Analysis of IMP3 Expression in Prostate Adenocarcinomas

Prostat Adenokarsinomlarında IMP-3 Ekspresyonunun Araştırılması

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ABSTRACT

Objective: Prostate cancer is the second most common cause of male cancer deaths after lung cancer in developed countries. The prognostic factors currently identified for prostate carcinoma include preoperative serum PSA, TNM staging system, histological grade and surgical margin status and are composed of the clinically most important and useful parameters. However, all the markers studied have not been applied in clinical practice. The oncofetal protein Insulin-Like Growth Factor II has been demonstrated to be associated with aggressive tumor behavior in many organs including urothelial tumors and renal cell carcinoma. Our aim was to investigate the expression status of Insulin-Like Growth Factor II in benign prostate glands, high grade PIN and prostate adenocarcinoma, and to determine the role of Insulin-Like Growth Factor II in pathogenesis of prostate adenocarcinoma.

Material and Method: A total of 70 prostate adenocarcinoma cases accompanied by high grade PIN and benign prostate glands were evaluated by immunohistochemistry for the expression of Insulin-Like Growth Factor II.

Results: Insulin-Like Growth Factor II expression was not seen in any of the 70 prostate adenocarcinoma and high grade PIN cases and benign prostate glands.

Conclusion: Although the number of our cases was limited, our results suggested that Insulin-Like Growth Factor II protein expression was not included in the pathogenesis of the prostate adenocarcinomas and Insulin-Like Growth Factor II expression status cannot be used for diagnosis of prostate adenocarcinomas.

Key Words: Prostate, Adenocarcinoma, Insulin-like growth factor II, Pathogenesis

ÖZ

Amaç: Prostat adenokarsinomu, gelişmiş ülkelerde erkeklerde, kansere bağlı ölümler sıralamasında, akciğer kanserinden sonra ikinci sırada yer almaktadır. Günümüzde prostat karsinomlarında tanımlanan prognostik faktörler içinde preoperatif serum prostat spesifik antijen değeri, TNM sistemi esas alınarak evreleme, histopatolojik derece ve cerrahi sınırlar klinik olarak hasta takibinde en önemli ve yararlı parametreleri oluşturmaktadır. Bununla birlikte, prostat adenokarsinomlarıyla ilgili çalışmalarda kullanılan belirteçlerin hiçbirisi, klinik uygulamaya geçirilememiştir. Onkofetal bir protein olan insülin benzeri büyüme faktörü II, mesane ve böbrek tümörlerini içeren birçok organda yapılan çalışmada, agresif gidişli tümörlerle ilişkili bulunmuştur. Çalışmada amacımız, benign prostatik glandlar, yüksek dereceli prostatik intraepitelyal neoplazi ve prostat adenokarsinomlarında insülin benzeri büyüme faktörü II ekspresyon farkını değerlendirerek, prostat adenokarsinomlarının patogenezinde insülin benzeri büyüme faktörü II'nin rolünü aydınlatmaya çalışmaktır.

Gereç ve Yöntem: Çalışmada 70 prostat adenokarsinomu tanılı olgu yer aldı. Her olguda tümör alanı ve buna eşlik eden yüksek dereceli PIN alanları ile benign glandüler yapılar, immünohistokimyasal olarak insülin benzeri büyüme faktörü II ekspresyonu açısından değerlendirildi.

Bulgular: Çalışmada yer alan 70 prostat adenokarsinom olgusunda ve bunlarda tümöre eşlik eden yüksek dereceli PIN alanları ile benign glandüler yapılarda insülin benzeri büyüme faktörü II ekspresyonu saptanmadı.

Sonuç: Olgu sayımız sınırlı olmakla birlikte elde ettiğimiz bulgular, İnsülin benzeri büyüme faktörü II proteinin prostat adenokarsinomlarının patogenezinde yer almadığını ve insülin benzeri büyüme faktörü II ekspresyon durumunun prostat adenokarsinomlarında tanısal amaçlı kullanılamayacağını göstermektedir.

Anahtar Sözcükler: Prostat, Adenokarsinom, İnsülin benzeri büyüme faktörü II, Patogenez

INTRODUCTION

Prostate adenocarcinoma takes second place following lung cancer as a cause of male cancer-related deaths in developed countries (1). The incidence of prostate cancer increases with age and 75% of the cases are 65 years of age or older (2). It is quite rare in children, adolescents and young adults (1).

The etiopathogenesis of prostate cancer is still not clear but hormonal, genetic and environmental factors are thought to play a role in the tumor pathogenesis. Prognostic factors

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for prostate carcinoma that have currently been defined are preoperative serum prostate-specific antigen (PSA) value, TNM system-based staging, histopathological grade and surgical margins, which constitute the most important and beneficial parameters for patient follow-up while none of the markers used for prostate adenocarcinomas in relevant studies have actually entered clinical practice (2).

The status of insulin-like growth factor-II mRNA binding protein-3 (IMP-3) has been investigated in many solid organ tumors in recent years and is held mainly responsible for cellular proliferation, adhesion and invasion in malignant tumors (3). Although IMP-3 expression has recently been studied in various organs and tissues and especially the urogenital system, kidney and the bladder, there is only one study as far as we know on IMP-3 expression in prostate adenocarcinomas (4-9). Our aim in this study was to try to elucidate the role of IMP-3 in the pathogenesis of prostate adenocarcinomas by checking the IMP-3 expression difference between benign prostate glands, high-grade prostatic intraepithelial neoplasia (PIN) and prostate adenocarcinomas. Finding a significant difference for expression between the groups would indicate that IMP-3 could be an immunohistochemical marker to use in the routine diagnosis of prostate adenocarcinoma.

MATERIAL and METHODS

We retrospectively evaluated 70 radical prostatectomy material diagnosed as prostate adenocarcinoma between January 2005 and December 2010 in this study. Sections obtained from paraffin-embedded tissue samples fixed in 10% formaldehyde solution were reevaluated for Gleason score, high-grade PIN, perineural invasion and surgical margins. All cases were also re-evaluated regarding the World Health Organization (WHO) 2004 classification and pathological T staging was performed (3). The clinical information for the cases including age, gender and preoperative serum PSA values were obtained from pathology reports.

Paraffin blocks that included high-grade PIN, perineural invasion and benign glandular structures together with tumor were chosen for each case. Sections 4-5 micron thick were placed on poly-L-lysine coated slides for IMP-3 immunohistochemical investigation. The sections were kept in a 56-60°C autoclave for one night for the first deparaffinization procedure. The immunohistochemical staining of the sections was then performed on fully automatic immunohistochemistry device (VENTANA Bechmark/LT, Ventana Medical Systems, USA). Primary antibody used for the sections was IMP-3 monoclonal

antibody (dilution: 1/50, Clone: 69.1, Code: L523S, Dako SA, Glostrup, Denmark). Cytoplasmic staining seen in neuroendocrine lung carcinoma tumor cells was used as the positive control.

The presence of benign glandular structures, high grade PIN and presence of IMP-3 protein expression in tumor tissue were evaluated immunohistochemically. When evaluating the immunohistochemical stains for IMP-3 antibody, the total section was revealed for each case using 10x magnification of the microscope (NIKON Eclipse E200) and the presence or absence of positive staining was evaluated. Positive staining for IMP-3 was accepted in the presence of dark brown cytoplasmic staining in epithelial cells that could be easily seen with low magnification (≤40x). The staining was accepted as negative in case of weak, fine granular background staining in epithelial cells that could not be seen under low magnification (≤40x) or when there was no staining at all.

All analyses were made with the SPSS software (Version 11.0, SPSS Inc., Chicago, IL, USA) and χ^2 tests. A p value <0.05 was considered significant for the obtained results.

RESULTS

The age of the cases ranged from 51 to 74 years (mean age 61.94±5.16), and the preoperative serum PSA values were 2.0-46.2 ng/ml (mean 10.64±8.03 ng/ml).

According to the Gleason scoring system, 20 cases (28.6%) were Gleason score 6, 44 cases (62.9%) Gleason score 7, 1 case (1.4%) Gleason score 8, and 5 cases (7.1%) Gleason score 9. The histopathological evaluation of the cases revealed 20 cases (28.6%) as grade 2 (moderately differentiated), and 50 cases (71.4%) as grade 3-4 (poorly differentiated). All cases were reevaluated according to the WHO 2004 classification, and 4 cases (5.7%) were pT2a, 4 cases (5.7%) pT2b, 30 cases (28.6%) pT2c, 20 cases (28.6%) pT3a, 10 cases (14.3%) pT3b, and 2 cases (2.9%) pT3c.

High grade PIN was present in 60 (85.7%) of the 70 cases and absent in 10 (14.3%). There was perineural invasion in 48 (68.6%) cases and no perineural invasion in 22 (31.4%). The surgical margins were positive in 12 (17.1%) cases and negative in 58 (82.9%). Table I summarizes the histopathological features.

Statistical evaluation revealed a statistically significant relationship between histopathological grade and stage (p=0.012). More advanced pT stages were found in cases with higher histopathological grade. There was also a statistically significant relationship between the histological grade of the cases and perineural invasion status (p=0.034).

Table I: Histopathological findings of the study cases

|	**Number of patients**	**Percentage (%)**
Gleason Score		
Gleason Score 6	20	28.6
Gleason Score 7	44	62.9
Gleason Score 8	1	1.4
Gleason Score 9	5	7.1
Histopathological evaluation		
Grade 2	20	28.6
Grade 3-4	50	71.4
pT staging		
pT2a	4	5.7
pT2b	4	5.7
pT2c	30	42.9
pT3a	20	28.6
pT3b	10	14.3
pT3c	2	2.9
High Grade PIN		
Yes	60	85.7
No	10	14.3
Perineural invasion		
Yes	48	68.6
No	22	31.4
Surgical margins positive		
Yes	12	17.1
No	58	82.9

We found no statistically significant relationship between histopathological grade of the cases and high-grade PIN, surgical margin positiveness and preoperative serum PSA value (p=0.388; p=0.764; p=0.612 respectively).

There was no IMP-3 expression in the 70 prostate adenocarcinoma cases and the accompanying high grade PIN areas and benign glandular structures (Figure 1).

DISCUSSION

Prostate cancer is the most common malignancy in males in developed countries and takes second place after lung cancer among causes of cancer-related mortality. Prostate adenocarcinoma is usually asymptomatic in the early stages since it develops from the peripheral zone and as multifocal small foci. These cases are detected with a suspicious nodule during rectal examination or with an elevated serum PSA level (1). The presence of symptoms usually indicates locally advanced or metastatic disease (2). Early diagnosis is therefore important for effective prostate

adenocarcinoma treatment (4, 10). Major advances are especially urgently needed for the diagnostic algorithms of
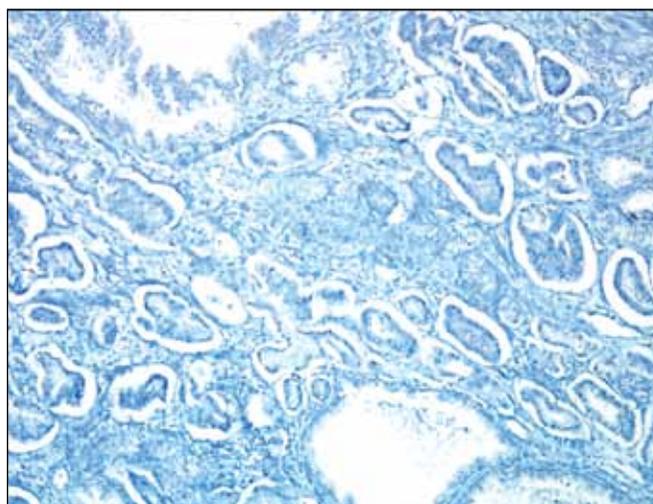
Figure 1: Grade 2 prostate adenocarcinoma with no IMP-3 expression (x200).

prostate adenocarcinoma regarding the reliable diagnosis of clinically insignificant aggressive prostate adenocarcinomas (4).

High-grade PIN is structurally benign and consists of large ducts and acini lined by atypical cells cytologically. It is frequently seen as multifocal foci in the peripheral zone. High grade PIN is seen in most of the moderately and poorly differentiated prostate adenocarcinomas. Genetic changes similar to prostate adenocarcinoma can also be seen with high-grade PIN. High-grade PIN is therefore assumed to be premalignant and considered a preliminary lesion of prostate adenocarcinoma (1).

Samaratunga et al. defined low risk groups in prostate adenocarcinomas in their study and found that cases with a low Gleason score (histopathological grade) were usually classified in pT1 and pT2a group (11). A study by Andren et al. consisting of 253 prostate adenocarcinoma cases followed up for 20 years found more advanced pT stages in cases with high Gleason scores and reported that the Gleason score was an independent predictive factor for tumor progression (10). Similar to this study, we found advanced pT stages in cases with high histopathological grade.

Lee et al. compared the perineural invasion status and clinicopathological parameters in prostate adenocarcinoma cases of 361 patients and found perineural invasion at a statistically significantly higher rate in cases with high histopathological grades (Gleason score) and reported that the perineural invasion status was significantly related to the tumor's biological aggressive behaviour (12). Similar to this study, we found a higher grade of perineural invasion in cases with higher histopathological grade.

Although the etiopathogenesis of prostate cancer is not clear, it is postulated that hormonal, environmental and genetic factors play a role in the pathogenesis (2). Insulin, one of the hormonal factors, plays a role in cancer etiopathogenesis through cellular proliferation, differentiation and apoptosis. The effects of insulin on prostate cancer development are realized through various mechanisms such as a sympathetic stimulating effect, sex hormone metabolism, the Insulin-like growth factor (IGF) pathway, signal transaction pathway, dyslipidemia and inflammation (13). The IGF family plays a key role in cellular metabolism, differentiation, proliferation, transformation and apoptosis during normal development and malignant growth. The IGF family seems to be necessary for bone metastasis, angiogenesis and androgen-independent progression of prostate cancer (14).

IMP-3 is a member of the IMP family that also contains IMP-1 and 2. The IMP protein family members play a role in RNA interaction and stabilization, cell growth and cell migration of the early stage of embryogenesis (7). The IMP-3 gene is localized in chromosome 7p11.2, and IMP-3, a product of this gene, is a 580 amino acid oncofetal protein. IMP-3 is equivalent to the K homolog domain containing protein overexpressed in cancer (KOC) protein cloned from pancreatic tumors (15). IMP-3 is expressed in normal epithelium, muscle and placenta during the early stages of human and mouse embryogenesis while it is expressed at very low or undetectable levels in adult tissues (3).

IMP-3 expression status has been investigated in many solid organ tumors in recent years and it is primarily held responsible for cellular proliferation, adhesion and invasion in malignant tumors. IMP-3 regulates the gene expression of IGF-II by binding to the 3 m-RNA region of IGF-II. IGF-II binds to IGF-I and activates IGF-I while stimulating the tyrosine phosphorylation of this receptor. The tyrosine phosphorylated IGF-I receptor sends mitogenic signals to the cell. This is followed by cell cycle regulation loss and apoptotic cycle disturbance and resulting uncontrolled cell proliferation, i.e. carcinogenesis (16).

Overexpression of IMP-3 has been found in many malignant tumors including hepatocellular carcinoma, extrahepatic biliary system, melanocytic lesions, and exocrine pancreas, esophagus and gastric cancers but expression has not been found in adjacent benign tissues (17-22).

Lu et al. have compared IMP-3 expression in invasive esophageal adenocarcinoma, metastatic esophageal adeno-carcinoma and high-grade dysplasia with the expression in benign glandular structures, low grade dysplasia and Barett esophagus in their 2009 study and found significantly higher rates in the first group. They stated that IMP-3 possibly plays an important role in the malignant transformation of esophageal adenocarcinoma with these findings (21). Similarly, Riener et al. found significantly higher degrees of strong positive IMP-3 expression in the extrahepatic biliary system in high degree dysplasia than in normal, inflamed and low-grade dysplasia cases. They also found IMP-3 expression to be significantly associated with decreased survival in carcinoma cases (18). So, the oncofetal protein IMP-3 seems to play a critical role in arranging cellular proliferation, tumor invasion and aggressive behaviour (6).

IMP-3 expression has been extensively studied in kidney and bladder tumors in the urogenital system (5-8). Jiang et al. studied 501 localized primary and metastatic renal cellular carcinoma (RCC) cases and found IMP-3

expression to be significantly higher in the metastatic RCC group than the localized primary RCC group. They also found the metastasis-independent 5 year survival rate to be significantly lower in IMP-3 positive localized primary RCC cases than IMP-3 negative localized primary RCC cases (7). Jiang et al. studied 334 primary papillary and chromophobe RCC cases and found IMP-3 expression to be significantly increased in the metastasis developing groups for both RCC subtypes (8). Hoffman et al. have studied IMP-3 expression in 716 clear cell RCC cases and reported similar to Jiang et al. that IMP-3 expression was an independent predictive factor for aggressive behaviour (7, 8, 23).

Sitnikova et al. studied IMP-3 expression in a total of 242 primary superficial bladder urothelial carcinoma and metastatic urothelial carcinoma cases and found IMP-3 expression to be positive in 20% of primary superficial bladder urothelial carcinoma cases and 93% of metastatic urothelial carcinoma cases. They also found IMP-3 positive urothelial carcinoma cases to have lower progression-independent and disease-independent survival rates (6). Li et al. investigated IMP-3 expression in benign urothelium and urothelial tumors and did not find IMP-3 expression in low grade urothelial tumors including benign urothelium and urothelial dysplasia, papillary urothelial neoplasms with low malignant potential and low grade papillary urothelial carcinomas. However, they found significantly higher IMP-3 expression in high grade urothelial tumors including high grade papillary urothelial carcinoma, urothelial carcinoma in situ and invasive urothelial carcinoma (5). A study by Özdemir et al. on benign urothelium, non-invasive and invasive urothelial carcinomas found low IMP-3 expression in benign urothelium and low and high grade non-invasive urothelial carcinomas while there was a statistically significantly higher IMP-3 expression in low and high grade invasive urothelial carcinoma cases. These finding and the other studies indicate that IMP-3 expression can be related to aggressive tumor behaviour in urothelial carcinomas (9).

The cases in our study were classified according to the WHO 2004 classification. Benign prostate tissue and high-grade PIN were also included in the study. Metastatic prostate adenocarcinomas were not included in our study. All cases were analysed for IMP-3 expression. Although we found IMP-3 expression in positive controls and internal controls, we did not find IMP-3 expression in the 70 prostate adenocarcinoma cases and the accompanying high-grade PIN areas and benign glandular structures in our study. Ikenberg et al. have investigated IMP-3 expression with the tissue microarray method in total of 505 cases consisting

of 31 normal prostate tissues, 425 primary prostate adenocarcinomas and 51 metastatic or castration resistant prostate adenocarcinomas. The single study investigating IMP-3 expression in prostate adenocarcinoma has found no IMP-3 expression in 16.7% of normal prostate tissue and primary prostate adenocarcinomas (71 cases) while weak expression was found in 69.2% (294 cases), moderate expression in 13.4% (57 cases) and strong expression in 0.7% (3 cases) of the primary prostate adenocarcinomas. IMP-3 expression was not observed in 25.5% of the metastatic or castration-resistant prostate adenocarcinoma cases (13 cases) while there was weak expression in 58.8% (30 cases) moderate expression in 5.9% (3 cases) and strong expression in 9.8% (5 cases). When compared to normal prostate tissue, they found IMP-3 expression to be significantly higher in prostate cancer. However, this expression was not found to be associated with the pT stage, Ki-67 proliferation index, preoperative serum PSA value and surgical boundaries. They have only stated that IMP-3 expression may be weakly or mildly significantly associated with the Gleason score but this had little value regarding the prognostic significance in the clinical and pathologic correlation analysis of prostate adenocarcinomas (4). When we compare the Ikenberg et al. study on IMP-3 expression in prostate adenocarcinomas and our study, we were unable to show staining in any of our cases although we used the antibody from the same clone as theirs and in a more concentrated manner. Our number of cases was quite limited compared to the Ikenberg et al. study and did not include any metastatic cases. Despite our limited number of cases, our findings indicate that the IMP-3 protein does not play a role in prostate adenocarcinoma pathogenesis and IMP-3 expression status cannot be used for diagnostic purposes in prostate adenocarcinomas.

In conclusion, IMP-3 oncofetal protein has been shown to play a role in malignant transformation in many malignant tumors including the hepatobiliary system, esophagus, gastric, pancreas, and urothelial tumors, and melanocytic lesions. It has also been said to possibly be a sensitive and specific marker for the diagnosis of the invasive tumor and high-grade dysplasia in these tumors. However, our findings show that IMP-3 plays no role in the malignant transformation of prostate adenocarcinomas in contrast to tumors in many other systems. It therefore does not seem possible to use it in diagnostic algorithms for the reliable diagnosis of clinical insignificant aggressive prostate cancers.

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