Monocyte Chemoattractant Protein-1 Serum Levels in Patients with Oral Squamous Cell Carcinoma

A. Andisheh-Tadbir, B. Khademi, M. Malekzadeh and B. Zareifar
1Oral and Dental Health Care Research Center, Department of Oral and Maxillofacial Pathology, School of Dentistry,
2Department of Otolaryngology, Khalili Hospital, Shiraz Institute for Cancer Research,
3Shiraz Institute for Cancer Research,
4Student Research Committee, School of Dentistry, International Branch, Shiraz University of Medical Sciences, Shiraz, Iran

Abstract: Monocyte chemoattractant protein-1 (MCP-1) has been shown to be a potent chemotactic factor for monocytes. It acts as an important factor in the cytokine network which regulates tumor proliferation. The association between serum MCP-1 level and oral squamous cell carcinoma has not been clarified yet. The aim of this study was to determine MCP-1 serum levels in patients with oral squamous cell carcinoma and investigate if it is correlated with clinicopathological features of tumor. Using an ELISA kit, the circulating levels of MCP-1 in blood serum of 54 oral squamous cell carcinoma patients with 32 healthy control samples were assessed. The serum MCP-1 concentration in OSCC patients was significantly lower (573.1±238.6 pg mL⁻¹, n = 54) compared with healthy controls (719.7±354.5 pg mL⁻¹, n = 32, p = 0.02). There was no apparent correlation in serum MCP-1 concentration with the clinicopathological features such as stage, tumor size, nodal status and histological grade. Serum levels of MCP-1 decreased in patients with oral squamous cell carcinoma but no clear-cut relationship was detected between MCP-1 levels and clinicopathologic factor. These results suggest that MCP-1 may not be a useful marker for recognition of clinical behavior of oral squamous cell carcinoma but further studies are recommended.

Key words: Chemokine, monocyte chemoattractant protein-1, oral squamous cell carcinoma

INTRODUCTION

Regulating cell trafficking and inducing the chemotaxis of different leukocyte subtypes is performed by chemokines (chemotactic cytokines) which are the small heparin-binding proteins. They are structurally related to cytokines and constitute a large family of peptides (60-100 amino acids) (Deshmane et al., 2009).

Up to now, more than 50 chemokines have been known. According to the organization of positionally conserved cystein residues, they are categorized into four major groups but only two of them have been widely studied, namely the CC and CXC chemokines (Antonelli et al., 2006).

The genes for CXC chemokines and the members of CC chemokines are located on chromosome 4 and chromosome 17, respectively (Deshmane et al., 2009).

Generally speaking, chemokines of the CC family are chemoattractant for T lymphocytes, monocytes and natural killer cells whereas CXC chemokines are attractant for neutrophils. They also increase neutrophils adherence to the endothelial cells (Kemp et al., 2003).

The monocyte chemoattractant protein-1 (MCP-1/CCL2), is a member of the CC chemokine family and a potent chemotactic factor for monocytes. It was located on chromosome 17 and composed of 76 amino acids and 13 KDa in size, (Deshmane et al., 2009). At first, it was obtained from the culture supernatant of a human malignant glioma (Yoshimura et al., 1989) and a monocytic leukemia cell line (Matsushima et al., 1989) and later it was shown to be the same as other chemotactic factor, thus tumor cells can produce MCP-1 (Yoshimura et al., 2013).

A wide variety of cells such as mononuclear leukocytes, fibroblasts, endothelial and epithelial cells,
smooth muscle cells, melanocytes and various tumor cells are able to express MCP-1 after being stimulated (Sullivan et al., 2011).

In the immunological responses to malignant growth, MCP-1 is known to have a key role via attraction and activation of Tumor-Associated Macrophage (TAM) (Leonard and Yoshimura, 1990).

In relation to tumor progression in several malignancies, a high tumor levels of MCP-1 has been reported by a number of studies (Melgarejo et al., 2009; Ohta et al., 2002; Bektas-Kayhan et al., 2012; Marcus et al., 2004).

Most studies assessed MCP-1 tissue expression in tumoral tissues and only few studies evaluated clinical utility of its serum measurement (Sullivan et al., 2011; Wu et al., 2013; Lu et al., 2011). Therefore this study aimed to evaluate the serum level of MCP-1 in patients with oral squamous cell carcinoma and investigate its relation with clinicopathologic parameters.

RESULTS AND DISCUSSION

Table 1 shows the clinical data and serum MCP-1 level of the patients assayed. There were 28 males and 26 females diagnosed with OSCC in this study.

The serum MCP-1 concentration in OSCC patients was significantly lower (573.1±238.6 pg mL⁻¹, n = 54) compared with healthy controls (719.7±354.5 pg mL⁻¹, n = 32; p = 0.02).

There was no significant difference in MCP-1 concentration between males (615.2±273.9) and females (527.8±188.7) (p = 0.1), nor was there a correlation between serum MCP-1 levels and age (p = 0.7).

The serum levels of MCP-1 were higher in the patients with an advanced clinical stage, higher tumor grade and lymph node involvement but the mean MCP-1 levels between groups didn't show statistically significant differences. There was no relation between the mean MCP-1 levels and tumor size (p = 0.8) (Table 1).

A wide range of normal host activities that can affect cancer are governed by chemokines, so it is possible that they have important impacts on cancer pathogenesis. As a result of this, chemokines are expected to have some influences either on promotion or inhibition on cancer cells growth according to the particular setting by which they are generated. Furthermore, because of their attracting and activating effects on lymphocytes some chemokines might be able to excite host antitumor responses. Additionally, some of the chemokines are thought to have angiogenic activities, by which can induce tumor growth and progression (Deshmule et al., 2009).

<table>
<thead>
<tr>
<th>Parameters</th>
<th>No. (%)</th>
<th>Mean MCP-1 (level=SD)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>28 (51.8)</td>
<td>615.0±273.9</td>
<td>0.1</td>
</tr>
<tr>
<td>Female</td>
<td>26 (48.2)</td>
<td>527.8±188.7</td>
<td></td>
</tr>
<tr>
<td><strong>Tumor size</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>21 (38.9)</td>
<td>578.9±257.9</td>
<td>0.8</td>
</tr>
<tr>
<td>T2</td>
<td>17 (31.5)</td>
<td>599.5±217.8</td>
<td></td>
</tr>
<tr>
<td>T3</td>
<td>16 (29.6)</td>
<td>557.1±242.7</td>
<td></td>
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<tr>
<td><strong>Lymph node involvement</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N0</td>
<td>42 (77.7)</td>
<td>559.6±217.0</td>
<td>0.8</td>
</tr>
<tr>
<td>N1</td>
<td>5 (9.3)</td>
<td>642.1±303.1</td>
<td></td>
</tr>
<tr>
<td>N2</td>
<td>5 (9.3)</td>
<td>751.2±66.8</td>
<td></td>
</tr>
<tr>
<td>N3</td>
<td>3 (5.7)</td>
<td>926.3±632.5</td>
<td></td>
</tr>
<tr>
<td><strong>Stage</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>15 (27.7)</td>
<td>513.1±139.8</td>
<td>0.6</td>
</tr>
<tr>
<td>II</td>
<td>15 (27.7)</td>
<td>551.1±208.3</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>13 (24.2)</td>
<td>610.5±230.4</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>11 (20.4)</td>
<td>652.2±302.4</td>
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</table>

Table 1: Mean MCP-1 levels in the patients with oral squamous cell carcinoma according to clinicopathological features.
It is well known that tumors are unable to grow beyond the critical size of 2-3 mm, without neovascularization. Therefore angiogenesis ability and tumor growth seems to be necessary for tumor metastasis (Zetter, 1998).

A number of proangiogenic and antiangiogenic factors have been identified as central to angiogenesis. It has been shown that in addition to the tumor itself, macrophages, act as a source of pro angiogenic cytokines (Kataki et al., 2002). So, the infiltration of TAMs might play an effective and necessary role for tumor growth and metastasis (Marcus et al., 2004).

Ohita et al. (2003) have been shown that MCP-1 expression in tumor cells can increase macrophage infiltration and macrophage mediated angiogenesis.

Increased expression of MCP-1 in relation to tumor progression has been reported in several malignancies (Melgarejo et al., 2009; Koide et al., 2004; Vande Broek et al., 2003; Johrer et al., 2004; Nakashima et al., 1995).

Several studies have investigated the circulating level of MCP-1 in patients with different malignant tumors. Elevated serum levels of MCP-1 were observed in patients with nasopharyngeal carcinoma (Lu et al., 2011), gastric cancer (Wu et al., 2013) and pancreatic cancer (Sullivan et al., 2011). Tonouchi et al. (2002) reported that the serum concentration of MCP-1 in patient with gastric cancer was significantly lower than controls. Present study, is the first report which evaluates the circulating level of MCP-1 in OSCC patients.

This study has shown that circulating MCP-1 level was significantly lower in patients compared to control group and this result was in line with Tonouchi et al. (2002) findings. Decreasing in serum levels of MCP-1 may reflect increased local consumption in tumor (Tonouchi et al., 2002).

In some studies it was reported that obese individuals are have a higher levels of MCP-1 (Murdolo et al., 2007; Kim et al., 2006). Interestingly significant reduction in serum level of MCP-1 after weight loss in those patients has been shown (Kim et al., 2006). Weight loss due to SCC may be associated with MCP-1 level reduction in OSCC patients, because many patients with OSCC, may have lost a considerable amount of weight by the time they presented for surgical intervention. It seems that further studies are needed to clarify this hypothesis and investigated the relationship between circulating levels of MCP-1 and Body Mass Index (BMI) in OSCC patients.

Yoshimura et al. (1989) in their study demonstrated that level of MCP-1 in sera of mice significantly increased 1 week after injection of tumoral cells, peaked at 3 week and then decreased at 4 week.

It can be possible that decreased MCP-1 levels in OSCC patients are because of changing in MCP-1 concentration with the tumor progression.

The fact that this study just focused one shot serum evaluation of MCP-1 but not multiple sessions of serum analysis could be considered as a limitation. Therefore further studies can be designed where multiple samples from the same patients can be collected at different time intervals and the changes in concentration of MCP-1 during the progress of the disease can be assessed.

Tse et al. (2007), demonstrated that the Single Nucleotide Polymorphism (SNP) of the MCP-1 gene promoter region creates three distinct genotypes: AA, AG and GG.

There is a correlation between GG genotype and circulating levels of MCP-1 (Tse et al., 2007). Decreased circulating levels of MCP-1 in patients compared with healthy individuals, might be due to different genotypes and so in the future studies assessment the relation between variations of genotypes and MCP-1 levels in patients and controls is recommended.

In the present study it was found that patients with advanced OSCC have higher serum MCP-1 levels compared with early stage but the difference was not statistically significant.

This result indicates that MCP-1, may play a role in tumor progression. Furthermore, although it was not statistically significant, serum MCP-1 has had an increase with advanced lymphatic spread to the regional lymph nodes.

In the present study MCP-1 serum levels in patients with well differentiated tumors was lower in compared with moderately and poorly differentiated tumors, although MCP-1 levels didn’t show statistically significant difference between groups, these findings indicate that dedifferentiation of tumor cells provokes a more aggressive host immune responses.

Current study showed that MCP-1 serum levels were not associated with tumor size. This finding indicates that MCP-1 serum levels in OSCC are not reflecting tumor bulk. As the findings of this study are limited to surgically resected patients with OSCC the temporal relationship between MCP-1 level changes in the serum and the progression of OSCC remains unknown. Therefore, additional studies on this protein in unresectable malignant lesions is recommended.

CONCLUSION

Serum levels of MCP-1 decreased in patients with oral squamous cell carcinoma but no clear-cut relationship was detected between MCP-1 levels and clinicopathologic factors. These results suggest that MCP-1 may not be a
useful marker for recognition of clinical behavior of oral squamous cell carcinoma but further studies is recomended.

ACKNOWLEDGMENTS

This study has been extract from Mrs. Eita Zareifar DDS thesis which was conducted under supervision of Dr. Azadeh Ardikesh Tadbir and Dr. Bijan Khademi.

The study was approved, registered with ID Grant No. 8591016 and supported by the Vice-Chancellor of International Branch of Shiraz University of Medical Sciences.

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