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HIGH MATRIX METALLOPROTEINASE 9 EXPRESSION AS A RISK FACTOR OF LYMPHOVASCULAR INVASION IN CERVICAL CARCINOMA

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Abstract

Background: Cervical carcinoma is an epithelial cancer of the cervix that causes the highest mortality among all female genital cancers. Its mortality is influenced by metastasis to various organs, and lymphovascular invasion (LVSI) has been known to be an early stage of the distant metastatic process. Still, it is very difficult to predict early. The ability of cancer cells to penetrate the surrounding tissue and then carry out LVSI occurs through the cancer cells' proteolytic enzymes. Various molecular parameters have been developed in predicting the possibility of cervical carcinoma LVSI. One of the controversial proteolytic proteins is matrix metalloproteinase 9 (MMP-9).

Objective: This study will prove MMP-9 as a risk factor for LVSI in cervical carcinoma

Methods: This case-control study used 40 paraffin blocks from patients with cervical carcinoma at BaliMed Denpasar Hospital. Paraffin blocks were then processed with an immunohistochemical stain to evaluate MMP-9 expression and an H&E stain to evaluate the LVSI. Data analysis was performed using the chi-square test with the SPSS 25 program.

Results: The study showed that 85,7% of cervical carcinomas with LVSI have high MMP-9 expression, with a significant result compared to cervical cancer without LVSI (p=0.001).

Conclusions: The MMP-9 expression was significantly associated with the risk of LVSI in cervical carcinoma

Cite this Article

INTRODUCTION

Cervical carcinoma is an epithelial cancer of the cervix that causes the highest mortality among all female genital cancers in developing countries, including Indonesia (1,2). The progression of cervical carcinoma is relatively fast, and it is even very susceptible to causing distant metastasis. One of the triggering factors for distant metastasis in cervical carcinoma is lymphovascular invasion (LVSI). Until now, predicting the possibility of metastasis in cervical carcinoma has been an obstacle. The finding of metastasis can occur several months or years after the histopathological diagnosis of cervical carcinoma is confirmed. In reporting the histopathological results of cervical carcinoma, the diagnosis will be accompanied by the stage, grade of cancer, and findings of LVSI. LVSI is the initial process that triggers metastasis, which is confirmed histopathologically if there is a picture of cancer cell emboli in the lumen of blood vessels lined with endothelial cells (1,3). However, until now, it has been tough to predict the possibility of intravascular invasion earlier.

Clinically, LVSI is one of the three Sedlis criteria in determining the need for adjuvant therapy, such as chemoradiation, after radical hysterectomy. The finding of LVSI is one of the critical factors that affect the prognosis and management of cervical carcinoma. LVSI is the process by which cancer cells infiltrate the lymphatic and blood vessels, spreading cancer cells to other body parts (1,4,5). This process is very complex and involves various molecules and different signaling pathways. One group of enzymes that plays a vital role in invasion and metastasis is matrix metalloproteinases (MMPs), especially MMP-9. MMP-9, or gelatinase B, is a proteolytic enzyme that can degrade extracellular matrix (ECM) components, such as type IV collagen and gelatin (2,6,7,8). Degradation of the ECM by MMP-9 facilitates the movement of cancer cells through the surrounding tissue and into the blood and lymphatic vessels (9). In addition, MMP-9 is also involved in modulating the tumor microenvironment, which can support the growth and spread of cancer cells. Previous studies have shown that MMP-9 expression is increased in various types of cancer, including cervical carcinoma, and that the level of MMP-9 expression correlates with tumor aggressiveness and poor prognosis (9,10,11,12,13). Other studies have also found a positive correlation between MMP-9 and lymph node metastasis (14,15,16,17,18). However, the specific mechanism by which MMP-9 affects LVSI in cervical carcinoma is still not fully understood.

MATERIALS AND METHODS

This research used a case-control analytical study design at BaliMed Denpasar Hospital on 40 patients with cervical carcinoma who met the inclusion and exclusion criteria using simple random sampling. The samples in this study were paraffin blocks from patients diagnosed with cervical carcinoma stored at the BaliMed Denpasar Hospital during the 2022-2023 period. Inclusion criteria were all paraffin blocks of cervical carcinoma that had been diagnosed histopathologically. Exclusion criteria were paraffin blocks that were damaged or did not contain enough tumor mass.

The age and size of the tumor data were obtained from medical records. Meanwhile, MMP-9 expression data were obtained from immunohistochemical (IHC) examination, and the grade of tumor budding data was obtained from hematoxylin and eosin (H&E) staining. Age is divided into>50 years and ≤50 years. The tumor size is divided into < 2 cm and >/= 2 cm. Paraffin blocks of cervical carcinoma were subjected to IHC staining using MMP-9

antibodies to evaluate MMP-9 expression. Cells expressing MMP-9 will appear brown in the cytoplasm of malignant epithelial cells. Interpretation of IHC staining is determined by high expression if the cytoplasm of tumor cells that is stained is >10% while low expression if the one that is stained is <10% (19). An anatomical pathologist observed using a microscope with 400x magnification in five different fields of view.

All data were then tabulated and analyzed. Univariate analysis was conducted to obtain a frequency distribution and characterize the subjects. Bivariate analysis was carried out with the Chi Square Test using the IBM SPSS version 25 application to determine whether high expression of MMP-9 is a risk factor for lymphovascular invasion in cervical carcinoma.

RESULTS AND DISCUSSIONS

This study found that the most significant sample was in the age group <50 years, which was 55%, with the majority in that age group being in the 4th decade. The results of this study indicate consistency with similar research at the Prof. Dr. I.G.N.G. Ngoerah Central General Hospital in 2017, which stated that the highest incidence of cervical cancer was at the age of 41-50 years (20).

Furthermore, a previous study conducted at Dr. Kariadi General Hospital, Semarang, reported the highest incidence of cervical cancer among women aged 41–50 years (21). In the present study, the distribution of tumor sizes within the sample was relatively balanced, with 52.5% of cases in the cervical carcinoma group having tumors ≥2 cm and 47.5% with tumors <2 cm. To minimize potential bias from tumor size on the study outcomes, tumor size categories were standardized across both groups.

Previous research by Huang et al. (2016) demonstrated a significant association between tumor size and both the degree of tumor budding and invasiveness ($p = 0.002$). Similarly, Park et al. (2020) reported that tumor size holds prognostic significance in cervical carcinoma, with larger tumors being more likely to metastasize distantly via the parametrium or vascular invasion, resulting in poorer prognosis ($p = 0.0129$). Consequently, tumor size was considered a critical confounding factor that required control in the present study.

As in Table 1 this study found that MMP-9 expression was closely related to LVSI in cervical carcinoma with a significance value of $p = 0.001$ ($p < 0.05$). MMP-9 expression can be seen in Figure 1, which shows that more than 10% MMP-9 is stained in the cytoplasm of cervical carcinoma with positive LVSI (B), in contrast to cervical carcinoma with negative LVSI, which shows negative staining of MMP-9 IHC. Previous studies on thyroid carcinoma found that MMP-9 was related to extracompartmental invasion and metastasis to the lymph node (21).

MMP-9 is a proteolytic enzyme that plays a role in the degradation of extracellular matrix components, which allows cancer cells to invade surrounding tissues and spread to blood vessels and lymphatics.

Based on various research results in the field of cancer, increased expression of MMP-9 is often found in more aggressive tumors and may indicate the ability of the tumor to metastasize. MMP-9 can break down collagen and other extracellular matrix components, which support cancer cells in moving and adapting to their new microenvironment. The mechanism of MMP-9 in increasing the ability of tumor invasion is (16,17,18,19).

1. Extracellular Matrix Degradation: MMP-9 helps break down the physical barrier between the tumor and blood or lymph vessels, facilitating the migration of cancer cells.
2. Interaction with Immune Cells: MMP-9 can attract immune cells to the tumor site, affecting the invasion process and response to therapy. Recruited immune cells, such as macrophages, can also produce factors that further promote MMP-9 expression, creating a positive feedback loop that enhances the invasion process.
3. Production and regulation of signaling molecules: MMP-9 releases growth factors such as VEGF and various cytokines that induce tumor growth and metastasis.
Therefore, it can be concluded that high MMP-9 expression in tumor tissue, including cervical carcinoma, is associated with an increased risk of LVSI and metastasis.

Table 1. MMP-9 expression between the 2 group samples (n=40)

Variables	Lymphovascular invasion (LVSI) group		p value
	Positive N=20	Negative N=20	
MMP-9 Expression			
High	12(60.0%)	2(10.0%)	**0.001***
Low	8(40.0%)	18(90.0%)	

Remarks * explain the significant value of the statistical result

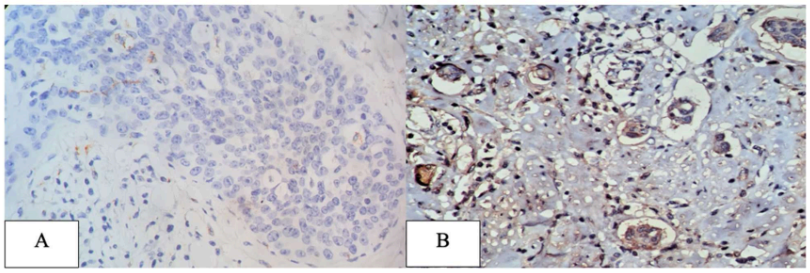

Figure 1. Comparison of MMP-9 expression between the 2 sample groups. A. Low MMP-9 expression in cervical carcinoma with negative LVSI, B. High MMP-9 expression in cervical carcinoma with positive LVSI

CLINICAL IMPLICATION

This study explores the role of MMP-9 in triggering LVSI in cervical carcinoma. A deeper understanding of this mechanism may provide new insights into the pathogenesis of cervical carcinoma and potentially identify new therapeutic targets to prevent or inhibit metastasis in patients with cervical carcinoma. Thus, this study has the potential to contribute significantly to improving treatment strategies and prognosis for patients with cervical carcinoma.

LIMITATIONS

This study did not consider whether or not there was a history of high-risk HPV infection. So, further research that sorts HPV dependent and HPV independent cervical carcinomas is needed. Further research is also needed on the role of MMP-9, specifically in LVSI, so that it can help develop more effective therapeutic strategies in the treatment of cervical carcinoma.

CONCLUSIONS

The expression of MMP-9 showed a significant correlation with an increased risk of lymphovascular invasion in cervical carcinoma. This suggests that MMP-9 may serve as a prognostic marker for the disease. Elevated MMP-9 expression appears to promote more aggressive tumor behavior, facilitating lymphovascular invasion and potentially driving further metastatic progression.

CONFLICT OF INTEREST

The authors affirm that this research was carried out without any commercial or financial involvement that could be interpreted as a potential conflict of interest.

AUTHOR CONTRIBUTIONS

Ni Wayan Armerinayanti: Conceptualization, Methodology, Writing – Original Draft, Visualization, Supervision, Project Administration, Funding Acquisition, and Resource Provision.

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