Preoperative Serum IL-6 Levels: Clinical Importance in Gastric Carcinoma with Lymph Node Metastasis

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ABSTRACT

***Aim**: The interleukin-6 (IL-6) pathway is one of the mechanisms that link inflammation and angiogenesis. The purpose of this study was to investigate the preoperative serum levels of IL-6 in gastric carcinoma with lymph node metastasis, and to correlate them with disease status.*

***Method**: A total of 100 patients who underwent gastrectomy were enrolled in this study. Serum levels of IL-6 were assessed enzyme linked immunosorbent assay (ELISA). Histological findings included tumor size, depth of tumor invasion, lymph node (LN) metastasis, and TNM stage.*

***Result**:Increases in cancer invasion and staging are generally associated with increases in preoperative serum IL-6 levels. IL-6 levels were correlated with invasion depth ($p<0.001$), LN metastasis ($p<0.001$), and TNM stage. The presence of peritoneal seeding metastasis is associated with IL-6 levels ($p<0.001$).*

***Conclusion**: Preoperative serum IL-6 levels might be markers of tumor invasion, LN metastasis, and TNM stage. These results suggest that IL-6 levels are potential molecular markers that predict lymphatic involvement in gastric carcinoma.*

***Key words**: IL-6, lymph node, metastasis, gastric carcinoma.*

Preoperatif Serum IL-6 Düzeyleri; Lenfnodu metastazlı mide kanserinde klinik önemi

Amaç: *İnterlökin-6 (IL-6) yolunun bağlantılı olduğu mekanizmalardan biri inflammasyon ve angiogenesisdir. Bu çalışmanın amacı, lenf nod metastazlı gastrik kanserli hastalarda preoperatif serum IL-6 düzeylerini incelemektir.*
Metod: *Çalışmaya 100 gastrektomi uygulanmış hastalar seçildi. IL-6 serum düzeylerini enzim bağlı immunosorbent ölçüm yöntemi (ELISA) ile ölçüldü. Histologik bulgular olarak, tümör büyüklüğü, tümör invazyon derinliği, lenf nod metastaz ve TNM evreleri alındı.*
Bulgular: *Artmış kanser invasyonu ve evreler genellikle artmış artmış preoperatif serum IL-6 düzeyleri ile ilişkilidir. IL-6 düzeylerini derin invazyon (p<0.001), LN metastazı (p<0.001) ve TNM evreleri (p<0.001) ile ilişkili bulduk. Aynı zamanda peritoneal seeding metastaz varlığı da serum IL-6 düzeyleri ilişkilidir (p<0.001).*
Sonuç: *Preoperatif serum IL-6 düzeyleri, tümör invazyonu, LN metastazı ve tumor evrelerinin markırıdır. Bu sonuçlar göstermiştir ki, IL-6 düzeyleri, gastrik karsinomada tahmin edilen lenfatik tutulumun potansiyel moleküler markırıdır.*
Anahtar kelimeler: *IL-6; lenf nod; metastaz; gastrik karsinoma.*

INTRODUCTION

Gastric cancer is one of the leading causes of death in the world. Metastasis to the regional lymph node is an indicator of tumor progression as well as an important prognostic factor in gastric cancer. Recent evidence suggests that tumor lymphangiogenesis promotes lymphatic metastasis (1-4). However, little is known about the mechanism of lymphangiogenesis in gastric carcinoma. Interleukin-6 (IL-6) is a multi-poietic cytokine that induces the growth and differentiation of immune cells, the expression of other cytokines, and acute-phase protein synthesis. IL-6 also marks various effects on cancer cells (5, 6).

In cancer, IL-6 is mostly known to be involved in crew defense mechanisms. Il-6 binds to the IL-6 receptor, activates the Janus kinase (JAK), and subsequently phosphorylates the signal transducers and activators of transcription (STAT). Suppressor of cytokine signaling-1 (SOCS-1) is one of the STAT-activated genes, which is upregulated by IL-6 and is involved in the down-regulation of the JAK/STAT pathway (7-9). In many cancer types, recent studies have demonstrated that the hypermethylation of SOCS-1 is not controlled by the JAK/STAT pathway, and IL-6 cannot perform a role in cancer defense; on the contrary, it is involved in cancer development and angiogenesis (7, 10). In the development of cancer, angiogenesis is a definite and elemental process. IL-6 is associated with angiogenesis by virtue of its capability to induce the mRNA of vascular endothelial growth factor (VEGF), which is typically a direct angiogen (5). Additionally, IL-6 activates the Rho protein, which is associated with cell-cell adhesion and invasion in malignancy (11).

The largely purpose of this study was to determine the relationship between serum IL-6 and lymphangiogenesis and prognosis in gastric cancer patients.

MATERIALS AND METHODS

This study enrolled 100 patients who underwent surgical resection for gastric adenocarcinoma at Haseki Education and Research Hospital between December 2007 and October 2009. Well-documented clinical data were collected from all patients. All patients provided informed consent, and the hospital review board approved the study. Venous blood sampling was enrolled within 7 days before the patients underwent operations. The blood collected for IL-6 serum level assessments was collected in plain tubes, and the levels of serum IL-6 were measured using commercially available enzyme-linked immunosorbent assay (ELISA) (Quantikine human IL-6 Immunassay, R&D Systems, USA). The blood samples were centrifuged for 10 min at 3000 r/min at -4°C. The serum was subsequently removed and stored at -80°C until biochemical analysis. Serum levels of IL-6 were expressed as the means ± SD. A p value of <0.05 was considered to be statistically significant. The Pearson chi-square test was performed to determine the correlation between IL-6 levels and various clinicpathological factors.

RESULTS

The patients were classified by their pathologic characteristics, including tumor size, depth of tumor invasion, status of lymph node metastasis, TNM staging, and peritoneal metastasis. The patients consisted of 58 men and 42 women, with a median age of 57 years (range, 35-78 years). The characteristics data of the study population are shown in Table 1. 51 patients evidence tumor sizes of ≥ 5 cm. The depth of tumor invasion was pT1 in 20 patients, pT2 in 34, pT3 in 31, and pT4 in 15. LN me-

Table 1. *Patients characteristics and IL-6 levels.*

Variables	*n*	*IL-6 (pg/ml)*	*p value*
Total	*100*		
Sex			
Male	*58*	*7.01±2.81*	
Female	*42*	*7.43±1.92*	*0.312*
Age			
<60	*49*	*5.89±3.03*	
≥60	*51*	*5.94±2.66*	*0.037*
Tumor size			
<5cm	*49*	*6.78±2.92*	
≥5cm	*51*	*7.24±3.18*	*0.019*
Tumor depth			
pT1	*20*	*5.43±1.29*	
pT2	*34*	*5.99±1.56*	
pT3	*31*	*7.82±2.34*	
pT4	*15*	*9.43±2.58*	*0.001*
LN metastasis			
N0	*11*	*5.97±1.56*	
N1	*29*	*6.41±1.68*	
N2	*30*	*7.38±2.11*	
N3	*10*	*9.47±1.28*	*0.001*
Peritoneal metastasis			
Met (-)	*90*	*6.17±3.05*	
Met (+)	*10*	*9.27±2.39*	*0.001*
TNM stage			
I	*27*	*7.36±3.12*	
II	*25*	*7.99±2.63*	
III	*30*	*8.78±2.91*	
IV	*18*	*9.54±3.05*	*0.001*

tastasis was detected in 81 patients. The postoperative stages of the patients were I, II, III, and IV in 27, 25, 30, and 18 patients, respectively. Ten patients in this study had peritoneal metastasis.

We noted that IL-6 levels were significantly correlated with IL-6 levels, and tumor size with higher IL-6 levels was detected in tumors sized ≥ 5cm. In addition, with increasing degrees of tumor invasion, the median levels of IL-6 evidenced an affinity to increase, and this difference in IL-6 levels was found to be statistically significant. In cases of LN metastasis, we also noted a significant difference between the serum level of IL-6 increased with the stage of the cancer, and this difference was statistically significant. In addition, serum IL-6 levels were significantly higher in patients with peritoneal metastasis than in those without peritoneal seeding.

DISCUSSION

In this study, the serum levels of IL-6 evidenced statistically significant differences in tumor size, tumor invasion depth, and LN metastasis. In the TNM stage, as the stage of the disease increased, serum IL-6 levels were significantly higher. In addition, the median levels of IL-6 were significantly higher in the patients with peritoneal seeding than in those without peritoneal seeding.

IL-6 was confirmed as independent factors. In some papers, it has been reported that IL-6 was an active prognostic indicator in stages II and III (12). There have been a great many studies conducted concerning the values and functions of IL-6 in malignancy. These studies have present that IL-6 levels were higher in malignancies than in non-malignancies, and increased with enhancing tumor size and depth (13,14). We determined a statistically significant relationship between IL-6 levels and LN metastasis. However, some studies have reported no relationship between IL-6 levels and LN metastasis (15). LN metastasis was shown to be affected by independent

predictors in cases of advanced cancers. Many studies have also showed that IL-6 levels enhanced in cases of distant metastasis, notably hepatic metastasis (13,14). This result has been imputed to a crew of mechanisms, including the autocrine and paracrine pathways. With regard to the autocrine pathway, IL-6 activated the production of IL-6 by tumor cells with the IL-6 receptor. With the regard to the paracrine pathway, IL-6 stimulated sttromal cells promoted the secretion of tumor growth and adhesion molecules containing (6,13,16). Lymphangiogenesis is one of the fundamental mechanisms which contribute to the progression of cancer. Because high IL-6 levels that block the some signaling pathway might block lymphangiogenous metastasis, IL-6 has been widely analyzed as a possible target for cancer treatment.

Preoperative serum IL-6 levels were related to cancer stage and might be markers of tumor invasion, LN metastasis and TNM stage. Particularly high IL-6 levels were presented as an important factor of lymphangiogenesis.

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