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ORIGINAL ARTICLE

The Value of STEAP1, C-Myc And P63 Immuno-Expression in Differentiation of Prostatic Carcinoma from Its Mimickers

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ABSTRACT

Background: Prostatic adenocarcinoma is the 2nd most common cancer in males. It is important to differentiate between prostatic adenocarcinoma and its benign mimickers with novel and reliable immunohistochemical markers for early diagnosis of prostatic adenocarcinoma, (6-transmembrane epithelial antigen of prostate (STEAP1), C-myc and basal cell marker P63 can be helpful in distinguishing prostatic adenocarcinoma from benign lesions. The aim of this study is to diagnose prostatic adenocarcinoma and differentiate it from its benign mimickers using STEAP1, C-myc and P63 immunoexpression and toevaluate the role of STEAP1 overexpression in prostate cancer initiation and progression. **Methods**: Retrospective cross-sectional study was conducted on 20 cases of prostatic adenocarcinoma, 8 cases of high grade prostatic intraepithelial neoplasia (HGPIN) and 18 cases of benign prostatic mimickers. All lesions were submitted for STEAP1, C-myc and P63 immunohistochemistry and the results were correlated with clinicopathological and histopathological parameters. **Results**: P63, STEAP1 and C-myc showed highly significant difference in expression in prostatic adenocarcinoma in relation to its benign mimickers (p-value<0.001). STEAP1 immunoexpression was significantly associated with Gleason score, grade grouping and perineural invasion of prostatic adenocarcinoma (p-value <0.05). Positive STEAP1 and C-myc expression along with negative P63 showed high sensitivity (80.0%, 85.0% and 95.0%) respectively and considerable specificity (86.9%, 73.1% and 96.2%) respectively for differentiating between prostatic adenocarcinoma and its benign mimickers. **Conclusion**: STEAP1, C-myc and P63 immunoexpression was helpful in differentiation between prostatic adenocarcinoma and benign mimickers. STEAP1 may have a valuable prognostic role in prostatic adenocarcinoma.

Keywords: Prostatic adenocarcinoma, STEAP1, C-myc, P63, HGPIN.

INTRODUCTION

Prostatic adenocarcinoma is the 2nd most common cancer in men leading to morbidity and mortality. The National Cancer Institute estimated that 174,650 new cases were diagnosed with prostate cancer in USA and 31,620 deaths during 2019. Over 80% of prostate cancers are diagnosed at or above age 65 years **[1].** In Egypt, prostate cancer represents about 4.9% of male cancers and currently ranks as the 4th most common cancer. Approximately 65% of men who are diagnosed with prostate cancer in Egypt will face mortality **[2].**

Mimickers of prostatic adenocarcinoma may represent normal gland structures, benign proliferations, atrophic lesions, hyperplastic or metaplastic changes, and inflammatory processes.

Most of the mimickers are easily

recognizable in large specimens, but they may have diagnostic problems when the evaluation is done on limited tissue, such as needle-core biopsies **[3].** It presents a challenge for pathologists for correct diagnosis especially with small numbers of atypical glands in a small tissue prostatic biopsy.

There are different immunohistochemical markers for differentiation between prostatic carcinoma and its benign mimickers. From which; **STEAP1** protein mostly located at cell-cell junctions, possibly involved in transmembrane electron transfer. STEAP1 seems to regulate intercellular communication, and invasion, perhaps through regulation of ion concentration such as sodium, potassium, and calcium. It may also regulate cancer cell invasiveness, increasing the potential of STEAP1 as a diagnostic, prognostic and immunotherapeutic target. STEAP1 overexpression was observed in several organ cancers **[4].**

C-myc, a well-known oncogene has a role in the regulation of prostate growth and carcinogenesis and it is amplified with increasing grade of prostatic adenocarcinoma, particularly in metastases **[5].** Malignancy is strongly diagnosed by the absolute absence of basal cell immunohistochemical staining in a morphologically suspicious lesion. The lack of basal cell layer staining should be supported by the simultaneous positive staining of a basal cell layer in adjacent benign glands (an internal quality control). Nuclear **p63** and basal cell cytokeratin (HMWK, CK 5/6, CK 14) are both used for basal cell staining **[6].**

METHODS

A comparative retrospective cross-sectional study was carried out on 46 prostatic tissue specimens that were collected randomly from archives of Pathology Department, Faculty of Medicine, Zagazig University and some private laboratories in the period 2016-2018. Biopsy specimens were obtained as follow: 21 cases by trans-rectal ultrasound guided biopsy (TRUS) procedure, 17 cases by transurethral resection prostatectomy (TURP) and 8 cases were obtained by radical prostatectomy. The selected specimens were diagnosed and classified into 18 cases of benign mimickers of prostatic carcinoma (5 adenosis, 5 basal cell hyperplasia, 4 atrophy, and 4 cribriform clear cell hyperplasia), 8 cases of HGPIN lesions and 20 cases of prostatic adenocarcinoma. Three experienced pathologists confirmed the histopathological diagnosis independently. Clinical data such as age, total serum PSA level and type of biopsy specimen were obtained from Patients' files.

Inclusion criteria:

1- Prostatic adenocarcinoma and prostatic lesions that mimic prostatic adenocarcinoma.
2- According to WHO classification, only the newly diagnosed and non-metastasizing prostatic adenocarcinomas.
3- All the studied cases included sufficient materials for the immunohistochemical study.

Exclusion criteria:

1- Non prostatic normal structures that mimic prostatic carcinoma as (seminal vesicles, Cowper's glands, nephrogenic adenoma and rectal glands).

Steps of the study:

I. Histopathological study: Paraffin embedded tissue blocks of all cases were processed routinely and stained with hematoxylin & eosin stain to confirm the diagnosis. Prostatic adenocarcinoma cases were classified according to the classification of WHO (2016) of prostatic tumors and were graded according to the modified Gleason scoring system **[7].**

II. Immunohistochemical study: Serial sections from the same blocks were submitted for immunohistochemical staining with P63, C-myc and STEAP1 and the results were recorded, analyzed and tabulated.

1. Immunohistochemical stains:

Primary antibodies:

1) P63: Mouse monoclonal antibody (Clone 4A4; isotype IgG2a, kappa Dako, Glostrup, Denmark; Dilution 1:50) which binds to all isoforms of p63.

2) STEAP1: Mouse monoclonal antibody, recombinant human STEAP1(1-70aa) purified

E-coli. (Clone J2D2; Catalog No. GTX53786; Dilution 1:100; GeneTex, Ivrine, California, USA).

3) C-myc: mouse monoclonal antibody (Clone 9E10.3; Catalog No. MS-139-R7 ready to use, Dilution 1-50; Lab Vision, Fremont, CA, USA).

4) Universal kit: Super sensitive link labile IHC detection system (Code No. QD000-5L Multilink. Detection kit, HRP, DAB, BioGenex, CA, USA), designated to detect specific antigens in formalin fixed, paraffin embedded blocks (FFPE) using modified labeled Avidin-Biotin technique (Dako-cytomation, Glostrup, Denmark).

Sections 5 µm thick were cut from (FFPE) blocks, mounted on positive charged slides, Briefly, the slides were deparaffinized and gradually rehydrated. Antigen retrieval was performed in a microwave oven using 10 mM citrate buffer (pH 6.0). The sections were incubated overnight with the primary antibodies of STEAP1, C-myc and P63. Incubation with horseradish peroxidase (HRP) conjugated anti-rabbit secondary antibody (Cat# K4010, Dako, Carpinteria, CA) and visualized using 3,3'-Diaminobenzidine (DAB) chromogen solution. Finally, sections were counterstained with Mayer's hematoxylin and washed with distilled water and phosphate buffered saline (PBS).

Positive and negative controls:

1) Weak positive cytoplasmic and membranous brown staining of luminal cells of adjacent normal prostatic glands were used as internal positive control for STEAP1.

2) Burkitt's lymphoma was used as positive control of C-myc.

3) Squamous cell carcinoma was used as positive control for P63.

4) Sections incubated with (PBS) instead of the primary antibodies were used as negative controls.

2. *Interpretation and evaluation of immunostaining:*

1) STEAP1: STEAP1 immunoreactivity was assessed semi-quantitatively using a grade score system, as following:

The staining intensity was classified as: (0): No staining, (1): Weak staining, (2): High staining. **The percentage of stained cells were classified as:** (0): No staining, (1): ≤25% of stained cells, (2): 26 -50% of stained cells, (3): > 50% of stained cells. Subsequently, a final score was obtained by adding the percentage of stained luminal cells to the intensity of staining. Then, **score values were grouped into:** (0,1) = low score, (2,3) = Moderate score, (4-6) = High score **[8].**

2) C-myc: Immunohistochemical staining for nuclear C-myc in malignant cells was evaluated using **quick score (QS).** The QS represents the sum of a proportional score **(PS)** and intensity score (IS). The PS was calculated as the ratio of C-myc immunopositive tumor cells to the total number of tumor cells. The **PS** was classified as follows: **(**0): No nuclear staining. (1): 1%-30% of stained nuclei. (2): 31%-60% of stained nuclei. (3): 61%-100% of stained nuclei. The **IS** was classified as follows: 0, no immunostaining at high magnification.1, immunostaining only visible at high magnification. 2, immunostaining readily visible at low magnification. 3, immunostaining strongly visible at low magnification. Finally, the quick score **(QS)** of C-myc immunostaining **was divided into three groups**: Negative, (0); positive, (1-3); and strong positive, (4-6) **[9].**

3) P63: Immunoreactivity of p63 was scored by screening the slides at low power for any staining of basal cells; that evaluated semi-quantitatively as follows: no staining (0%), partial (focal) staining (<60%), complete diffuse staining (≥60%) **[10].**

Data management: The collected data were analyzed by computer using Statistical Package of Social Services (SPSS) version 24 **[11].** Descriptive and analytical methods were used. The Chi-square test ($\chi 2$) was used for comparing categorical variables. Pearson's correlation test (r) was used for correlations between immunoexpression of STEAP1, C-myc and P63. Roc curve was used to detect Sensitivity, Specificity and Accuracy of STEAP1, C-myc and P63 expression in detection malignant cases. The results were

considered statistically significant when the significant probability was (P <0.05). P-value < 0.001 was considered highly significant (HS), and P-value ≥ 0.05 was considered statistically nonsignificant (NS).

Ethical Considerations:

Written informed consent was obtained from all participants. The work has been carried out in accordance with The Code of Ethics of the World Medical Association (Helsinki Declaration of 1975, as revised in 2000) for studies involving humans **[12].** Institutional Review Board (IRB) of the faculty of Medicine Zagazig university approved the study protocol (No. 3275).

RESULTS

The cases were distributed in the age group of 50–84 years. The minimum age of patients was 50 years old and maximum age was 84 years old with the mean age was 66.4 years old. Serum PSA level ranged from 2.4 to 176 ng/ml for all studied groups. PSA level was detected in benign cases ≤ 4 ng/ml, while in the HGPIN cases ranged from 4.1-10 ng/ml, but its level was more than 10 ng/ml in malignant cases. Results showed that 40% of the studied cases of prostatic adenocarcinomas was Gleason score > 7 and perineural invasion presents in 45% of prostatic adenocarcinoma.

Immunoexpression of P63 in relation to clinicopathologic data.

Expression of P63 has highly significant difference in relation to serum PSA level (p-value<0.001). **[Table 1]**

Expression of P63 has highly significant difference in expression in prostatic adenocarcinoma in relation to its benign mimickers (p-value<0.001). **[Table 1]**

Expression of P63 has nonsignificant association with Gleason score, grade grouping and perineural invasion (p-value>0.05). **[Table 2]**

Immunoexpression of STEAP1 in relation to clinicopathologic data.

Expression of STEAP1 has highly significant difference in relation to serum PSA level (p-value<0.001). (Table.1)

Expression of STEAP1 has highly significant difference in expression in prostatic adenocarcinoma in relation to its benign mimickers (p-value<0.001). **[Table 1]**

Expression of STEAP1 was significantly associated with Gleason score, grade grouping system and perineural invasion of studied malignant cases (p-value<0.05). **[Table 2]**

Immunoexpression of C-myc in relation to clinicopathologic data.

Expression of C-myc has highly significant difference in relation to serum PSA level (p-value<0.001). (Table.1)

Expression of C-myc has highly significant difference in expression in prostatic adenocarcinoma in relation to its benign mimickers (p-value<0.001). **[Table 1]**

Expression of C-myc has nonsignificant association with Gleason scores, grade grouping system and perineural invasion (p-value>0.05). **[Table 2]**

Correlation between immunohistochemical markers in studied cases.

There was highly significant negative correlation between P63 and both STEAP1 & C-myc immunoexpression (r= -0.59 and -0.68) respectively, p-value <0.001), but there was highly significant positive correlation between both STEAP1 & C-myc immunoexpression (r= 0.80, p-value <0.001).

Diagnostic performance of STEAP1, C-myc & P63 expression in detection of malignancy in the studied cases:

P63 expression was 95.0% sensitive, 96.2% specific and 95.7% accurate, STEAP1 expression was 80.0% sensitive, 86.9% specific and 83.9% accurate and C-myc expression was 85.0% sensitive, 73.1% specific and 82.6% accurate in discrimination between prostatic adenocarcinoma and benign mimickers. **[Table 3]**

Table 1. Association between (P63, STEAP1 and C-myc expressions) and clinicopathologic parameters in studied cases

Parameters	N=46	P63			P value	STEAP1			P value	C-myc			P value
		Negative	Focal	Diffuse		Low	Moderate	High		Negative	positive	Strong positive	
		20	9	17		17	13	16		6	23	17	
Histopathology													
Benign mimics		1 (0.05)	2 (22.2)	15(88.2)	**<0.001 HS**	15(88.2)	3 (23.1)	0 (0.0)	**<0.001 HS**	6 (100)	12(52.2)	0 (0.0)	**<0.001 HS**
HGPIN		0 (0.00)	6(66.7)	2(11.8)		0 (0.0)	2 (15.4)	6 (16.7)		0 (0.0)	4 (17.4)	4 (23.5)	
Prostatic adenocarcinoma		19 (95)	1 (11.1)	0(0.0)		2(11.8)	8 (61.5)	10(83.3)		0 (0.0)	7 (30.4)	13(76.5)	
PSA level:													
< 4 ng/ml		1(0.05)	2 (22.2)	14(82.4)	**<0.001 HS**	14(82.3)	3 (23.1)	0 (0.0)	**<0.001 HS**	6 (100)	11(47.8)	0 (0.0)	**<0.001 HS**
4.1 – 10 ng/ml		0 (0.00)	6 (66.7)	3(17.6)		1 (5.9)	2 (15.4)	6 (16.7)		0 (0.0)	5 (21.7)	4 (23.5)	
> 10 ng/ml		19 (95)	1 (11.1)	0 (0.0)		2 (11.8)	8 (61.5)	10 (83.3)		0 (0.0)	7 (30.4)	13(76.5)	

Table 2. Association between (P63, STEAP1 and C-myc expressions) and histopathologic parameters in prostatic adenocarcinoma cases.

Parameter	*N= 20*	P63			P value	STEAP1			P value	C-myc			P value
		Negative	Focal	Diffuse		Low	Moderate	High		Negative	positive	Strong positive	
		19	1	---		2	8	10		---	7	13	
Gleason score:													
< 7		5 (26.3)	1(100)	---	**0.3**	2 (100)	4 (50.0)	0 (0.0)	**0.002 S**	---	4 (57.1)	2 (15.4)	**0.1**
7		6 (31.6)	0 (0.0)			0 (0.0)	4 (50.0)	2 (20.0)			1 (14.3)	5 (38.4)	
> 7		8 (42.1)	0 (0.0)			0 (0.0)	0 (0.0)	8 (80.0)			2 (28.6)	6 (46.2)	
Grades:													
1		5 (26.3)	1 (100)	---	**0.3**	2 (100)	4 (50.0)	0 (0.0)	**0.002 S**	---	4 (57.1)	2 (15.4)	**0.1**
2 – 3		6 (31.6)	0 (0.0)			0 (0.0)	4 (50.0)	2 (20.0)			1 (14.3)	5 (38.4)	
4 – 5		8 (42.1)	0 (0.0)			0 (0.0)	0 (0.0)	8 (80.0)			2 (28.6)	6 (46.2)	
Peri- neural invasion:				---						---			
Yes		9 (47.4)	0 (0.0)		**0.4**	0 (0.0)	1 (12.5)	2 (20.0)	**0.007 S**		4 (57.1)	5 (38.5)	**0.4**
No		10(52.6)	1 (100)			2 (100)	7 (87.5)	8 (80.0)			3 (42.9)	8 (61.5)	

Table 3. Diagnostic performance of STEAP1, C-myc and P63 expression in detection of malignancy in the studied cases:

Diagnostic performance	STEAP1 expression	C-myc expression	P63 expression
Area Under Curve (95% CI)	0.87 (0.80 – 0.94)	0.89 (0.80 – 0.98)	0.97 (0.92 – 1.0)
P-value	**<0.001 HS**	**<0.001 HS**	**<0.001 HS**
Sensitivity	80.0%	95.0%	95.0%
Specificity	86.9%	73.1%	96.2%
Accuracy	83.9%	82.6%	95.7%

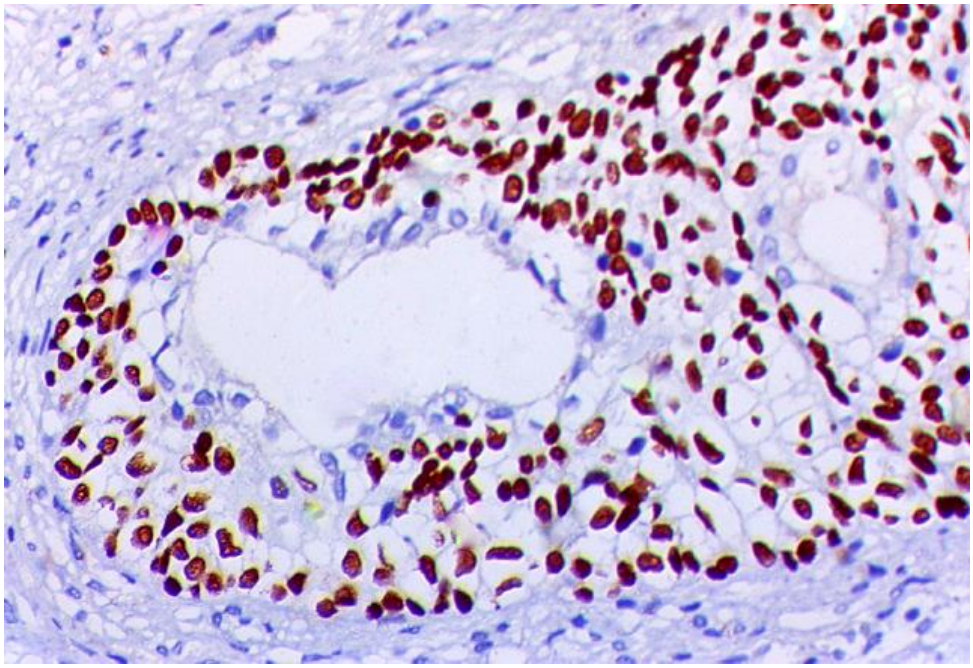

Figure 1. A case of clear cell cribriform hyperplasia showing benign looking clear cell that showed (complete) diffuse nuclear P63 expression (P63 immunoexpression, Mayer's H. x 400).

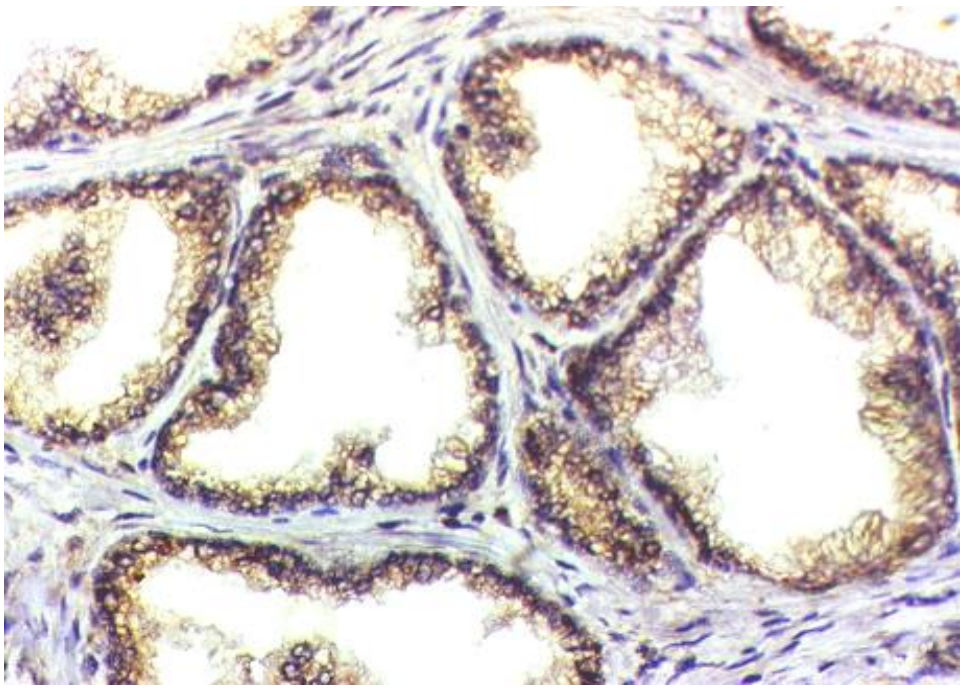

Figure 2. A case of prostatic adenomatous hyperplasia showing diffuse weak positive (score 1) STEAP1 cytoplasmic expression of the luminal cells (STEAP1 immunoexpression, Mayer's hematoxylin x 400).

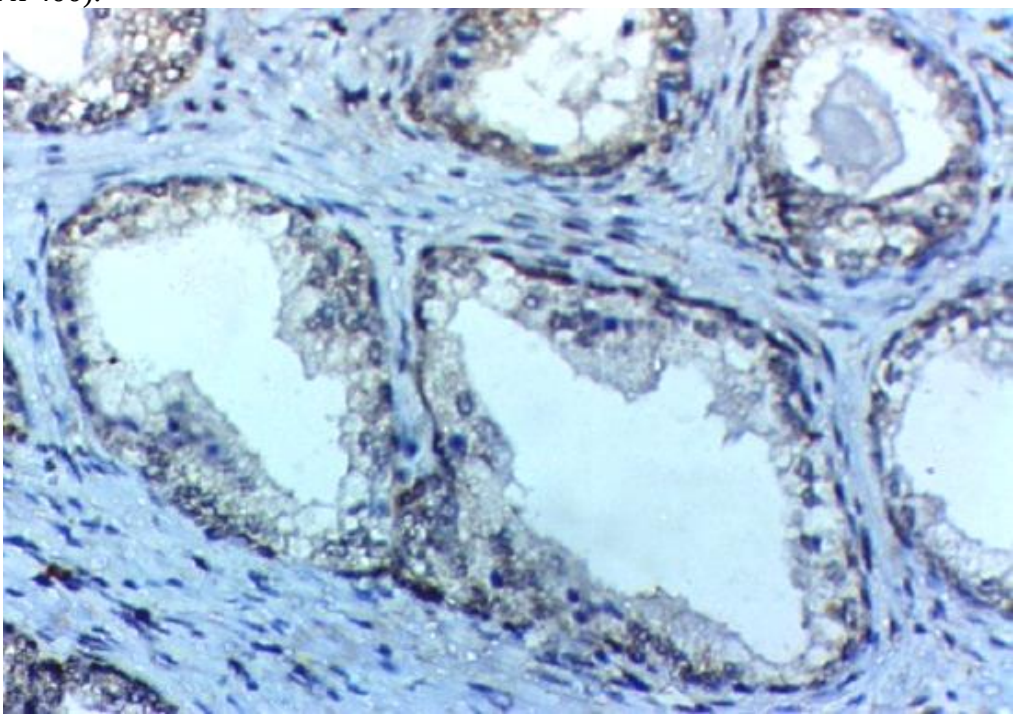

Figure 3. A case of prostatic adenomatous hyperplasia adenosis showing negative nuclear C-myc expression of the luminal cells of prostatic glands with non-specific cytoplasmic staining (C-myc immunoexpression, Mayer's H. counterstain x 400).

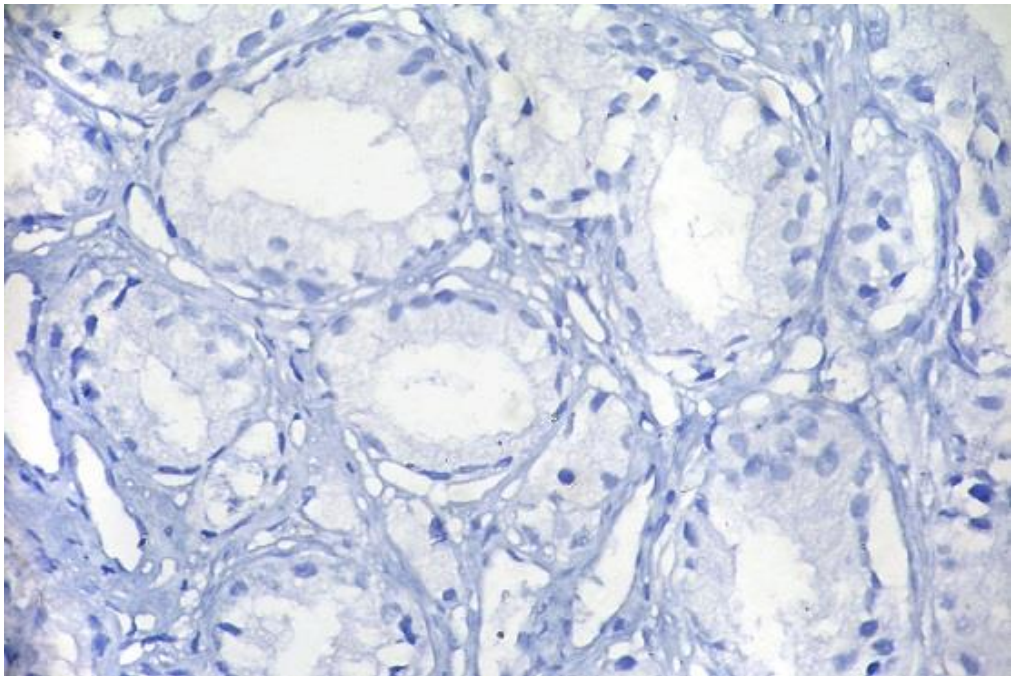

Figure 4. A case of of well differentiated prostatic adenocarcinoma (Gleason score 6) showing closely packed acini with scanty intervening stroma with negative nuclear P63 expression (P63 immunoexpression, Mayer's H. x 400).

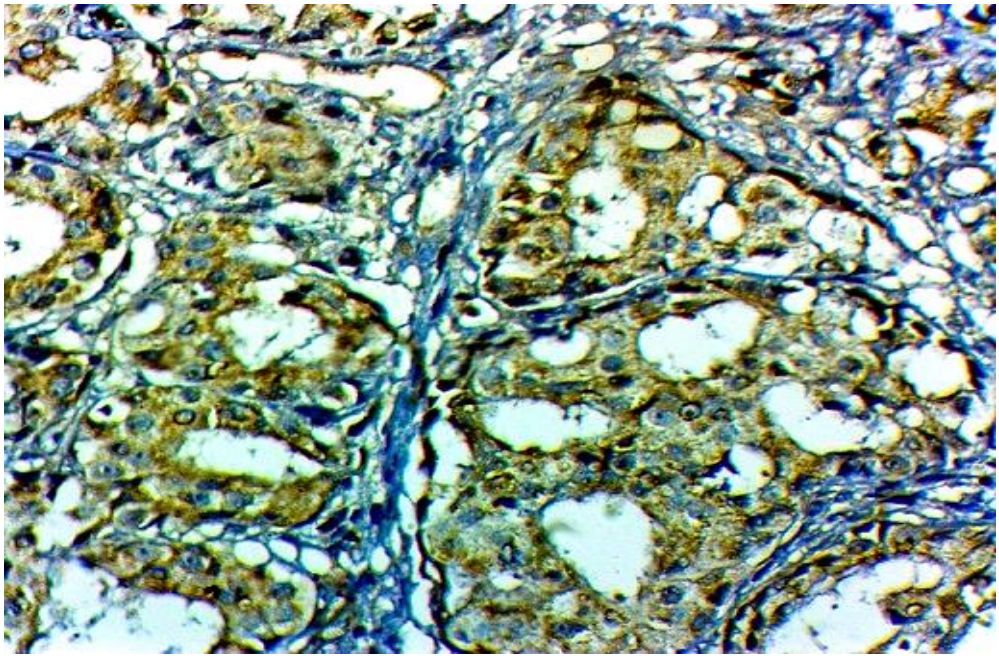

Figure 5. A case of prostatic adenocarcinoma showing fused closely packed acini (Gleason score 7) with diffuse moderate (score 3) STEAP1 cytoplasmic expression (STEAP1 immunoexpression, Mayer's hematoxylin x 400).

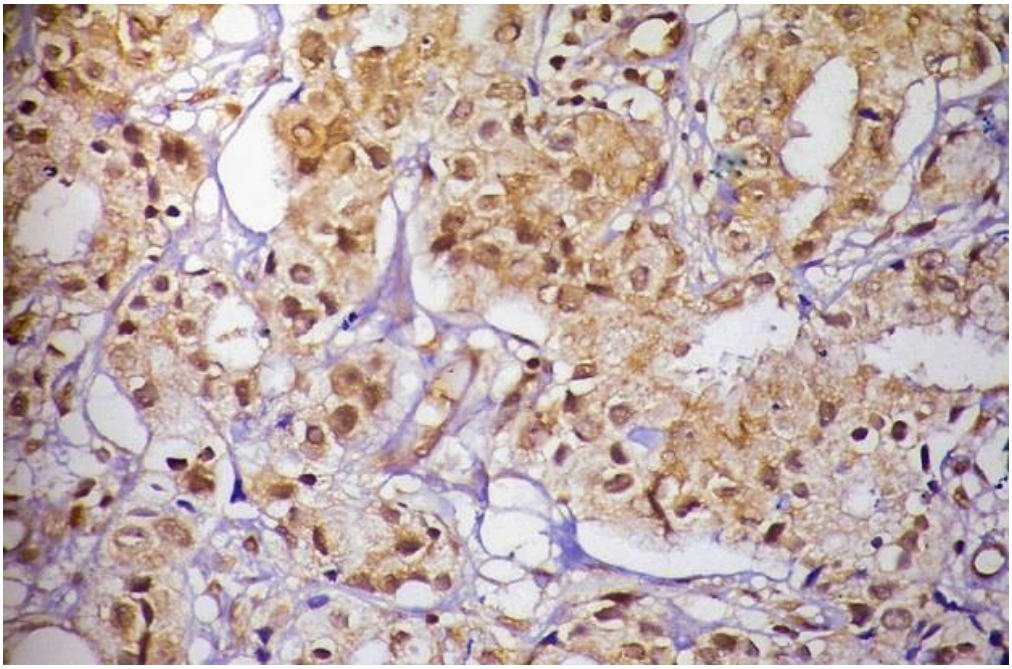

Figure 6. A case of prostatic adenocarcinoma showing fused closely packed acini (Gleason score 7) with strong positive nuclear C-myc expression (score 6) (C-myc immunoexpression, Mayer's hematoxylin x 400).

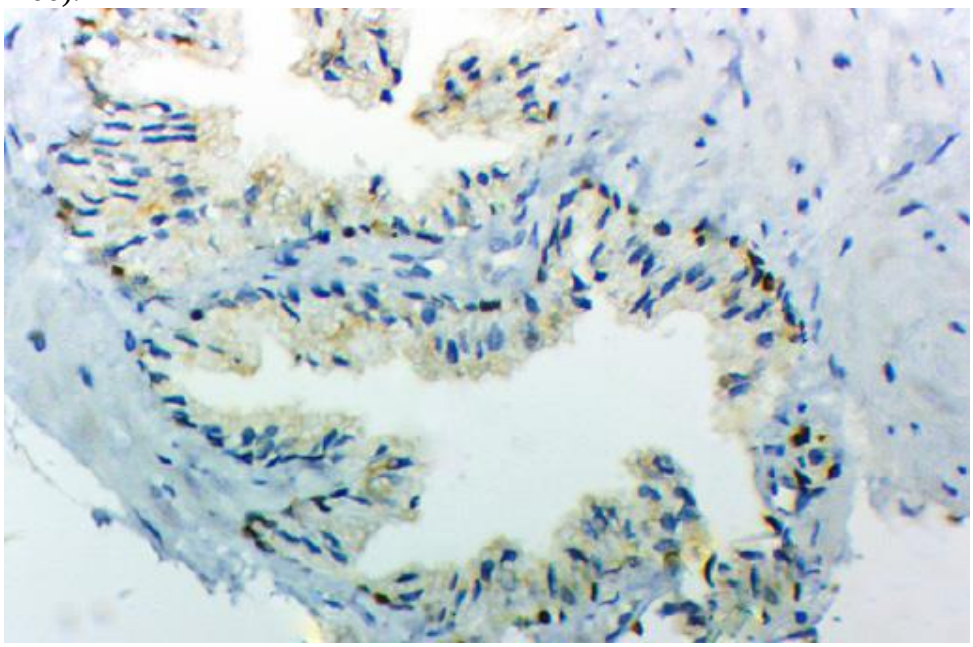

Figure 7. A case of high grade prostatic intraepithelial neoplasia showing closely packed prostatic glands with papillary infoldings and stratified epithelium with (partial) focal P63 expression of the basal cells (P63 immunoexpression, Mayer's H. x 400).

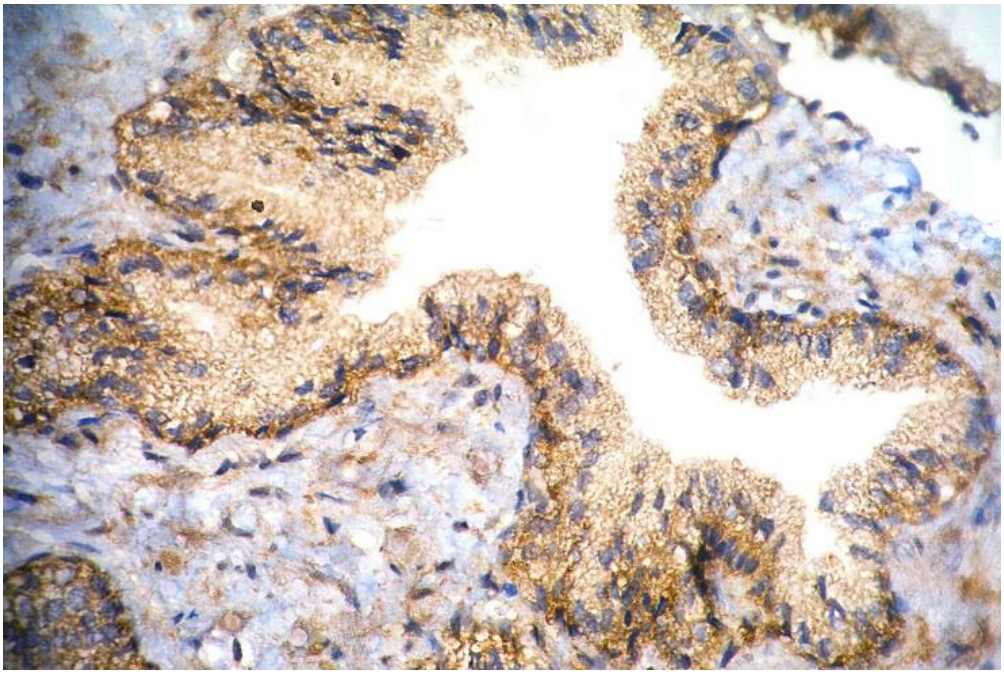

Figure 8. A case of high grade prostatic intraepithelial neoplasia showing prostatic glands with papillary infoldings and stratified epithelium with diffuse moderate cytoplasmic STEAP1 expression of the luminal cells (score 3) (STEAP1 immunoexpression, Mayer's H. x 400).

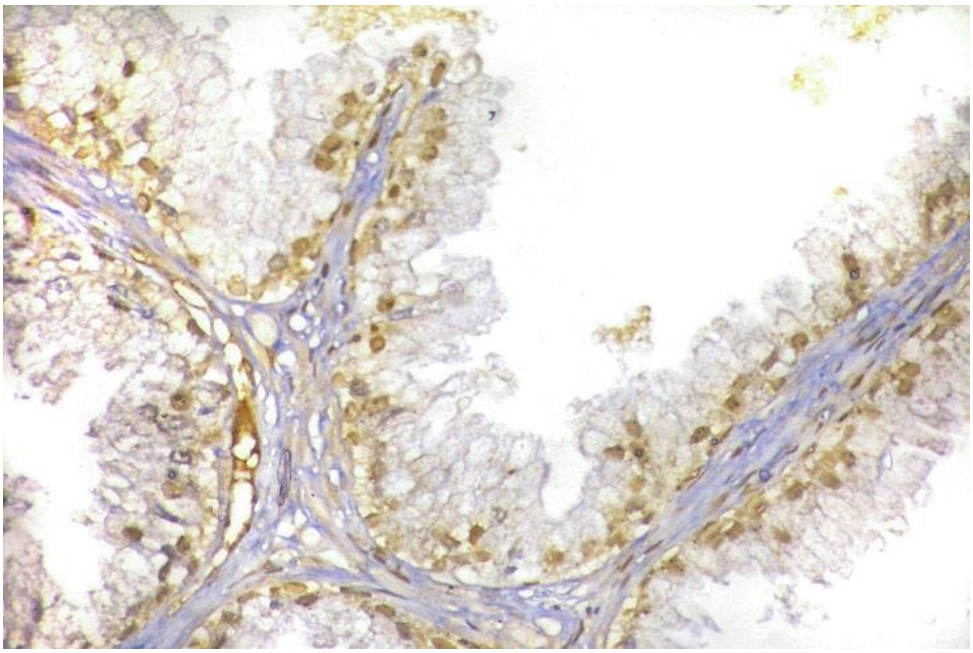

Figure 9. A case of high grade prostatic intraepithelial neoplasia showing prostatic glands with papillary infoldings with strong positive nuclear C-myc expression of the luminal cells (score 4) (C-myc immunoexpression, Mayer's H. x 400).

DISCUSSION

Prostatic adenocarcinoma is a clinically, morphologically and molecularly heterogeneous disease **[13].** Histological diagnosis of prostatic adenocarcinoma is usually based on histological evaluation of prostatic needle biopsies that can be challenging, particularly when malignant tissue is limited and admixed with benign prostatic glands, or because of the presence of benign mimickers of malignancy **[14].**

Considering the incidence and mortality of prostate cancer, it seems to be important to study a novel putative diagnostic and prognostic biomarker as STEAP1**[4]** in addition to diagnostic markers as C-myc and P63 for prostatic adenocarcinoma.

Regarding P63 immunoexpression, we found that P63 was closely related to benign mimickers with strong diffuse immunoexpression. This is in agreement with **Lu et al. [15].**

In our study, all HGPIN cases showed positive P63 immunoexpression. This is consistent with the results of previous studies **[16-17].** In contrast to our results, studies of **Lu et al. [15]** and **Tacha et al. [18]** showed that 86.67% and 70.20% of HGPIN cases were positive for P63 respectively. This might be due to deficient number of our studied HGPIN cases.

It is widely accepted that absence of basal cells is an important histological criterion for diagnosis of prostate adenocarcinoma **[15].** Most of our studied prostatic adenocarcinomas showed negative P63 expression. This is close to the results of **Lu et al. [15]** and **Uchida et al [19]** who demonstrated that some early invasive prostatic adenocarcinomas have residual basal cells.

In our study we observed that P63 expression had high specificity and sensitivity in detection of prostatic adenocarcinoma. That is close to the results recorded by **Kalantari et al. [16].**

As regards STEAP1 immunoexpression, a significant difference was detected in STEAP1 immunoexpression in relation to PSA level (p-value<0.001). This finding was in agreement of the results of **Ihlaseh-Catalano et al**. **[13].**

We found that a significant difference was detected between STEAP1 immunoexpression in prostatic adenocarcinoma and its benign mimickers (p-value<0.001). This finding was in agreement with the results of **Ihlaseh-Catalano et al**. **[13]** who demonstrated that STEAP1 was significantly overexpressed in prostatic adenocarcinoma in comparison to adjacent prostatic tissues and BPH samples.

We found that all studied HGPIN cases showed cytoplasmic or membranous STEAP1 expression. These results are steady with the results of **Gomes et al. [20]** and **Ibrahim et al. [8].** This may suggest that STEAP1 overexpression has a valuable role in prostatic adenocarcinoma initiation and progression.

In our study, we showed a significant relation (P-value< 0.05) between STEAP1 immunoexpression and both Gleason scoring, grade grouping and perineural invasion of studied prostatic adenocarcinoma cases. This is consistent with several studies [8,13,20].

We showed that STEAP1 sensitivity was 80%, specificity was 86.9% with 83.9% accuracy in distinguishing between prostatic adenocarcinoma and its benign mimickers, that is near to the results recorded by **Ibrahim et al. [8].**

Regarding C-myc immunoexpression, we found that there was highly significant difference in C-myc immunoexpression in prostatic adenocarcinomas and benign mimickers (p-value<0.001). This is consistent with the results of **Sadiq et al. [21].** We also observed that 50% of HGPIN in our work showed strong C-myc immunoexpression that is similar to the results of **Hubbard et al**. **[22].**

We observed that nonsignificant relation was found between C-myc immunoexpression and other clinicopathological parameters as Gleason scoring, grade grouping and perineural invasion (p-value>0.05). These results are in agreement with the results of **Sadiq et al. [21]**

and **Pettersson et al. [23].** However, **Zeng et al. [9]** and **Udager et al [24]** studies showed different results as they observed positive correlation between C-myc and staging, grading and distant metastasis, this might be due to different clone or different cut-off value for overexpression.

We observed that C-myc expression was 85.0% sensitive, 73.1% specific with 82.6% accuracy that is close to the results of **Rastogi et al. [25]** who showed 68.5% sensitivity of C-myc expression in detection of malignancy.

In our study, we demonstrated that there was highly significant positive correlation between both STEAP1 and C-myc immunoexpression in differentiation between prostatic adenocarcinoma and benign mimickers (r= 0.80, P value <0.001). While there was highly significant negative correlation between P63 and both STEAP1 and C-myc (r= -0.59, P value <0.001) and (r= -0.68, P value <0.001) respectively. This is in accordance with **Trudel et al. [26]** and **Fonseca-Alves et al. [27]** who showed significant negative correlation between P63 and C-myc expression.

CONCLUSION

This study concluded that positive STEAP1, C-myc and a negative P63 can improve the differentiation between prostatic adenocarcinoma and benign mimickers. STEAP1 may have a valuable prognostic role in prostatic adenocarcinoma.

Conflict of Interest: Nothing to declare.
Financial Disclosures: Nothing to declare

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