag Laboratories, Burlingame, CA, USA). The lymphocytes were washed after hemolysis. The CD3+T, CD4+T and CD8+T-cells were detected by a flow cytometer (Beckman Coulter, Fullerton, CA, USA) and the number of cells was counted.

LDH release

Lymphocyte were isolated by lymphocyte separation medium, followed by centrifugation for 15 min at 1700 r/min. NK cells collected from lymphocyte layer were then used as effector cells and washed two times with Hanks solution (1200 r/min × 5 min). Then the NK cells were washed by 0.5% bovine serum albumin for one time. GC BGC-823 cells were treated as target-cells. Effector cells and target-cells were made into cell suspension at a density of 2 × 106 cells/mL and 2 × 105 cells/mL and mixed in equal volumes, with cell number at a ratio of 10:1. Next, the effector cells and target-cells were incubated in a 5% CO_2 incubator at 37°C for 6 hr and centrifuged at 1500 r/min for 10 min, with the supernatant obtained. The absorbance value (A value) was measured by an automatic biochemical analyzer at a wavelength of 340 nm according to the instructions of the LDH reagent. Three replicated tubes were set in each sample, and the experiment was repeated 3 times. The activity of NK cells (%)=(A value of the experimental group-A value of the natural release of effector cells group)/(A value of the maximum release of target T-cells group-A value of the natural release of target-cells group) × 100%.

Statistical analysis

Statistical analyses were conducted by using SPSS 21.0 (IBM Corp. Armonk, NY, USA). Measurement data were expressed as mean ± standard deviation. Comparisons between two groups were conducted by t test while comparisons among multiple groups were conducted by one-way Analysis of Variance (ANOVA). All experiments were conducted three times independently. $p<0.05$ was considered significant.

RESULTS

General data of TCM syndrome types and TNM classification

There are 103 patients consisting of 68 males and 35 females aged 31-74 years. According to TNM classification of GC, there were 10 cases at stage I, 38 cases at stage II, 44 cases at stage III, and 11 cases at stage IV. According to TCM syndrome types of GC, there were 21 cases of liver qi invading the stomach type, 20 cases of qi stagnation and blood stasis type, 15 cases of Phlegm-dampness accumulation type, 7 cases of yin deficiency due to stomach heat type, 17 cases of qi and blood deficiency type, and 23 cases of deficiency-cold of the spleen and stomach type.

TCM syndrome types are correlated with TNM classification in GC

Next, the GC specimens were classified according to TNM classification (Table 1). At stage I, most of the patients were observed with liver qi invading the stomach type (4 cases, 40.00%), and yin deficiency due to stomach heat type accounted for the least (0 case, 0.00%). At stage II, most of the patients with liver qi invading the stomach type were observed (13 cases, 34.21%), and phlegm-dampness accumulation type accounted for the least (1 case, 2.63%). At stage III, most of the patients were observed with phlegm-dampness accumulation type (13 cases, 29.55%), and yin deficiency due to stomach heat type accounted for the least (2 cases, 4.55%). At stage IV, most of the patients with qi and blood deficiency type were observed (6 cases, 54.55%), and phlegm-dampness accumulation type accounted for the least (0 case, 0.00%).

Patients with deficiency syndromes exhibits higher T-cell dysfunction and decreased NK cell activity

Then the T-cell subsets and NK cell activity in peripheral blood of patients with sufficiency and deficiency syndrome were detected by flow cytometry and LDH release assay (Table 2). The total T-cells in the peripheral blood of deficiency syndrome patients were significantly different from those in the control group ($p<0.05$), while the total T-cells in the peripheral blood of the patients with sufficiency syndrome were basically normal. Compared with the control group, the number of CD8+ T-cells in the sufficiency syndrome group was significantly increased, the ratio of CD4+/CD8+ T-cells was significantly decreased ($p<0.05$), the number of CD3+ T-cells, the number of CD4+ T-cells and the NK cell activity had no significant difference (all $p>0.05$); the number of CD8+ T-cells in the peripheral blood of the deficiency syndrome group was significantly increased, and the number of CD3+ T-cells, the number of CD4+ T-cells, the ratio of CD4+/CD8+, and the activity of NK cells were significantly decreased (all $p<0.05$). Compared with the sufficiency syndrome group, the number of CD4+ T-cells, ratio of CD4+/CD8+ T-cells and NK cell activity in peripheral blood of the deficiency syndrome group were significantly decreased ($p<0.05$). These results indicated that patients with deficiency syndromes were observed with T-cell dysfunction and reduced NK cell activity.

Table 1: Relationship between TCM syndrome types of GC and TNM classification.

TCM syndrome type	TNM Classification			
	Stage I	Stage II	Stage III	Stage IV
Liver qi invading the stomach (n=21)	4(40.00%)	13(34.21%)	3 (6.82%)	1 (9.09%)
Qi stagnation and blood stasis (n=20)	1(10.00%)	6 (15.79%)	11(25.00%)	2(18.18%)
Phlegm-dampness accumulation (n=15)	1(10.00%)	1 (2.63%)	13(29.55%)	0 (0.00%)
Yin deficiency due to stomach heat (n=7)	0 (0.00%)	4 (10.53%)	2 (4.55%)	1 (9.09%)
Qi and blood deficiency (n=17)	1(10.00%)	2 (5.26%)	8 (18.18%)	6(54.55%)
Deficiency-cold in spleen and stomach (n=23)	3(30.00%)	12(31.58%)	7 (15.91%)	1 (9.09%)
Total (n=103)	10	38	44	11

Abbreviations: TCM:Traditional Chinese Medicine; TNM:Tumor Node Metastasis; GC:Gastric Cancer

Patients with deficiency syndromes exhibits higher T-cell dysfunction and decreased NK cell activity

Finally, the number of T-cell subsets and NK cell activity in peripheral blood of patients with various TCM syndromes were detected by flow cytometry and LDH release assay (Table 3). The total number of T-cells in peripheral blood had no significant difference in liver qi invading the stomach, qi stagnation and blood stasis, phlegm-dampness accumulation, deficiency-cold of the spleen and stomach, yin deficiency due to stomach heat, and qi and blood deficiency types (all $p>0.05$). The CD3+ T-cell number had no significant difference in the six types (liver qi invading the stomach type>qi stagnation and blood stasis type>Phlegm-dampness accumulation type>deficiency-cold of the spleen and stomach type>yin deficiency due to stomach heat type>qi and blood deficiency type). The number of CD4+ T-cells and NK cell activity was the lowest in qi and blood deficiency type, which showed a significant difference with liver qi invading the stomach type ($p<0.05$) and there was no statistical difference in the other groups (all $p>0.05$) (liver qi invading the stomach type>qi stagnation and blood stasis type>phlegm-dampness accumulation type>yin deficiency due to stomach heat type>deficiency-cold of the spleen and stomach type>qi and blood deficiency type). The number of CD8+ T-cells and NK cell activity was the highest in qi and blood deficiency type, which showed a significant difference with liver qi invading the stomach type ($p<0.05$) and there was no statistical difference in the other groups (all $p>0.05$) (liver qi invading the stomach type<qi stagnation and blood stasis type<phlegm-dampness accumulation type<yin deficiency due to stomach heat type<deficiency-cold of the spleen and stomach type<qi and blood deficiency type). The ratio of CD4+/CD8+ in qi and blood deficiency type was significantly lower than that of liver qi invading the stomach type and qi-stagnation and blood-stasis type (all $p<0.05$), and the ratio of CD4+/CD8+ in yin deficiency due to stomach heat type and deficiency-cold of the spleen and stomach type were significantly lower than that of liver qi invading the stomach type ($p<0.05$) (liver qi invading the stomach type>qi stagnation and blood stasis type>Phlegm-dampness accumulation type>yin deficiency due to stomach heat type>deficiency-cold of the spleen and stomach type>qi and blood deficiency type). From the above findings, we can conclude that T-cell dysfunction and

Table 2: The T-cell subsets and NK cell activity in peripheral blood of patients with sufficiency and deficiency syndrome.

Group	CD3+ (%)	CD4+ (%)	CD8+ (%)	CD4+/CD8+ (%)	NK (%)
Control group (n=30)	69.32 ± 7.50	45.24 ± 4.32	27.80 ± 4.20	1.66 ± 0.30	16.69 ± 2.30
Sufficiency syndrome group (n=56)	67.27 ± 7.15	42.82 ± 7.04	31.87 ± 4.24*	1.36 ± 0.24*	16.78 ± 2.75
Deficiency syndrome group (n=47)	64.40 ± 6.53*	38.53 ± 5.17*#	33.95 ± 4.99*	1.15 ± 0.19*#	13.28 ± 3.18*#

Note: * p<0.05 compared with the control group; #, p<0.05 compared with sufficiency syndrome group; NK:Natural Killer

Table 3: The relationship of T-cell subsets and NK cell activity in peripheral blood of patients with various TCM syndrome types.

Group	CD3+ (%)	CD4+ (%)	CD8+ (%)	CD4+/CD8+ (%)	NK (%)
Control group (n=30)	69.32 ± 7.50	45.24 ± 4.32	27.80 ± 4.20	1.66 ± 0.30	16.69 ± 2.30
Sufficiency syndrome group (n=56)	67.27 ± 7.15	42.82 ± 7.04	31.87 ± 4.24*	1.36 ± 0.24*	16.78 ± 2.75
Deficiency syndrome group (n=47)	64.40 ± 6.53*	38.53 ± 5.17*#	33.95 ± 4.99*	1.15 ± 0.19*#	13.28 ± 3.18*#
TCM syndrome type	CD3+ (%)	CD4+ (%)	CD8+ (%)	CD4+/CD8+ (%)	NK (%)
Liver qi invading the stomach (n=21)	67.56 ± 7.01	44.23 ± 7.01	30.18 ± 3.23	1.47 ± 0.19	17.30 ± 3.01
Qi stagnation and blood stasis (n=20)	67.39 ± 7.30	42.23 ± 7.26	32.58 ± 4.40	1.30 ± 0.21	16.85 ± 2.70
Phlegm-dampness accumulation (n=15)	66.70 ± 7.59	41.65 ± 6.93	33.30 ± 4.71	1.28 ± 0.29	15.96 ± 2.40
Yin deficiency due to stomach heat (n=7)	64.06 ± 5.64	39.09 ± 2.81	33.34 ± 4.74	1.20 ± 0.20*	15.68 ± 2.31
Qi and blood deficiency (n=17)	63.49 ± 7.40	37.75 ± 6.82*	34.79 ± 4.98*	1.10 ± 0.18*#	10.37 ± 2.01*
Deficiency-cold in spleen and stomach (n=23)	65.17 ± 6.28	38.93 ± 4.38	33.51 ± 5.20	1.18 ± 0.18*	14.70 ± 2.50

Note: *, p<0.05 compared with liver qi invading the stomach type; #, p<0.05 compared with qi stagnation and blood stasis type; NK: Natural Killer; TCM: Traditional Chinese Medicine

reduced NK cell activity were associated with the lowest in qi and blood deficiency type and highest in liver qi invading the stomach type.

DISCUSSION

The recurrence and metastasis of GC are a critical cause of mortality, and TCM is a good option for the prevention and treatment, as well as improving the quality of life [18]. Notably, TCM has been pointed out to exert anticancer activities in multiple human cancers including GC, but the mechanisms of action of TCM have not been clearly defined [19]. The distribution of TCM syndrome types of GC is associated with the pathological types [20]. Therefore, this present study observed the association of TCM syndrome types with TNM classification of GC patients, and identified the underlying mechanism involved with cellular immune function.

Initially, the statistical analysis indicated that TCM syndrome types were correlated with TNM classification in GC. At stage I and stage II, most of the patients were observed with liver qi invading the stomach type and liver qi invading the stomach type. At stage III and stage IV, most of the patients were observed with phlegm-dampness accumulation type and qi and blood deficiency type. It has been reported that the correlation between different clinical TNM staging in lung cancer patients and TCM syndrome types showed statistical significance; specifically, at stage III and stage IV, the most common syndrome type is qi and blood deficiency type [21]. The TCM syndromes have statistical relationships with histopathological types in primary bronchogenic carcinoma [22].

Then the T-cell subsets and NK cell activity in peripheral blood of patients with sufficiency and deficiency syndrome were detected by flow cytometry and LDH release assay. We observed that patients with deficiency syndromes exhibits higher T-cell dysfunction and decreased NK cell activity. For the patients with sufficiency syndromes, the T-cell subsets and NK cell activity were basically normal. Concordant with the present study, T-regulatory lymphocytes, the subset of CD4+T-cells, play a significant role in immune tolerance to self and allo-antigens and show a decreased level in peripheral blood of patients suffering from GC [23]. Subsequently, we demonstrated that the NK cell activity is decreased and different in advanced GC with different TCM syndrome types. In accordance with our results, a recent study reported that NK cells are enabling to kill and clear up abnormal cells and cancer cells and the decreased cytotoxic activity of NK cells is implicated in a vast majority of carcinomas like GC [24,25]. Also, Szkaradkiewicz, et al. also illustrated that the anti-tumor function and activity of NK cells was diminished in the tumor progression of GC.

Moreover, another study reported by Mimura, et al. has elucidated that the up-regulation of NK cells is important anti-GC factor [26]. Consistent with our study, Okita, et al. found that CD4+ T-cells are conducive to the certification of cellular activities occurring in the tumor microenvironment in regional lymph nodes of GC and the decrease of effector memory CD4+ T-cell number is observed

in regional lymph nodes of GC [27]. Besides, it is reported that the ratio of CD4+/CD8+ was also decreased in patients suffering from GC [28-31].

CONCLUSION

To be more specific, patients with qi and blood deficiency had the most significant T-cell dysfunction and decreased NK cell activity. The T-cell subsets secreted by peripheral blood and Th1 and Th2 cells correspond to TCM syndrome types in patients with chronic hepatitis B. To identify the relation between immune function of endometriosis and TCM syndrome types, the ratio of CD4+/CD8+ is closely relation with TCM syndrome types of endometriosis. In advanced GC, qi and blood deficiency was frequently observed. When it was effectively managed by Biejiahuajian Decoction united Gio therapy, the clinical efficacy was improved, the gastrointestinal tract was protected, and even white blood cells didn't increase side effects.

AUTHOR CONTRIBUTIONS

Authorship must be limited to those who have contributed substantially to the work reported. For research articles with several authors, the following statements should be used "All authors have read and agreed to the published version of the manuscript". Conceptualization, and BB methodology, CC software, DD validation, AA BB and EE formal analysis, writing-original draft preparation.

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CONFLICT OF INTEREST

Declare conflicts of interest or state "All authors declare no conflict of interest."

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