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Original article

Clinical significance of interleukin-6 (IL-6) in the spread of gastric cancer: role of IL-6 as a prognostic factor

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Abstract

Background. **It is becoming clear that various cytokines are associated with the spread of cancer cells. The purpose of this study was to compare interleukin (IL)-6 levels in patients with gastric cancer to elucidate the role of IL-6 in predicting the spread of tumors.**

Methods. **In 60 patients, we assessed the correlation of serum IL-6 (pg/ml) with stage, histological findings, hepatic metastasis, and related factors (hepatocyte growth factor [HGF], IL-1β, tumor necrosis factor [TNF]-α, and transforming growth factor [TGF]-β1). We also investigated the diagnostic significance of the IL-6 level for advanced gastric cancer and lymph node metastasis, as well as the association between IL-6 elevation and outcome. Finally, we examined the expression of IL-6 in tumor tissue.**

Results. **Significant relationships were seen between serum IL-6 and stage, depth of tumor invasion (pT), lymphatic invasion (ly), venons invasion (v)*, lymph node metastasis (pN), hepatic metastasis (cH), and HGF ($P < 0.01$; $^*P < 0.05$). With regard to the diagnostic significance of the IL-6 level for advanced gastric cancer and lymph node metastasis, when the cutoff value of IL-6 was set at 1.97 pg/ml, the sensitivity was 81.8% and 87.5%; specificity was 66.7% and 58.3%; and accuracy was 77.1% and 72.9%, respectively. The 1- and 3-year cumulative survival rates for patients with an IL-6 value of more than 1.97 pg/ml (69.0% and 43.4%, respectively) were significantly lower than those for patients with an IL-6 value of 1.97 pg/ml or less (94.4% and 87.2%, respectively; $P < 0.05$). Immunohistochemical staining was positive for IL-6 in the cytoplasm of cancer cells.**

Conclusion. **We suspect that IL-6 is involved in cancer invasion and lymph node and/or hepatic metastasis. Our results indicate that IL-6 could be used as a prognostic factor for survival.**

Key words IL-6 · HGF · Advanced gastric cancer · Lymph node metastasis · Hepatic metastasis · Outcome · Prognostic factor

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Introduction

A cancer cell has the ability to invade host stroma and to metastasize. Metastasis refers to the ability of cancer cells to invade the stroma and to generate secondary tumors at sites distant from the primary tumor. It is well known that the spread of tumors can be enhanced not only by cancer cells but also by interstitial cells. It is becoming clear that various cytokines, produced by cancer tissues, including interstitial cells, are associated with invasion and metastasis [1,2]. Cytokines are considered to form a cytokine network, either autocrine or paracrine, and to be involved in the system of invasion and metastasis through receptors expressed on cancer cells.

The purpose of this study was to compare the serum levels of IL-6 in patients with gastric cancer to elucidate the possible role of IL-6 in predicting the spread of tumors in relation to the grade of histological findings (depth of tumor invasion [pT], lymphatic invasion [ly], venous invasion [v], and lymph node metastasis [pN]) and hepatic metastasis (cH). We also examined the role of IL-6 as a prognostic factor and its diagnostic significance for advanced gastric cancer and lymph node metastasis.

Patients and methods

Patients

Sixty patients with gastric cancer diagnosed histopathologically, without pre-treatment, who underwent gastrectomy at our department between January 1998 and March 2003 were enrolled in this study. The patients consisted of 43 men and 17 women (mean age, 64.1 years; range, 40–83 years). Twenty healthy volunteers were also analyzed as controls. Twelve patients were considered to have hepatic metastasis clinically. In the

remaining 48 patients, the depth of tumor invasion was pT1 in 15 patients, pT2 in 16, pT3 in 15, and pT4 in 2; lymphatic invasion was ly0 in 16 patients, ly1 in 15, ly2 in 8, and ly3 in 9; venous invasion was v0 in 18 patients, v1 in 12, v2 in 12, and v3 in 6; and lymph node metastasis was pN0 in 24 patients, pN1 in 13, pN2 in 7, and pN3 in 4. There were 21 patients with stage I disease, 9 with stage II, 13 with stage III, and 17 with stage IV (Table 1).

Methods

In the 60 patients with gastric cancer, we statistically assessed the correlation of preoperative serum levels of IL-6 (pg/ml) with the stage, the grade of histological findings (pT, ly, v, pN), hepatic metastasis (cH), and IL-6 related cytokines (hepatocyte growth factor [HGF; ng/ml], IL-1β (pg/ml), tumor necrosis factor-α [TNF-α; pg/ml], and transforming growth factor-β1 [TGF-β1; ng/ml]).

We determined the diagnostic significance of IL-6 for advanced gastric cancer and lymph node metastasis.

Table 1. Patients' characteristics

Number of patients	60
Age (years)	
Median	64.1
Range	40–83
Sex (%)	
Male	43 (71.7)
Female	17 (28.3)
Hepatic metastasis (cH), *n* (%)	
1	12 (20.0)
0	48 (80.0)
Depth of tumor invasion (pT), *n* (%)	
1	15 (31.3)
2	16 (33.3)
3	15 (31.3)
4	2 (4.1)
Lymphatic invasion (ly), *n* (%)	
0	16 (33.3)
1	15 (31.3)
2	8 (16.7)
3	9 (18.7)
Venous invasion (v), *n* (%)	
0	18 (37.5)
1	12 (25.0)
2	12 (25.0)
3	6 (12.5)
Lymph node metastasis (pN), *n* (%)	
0	24 (50.0)
1	13 (27.1)
2	7 (14.6)
3	4 (8.3)
Stage, *n* (%)	
I	21 (35.0)
II	9 (15.0)
III	13 (21.7)
IV	17 (28.3)

We studied the association between IL-6 elevation and outcome, and compared IL-6 and clinicopathological prognostic factors (pT, ly, v, pN, cH) with regard to outcome. We also examined the expression of IL-6 in tumor tissue by immunohistochemical staining, using an anti-human IL-6 monoclonal antibody (Cosmo Bio, Tokyo, Japan). Histological findings were described according to the *Japanese classification of gastric carcinoma*, 13th edition [3].

Assay of serum cytokine values

The serum level of IL-6 was measured by chemiluminescent enzyme immunoassay (CLEIA), using a commercial kit (Fujirebio, Tokyo, Japan). The serum values of other cytokines were measured by enzyme-linked immunosorbent assays (ELISAs), by means of commercially available methods: HGF (Otsuka Pharmaceutical, Tokyo, Japan), IL-1β (Biosource Europa, Camarillo, CA, USA), TNF-α (Japan Immunoresearch Laboratories, Gunma, Japan), and TGF-β1 (R&D System, Minneapolis, MN, USA).

Statistical analysis

Spearman's rank correlation coefficient (*r*s) was used to assess the correlation of IL-6 with stage, histological findings, hepatic metastasis, and IL-6 related cytokines. The comparison of IL-6 in relation to the stage and histological variables was assessed by the Kruskal-Wallis *H*-test and Mann-Whitney *U*-test with Bonferroni correction. Comparisons of IL-6 in regard to cH were assessed by unpaired *t*-test. Survival curves for patients were plotted using the Kaplan-Meier method, and differences were assessed by the log-rank test and the generalized Wilcoxon test. A P value of less than 0.05 was considered to indicate a statistically significant difference. IL-6 and clinicopathological prognostic factors were compared with regard to survival using Cox proportional analysis.

Results

Correlation of IL-6 values with disease stage

A significant relationship was seen between IL-6 and the four disease stages (rs = 0.67018; $P < 0.01$). The mean IL-6 values in stage I (2.14 ± 1.57 pg/ml) and stage IV (11.77 ± 10.58 pg/ml) patients were statistically significantly higher than those in healthy volunteers (1.05 ± 0.46 pg/ml; $H = 52.292$; $P < 0.01$). However, there was no significant difference in IL-6 values among stage I, stage II (4.97 ± 2.52 pg/ml), stage III (5.19 ± 3.38 pg/ml), and stage IV patients (Fig. 1).

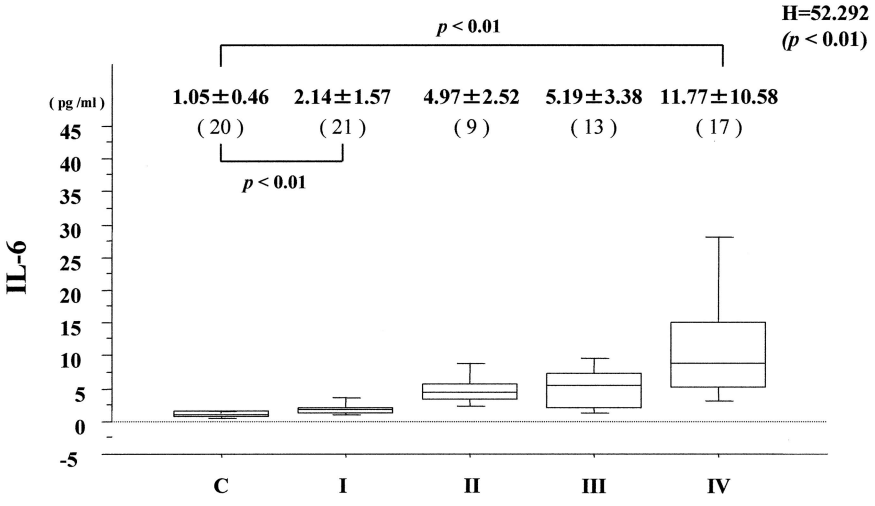

Fig. 1. Comparison of serum interleukin-6 (*IL-6*) values in control subjects (*C*) and patients according to disease stage. *Numbers in parentheses* are numbers of patients

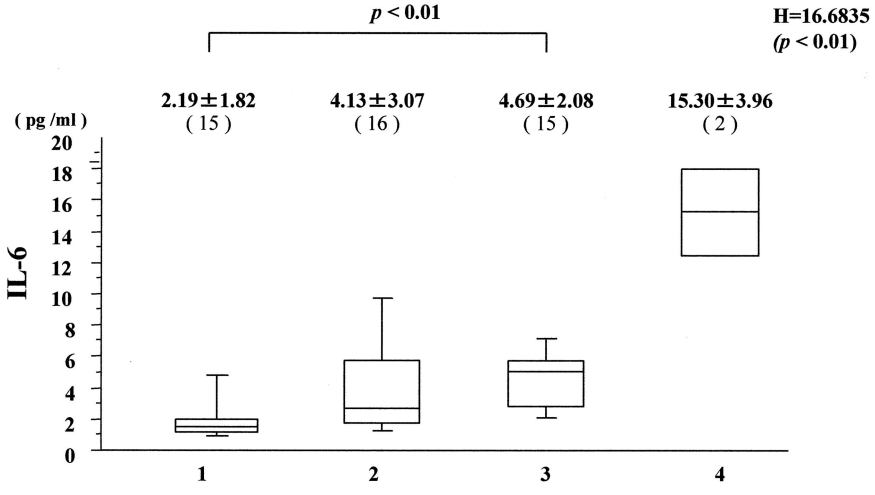

Fig. 2. Comparison of serum IL-6 values in patients according to depth of tumor invasion (*numbers on horizontal axis*). *Numbers in parentheses* are numbers of patients

Correlation of IL-6 values with grade of histological findings

Depth of tumor invasion (pT)

A significant relationship was seen between IL-6 and the four grades of pT ($rs = 0.5778$; $P < 0.01$). The mean IL-6 value was statistically significantly higher in pT3 patients (4.69 ± 2.08 pg/ml) than in pT1 patients (2.19 ± 1.82 pg/ml; $H = 16.6835$; $P < 0.01$). However, there was no significant difference in IL-6 values among pT1, pT2 (4.13 ± 3.07 pg/ml), pT3, and pT4 (15.3 ± 3.96 pg/ml) patients, except for pT1 vs pT3 (Fig. 2).

Lymphatic invasion (ly)

A significant relationship was seen between IL-6 and the four grades of ly ($rs = 0.49851$; $P < 0.01$). The mean IL-6 value was statistically significantly higher in ly2 patients (4.65 ± 1.73 pg/ml) than in ly0 patients (2.31 ± 1.80 pg/ml; $H = 11.8992$; $P < 0.05$). However, there was no significant difference in IL-6 values among ly0, ly1 (4.51 ± 3.91 pg/ml), ly2, and ly3 (6.44 ± 4.84 pg/ml) patients, except for ly0 vs ly2 (Fig. 3).

Venous invasion (v)

A significant relationship was seen between IL-6 and the four grades of v ($rs = 0.36304$; $P < 0.05$). The mean IL-6 value was statistically significantly higher in v2 patients (7.05 ± 4.55 pg/ml) than in v0 patients (2.79 ± 2.59 pg/ml; $H = 11.9274$; $P < 0.05$). However, there was no significant difference in IL-6 values among v0, v1 (3.70 ± 2.46 pg/ml), v2, and v3 patients (3.43 ± 2.35 pg/ml), except for v0 vs v2 (Fig. 4).

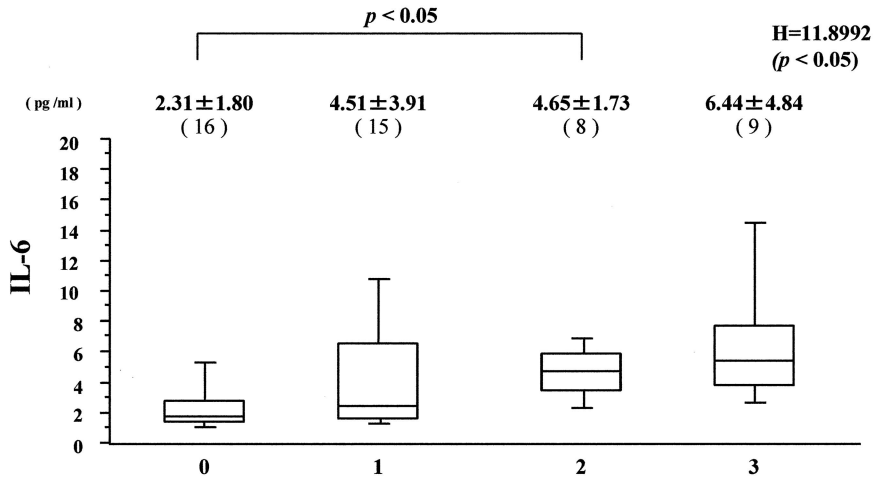

Fig. 3. Comparison of serum IL-6 values according to lymphatic invasion (*numbers on horizontal axis*). *Numbers in parentheses* are numbers of patients

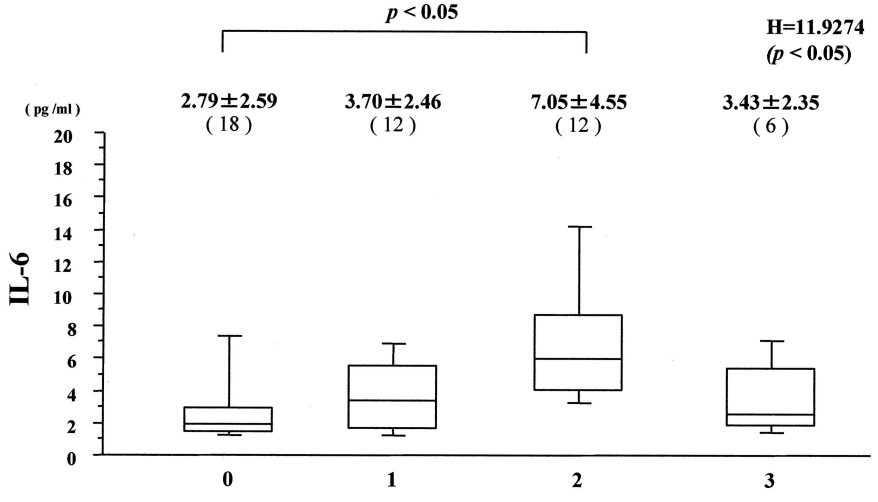

Fig. 4. Comparison of serum IL-6 values according to venous invasion (*numbers on horizontal axis*). *Numbers in parentheses* are numbers of patients

Lymph node metastasis (pN)

A significant relationship was seen between IL-6 and the four grades of pN ($rs = 0.55876$; $P < 0.01$). The mean IL-6 value was significantly higher in pN1 patients (5.48 ± 3.32 pg/ml) than in pN0 patients (2.35 ± 1.61 pg/ml; $H = 16.0375$; $P < 0.01$). However, there was no significant difference in IL-6 values among pN0, pN1, pN2 (6.77 ± 5.69 pg/ml), and pN3 patients (6.15 ± 2.81 pg/ml), except for pN0 vs pN1 (Fig. 5).

Correlation of IL-6 with hepatic metastasis (cH)

The mean IL-6 value was significantly higher in cH1 patients (13.12 ± 11.99 pg/ml) than in cH0 patients (4.16 ± 3.50 pg/ml; $P < 0.0001$); thus, a significant relationship was seen between IL-6 value and hepatic metastasis ($rs = 0.44149$; $P < 0.01$; Fig. 6).

Correlation of IL-6 with related cytokines

A significant relationship was seen between IL-6 and HGF ($rs = 0.43527$; $P < 0.01$). However, there was no significant relationship between IL-6 and IL-1β ($rs = 0.21125$; not significant [NS]), TNF-α (rs not calculated; NS), or TGF-β1 ($rs = 0.26446$; NS).

Diagnostic significance of IL-6 for advanced gastric cancer and lymph node metastasis

When the cutoff value of IL-6 was set at 1.97 pg/ml (mean + 2SD for 20 healthy volunteers), with regard to diagnostic significance for advanced gastric cancer (pT2, pT3, and pT4 patients), the sensitivity was 81.8% (27/33); specificity, 66.7% (10/15); positive predictive value, 84.4% (27/32); negative predictive value, 62.5% (10/16); and accuracy, 77.1% (37/48). With regard to

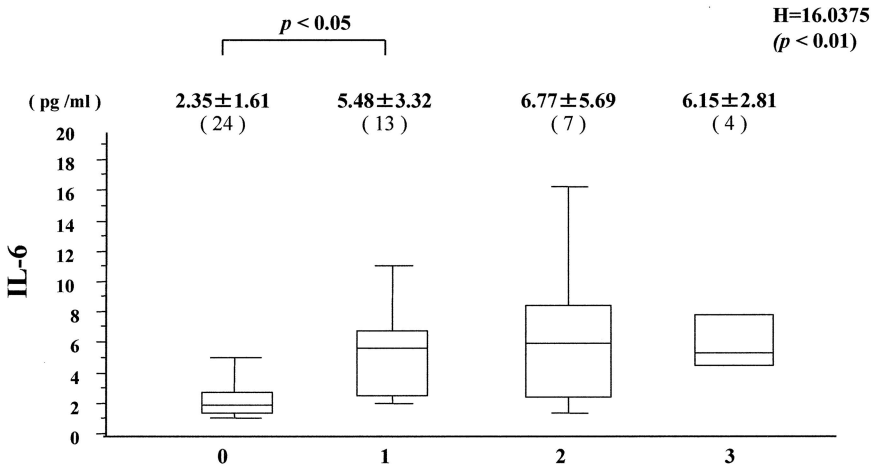

Fig. 5. Comparison of serum IL-6 values according to lymph node metastasis (*numbers on horizontal axis*). *Numbers in parentheses* are numbers of patients

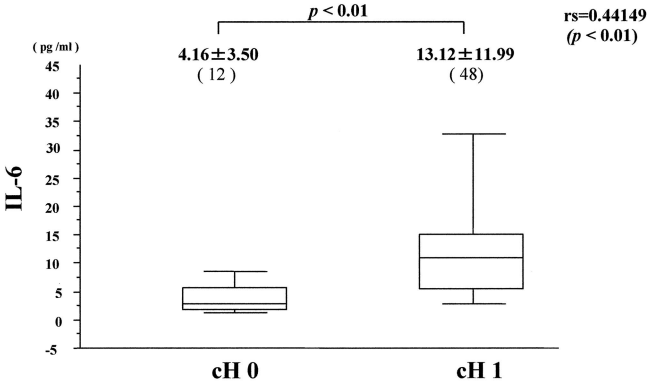

Fig. 6. Comparison of serum IL-6 values according to hepatic metastasis (*cH*). *Numbers in parentheses* are numbers of patients

diagnostic significance for lymph node metastasis (pN1, pN2, and pN3 patients), the sensitivity was 87.5% (21/24); specificity, 58.3% (14/24); positive predictive value, 67.7% (21/31); negative predictive value, 82.4% (14/17); and accuracy, 72.9% (35/48).

Outcomes

Analysis of survival was conducted in 60 patients. We assessed the correlation between the serum levels of IL-6 and outcome (survival time). Patients were divided into two groups based on the IL-6 cutoff value (1.97 pg/ml). The high-level group (43 patients) represented the population with levels higher than the cutoff value and the low-level group (17 patients) represented the population with levels equal to or lower than the cutoff value. The distribution of survival time was compared between the two groups. The 1- and 3-year cumulative survival rates for patients with an IL-6 value of more than 1.97 pg/ml (69.0% and 43.4%) were significantly lower than those for patients with an IL-6 value of 1.97 pg/ml or less (94.4% and 87.2%) as assessed by the log-rank test ($P < 0.05$) and the generalized Wilcoxon test ($P < 0.05$; Fig. 7).

The Cox proportional hazards model was applied to multivariate analysis to test the relationship of regression parameters with outcome. When the six variables (i.e., IL-6, pT, ly, v, pN, and cH) were applied to the model, IL-6 ($P = 0.0276$) was inferior to pN ($P = 0.0089$) as a prognostic factor, but it had a relatively stronger correlation with the survival rate than pT ($P = 0.1849$), ly ($P = 0.2256$), v ($P = 0.2427$), and cH ($P = 0.0989$).

Immunohistochemical staining

In all four patients with very high serum levels of IL-6 (more than 15.0 pg/ml), immunohistochemical staining showed positive findings for IL-6 in the cytoplasm of cancer cells. On the other hand, there was no evidence of positive findings for IL-6 in five patients with low serum levels of IL-6 (less than 1.5 pg/ml).

Case example

We report representative findings in an a 83-year-old-woman who suffered from gastric cancer and presented with a high temperature (37.5°C–38.5°C). Although laboratory data showed elevations of the white blood cell count (WBC; 9000–12 000/μl), and of levels of C-reactive protein (CRP; 6–8 mg/dl), HGF (1.58 ng/ml), and IL-6 (30.5 pg/ml), no evidence of an inflammatory focus was observed upon further clinical examination. After distal gastrectomy and lymph node dissection, a reduction of the temperature and a decrease of WBC, CRP, HGF, and IL-6 occurred. The resected specimen revealed poorly differentiated adenocarcinoma (Fig. 8A) (por2, pT4, ly3, v2, pN3, cH1, stage IV). An immu-

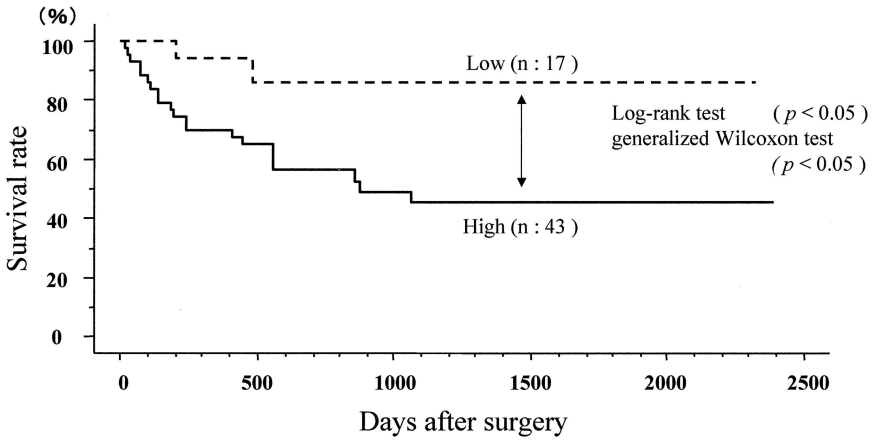

Fig. 7. Cumulative survival curves in patients with high or low serum values of IL-6 (Kaplan-Meier method)

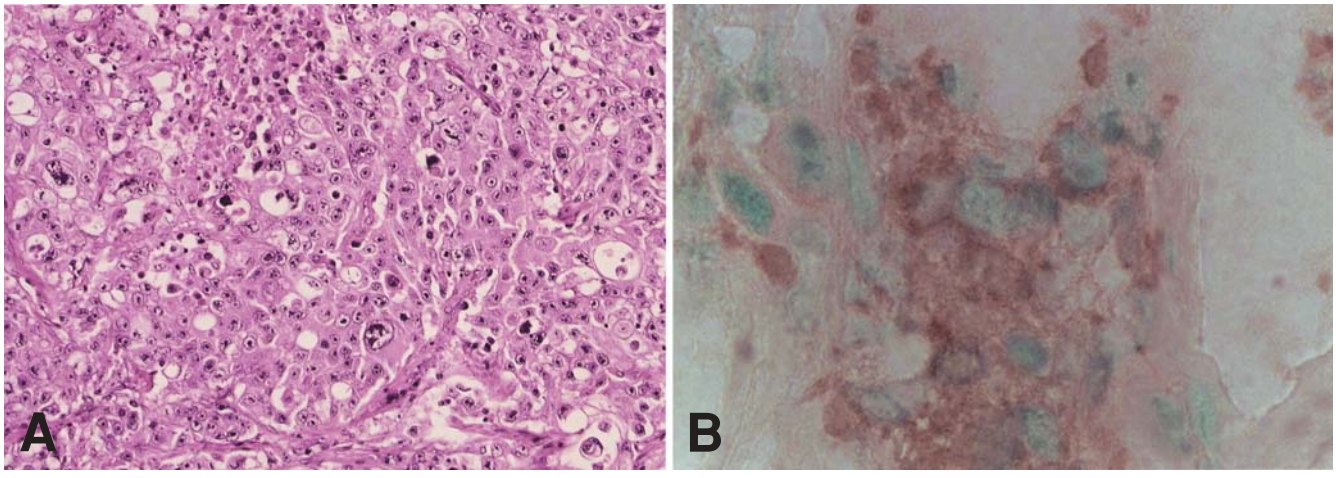

Fig. 8A,B. Microscopic findings. **A** The main tumor shows poorly differentiated adenocarcinoma. **B** Immunohistochemical study shows positive staining for IL-6 in the cytoplasm of the adenocarcinoma cells. **A** H&E, ×200; **B** ×400

nohistochemical study showed positive staining for IL-6 in the cytoplasm of the adenocarcinoma cells (Fig. 8B).

Discussion

In 1986, the deduced nucleotide and amino-acid sequences of cloned human IL-6 cDNA were purified. Human IL-6 consists of 212 amino acids, including a hydrophobic signal sequence of 28 amino acids [4–6]. On the other hand, the IL-6 receptor (IL-6R) system consists of an 80-kD glucoprotein (IL-6R) and a 130-kD glucoprotein (gp130), and signals are transferred into cells by IL-6 combined with IL-6R on the cell membrane [7]. It has been found that IL-6 is produced by many different types of lymphoid and nonlymphoid cells. It is now also known that IL-6 is involved in the following multiple biological activities: (1) T-cell growth and differentiation; (2) IL-2 production and IL-2 receptor expression in T cells; (3) B-cell growth and differentiation; (4) hematopoietic stem cell growth; (5) megakaryocyte maturation; (6) acute phase protein synthesis; (7) macrophage differentiation; (8) mesangial cell, keratinocyte, and osteoclast cell growth; (9) hybridoma, plasmacytoma, and myeloma growth; and (10) stimulation of cancer-cell growth [8–11]. We therefore considered "stimulation of cancer-cell growth by IL-6", and investigated the possible role of IL-6 in predicting the spread of tumors, including invasion and metastasis.

Cancer metastasis is a complex process involving coordinated cellular responses of both cancer cells and normal cells. The steps involved in metastasis are as follows: (1) invasion of the stroma; (2) intravasation of blood vessels; (3) circulation in the blood; (4) lodging and adhesion in target capillaries; (5) extravasation from the blood vessels; and (6) proliferation of secondary tumors [12]. IL-6 is thought to be involved in steps 1, 2, and 3 of the metastatic process.

As proof of the mechanism of IL-6 action, Tamm et al. [13] showed that IL-6 makes cancer cells increase

their motogenic activity, by autocrine pathway (IL-6 secreted from the cancer cells combines with the IL-6R, which is expressed on the surface of cancer cells, and together, IL-6 and IL-6R act the cancer cells directly). It also became clear by subsequent research that a paracrine pathway was involved in the effects of HGF and IL-6 on the invasion and metastasis of cancer cells [14–16]. When IL-6 produced by cancer cells stimulates interstitial cells to secrete HGF, HGF combines with the HGF receptor (c-Met) expressed on the cancer cells. HGF raises the motogenic activity of cancer cells, and it is thought that such cancer cells are then moved to the metastasis site. An association was seen between IL-6 and HGF in this research, and IL-6 may act through HGF on cancer cells, by the promotion and acceleration of invasion and lymph node and/or hepatic metastasis. In regard to the tumor, it is rational to say that IL-6 affects the environmental structure of the region in which metastasis tends to occur, not only acting on the cancer cells but also acting on the target organs, by the promotion of its action through HGF. It has been reported that intercellular adhesion molecule (ICAM)-1, vascular cell adhesion molecule (VCAM)-1, and E-selectin are expressed on endothelial cells by proinflammatory cytokines such as IL-1β and TNF-α, which are located upstream of IL-6 [17,18], and which, combined with IL-6, promote the adhesion of cancer cells and endothelial cells [19]. However, IL-6 did not correlate significantly with IL-1β or TNF-α in this research. Because the ability of the measurement kits we used in the present study for IL-β and TNF-α was inadequate measure very small quantities, the level measured in most patients (52 of 60 patients; 86.7%) for IL-1β, and 60 of 60 (100%) patients for TNF-α) was below the detection limit. Therefore, these two cytokines were compared in terms of marginal serum detection values (IL-1β, 10 pg/ml; TNF-α, 5 pg/ml) in these 112 patients.

Although specific IL-6 immunostaining was observed in the cytoplasm of cancer cells in patients with a very high IL-6 level (more than 15.0 pg/ml), IL-6 immunostaining was not shown in patients with a low IL-6 level (less than 1.5 pg/ml), strongly suggesting that a high serum level of IL-6 reflects IL-6 secretion by cancer cells. However, it remains unclear what upregulates IL-6 production in cancer cells.

Experimental studies have recently demonstrated that the in vitro treatment of Kupffer cells with carcinoembryonic antigen (CEA) induces the expression of cytokines such as IL-1α, IL-1β, IL-6, and TNF-α [19]. In addition, the injection of CEA into mice resulted in a significant dose-dependent IL-6 response [20]. Furthermore, Belluco et al. [21] reported that the preoperative serum concentration of IL-6 was associated with CEA in 208 patients with colorectal cancer. These data suggest that CEA induces the systemic production of IL-6. However, there was no significant relationship between IL-6 and CEA in the present study (data not shown; rs = 0.1006). The role of CEA in the upregulation of IL-6 in cancer cells is considered to be an important research subject, and such research would need to examine the relevance of IL-1β and TNF-α, which are located upstream of IL-6. Further studies are needed to clarify the mechanism underlying IL-6 production and its effect in patients with gastric cancer.

Because IL-6 is affected by various clinical conditions, such as sepsis, trauma, surgery, inflammation, and other forms of chronic stress, its serum level may reflect much indefinite bias, and it is therefore not necessarily suitable as a screening modality to rule out malignancy. Based on our results, the clinical significance of IL-6 is limited to evaluating the spread of gastric cancer, and it should be used as a tumor marker of advanced gastric cancer and lymph node metastasis. Actually, with regard to the diagnostic significance of IL-6 serum levels for advanced gastric cancer and lymph node metastasis, when the cutoff value of IL-6 was set at 1.97 pg/ml, the sensitivity was 81.8% and 87.5%; specificity was 66.7% and 58.3%; and accuracy was 77.1% and 72.9%, respectively. Although it cannot be said that the specificity is high enough, the sensitivity and accuracy are high and are not inferior to those for other tumor markers, such as CEA and carbohydrate antigen (CA) 19–9 [22]. Moreover, we found that patients with a high serum level of IL-6 exhibited a significantly poor outcome compared with patients with a low level of IL-6. Therefore, serum IL-6 may be valuable as a prognostic factor for survival, and it is recommended for the preoperative prediction of disease stage. In patients with IL-6-producing gastric cancer who show high levels of C-reactive protein (CRP) before operation [23,24], examination of the serum IL-6 level and IL-6 expression in cancer cells would be useful to estimate whether there is a high risk of lymph node and/or hepatic metastasis after surgical removal of the primary tumor.

Elevations of IL-6 levels can be seen temporarily after surgery, with the levels depending on the type of surgical intervention [25,26]. It is also well known that there are some cases of the spread of malignant tumor being accelerated after surgical treatment [27]. It cannot be denied that elevations of IL-6 may be involved in accelerating the activity and spread of cancer cells. Therefore, if a curative operation cannot be performed, we should not perform unnecessary procedures for patients with far-advanced gastric cancer.

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