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Expression of matrix metalloproteinase-9 in the neoplastic and interstitial inflammatory infiltrate cells in the different histopathological types of esophageal cancer

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Abstract: Metalloproteinase-9 (MMP-9) is the proteolytic enzyme degrading type IV collagen, and plays important role in the invasiveness and metastatic potential of tumor cells. The aim of the current study was to compare the association between the intensity of MMP-9 expression in neoplastic cells and in the interstitial inflammatory infiltrate cells in esophageal cancer with clinicopathological features of esophageal cancer (EC) and in different histopatological types of EC, *e.g.* adenocarcinoma and esophageal squamous cell carcinoma. The study included 32 EC patients, 17 cases of squamous cell carcinoma and 15 cases of adenocarcinoma, verified histopatologically. The presence of MMP-9 in cancer tissue was investigated by immunohistochemistry on formalin-fixed, wax-embedded sections of esophageal cancers. The light microscopy was used to evaluate the expression of metalloproteinase-9 in cancer cells and in inflammatory infiltrate in the neoplastic interstitium in semi-quantitative scale. The expression of MMP-9 in cancer cells was positive in 81% of cases whereas in inflammatory cells – in 75% and increased with tumor stage, depth of tumor invasion (T factor) and lymph node metastases (N factor). In squamous cell cancer the MMP-9 expression in cancer cells and in inflammatory infiltrate was higher than those in adenocarcinoma. Mean value of MMP-9 expression in inflammatory cells was higher in early stages of EC, whereas mean expression of this enzyme in cancer cells increased with tumor stage. In conclusion, this is the first study comparing the expression of metalloproteinase-9 in cancer and inflamatory infiltrate cells in different histopatological types of esophageal cancer. We proved the synthesis of MMP-9 by cancer cells as well as by inflammatory cells and its correlation with tumor stage, tumor size, depth of tumor invasion and lymph node metastases. The results suggest the role of MMP-9 in esophageal tumorigenesis, although this issue requires further investigations.

Key words: esophageal cancer, matrix metalloproteinases, MMP-9

Introduction

Matrix metalloproteinases (MMPs) are the family of structurally related zinc dependent endopeptidases [1]. They are classified into subgroups of collagenases, stromelysins and gelatinases. Metalloproteinase-9 (MMP-9) is one of gelatinases, which is capable of degrading type IV collagen, main component of basement membrane. MMP-9 plays important role in the invasiveness [1] and metastatic potential of tumor cells through increased vessel permeation [2].

Esophageal cancer (EC) is one of the most aggressive malignant tumors and relatively common [3], especially in developing countries [4]. The mortality rates of this tumor are similar to the incidence rates, because of rapid progression, late stage of diagnosis, and poor prognosis [5]. Several studies showed high MMP-9 protein expression in tumor tissues of esophageal cancer patients [6-8]. Moreover, high MMP-9 expression in esophageal cancer correlated significantly with the depth of tumor invasion, lymphatic vessel permeation, nodal metastases and differentiation grade [2,9]. In addition, in multivariate analysis, high expression of MMP-9 in esophageal

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Table 1. Characteristics of esophageal cancer patients.

Variable		No of patients
Esophageal cancer patients		32
Gender	Female	4
	Male	28
Age	< 65 years	17
	>= 65 years	15
	Range	49 - 77
Tumor stage	I+II	11
	III+IV	21
Tumor size	< 4 cm	12
	>=4 cm	20
Depth of tumor invasion	T1+T2	5
	T3+ T4	27
Lymph node metastases	N0	10
	N1	22
Survival of patients	Alive	17
	Died of cancer	15

cancer tissue was a negative prognostic factor [9]. The recent study has shown that the preoperative serum levels of MMP-9 in esophageal cancer patients were statistically higher than in healthy subjects and correlated with clinical stage of disease as well as with tumor size [10]. The diagnostic sensitivity of serum MMP-9 measurement was higher than for classical tumor markers (carcinoembryonic antigen, CEA and squamous cell cancer antigen, SCC-Ag) and increased in the combination of MMP-9 with SCC-Ag [10]. Moreover, the presence of MMP-9 in esophageal cancer cells was proved by the immunohistochemical staining [10].

The aim of the current study was to compare the association between the intensity of MMP-9 expression in neoplastic cells and in the interstitial inflammatory infiltrate in esophageal cancer with clinicopathological features of esophageal cancer. Additionally, we evaluated the expression of MMP-9 in different histopatological types of esophageal cancer, *e.g.* adenocarcinoma and esophageal squamous cell carcinoma.

Materials and methods

Patients. Thirty-two patients with esophageal cancer were enrolled in this study (28 males and 4 females, aged 49-77 years). The samples for immunohistochemical staining were collected during surgery. All tumors were verified histopathologically (17 cases of squamous cell carcinoma and 15 cases of adenocarcinoma). Clinical status of patients was classified according to the pathological tumor, node, metastasis (pTNM) classification system [11]. TNM staging of the tumor showed 11 patients in stage I+II (early stage) and 21 patients in stage III+IV (advanced). The patients were grouped based on the tumor size, depth of tumor invasion (T factor) and lymph node metastases (N factor) (Table 1).

Immunohistochemical (IHC) staining. The tissue samples were fixed in 10% buffered formalin, dehydrated and embedded in paraffin. Mice monoclonal antibodies against human matrix metalloproteinase-9 (Novocastra; clone15W2; dilution 1:40) were used for detection of metalloproteinase-9 expression. RE7110-K Novocastra Peroxidase Detection System was used for the visualization of the antigen presence. The antigen retrieval was preformed by microvawe boiling of the paraffin sections 4 µm thick Tissue samples were elaborated according to the protocol recommended by manufacturer of assay kits (Novocastra). All the procedures were accompanied by positive (human liver) and negative (without primary antibody) controls. The light microscopy was used to evaluate the expression of metalloproteinase-9 in neoplastic tissue using semi-quantitative scale: 0 pt – no reaction; 1 pt – weak reaction; 2 pts – moderate reaction; 3 pts – intense reaction. Intensity of the metalloproteinase positive inflammatory infiltrate (macrophages, polinuclears and lymphocytes) in the neoplastic interstitium was evaluated in the same scale.

Statistical analysis. It was revealed in Chi-square test as preliminary statistical analysis that the intensity of MMP-9 expression did not follow a normal distribution. Therefore the nonparametric Mann – Whitney U-test was used. Data are presented as percent and mean value of MMP-9 expression in each analyzed subgroup. Statistically significant differences were defined as comparison resulting in $p<0.05$. Statistical analyses were performed using the STATISTICA 5.1 PL software (StatSoft Inc., Tulsa, OK, USA).

Results

The expression of matrix metalloproteinase-9 in esophageal cancer cells

The expression of MMP-9 (Fig. 1) was evaluated using semi-quantitive scale. Intensity of expression was individually different, from null (0 pt) to intense reaction (3 pts). A positive reaction (Table 2) was observed in 81% of all esophageal cancer tissue samples, in which weak (1 pt) in 53%, moderate (2 pts) in 16% and an intense expression (3 pts) in 12% of cases.

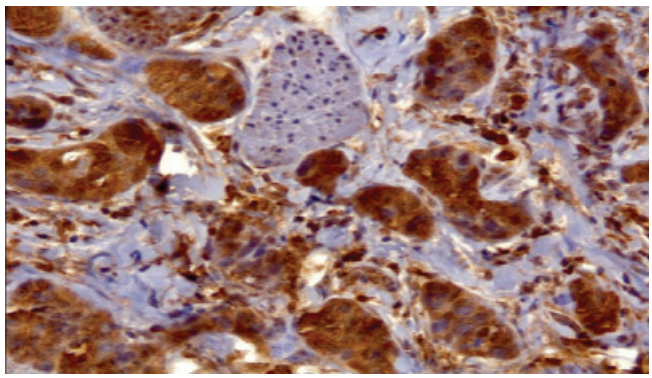

Fig. 1. The expression of matrix metalloproteinase-9 in esophageal cancer cells.

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Table 2. The expression of matrix metalloproteinase-9 in esophageal cancer cells in relation to clinicopathological features of tumor.

Group tested			Expression of MMP-9				
			positive				negative
			+	+ +	+++	all	
Espophageal cancer patients (n=32)		Cases	17	5	4	26	6
		%	53	16	12	81	19
TNM stage	I+II (n=11)	Cases	6	1	1	8	3
		%	19	3	3	25	9
	III+IV (n=21)	Cases	11	4	3	18	3
		%	34	13	9	56	9
Tumor size	< 4 cm (n=12)	Cases	5	3	1	9	3
		%	16	9	3	28	9
	>=4 cm (n=20)	Cases	12	2	3	17	3
		%	38	6	9	53	9
Depth of tumor invasion	T1+T2 (n=5)	Cases	2	1	0	3	2
		%	6	3	0	9	6
	T3+T4 (n=27)	Cases	15	4	4	23	4
		%	47	13	13	72	13
Lymph node metastases	N0 (n=10)	Cases	6	1	1	8	2
		%	19	3	3	25	6
	N1 (n=22)	Cases	11	4	3	18	4
		%	34	13	9	56	13
Histological type	Squamous cell carcinoma (n=17)	Cases	10	3	2	15	2
		%	31	9	6	47	6
	Adenocarcinoma (n=15)	Cases	7	2	2	11	4
		%	22	6	6	34	13

The relationship between the intensity of MMP-9 expression in neoplastic tissue and clinicopathological features of esophageal cancer were compared (Table 2). The percentage of positive MMP-9 expression was higher in advanced stage of tumor (III+IV) when compared to early stage of EC (I+II). Immunostaining revealed a positive reaction in 25% of cases in early stage of disease whereas 56% of those from patients being in advanced stage. There were more of weak, moderate and intense reactions in subgroup III+IV (34%, 13% and 9%, respectively) than in tumor samples from patients with early stage (19%, 3% and 3%, respectively).

Similar results were observed when analyzed relationships between MMP-9 expression with tumor size (diameter). In patients with tumors of 4 cm or greater the immunostaining revealed that the expression of MMP-9 was higher (53%) than in subgroup with tumors smaller than 4 cm (28%). Additionally, the number of weak (1 pt) and intense reactions (3 pts) in tumors above 4 cm (38% and 9%, respectively) was higher than in smaller tumors (16% and 3%, respectively).

It was shown that expression of MMP-9 in cancer cells was dependent on the depth of tumor invasion (T factor). There were eight times more cases with positive reactions (72%) in the T3+T4 subgroup of EC samples than in the T1+T2 patients (9%). Moreover, there were more of weak, moderate and intense reactions in subgroup T3+T4 (47%, 13% and 13%, respectively) than in tumor samples from subroup T1+T2 (6%, 3% and 0%, respectively).

The MMP-9 expression in tumor samples from patients with lymph node metastases (N1) was higher than in samples from N0 subgroup. There were more positive reactions in N1 group (56%) than in patients without nodal metastases (N0 group – 25%). The results have also shown the higher number of moderate (34%), intense (13%) and positive reactions (9%) in patients with lymph node metastasis (N1) in comparison to the N0 subgroup (19%, 3% and 3%, respectively).

Additionally, the intensity of immunostainig in different histopatological types of cancer was analyzed. The percentage of MMP-9-positive reactions in the subgroup of squamous cell carcinoma (47%) was

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Table 3. The expression of matrix metalloproteinase-9 in interstitial inflammatory infiltrate cells of esophageal cancer in relation to clinicopathological features of tumor.

Group tested			Expression of MMP-9				
			positive				negative
			+	+ +	+++	all	
Espophageal cancer patients (n=32)		Cases	11	6	7	24	8
		%	34	19	22	75	25
TNM stage	I+II (n=11)	Cases	4	4	2	10	1
		%	13	13	6	31	3
	III+IV (n=21)	Cases	7	2	5	14	7
		%	22	6	16	44	22
Tumor size	< 4 cm (n=12)	Cases	6	4	2	12	0
		%	19	13	6	38	0
	>=4 cm (n=20)	Cases	5	2	5	12	8
		%	16	6	16	38	25
Depth of tumor invasion	T1+T2 (n=5)	Cases	3	1	0	4	1
		%	9	3	0	12	3
	T3+T4 (n=27)	Cases	8	5	7	20	7
		%	25	16	22	63	22
Lymph node metastases	N0 (n=10)	Cases	3	4	2	9	1
		%	9	13	6	28	3
	N1 (n=22)	Cases	8	2	5	15	7
		%	25	6	16	47	22
Histological type	Squamous cell carcinoma (n=17)	Cases	8	4	3	15	2
		%	25	13	9	47	6
	Adenocarcinoma (n=15)	Cases	3	2	4	9	6
		%	9	6	13	28	19

found to be higher than in adenocarcinoma subgroup (34%).

The expression of matrix metalloproteinase-9 in inflammatory infiltrate cells

Table 3 shows the expression of MMP-9 in interstitial inflammatory infiltrate in esophageal cancer cells in relation to clinicopathological features of tumor. Positive reaction was observed in 75% of cases, where weak expression of MMP-9 was identified in 34%, moderate in 19% and intensive in 22% of tumor samples. Additionally, we analyzed the relationship between MMP-9 expression in inflammatory cells (macrophages, polinuclears and lymphocytes) and clinicopathological parameters of tumor. There were more positive cases in advanced stage (44%) in comparison to subgroup of early cancer (31%). However, we have observed higher number of positive cases with weak (1 pt) and intense (3 pts) expression of MMP-9 in advanced stage subgroup.

In the analysis of relationship between MMP-9 expression in inflammatory infiltrate with tumor size the same number of positive cases in both subgroups (38%) was observed, although the percentage of intense expression was higher in samples from patients with tumor size above 4 cm (16%) than in subgroup with smaller tumors (6%) (Table 3).

We have observed more cases of positive MMP-9 staining in T3+T4 subgroup (63%) than in T1+T2 (12%). Similarly, the percentage of weak, moderate and high intensity of expression was identified in T3+4 group (25%, 16% and 22%, respectively) in comparison with T1+T2 subgroup (9%, 3% and 0%, respectively).

Moreover, the number of positive reactions (47%) in patients with lymph node metastases (N1 subgroup) was found to be higher when compared with patients in N0 subgroup (28%). The percentage of weak (1 pt) and intense reactions (3 pts) were higher in N1 patients (25% and 16%, respectively) versus subgroup N0 (9% and 6%, respectively).

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Table 4. Mean values of MMP-9 expression in esophageal cancer and inflammatory cells.

Group tested		Mean value of MMP-9 expression	
		esophageal cancer	inflammatory cells
Espophageal cancer patients (n = 32)		1.21	1.37
TNM stage	I+II (n=11)	1.0	1.64
	III+IV (n=21)	1.33	1.24
Tumor size	< 4 cm (n=12)	1.0	1.67
	>=4 cm (n=20)	1.25	1.2
Depth of tumor invasion	T1+T2 (n=5)	0.8	1.0
	T3+T4 (n=27)	1.3	1.44
Lymph node metastases	N0 (n=10)	1.1	1.7
	N1 (n=22)	1.27	1.23
Histological type of tumor	Squamous carcinoma (n=17)	1.29	1.47
	Adenocarcinoma (n=15)	1.13	1.27

Additionally, we analyzed immunostainig in different histopatological types of cancer. We observed almost two-fold higher percentage of positive MMP-9 reactions in inflammatory cells in the subgroup of squamous cell carcinoma (47%) than in adenocarcinoma subgroup (28%). In the subgroup of squamous cell carcinoma weak (1 pt) and moderate expression (2 pts) of MMP-9 was higher (25% and 13%, respectively) than in the adenocarcinoma subgroup (9% and 6%, respectively).

Mean values of MMP-9 expression

Table 4 shows mean values of MMP-9 in esophageal cancer tissue and in inflammatory cells, which were evaluated using semi-quantitative scale. The mean value of MMP-9 expression was higher in inflammatory infiltrate (1.37) than in cancer cells (1.21), although this difference was not statistically significant. We have assessed the relationship between mean MMP-9 expression and clinicopathological characteristic of tumors. The mean expression of this enzyme in cancer cells was higher in advanced stage (III+IV subgroup) of esophageal cancer (1.33) than in early stage of tumor (1.33), but in inflammatory cells lower in III+IV subgroup (1.64) than in I+II (1.24). Similar results were observed in relation to tumor size and node lymph metastases. The mean value for tumors above 4 cm and in N1 subgroup was higher in cancer cells and lower in inflammatory infiltrate than these values for smaller tumors as well as in N0 tumors. The mean expression of MMP-9 in T3+T4 group was higher than in T1+T2 tumors as well in cancer as in inflammatory infiltrate cells. All these differences were not statistically significant.

Additionally, we analyzed values of MMP-9 expression in different histopatological types of esophageal cancer. The mean values in squamous carcinoma were higer in esophageal cancer (1.29) and inflammatory cells (1.47) in comparison to adenocarcinoma (1.13 and 1.27, respectively), but these differences were not statistically significant.

Discussion

Esophageal cancer is one of the most aggressive malignant tumors. Despite recent advances in diagnosis and treatment of this malignancy, the prognosis for EC patients is still poor in comparison with other tumors of digestive tract. Degradation of extracellular matrix (ECM) is thought to be one of key steps of invasion and metastasis of esophageal cancer. Matrix metalloproteinases are able to degrade ECM and facilitate progression of neoplastic tumors.

High MMP-9 protein expression in tumor tissues from EC patients was shown in several studies [6-8] while normal esophagus epithelium expressed no detecTable tissue level of this enzyme [7,8]. The expression of MMP-9 correlated with clinicopathological factors, such as depth of tumor invasion (T), lymphatic vessel permeation, nodal metastasis (N) and pathological differentiation of tumor (G) [2,9]. The most common technique to investigate MMPs protein expression is the evaluation in immunohistochemical staining, a semiquantitive and subjective method, employing tissue samples preparation. In this study we assessed the expression of MMPs in tumor tissue samples – as well in esophageal cancer cells as in the inflammatory infiltrate cells in surrounding tissue.

In our study we proved the presence of MMP-9 in the tumor by immunostaining. The deposits of MMP-

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9 were localized as well in the cytoplasm of neoplastic cells as well in inflammatory cells, *e.g.* macrophages, polinuclears and lymphocytes. The intensity of the enzyme expression in cancer cells was assessed, using semi-quantitative scale: 0 pt – no reaction, 1 pt – weak, 2 pts – moderate and 3 pts – intense reaction. Mean values of MMP-9 expression intensity was determined for each analyzed subgroup of patients.

The positive reaction in cancer cells was observed in 81% of specimens. Moreover, there was a tendency to increase the intensity of immunostaining in more advanced stages of tumor – 25% MMP-9 positive cases in early and 56% in advanced stage of EC, although we have not found statistically significant differences between mean tissue expression and TNM stage. We found that mean value of expression of MMP-9 in EC was higher in more advanced stage of disease (I+II versus III+IV) and increased with tumor size, depth of tumor invasion and presence of metastases in lymph nodes, what may probably be the result of enhanced production of this enzyme by cancer cells. The findings are in agreement with those obtained by El-Shahat *et al.* [7]. They showed a positive expression of MMP-9 in 36% of cases in stage I, 75% in stage II, 90% in stage III and 100% in stage IV of EC patients. Therefore, higher expression of MMP-9 in patients with more advanced esophageal cancer might be a result of the enzyme production by cancer cells [7].

Moreover, we observed higher percentage and mean values of MMP-9 expression in the subgroup of squamous cell carcinomas in comparison to the adenocarcinomas subgroup, although the two main types of EC invade and spread in a similar manner and have an equally poor prognosis [6]. The different expression of MMP in both histopatlogical types of EC may be the result of marked differences in the pathogenesis, tumor location, tumor biology of adenocarcinoma of esophagus and squamous cell carcinoma [12].

Additionally, the current study assessed the metalloproteinase expression in inflammatory cells. Infiltration of inflammatory cells is a prominent and characteristic feature of many malignant tumors. The inflammatory cells produce metalloproteinases to the peritumoral environment. These cells are also able to synthesize various cytokines enhancing expression of MMPs by both tumoral and stromal cells [13]. Intensity of the metalloproteinase positive inflammatory infiltrate (macrophages, polinuclears and lymphocytes) in the neoplastic interstitium was evaluated in the same score as in cancer cells. The positive reaction in inflammatory infiltrate cells was observed in 75% of specimens. There was also a tendency to increase the intensity of MMP-9 expression in advanced stages of tumor – 44% of MMP-9 positive cases in comparison to early stages – 31 %.

The mean expression of MMP-9 was higher in inflammatory infiltrate than in cancer cells. Interestingly, the mean value of MMP-9 expression in inflammatory infiltrate cells was higher in early stages of EC than those in advanced stages, whereas the percentage of positive reactions and mean expression of this enzyme in cancer cells increased with tumor stage. This more intense reaction in less advanced stage of disease may be the result of synthesis of MMP 9 rather by inflammatory cells, *e.g.* tumor associated macrophages, polynuclear granulocytes and lymphocytes than by cancer cells [14]. In cancer tissue, infiltration of inflammatory cells has been suggested to be a mechanism of host resistance [15].

This is the first study comparing the expression of metalloproteinase-9 in cancer and inflamatory infiltrate cells in different types of esophageal cancer, *e.g.* squamous cell cancer and adenocarcinoma of esophagus. We proved the synthesis of MMP-9 by cancer cells as well as by inflammatory cells and its correlation with tumor stage, tumor size, depth of tumor invasion and lymph node metastases. In conclusion, high incidence of MMP-9 expression in esophageal cancer tissue samples and its increased intensity in higher stages of EC suggest the important role of matrix metalloproteinase-9 in esophageal tumorigenesis, although this issue requires additional studies.

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