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ORIGINAL ARTICLE

Detection of CD155 Marker in Benign Prostate Hyperplasia Patients Infected with Human Papillomavirus

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ABSTRACT

Background: *Human Papillomavirus (HPV) has been implicated in the pathogenesis of Benign Prostate Hyperplasia (BPH), suggesting a potential viral influence on the disease's development and progression* ***Objctive:*** *This study aims to Detection of CD155 marker in molecular Diagnosed Human papillomavirus patients infected with Benign Prostate Hyperplasia (BPH).* ***Methodology:*** *Prostate tissue samples from 50 BPH patients in Ramadi City were collected between December 2023 and April 2024. After PSA and ultrasound confirmed BPH cases, PCR-based HPV16 and HPV18 genotyping was carried out. Twelve of the 39 samples with positive HPV16 tests also tested positive for HPV18. In the eleven samples that did not test positive for HPV16 or HPV18 by PCR, further analysis was performed to confirm the expression of CD155.* ***Results:*** *In 50 prostate tissue samples, total PSA was higher in patients with enlarged prostates (9.82 ± 4.33 ng/ml) than in those with normal prostates (7.04 ± 4.51 ng/ml), while free PSA was lower (0.35 ± 0.12 ng/ml vs. 0.48 ± 0.23 ng/ml), though differences were not statistically significant (p=0.272, p=0.171.(For PCR16-positive patients (n=39), total PSA was slightly higher (11.95 ± 6.39 ng/ml) than in PCR16-negative patients (9.50 ± 4.65 ng/ml), with free PSA levels of 0.38 ± 0.14 ng/ml and 0.31 ± 0.12 ng/ml, respectively (p=0.648, p=0.412). PCR18-positive patients (n=12) had a total PSA of 9.05 ± 5.01 ng/ml, compared to 12.16 ± 7.55 ng/ml in PCR18-negative patients (p=0.550), while free PSA levels were similar (p=0.738.(CD155 expression was significantly associated with HPV infection. Among PCR16-positive patients, 92.1% had positive CD155 expression (p<0.001), while all PCR18-positive patients (100%) showed CD155 positivity, compared to only 2.6% of PCR18-negative patients (p<0.001.* ***Conclusion:*** *With a substantial association between HPV16 and CD155 marker expression, our work demonstrates the significant occurrence of HPV16 and HPV18 in BPH patients. According to these results, HPV infection may have a part in modifying CD155 expression, which could aid in the pathophysiology of BPH. The underlying processes and possible diagnostic and therapeutic consequences of this connection require more investigations.*

INTRODUCTION

Benign Prostate Hyperplasia (BPH) is a common condition affecting older men, characterized by an increase in prostate size that can lead to urinary symptoms and complications[1,2].

While the exact etiology of BPH remains unclear, emerging evidence suggests that viral infections, particularly those caused by Human Papillomavirus (HPV), may play a significant role in its pathogenesis[3–5].

HPV is known for its association with various cancers, notably cervical cancer, and recent studies have begun to explore its potential link to prostate conditions[6,7].Among the numerous HPV serotypes, types 16 and 18 have been identified as high-risk strains associated with malignancies[8].

Their presence in the prostate may contribute to inflammatory processes or immune dysregulation, thereby influencing the development of BPH[9,10]. The CD155 marker, a known immune checkpoint protein, has garnered attention for its role in modulating immune responses in various malignancies and infections[10,11].

Investigating the expression of CD155 in relation to HPV infection could provide insights into the immunological landscape of BPH and its potential viral associations[12,13].

In assessing prostate health, Prostate-Specific Antigen (PSA) measurements serve as critical biomarkers for disease surveillance and diagnosis[14,15].

Of particular importance is free PSA, which constitutes a distinct fraction of the total PSA and has proven to be a valuable diagnostic indicator. The ratio of free to total PSA becomes particularly relevant in cases where total PSA levels range between 4 and 10 ng/mL, providing enhanced diagnostic accuracy[16].

Clinical studies have established a clear inverse correlation between free PSA percentages and cancer risk assessment: patients presenting with free PSA levels below 10% face an elevated cancer risk of approximately 50%, whereas those with levels exceeding 25% typically demonstrate a significantly lower risk, generally below 10%. This risk stratification has become instrumental in guiding clinical decision-making and patient management strategies[17].

Further refinements in PSA analysis include PSA density, calculated by dividing total PSA by prostate volume, with values ≥0.15 warranting closer investigation. PSA velocity and doubling time also serve as valuable prognostic indicators, with annual increases exceeding 0.75 ng/mL or 25% suggesting potential malignancy. The PSA doubling time, particularly relevant in known prostate cancer cases, correlates significantly with mortality rates – doubling times of less than one year are associated with a 50% five-year mortality rate, compared to 10% for doubling times exceeding 12 months.This study aims to detect the presence of HPV serotypes 16 and 18 in tissue samples from patients diagnosed with BPH and assess their correlation with CD155 expression by elucidating these relationships.

METHODOLOGY

Patient Selection and Sample Collection:

In this study, 50 patients who were suspected of having benign prostatic hyperplasia (BPH) were included. In order to confirm BPH, ultrasound imaging was performed after prostate-specific antigen (PSA) testing, which was the first step in the sequential diagnosis process. Urine samples were obtained after diagnosis in order to use PCR to detect HPV. In order to determine its correlation with HPV infection in cases of BPH, prostate tissue samples from patients were analyzed further.

Ethical Approval:

The "Research Ethics Committee of the Ministry of Higher Education in Iraq, as well as the Institutional Review Board of the Iraqi Ministry of Health" granted ethical approval for the study. Before beginning any study-related procedures, we requested written informed permission from the subjects. The University of Anbar's College of Medicine served as the study's site.

DNA Extraction and PCR Analysis:

To identify HPV serotypes 16 and 18, polymerase chain reaction (PCR) was carried out after DNA extraction using the Quick-DNA Viral Kit (ZymoResearch, USA). The intended sequences were amplified using particular forward and reverse primers. Information about the primers is given in Table (1) We used an Applied Biosystems 2720 heat cycler to perform PCR reactions. In every 25 µl PCR reaction, there was 12.5 µl of OneTaq (NEB®) Mastermix present.1.5% (10 pmol/µl) of each primer and 3 µl of isolated DNA• Nuclease-free water (6.5 µl).

Table 1: Primer Sequences of HPV Serotype and their size Gene

Gene		Sequence of forward and reverse Primer (5´-3´)	PCR Product Size bp	Annealing Temp.	Reference
HPV16	F	5-AGCTTTGCAATATCCCCTGTGA -3	**353 bp**	**60**	**NCBI**
	R	3- CCAAATAGAAGTCACGTCGAGGA-5			
HPV18	F	5- TCTAAACCTGCCAAGCGTGT -3	**681 bp**	**64**	
	R	3- AAGGGTAGACAGAATGTTGGACA -3			

Tissue Sample Processing and Histological Analysis:

Histological Analysis and Tissue Sample Processing Samples of prostate tissue were taken from patients with HPV following molecular diagnosis. Fifty prostate tissue biopsies in all were chosen using stringent inclusion criteria. The tissue samples were gathered and maintained by paraffin embedding and formalin fixation (FFPE). For additional analysis, fresh samples were also preserved at -80°C after being snap-frozen in liquid nitrogen at -196°C. Freeze tissue sections were immersed in an OCT compound, cryosectioned into 5-µm slices, and then placed on glass slides for histological analysis. Before staining, the slices were fixed for 10 minutes in cold acetone (-20°C) to maintain tissue structure. Sections that had been paraffin-fixed were deparaffinized, rehydrated with 70%, 95%, and 100% graded ethanol solutions, and then washed with distilled water. Retrieval of antigen was done previously incubation with 3% hydrogen peroxide to block endogenous peroxidase activity, cut with a cryostat into 5-µm slices, and then placed on glass slides for histopathological analysis [18 19].

Immunohistochemical Staining for CD155:

Immunohistochemical staining was carried out using the CD155/PVR Polyclonal Antibody (Elabscience, China; Catalog Number: E-AB-61100). Visualization was performed using 3,3'-diaminobenzidine (DAB). Positive CD155 expression was indicated by brownish, chocolate-colored staining in tissue sections, particularly in samples infected with HPV16 and HPV18, suggesting a potential link between HPV infection and CD155 expression in BPH patients.

Statistical Analysis: Data analysis was performed using the available statistical package SPSS-22(Statistical Package for the Social Science). Data was reflected in simple frequency, and percentage measurements. The significance of differences in different percentages (quality data) was evaluated using the One 00Way Analysis of Variance (ANOVA) and Chi-square test (X2). Statistical significance is considered whenever the P-value for the relevance check was equal to or less than the P-value for the relevance check (0.05).

RESULTS

The age distribution of patients diagnosed with benign prostatic hyperplasia (BPH). The highest proportion of cases is observed in the 55–64 age group, accounting for 36% of the total, followed by individuals aged 65 and above at 30%. Patients within the 45–54 age range constitute 22% of cases, while those under 45 represent the lowest percentage at 12%. These findings reinforce the established correlation between advancing age and the increased prevalence of BPH, reflecting the progressive nature of prostatic hyperplasia in older populations.

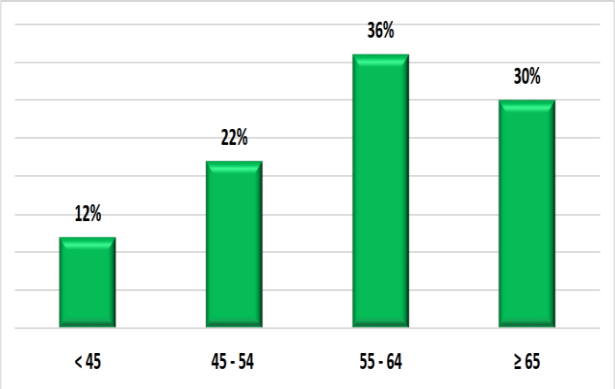

Fig 1: Distribution of BPH patients according to age group

The results in table 2 indicate a comparative evaluation of total and free prostate-specific antigen (PSA) levels in individuals with normal and enlarged prostates. Statistical analysis revealed no significant variation in total PSA (P = 0.272) or free PSA (P = 0.171) between the groups.

Table 2: Comparison of free and total PSA according to the prostate size

Characteristics	Prostate size		P-Value
	Enlarged (n= 7)	Normal (n= 43)	
Total PSA (ng/ml) Mean ± SD	**9.82 ± 4.33**	**7.04 ± 4.51**	**0.272**
Free PSA (ng/ml) Mean ± SD	**0.35 ± 0.12**	**0.48 ± 0.23**	**0.171**

Total and free prostate-specific antigen (PSA) levels were assessed in relation to HPV16 and HPV18 PCR status. The statistical analysis demonstrated no significant variations in PSA levels between HPV-positive and HPV-negative groups for HPV16 (Table3).

Table 3: Comparison of free and total PSA according to PCR of HPV serotype16 and PCR of serotype HPV18

Characteristics	PCR16		PCR18	
	Positive (n= 39)	Negative (n= 11)	Positive (n= 12)	Negative (n= 38)
Total PSA (ng/ml) Mean ± SD	11.95 ± 6.39	9.50 ± 4.65	9.05 ± 5.01	12.16 ± 7.55
	P = 0.648		**P = 0.550**	
Free PSA (ng/ml) Mean ± SD	0.38 ± 0.14	0.31 ± 0.12	0.39 ± 0.16	0.36 ± 0.13
	P = 0.412		**P = 0.738**	

The results show (Table 4) the distribution of CD155 expression among patients categorized by HPV16 PCR status. A markedly higher percentage of HPV16-positive patients (92.1%) demonstrated CD155 expression compared to HPV16-negative individuals (7.9%), with statistical analysis indicating a highly significant association ($P < 0.001$).

Table 4: Distribution of the study patients according to results PCR of HPV serotype16 and expression of CD155

Variable	PCR16		Total (n= 50) No. (%)	P- Value
	Positive (n= 39) No. (78%)	**Negative (n= 11) No. (22%)**		
CD155				
Positive	35 (92.1)	3 (7.9)	38 (76.0)	**< 0.001**
Negative	4 (33.3)	8 (66.7)	12 (24.0)	

Table 5 demonstrates a strong relationship ($P < 0.001$) between BPH patients' expression of CD155 and HPV-18 infection. Whereas 97.4% of cases (100%) did. These results indicate a substantial correlation between HPV-18 infection and the overexpression of CD155, suggesting that CD155 may play a role in alterations to prostatic tissue

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Table 5 :Distribution of the study patients according to results of PCR of serotype HPV18 and expression of CD155

Variable	PCR18		Total (n= 50) No. (%)	P- Value
	Positive (n= 12) No. (24%)	**Negative (n= 38) No. (76%)**		
CD155				
Positive	11 (100.0)	0 (0)	11 (22.0)	**< 0.001**
Negative	1 (2.6)	38 (97.4)	39 (78.0)	

The results which shown in Figure (2) displays a prostate tissue biopsy stained with immunohistochemistry using DAB, which produces a brown color to indicate CD155 expression.

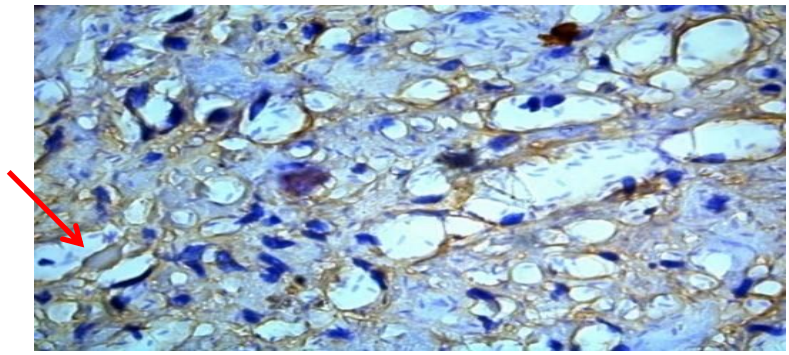

Fig 2: Immunohistochemical Staining of CD155 Expression in Prostatic Tissue of BPH Patients Infected with HPV16 (DAB Immunohistochemical Staining)

Prostate tissue from BPH patients that was PCR-confirmed to be HPV-negative (Figure 3). DAB immunohistochemical testing showed no brown staining, demonstrating no immune evasion linked to HPV and the lack of CD155 expression.

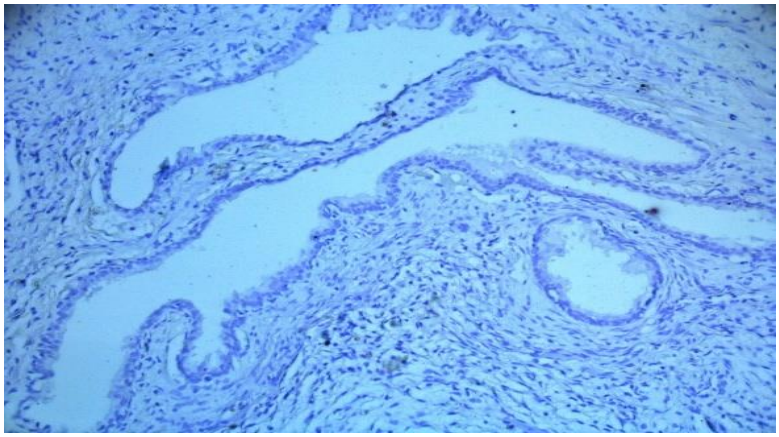

Fig. 3: Lack of CD155 Expression in Prostatic Cells of BPH Patients

DISCUISSION

The data indicates that benign prostatic hyperplasia (BPH) becomes more prevalent with advancing age, peaking in individuals aged 55 to 64. This pattern is likely due to hormonal changes, increased prostate cell growth, and a weakening immune system as men age, all of which contribute to BPH development. These age-related factors may also increase susceptibility to infections like human papillomavirus (HPV) and other risk factors. In contrast, younger men tend to have lower BPH rates, possibly because of more stable hormone levels, fewer prostate cells, and a stronger immune response to infections. These observations are consistent with previous research showing that BPH prevalence rises with age.[20,21]

The data analysis which presented in the (table2) indicates that, although patients with enlarged prostates had higher mean total and free PSA levels compared to those with normal prostates, the differences were not statistically significant. This suggests that PSA levels alone may not be a reliable indicator of prostate enlargement, as they can vary widely among individuals. Therefore, relying solely on PSA testing for diagnosing benign prostatic hyperplasia (BPH) is insufficient. Integrating PSA testing with imaging techniques, such as transracial ultrasonography (TRUS), enhances diagnostic accuracy and helps distinguish BPH from other prostate conditions, including prostate cancer. This approach aligns with findings from previous studies, which support the combined use of PSA testing and imaging for more precise diagnosis. [22,23]. The findings of this investigation, however, were different from ours in that individuals with benign prostatic hyperplasia (BPH) frequently have elevated serum levels of prostate-specific antigen (PSA). According to studies, BPH patients may experience PSA levels that are two to three times higher than usual.[24,25]

The data in Table (3) show that HPV16 or HPV18 infection does not have a significant effect on PSA levels in patients with benign prostatic hyperplasia (BPH). This suggests that HPV infection may not notably influence PSA levels in BPH patients. It is possible that, during the PSA test, the virus could be in a dormant or latent phase, without causing active inflammation. Moreover, the sensitivity of current PSA tests might not be sufficient to detect the impact of HPV infection, highlighting the need for more targeted HPV testing. These results are in line with prior studies, which have similarly found no significant relationship between HPV infection and PSA levels in BPH patients.[26,27]

In this study the table (4) a notable difference in CD155 expression was found between HPV16-positive and HPV16-negative BPH patients. Most HPV16-positive patients showed positive CD155 expression, while a smaller proportion of HPV16-negative patients exhibited positive CD155 expression. This indicates that HPV16 infection may play a role in influencing CD155 expression in BPH patients HPV16, a high-risk strain, produces the E6 and E7 oncoproteins that disrupt normal cell cycle regulation. E6 binds to and promotes the degradation of the tumor suppressor protein p53, preventing the apoptosis of damaged cells. Meanwhile, E7 inactivates the retinoblastoma protein (pRb), allowing the cell cycle to bypass its usual checkpoints. This leads to uncontrolled cell division and may contribute to CD155 overexpression. The overexpression of CD155 could enable the virus to evade immune detection, thereby promoting its persistence and the potential carcinogenic effects of HPV16. These findings are consistent with previous studies, which have found a link between HPV16 infection and changes in immune markers like CD155, suggesting that CD155 may serve as a marker for HPV-induced alterations in prostatic tissues. [28–30]. These results imply that CD155 may be an effective

immunological marker for changes in prostatic tissues linked to HPV. [31,32].

This study found a significant association between HPV18 infection and CD155 expression, with all HPV18-positive patients showing positive CD155 expression. This suggests that CD155 might help HPV18 evade immune detection, potentially aiding the virus's persistence. However, the small number of HPV18-positive cases limits the ability to confirm the full significance of CD155 in HPV18-related malignancies and its potential as a biomarker or therapeutic target

HPV18 is generally less common and lower expression in the Middle East, which aligns with findings with our study this show in the table(5). Despite its lower prevalence, the potential role of CD155 in HPV18-related conditions, especially in cancer treatment, remains significant. For example, previous studies have noted that CD155 expression is higher in hormone-resistant prostate cancer, suggesting its potential as a therapeutic target. These findings support the idea that CD155 could be a useful marker for HPV18-related changes in prostatic tissues, but further research with larger sample sizes is necessary to fully understand its clinical implications. [33,34]

Image (1) displays a prostate tissue biopsy stained with immunohistochemistry using DAB, which produces a brown color to indicate CD155 expression. The staining showed that CD155 was predominantly expressed in the epithelial cells of the prostate, particularly in cells linked to HPV serotype 16. The majority of CD155-positive results were found in patients with HPV16, suggesting a stronger correlation of this serotype with BPH compared to HPV18. This observation points to the potential involvement of HPV16 in regulating CD155 expression in BPH patients.[35] Another study emphasizes how CD155 may be involved in HPV infection. [36].

The lack of CD155 expression in image (2) in normal benign prostatic hyperplasia (BPH) tissues suggests it is not involved in regular prostate cell functions. CD155 is associated with tumor growth, cell adhesion, and immune modulation, and its expression increases in pathological conditions like cancer, inflammation, or viral infections. This study suggests that CD155 could be a useful biomarker for differentiating healthy prostate tissues from diseased ones, especially in prostate or HPV-related cancers. High CD155 expression has been linked to tumor progression and metastasis, highlighting its potential as a diagnostic marker and therapeutic target for prostate diseases. [31,37].

CONCLUSION

A substantial association between HPV16 and CD155 marker expression, our work demonstrates the significant occurrence of HPV16 and HPV18 in BPH patients. According to these results, HPV infection may have a part in modifying CD155 expression, which could aid in the pathophysiology of BPH. The underlying processes and possible diagnostic and therapeutic consequences of this connection require more investigations.

Declarations:

Consent for publication: Not applicable

Availability of data and material: Data are available upon request.

Competing interests: The author(s) declare no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

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