Serum Interleukin-6 Levels in Patients with Gastric MALT Lymphoma Compared to Gastric and Pancreatic Cancer

RUPERT BARTSCH, STEFAN WOEHRER, MARKUS RADERER and MICHAEL HEJNA

Department of Internal Medicine I, Division of Oncology, Medical University of Vienna, Vienna, Austria

Abstract. Background: Interleukin-6 (IL-6) plays a major role in inflammatory processes and various malignancies. Serum IL-6 levels from patients with gastric MALT lymphoma, gastric cancer and pancreatic cancer was investigated. Patients and Methods: The serum IL-6 levels were obtained in a total of 86 patients. A two-tailed Mann-Whitney-test was performed to compare the results. A p-level <0.05 was deemed statistically significant. Results: In lymphoma patients, the mean IL-6 levels were 12.633 pg/ml (SD 10.465). The levels for gastric cancer were 6.324 pg/ml (SD 11.497) and 27.4 pg/ml (SD 86.272) for pancreatic cancer. A comparison between MALT lymphoma and gastric cancer revealed a significant difference (p=0.0030), while no difference was found between MALT lymphoma and pancreatic cancer. The IL-6 levels, however, were higher in pancreatic cancer than gastric cancer (p=0.0040). Conclusion: Our results might reflect a greater importance of IL-6 in the development and growth of MALT lymphoma and, possibly, pancreatic cancer than in gastric cancer.

Interleukin (IL)-6, a pleiotropic cytokine with varied systemic functions, plays a major role in inflammatory processes. It is part of an entire family of IL-6-type cytokines, comprising IL-6, IL-11, leukaemia inhibitory factor (LIF), oncostatin M (OSM), ciliar neurotrophic factor (CNTF), cardiotrophin-1 (CT-1) and cardiotrophin-like cytokine (CLC) (1). These cytokines share a common glycoprotein 130 receptor component (2) modulating the transcription of several liver-specific genes during acute inflammatory states, particularly C-reactive protein. IL-6 was also found to act as a co-factor in haematopoiesis, stem cell amplification and differentiation (3). It further interacts with vascular endothelial growth factor (VEGF), thereby stimulating angiogenesis and tumour vascularisation (4).

In general, IL-6 appears to play an important role in the development and growth of lymphomas and also of solid malignancies. IL-6 signal transduction involves the activation of JAK (janus kinase) tyrosine kinase family members, leading to the activation of transcription factors of the STAT (signal transducers and activators of transcription) family. An alternative pathway for IL-6 signalling is the MAPKinase cascade (1).

Gastric mucosa-associated lymphoid tissue (MALT) lymphoma is preceded by Helicobacter pylori (HP) gastritis (5) in the large majority of cases and, patients with early stage gastric MALT lymphoma have a favourable long-term outcome using HP eradication as the sole treatment modality (6). Activated local defence mechanisms cause a chronic inflammatory response, creating the clinical symptoms and tissue damage typical of HP-associated gastritis. This response results in an up-regulation of inflammatory cytokines, both in patient blood and the gastric fluid. In different studies, chronic HP infection was found to correlate with increased levels of inflammatory cytokines, especially IL-6 and TNF alpha, while data concerning IL-8 are inconsistent throughout the literature (7-8). As IL-6 is known to have a major anti-apoptotic role in various types of non-Hodgkin’s lymphoma and multiple myeloma (4, 9), the serum IL-6 levels in patients with gastric MALT lymphoma were investigated. Patients with gastric cancer or pancreatic cancer were selected as controls. This was due to the fact that the IL-6 levels had previously been reported to correspond to advanced disease status (10) in gastric cancer, and have also been shown to be markedly elevated in pancreatic cancer (11). In addition, both diseases have been linked to HP infection to some extent (12-14).

Patients and Methods

All the data were collected at the Department of Internal Medicine I, Division of Oncology at the Medical University of Vienna, Vienna, Austria. The study was performed in accordance with the ethical regulations of the Medical University of Vienna.
Patients. A total of 86 consecutive patients were included in this analysis. Eighteen had localised gastric MALT lymphoma (Stage I), 21 were suffering from gastric cancer (Stage IV in all cases) and 47 from pancreatic cancer (16 patients with locally inoperable and 31 with metastatic disease). The median age at diagnosis was 59 years (range; 27-88 years). In addition, the HP status of the patients was assessed using serological testing for anti-HP antibodies.

The criteria for inclusion were as follows: histological proof of gastric MALT lymphoma, gastric cancer or pancreatic cancer, no concurrent treatment for other malignancies, no clinical signs of chronic infections other than HP or chronic inflammation and informed consent. In order to rule out a potential confounding factor, all patients were tested for the presence of autoimmune diseases by evaluation of antinuclear-antibodies (ANAs), rheumatoid factor, c3, c4 and thyroid antibodies.

Blood was drawn from patients after primary diagnosis of disease and the serum concentration of interleukin 6 was determined by a solid-phase enzymoimmunoassay technique (ENDOGEN IL-6; Endogen Inc., Woburn, Massachusetts, USA) and results are given in pg/ml.

Statistical analysis. All statistics were done with Graph pad-Prism 4.1 software. The mean, standard deviation and standard error are provided from the sampled serum IL-6 levels. The results were compared with a two-tailed Mann-Whitney test. P values less than 0.05 were considered to indicate statistical significance.

Results

The mean IL-6 level (all patients) was 19.162 pg/ml (standard deviation 64.634; standard error 6.970), 95% CI 5.304-33.019. Corresponding numbers for gastric MALT lymphoma were 12.633 pg/ml (SD 10.465, SE 2.467), 95% CI 7.429-17.837; gastric cancer 6.324 pg/ml (SD 11.497, SE 2.509), 95% CI 1.091-11.557; and for pancreatic cancer, 27.400 pg/ml (SD 86.373, SE 12.599) and 95% CI 2.04-52.76, respectively. The IL-6 levels are shown in Figure 1.

Statistical analysis showed significantly higher IL-6 levels in MALT lymphoma than in gastric cancer ($p=0.0030$) while no significant difference was found between MALT lymphoma and pancreatic cancer ($p=0.7140$). A comparison between the IL-6 levels in gastric and pancreatic cancer also showed significantly lower IL-6 levels in gastric cancer ($p=0.0040$). No significant difference was found between pancreatic cancer patients with locally inoperable versus metastatic disease.

None of our patients showed evidence of an underlying autoimmune disease.

Elevated HP-antibodies were detected in 12/21 patients (55%) with gastric and 32/47 (69%) patients with pancreatic cancer. In addition, 17/18 (94%) patients with MALT lymphoma had a positive HP-serology. No significant correlation was observed between the IL-6 levels and HP status.

Discussion

IL-6 is a pleiotropic cytokine that has been implicated in the pathogenesis of several autoimmune diseases, as well as lymphoproliferative disorders, including multiple myeloma, lymphoma and Castleman’s disease (15-18). Low serum IL-6 levels were observed in some diseases (e.g., monoclonal gammopathies), while elevated serum IL-6 levels were found in others such as diffuse large B-cell lymphomas. The latter are usually associated with adverse prognostic features and are predictive of a poor failure-free and overall survival in multivariate analysis (19). The adverse prognostic significance of the elevated serum IL-6 levels has been shown in patients with Hodgkin disease, various indolent non-Hodgkin lymphomas including CLL, renal cell carcinoma, breast cancer, ovarian carcinoma, prostate carcinoma, esophageal cancer, gastric cancer, pancreatic cancer and colorectal carcinoma (20-27).

The results from our series showed that the serum IL-6 levels were significantly higher in patients with stage I gastric MALT lymphoma than in gastric cancer. MALT lymphoma and gastric cancer are both associated with chronic HP infection. To date, no comparison of the cytokine levels between these two HP-associated malignancies has been performed. In view of the literature, the significantly higher levels in MALT lymphoma might reflect the greater role of HP in its development compared to gastric cancer. This is highlighted by the fact that MALT lymphoma is preceded by HP-positive follicular gastritis in about 90% of cases (5), and the observation that selected patients developed long-lasting complete remission following HP eradication (6). The results of a recent trial reporting that IL-6 reduced the level of apoptosis among antigen-stimulated cells (28) is also in keeping with an important role in the development of gastric MALT lymphoma.

Figure 1. IL-6 levels (pg/ml) in gastric MALT lymphoma, gastric cancer and pancreatic cancer (mean±SD).
In gastric cancer, however, conflicting results have been published. The results from Yamaoka et al. (29) differ from those of Wu and colleagues (10), who reported that there was no relationship between the serum anti-HP antibody and the serum IL-6 levels in patients with gastric cancer. Nevertheless, one in vitro study showed an anti-apoptotic effect of IL-6 in gastric cancer (30). In gastric cancer, IL-6 was also associated with elevated levels of VEGF and advanced disease status, thus indicating a potential role of IL-6 in the angiogenesis of gastric cancer via modulation of VEGF (31). It must be taken into account that the patients with gastric or pancreatic cancer in this trial were suffering from inoperable, locally advanced or metastatic disease, while virtually all patients of the MALT group presented with stage I disease, rendering the elevated IL-6 levels even more remarkable.

When the IL-6 levels, obtained from patients with pancreatic cancer, were compared to those with gastric cancer, again significantly higher IL-6 levels were encountered in the former. On the other hand, no difference was observed between MALT lymphoma and pancreatic cancer. Several observations suggest that IL-6 is involved in the clinical course of pancreatic carcinoma (32). In contrast to MALT lymphoma and gastric cancer, no strong association between pancreatic cancer and HP was found until now. While there is some evidence from two studies that patients with pancreatic cancer have a higher rate of HP-seropositivity than controls, the possible mechanisms have not been elucidated yet (12-14).

In our trial, no significant difference was found between HP-positive and HP-negative individuals, indicating that the observed IL-6 levels were not influenced by the HP status, but most probably by the malignant disorder.

Our data suggest that IL-6 plays a major role in MALT lymphoma of the gastric mucosa, as reflected by the significantly higher IL-6 in MALT lymphoma than in gastric cancer. In view of this, anti-IL-6 therapy might be useful in the treatment of MALT lymphoma. Antibiotic agents regularly used for HP-eradication, i.e., clarithromycin and amoxicillin, have been shown to interact with IL-6, which thus might constitute an additional therapeutic mechanism of antibiotic combinations (33). Further trials are warranted to fully elucidate the role of IL-6 in the development and therapy of gastric MALT lymphoma.

References

Received March 16, 2006
Accepted May 15, 2006