CORRELATION BETWEEN BLOOD SERUM PSA LEVEL AND MMP-2 IN PROSTATE ADENOCARCINOMA

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CORRELATION BETWEEN BLOOD SERUM PSA LEVEL AND MMP-2 IN PROSTATE ADENOCARCINOMA

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ABSTRACT

Objective: *This study aims to prove the correlation between Prostate Specific Antigen (PSA) blood level and Matrix Metalloproteinase-2 (MMP-2) expression in patients with prostate adenocarcinoma.* ***Material & method:*** *Prostate cancer patients' data from January 2009 to May 2012 were collected at the Department of Pathology, Soetomo General Hospital Surabaya. Data collected included patient medical documents, PSA blood examination, and histopathological examination. Histopathology slides and paraffin blocks of needle biopsies, Transurethral Resection of Prostate (TURP) and radical prostatectomy of prostate cancer patients were re-read, then the samples that met the inclusion criteria were stained by immunohistochemistry using antibodies MMP-2.* ***Results:*** *Data collection was done to obtain data samples of prostate cancer patients in 2009 to 2012 comprising as many as 22 patients between the ages of 52-91 years. Prostate adenocarcinoma in age of 70-79 was found in 8 patients, with a mean age of 68 years. PSA values obtained from medical documents were between 8.6-594.41 ng/ml. Spearman's test performed in this study showed a positive correlation (one-tailed) (correlation coefficient (r) 0431, $p < 0.05$) between blood PSA level and MMP-2 expression in patients with prostate adenocarcinoma.* ***Conclusion:*** *Blood PSA level correlates positively with MMP-2 expression in prostate adenocarcinoma.*

Keywords: *Prostate specific antigen, matrix metalloproteinase-2, prostate adenocarcinoma.*

ABSTRAK

Tujuan: *Penelitian ini bertujuan untuk membuktikan hubungan antara kadar Prostate Specific Antigen (PSA) darah dengan Ekspresi Matrix Metalloproteinase-2 (MMP-2) pada penderita Adenokarsinoma Prostat.* ***Bahan & cara:*** *Data arsip penderita kanker Prostat dikumpulkan di Departemen/SMF/Instalasi Patologi Anatomi RSUD Dr. Soetomo Surabaya, mulai Januari 2009 sampai Mei 2012. Pengumpulan data meliputi dokumen medik penderita, data pemeriksaan PSA darah, dan data pemeriksaan Histopatologi. Slide Histopatologi dan blok parafin hasil biopsi jarum, Transurethral Resection of Prostate (TURP) dan Radikal Prostatectomy penderita kanker prostat dibaca ulang, kemudian sampel memenuhi kriteria inklusi dipulas secara imunohistokimia dengan menggunakan antibodi MMP-2.* ***Hasil:*** *Pengumpulan data yang dilakukan memperoleh data sampel penderita kanker prostat pada tahun 2009 sampai 2012 sebanyak 22 orang, yang terjadi antara usia 52-91 tahun. Adenokarsinoma prostat terbanyak terjadi pada usia 70-79 yaitu 8 orang, dengan rerata pada usia 68 tahun. Nilai PSA yang didapatkan pada dokumen medik antara 8.6-594.41 ng/ml. Uji Spearman yang dilakukan pada penelitian ini diperoleh hasil korelasi yang positif (1-tailed) (koefisien korelasi (r) 0.431, $p < 0.05$) antara kadar PSA darah dan ekspresi MMP-2 pada penderita adenokarsinoma prostat.* ***Simpulan:*** *Terdapat korelasi positif antara kadar PSA darah dengan ekspresi MMP-2 pada adenokarsinoma prostat.*

Kata Kunci: *Prostate specific antigen, matrix metalloproteinase-2, adenokarsinoma prostat.*

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INTRODUCTION

Prostate cancer is a malignancy of the sixth most-common of all types of malignancies in the world, and becomes the second leading cause of death from cancer in men caused by the incidence of metastasis.[1,2] The incidence of prostate cancer in the United States amounted to about 29% of the incidence of all cancers and 10% of the causes of death.[2,3]

Factors contributing to the clinical application of prostate cancer, among others, are the level of Prostate Specific Antigen (PSA) in serum, Gleason grade, tumor stage, and operation edge.[4] These factors have been studied for the development of molecular prognostic markers in prostate cancer. Some literature suggests that malignant tumor cells produce some matrix that can degrade extracellular matrix (ECM), such as Matrix Metalloproteinase (MMP) family that plays a role in the invasion and metastasis of malignancy.[5]

PSA is produced by prostate gland luminal epithelial cells in the form of ductal and acinar, then secreted into the lumen of the gland and excreted along with semen within the seminal vesicles. In prostate cancer (adenocarcinoma) changes in luminal epithelial cells can penetrate and damage basal cells. Changes in luminal epithelial cells and damage in basal cells cause PSA out of the lumen and come into the blood circulation, resulting in increased concentration of PSA in the blood. The increase can be detected in the blood and used for post-therapy screening and evaluation of prostate cancer.[1,2,6]

Adenocarcinoma is a type of prostate cancer that is most commonly found, and in such malignancy there is an imbalance between MMP and Tissue Inhibitor Metalloproteinase (TIMP), which led the invasion into the surrounding tissue and the incidence of metastasis, both lymphogenic and hematogenous.[7-9] MMP-2 is a member of MMP family that has a special composition and function. MMP-2 (gelatinase A), in its function of invasion and metastasis, degrades collagen IV.[10] The invasion and metastasis that occurs in prostate adenocarcinoma can be assessed from the expression of MMP-2 in tumor cells.[11]

OBJECTIVE

The aim of this study was to prove the correlation between blood serum PSA level and MMP-2 in prostate adenocarcinoma, since studies on the correlation between blood serum PSA levels and MMP-2 expression in prostate adenocarcinoma is rare.

MATERIAL & METHODS

This study was an observational analytic study with cross-sectional approach conducted by collecting data from the archive on prostate cancer patients whose diagnosis was established histopathologically as adenocarcinoma of the prostate in the Department of Pathology, Soetomo General Hospital Surabaya, from January 2009 to May 2012. Data collected were in the form of medical documents of the patients, PSA blood examination and histopathological examination data. Histopathology slides and paraffin blocks of needle biopsies, TURP and Radical Prostatectomy from prostate cancer patients were collected, and then re-reading was done to those cases. Samples taken were patients who had data on blood serum PSA examination by ELISA and met the inclusion criteria. Immunohistochemical staining was done by using MMP-2 antibodies to eligible blocks. Results were obtained by conducting analytical testing with Spearman's correlation by comparing the patients' blood PSA with MMP-2 expression in tumor cells. The study was conducted at the Laboratory of Pathology, Faculty of Medicine, Universitas Airlangga, from May to August 2015.

Immunohistochemical staining on paraffin blocks of patients with a diagnosis of prostate adenocarcinoma was performed using antibodies MMP-2. Assessment of MMP-2 expression was done by assessing the expression in the cytoplasm or tumor cell membrane with staining intensity assessment and the percentage of stained tumor cells. Intensity scores are 0 = tumor cells not stained; 1 = light yellow; 2 = brownish yellow and 3 = brown, while the percentage of cell number is multiplied. The determination of the degree of expression was follows: 0 (negative) when the score is 0; 1+ = 1-3; 2+ = 4-6; and 3+ = 7-9.[12] Data on PSA and MMP-2 expression was tested using Spearman 'rho correlation test, with significant results if $p < 0.05$.

RESULTS

Data collection was done to obtain data on samples of prostate cancer patients from 2009 to 2012 as many as 22 people in ages of 52-91 years. Prostate adenocarcinoma occurred mostly in the age of 70-79, comprising 8 patients, with a mean age 68 years. PSA values obtained from medical documents were between 8.6 - 594.41 ng/ml.

All samples showed positive MMP-2 expression in the cytoplasm and tumor cells membrane, with the percentage as much as 30-70% and > 70%. The intensity varied from light yellow to brown. Then Spearman tests conducted in this study showed a positive correlation (one-tailed) (correla-

tion coefficient (r) 0.431, $p < 0.05$) between blood PSA level and MMP-2 expression in patients with prostate adenocarcinoma.

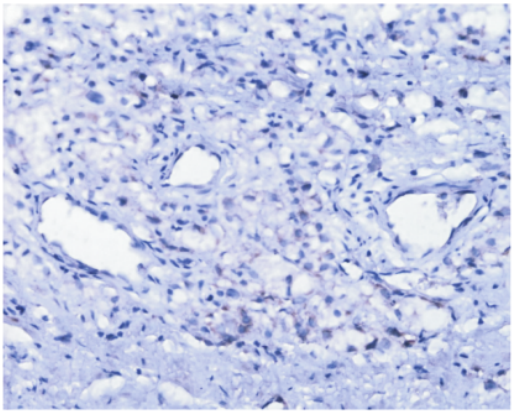


Figure 1. Preparation T. 3045/12, percentage > 70% (3+) and intensity 1 MMP-2 intensity 1 score +

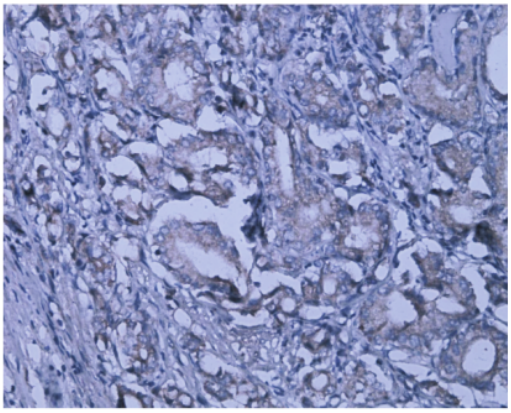
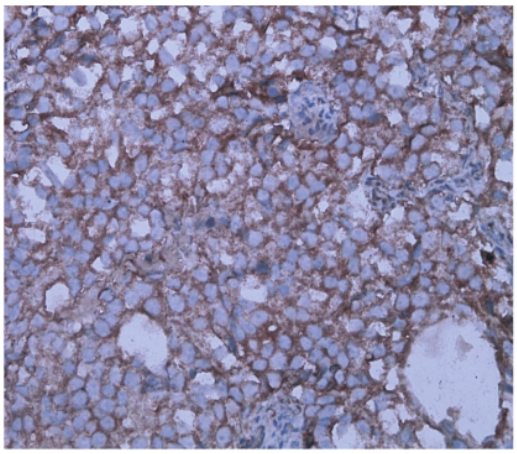


Figure 2. Preparation T. 1662/10 percentage > 70% (3+) and intensity 2.

Table 1. MMP-2 expression in prostate adenocarcinoma.

MMP-2 expression score	%	I	score
0	0	0	0
1	0	13	13
2	4	5	5
3	18	4	4
Total	22	22	22



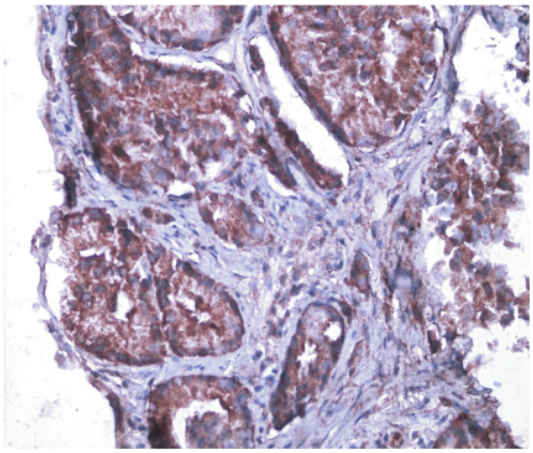


Figure 3. Preparation T. 3606/11 and 6324/10 percentage > 70% (3+) and intensity 3.

Blood PSA value in the sample was between 8.6–594.41 ng/ml, showing an increase in serum PSA level. Some literature mentions that the normal level is < 4 ng/ml, showing an increase in blood PSA levels compared to normal.[13,14]

DISCUSSION

The prostate is a retroperitoneal organ that surrounds the bladder neck and urethra, a gland shaped like a pear. Normal prostate gland is composed of two layers of cells: luminal epithelial cells and basal cells. Secretory/luminal cells have a

function to produce seminal fluid in the form of serine protease (prostate specific antigen/PSA).[1,2] Prostate cancer is most commonly in the form of adenocarcinoma, which is an invasive malignant tumor derived from luminal epithelial cells. In adenocarcinoma luminal epithelial cells change and able to penetrate basal cells, resulting in basal cell damage. Changes in luminal epithelial cells and damage in basal cells cause the produced PSA out of the lumen and enters blood circulation, resulting in increased PSA concentration in blood. The increase can be detected in blood and is used for screening and evaluation of prostate cancer post-treatment as well as indications for biopsy in patients. PSA is also a marker that is often used to diagnose prostate cancer.[1,2,6]

Murray in 2010 also stated that blood PSA value was positively related to the number of malignant epithelial cells stained with immuno-histochemical staining with PSA antibody. Increasing number of malignant epithelial cells results in increased blood PSA level, indicating that more malignant cells that damage the barrier will lead to higher levels of PSA detected in the circulation.[14]

The process of cell integrity disruption causes the release of PSA in circulation. This integration disorder also occurs in hyperplasia, inflammation and tumors. PSA value in benign prostate tissue: 0.5 ± 0.4 ng/ml, in BPH: 0:31 ± 0:25 ng/ml, so that up to now there is no definite value in cancer.[6]

Zivkovic in 2004 obtain levels of 4.0-10.0 ng/ml in benign hyperplasia, prostatitis and prostate cancer. Murray conducted a study in 2010 by measuring the weight of prostate tissue, giving results that each gram of prostate cancer tissue can increase PSA of approximately 2.3 ng/ml. Hyperplastic prostate tissue is 10 times lower than cancerous tissue. In addition, they also found that the highest PSA level was in the lumen of the prostate gland, and between gland lumen and capillary blood vessel, basal cells in the gland, prostate stromal and capillary endothelial cells they found barrier that prevents PSA to circulate in the circulation. Therefore, PSA can increase drastically in the state of prostatitis, but can return to normal after the infection resolved.[14]

All samples of this study showed positive expression of MMP-2, according to a study by Trudel (2003), who found that 70% of malignant epithelial cells had positive expression of MMP-2 due to the degradation of ECM by MMP-2.[15] There was a positive correlation between blood PSA levels with MMP-2 expression in prostate cancer, showing that increased blood PSA level is associated with increased MMP-2 expression in prostate cancer (correlation coefficient (r) 0.431, $p < 0.05$).

Malignant cells produce matrix that actively degrades with different specific substrates that act together in the degradation of Extracelluler Matrix (ECM), that is the Matrix Metalloproteinase (MMP) family, which is associated with the invasion and metastasis of tumor cells. This tumor metastases is the main cause of death in patients with cancer, particularly prostate cancer.[8,16]

Matrix Metalloproteinase (MMP), or matrix in, is a group of free endopeptidase structure that contain zinc, in cooperation with other proteolysis enzymes, such as cysteine proteinases, aspartic proteinase and serine proteinase, which plays a role in extracellular matrix degradation.[8,9] MMP is secreted in the form of proenzyme, then be activated by the proteolytic gap, and this process can be inhibited by Tissue Inhibitor Metalloproteinase (TIMP) in order to avoid degradation. Imbalance between MMP and TIMP is one of the causes of invasion and metastasis that occurs in malignant tumors.[7-10] Such imbalance is also an important factor that participates in tumor progression.[17] The expression of MMPs (MMP-2 and MMP-9) is often associated with tumor aggressiveness and overall survival, and it is also often used as a marker of malignancy.[18]

Degradation by MMP in malignancy process is taking place through several stages, including: 1) assisting the formation of a micro-environment through the release of extracellular matrix growth factor; 2) assisting the process of tumor angiogenesis, and enhancing the ability of the migration and invasion of tumor cells; 3) playing a role in angiogenesis at the site of metastasis; 4) playing a role in the damage to basal membrane of blood vessel walls, allowing intravasation and extravasation of tumor cells; and 5) playing a role in shaping new microenvirontment at metastasis site.[19]

Positive correlation between blood PSA levels with MMP-2 expression in prostate cancer showed that increased blood PSA level is associated with increased MMP-2 expression in prostate cancer (correlation coefficient (r) 0431, $p < 0.05$). Increased PSA levels in blood indicates barrier damage caused by invasion through the degradation of collagen type IV, as well as damage caused by MMP-2.[20]

According to Amalinei, Caruntu and Balan (2007), based on the substrate specificity, sequence similarity, and domain organization, MMP is divided into 6 groups: gelatinase (MMP-2, MMP-9); matrilysins (MMP-7, MMP-26); collagenases (MMP-1, MMP-8, MMP-13); stromelysin (MMP-3, MMP-10, MMP-11); membrane-type MMP (MT-MMP -> MMP-14, MMP-15, MMP-17, etc.); and other MMPs (MMP-12, MMP-19, etc.).[20]

Gelatinase-type MMP (MMP-2 and MMP-9) plays an important role because it can degrade collagen types IV, V, VII, X, XI, XIV, gelatin, elastin, proteoglycan core proteins, myelin basic protein, fibronectin, fibrillin-1, a precursor TNF-alpha and IL-1b. MMP-2 is able to break down collagen type I, which is the main component that forms the stroma and break down the molecular structure of collagen type IV which is a most protein constituent of basal membrane and the extra cellular matrix, which is instrumental in the invasion process.[7-10] Similarly, Murray in 2009 found that the expression of MMP-2 plays a role in the spread of malignant cells through invasion and metastasis.[14] MMP-2 expression (gelatinase A) in some malignant tumors has been widely studied. This relates to the prognostic value. Studies on the MMP-2 have also been started in prostate cancer (adenocarcinoma).

CONCLUSION

Blood PSA level correlates positively with MMP-2 expression in prostate adenocarcinoma and increased blood PSA can be used to predict ECM damage in MMP-2-induced prostate adenocarcinoma.

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