Biomedical & Pharmacology Journal, September 2019. Vol. **12**(3), p. 1403-1416

CD133 and CD166 Expression Predicting the Possibility of Prostatic Cancer Development in Cases of BPH

Khalida I. Noel[1]*, Mustafa M. Ibraheem[1], Basim S. Ahmed[2], Ahmed F. Hameed[1], Nibras H. Khamees[1] and Sameh S. Akkila[1]

[1]Department of Human Anatomy, College of Medicine, Mustansiriyah University, Baghdad, Iraq.
[2]Department of Pathology, College of Medicine, Mustansiriyah University, Baghdad, Iraq.
*Correspond to Dr. Khalida Noel, Email: dr.khalidanoel@uomustansiriyah.edu.iq

http://dx.doi.org/10.13005/bpj/1769

(Received: 18 June 2019; accepted: 06 September 2019)

Benign and malignant prostatic diseases are generallywell-known in the world. Accordingly, this research is planned to assess the immunohistochemicalanalysis of CD133 and CD166 in the prostatic epithelium in samples of benign prostatic hyperplasia (BPH) and normal looking epithelium around prostatic adenocarcinoma samples (PCa) and to explore the opportunity of malignant alterations in benign tissue. The prostate samples were divided into 2 groups; 50 BPH samples, and 50 normally looking tissue surrounding prostatic carcinoma samples (NPCA). The samples were treated for immunohistochemicalexamination of CD133 and CD166. Over expression of CD133 appeared in the BPH group which was statistically significant as compared to NPCA group. Conversely, over expression of CD166 stem cell marker in NPCA group than BPH group as it was significant statistically. CD166 is a stem cell marker for tissue tumorigenicity, while the positive expression of CD133 is not of value for cancer initiation.

Keywords: Immunohistochemistry, CD133, Prostatic cancer, BPH, CD166.

Prostate is a male exocrine gland, and a portion of the male reproductive system[1]. The adult human prostate tissue weighs roughly 20 g, and is 3 cm in length, 4 cm in width, and 2 cm in depth[2]. The prostate expands with age of men; prostate enlargement is also related with appearance of benign prostatic hyperplasia (BPH)[3]. Prostate carcinoma is one of the veryprevalenttumor in malesof developed countries. There were 1.3 million newlydiagnosed cases in 2018[4].

BPH is a chronic illnessdescribed by prostatic enlargement, which manifestedas lower urinary tract disorders[3]. There are numerous factors which can effectfor the development of BPH, such as metabolic syndromes, genetics and lifestyle. BPH is not supposed to be a straight risk factor or a pre-cancerous period in prostate cancer[5], but there are countless genetic, hormonal, and inflammatory causes have all been shared to be known pathophysiological dynamic mechanisms for the growth of both BPH and prostatic carcinoma (PCa), thus connecting these diseases together. Yet, on a cellular and molecular level, till now there is no revision shown that the change of BPH tissue has later transformed into an oncological ailment which is the core of the aims of this inquiry. Furthermore, the particular pathways of these prostatic diseases have yet to be fully assumed. This

is crucial to enhance future management strategies for both diseases[6].

Using stem cell markers like CD133 and CD166 can give a hint about the performance of the epithelial cells of prostatic gland in both BPH and normally looking tissue surrounding prostatic carcinoma, which specify that these cells have a stem cell-likecomportment. The presence of $CD133^+$ cells suggested that a high quantity of these tumor cells related to early lymph node metastasis, advanced cancer stages, and more poorly differentiated cancers[7,8]. Whereas, the expression of CD166 by prostate stem cellsproposethe possibility of using this cell surface molecule in targeted therapies of human prostate tumors[9].

Aims of the study

This researchdirected to estimate the behavior of benign prostatic hyperplasia and the likelihood ofalteration to cancerous lesion which requisite follow up later. In addition, to consider the role of the immunohistochemical (IHC) reaction types of glandular epithelium in normal tissue adjacent to prostatic carcinoma by using CD133 and CD166 markers as analyst to aid in choosing the best management for prostatic carcinoma. Finally, to compare the expression pattern of these markers in normal tissue adjacent to cancer and benign prostatic hyperplasia.

METHODS

Patients

The present work was enrolled during the period extended from February 2018 to March 2019 in Al- Yarmouk teaching hospital (histopathology unit) and two private histopathological labs. The study was conducted on human prostatic tissue specimens received from patients attending the abovementioned hospital and labs.

A total number of 100 specimens were selected for the study, some were prospective, with a majority of retrospective samples obtained from archives of histopathology units of those labs and hospital.

The specimens were divided as follows

Fifty primary prostatic carcinoma tissue samples were obtained from surgical resection of the prostate,biopsy was taken from normal tissue adjacent to the primary prostatic carcinoma (NPCA)(normal samples e" 5 cm distant from the cancer)[10] and fifty tissue samplesof benign prostatic hyperplasia (BPH) were obtained from transurethral resection surgery.

Patients were divided into two groups (table 1), according to case type, namely normal adjacent to cancer including 50 patients proved to have prostatic adenocarcinoma, their age ranged from 55-82 years with mean age 70 years.The

Table 1. Group categories by type and number

Group	Type	Age (years)	Mean age	No. of patients	Percentage
I	BPH	60- 86	71	50	50%
II	NPCA	55-82	70	50	50%
Total				100	100%

Table 2. Samples & marker type in relation to staining intensity (chi square)

Staining Intensity	Sample Type				p-value
	NPCA		BPH		
	CD133	CD166	CD133	CD166	
0	0%	8%	0%	46%	0.000
1+	56%	8%	18%	48%	
2+	32%	36%	38%	6%	
3+	12%	48%	44%	0%	

second 50 patients had BPH and their age range between 60-86 years with mean age 71 years.

Ethical approval for the study was obtained from the ethical board of Al-Yarmouk teaching hospital. The pathological diagnosis of prostatic carcinoma was confirmed by reviewing a freshly prepared hematoxylin and eosin stained slides.

Immunohisto chemistry

For each sample, 3 serial sections were taken, each with 4 micrometers thickness.The first serial section was placed on an ordinary slide and stained byhematoxylin/eosin stain to confirm the diagnosis and to determine the histological types and grades for the tumor. The second section was placed on positively charged slide for immunohistochemical staining with anti-CD133 antibody (Primary antibody from Abnova,EntrezGeneID 8842, Code PAB12663). The third section was treated with anti-CD166 antibody (Primary antibody from Abnova, Clone 10F1G12, Code MAB10485).Secondary antibody detection kit (Abcam, code ab64261, rabbit specific HRP/DAB)was used.

Formalin fixed samples and paraffin implanted tissue sections were dewaxed using xylene, and progressively hydrated. Antigen retrieval was done by pressure cooking using citrate buffer for 20 minutes.The primaryanti-CD133 and anti-CD166 antibodies were diluted 1:200 using abackground reducing dilution buffer (Abcam, code ab64211) and kept warm at room temperature for 30 minutes.

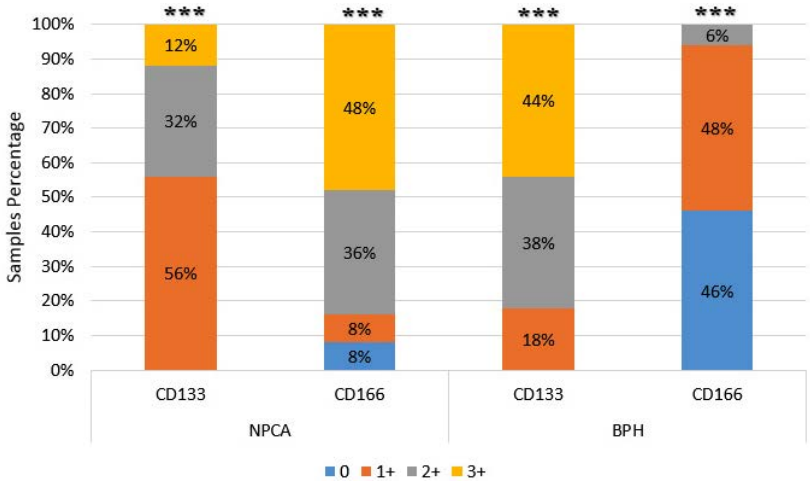

Fig. 1. Staining intensity distribution of IHC markers according to prostatic disorder.
***= p-value < 0.001

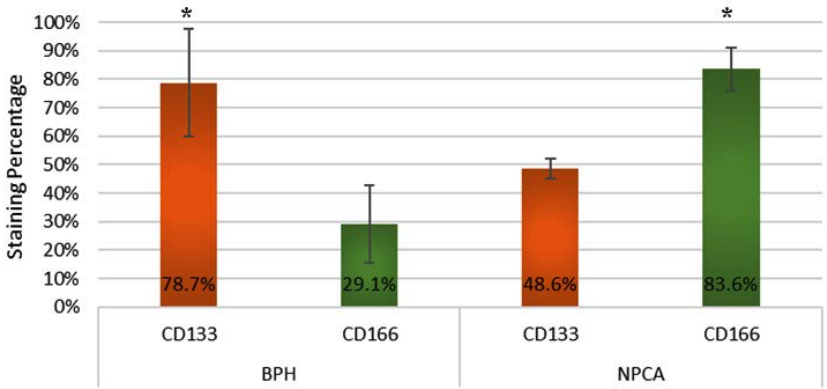

Fig. 2. Staining percentage of IHC markers according to prostatic disorder.
*= p-value < 0.05

Detection performedbylabeled streptavidin-biotin from Abcam secondary detection kit, followed by DAB and chromogen staining. The slides were quicklycounterstained with hematoxylin, hydrated and mountedby DPX[11].

Evaluation of the immunohisto chemical staining

For CD133, all tissue samples of NPCA, and BPH were assessed without prior knowledge, and correlated with the age of the patient. It showed both cytoplasmic and membranous staining with more pronounced membranous and nuclear staining in some of the samples.

Evaluation of anti-CD166 antibody, all tissue samples of NPCA, and BPH were assessed blindly, and interrelated with the age of the patient. It showed both cytoplasmic and membranous staining with more pronounced membranous staining[12,13].

Staining percentage and intensity for CD133 and CD166 were calculated as follows[14,15]:

Staining intensity was scored: 0 (no staining), 1+ (weak), 2+ (moderate) and 3+ (strong).

Extent of staining (percentage) was categorized by percentage: 0 = nil, 1= < 10 % of cell stained positively, 2= 10-50 %, 3= 51-80 %, 4= > 80 %

Statistical analysis

Statistical analysis was performed by using the SPSS – (Statistical Packages for Social Sciences) V18 .Categorical variables were evaluated by measuringthe percentage, mean, and range (min-max values). The qualitative data were verified using Pearson Chi–square test (X2 –test), and independent sample t-test.

RESULTS

Comparison of IHC marker expressions of CD133 and CD166 according to sample type:

Regarding the intensity of markers

Table 3. Sample & marker type in relation to staining percentage (t-test)

Sample Type	IHC Marker	Staining percentage Mean	SD	P-value
BPH	CD133	78.7%	18.9%	0.019
	CD166	29.1%	13.7%	
NPCA	CD133	48.6%	3.5%	0.027
	CD166	83.6%	7.5%	

Table 4. Sample & marker type in relation to total score (t-test)

Sample Type	IHC Marker	Total Score Mean	SD	p-value
BPH	CD133	1.86	0.8	0.013
	CD166	0.35	0.19	
NPCA	CD133	0.86	0.78	0.031
	CD166	2.08	0.9	

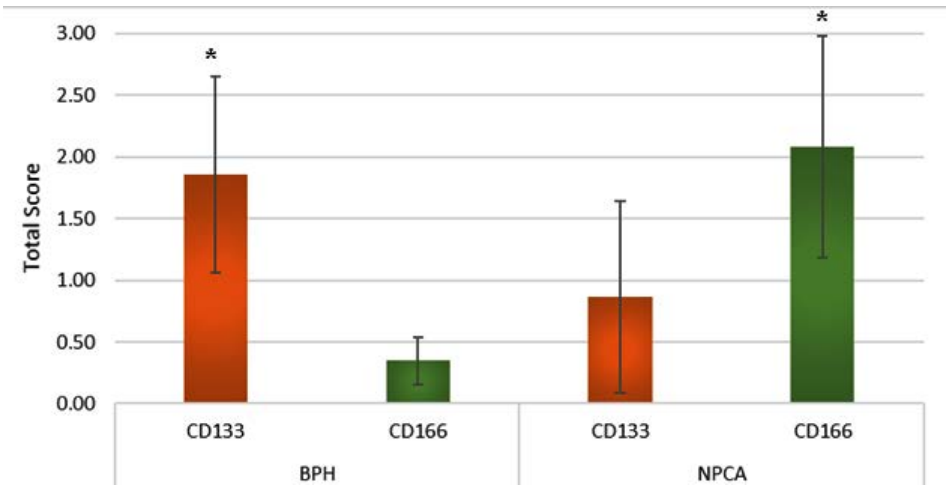

Fig. 3. Total score of IHC marker staining according to prostatic disorder.
*= p-value < 0.05

staining and by using Pearson's Chi-square test. In the BPH group, CD133 had the most intense response (3+, 44%) and none of the samples had a (0) response, while CD166 had the least response (1+, 48%) and none of the samples had a (3+) response (fig. 4, fig. 5, fig. 6, fig. 12, fig. 13, fig. 14). In the NPCA group, CD166 had the most intense response (3+, 48%) while the negative response was only 8%. On the other hand, 56% of cases in NPCA group obtained weak expression (1+) of CD133, but 0% of cases reflected the negative (0) expression of CD133 (fig. 8, fig. 9, fig. 10, fig. 15, fig. 16, fig. 17, fig. 18). Significant difference were obtained in between the two groups and markers as p-value= 0.000 (table 2 and figure 1).

For comparison of percentage of marker staining and by using t-test, the staining percentage was significantly different for the markers in each prostatic disorder. In the BPH group, CD133 was the mostly expressed marker in comparison to CD166 (p-value=0.019). In the NPCA group, CD166 was the mostly expressed marker in comparison to CD133 (p-value=0.027). CD133 was significantly more expressed in BPH group compared to NPCA group while CD166 had the opposite expression as shown on table 3 and figure 2.

The differences in total score of IHC marker expressions was assessed by t-test, and there was a statistical significance of different markers according to prostatic disorder. CD133 had the highest score in the BPH group in comparison to the NPCAgroup and the other marker (p-value=0.013). In the NPCA group, CD166 had the highest

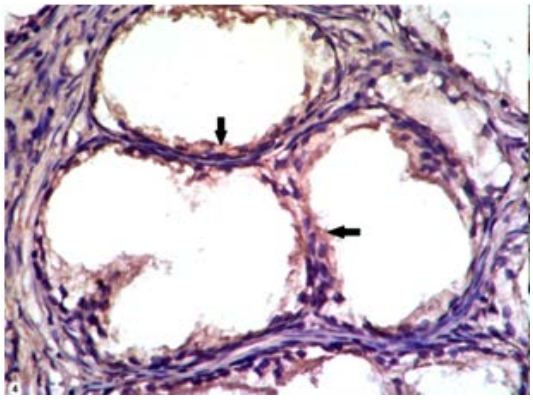

Fig. 4. Immunohistochemical expression of CD133 in BPH sample show 1+ staining (weak membranous staining) of CD133 (black arrows). X400

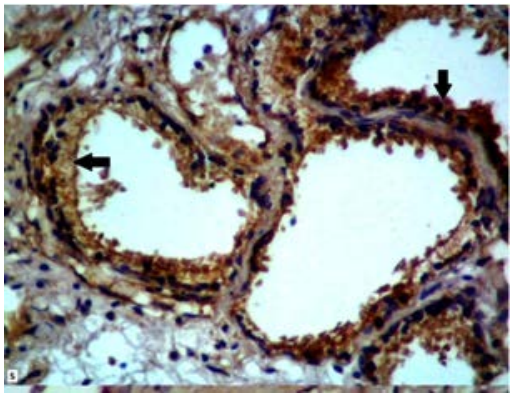

Fig. 5. Immunohistochemical expression of CD133 in BPH sample show 2+ staining (moderate membranous & cytoplasmic staining) of CD133 (black arrows). X400

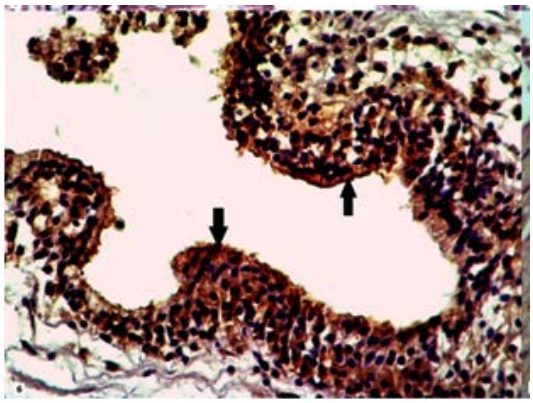

Fig. 6. Immunohistochemical expression of CD133 in BPH sample show 3+ staining (strong membranous & cytoplasmic staining) of CD133 (black arrows). X400

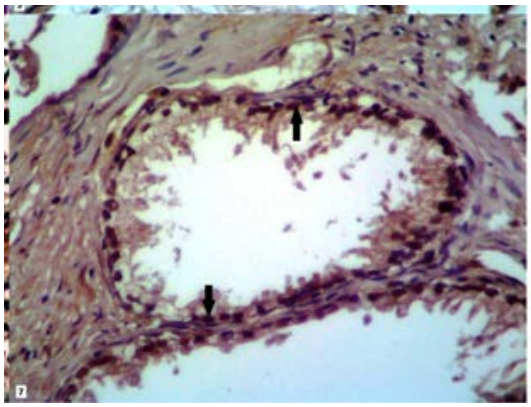

Fig. 7. Immunohistochemical expression of CD133 in BPH sample show 1+ staining (weak membranous &cytoplamic staining) of CD133 with nuclear involvement (black arrows). X400

scores compared to the other marker in the same group and the same marker in the BPH group as p-value=0.031 (table 4 and figure 3).

CD133 was expressed clearly in the cell membrane and cytoplasm of prostatic cells in both groups, in addition a few cases appeared with nuclear association in BPH and NPCA groups as appeared in fig. 7 and fig. 11. While CD166 was appeared in cell membrane and cytoplasm of the cells in both groups.

DISCUSSION

Expression of CD133 in BPH and NPCA groups

As appeared in our results, CD133 stem cell marker had greaterstaining percentage in BPH than in NPCA group and was significant statistically. Also, CD133 expressed more intensely in BPH group than NPCA group and was also statistically significant. As a result, the total score of expression of CD133 showed statistically significant higher levels in BPH group than NPCA group. On other hand, 44% of samples in BPH group showed strong expression of CD133, whereas, 56% of NPCA group samples showed weak appearance of CD133 stem cell marker. These finding are in agreement with other researchers[16,17]. All of these researchers showed the expression of CD133 positive cells in the prostatic epithelial cells in benign[18] and malignant status of the epithelium[19] as well as in the normal looking epithelial tissues[20].

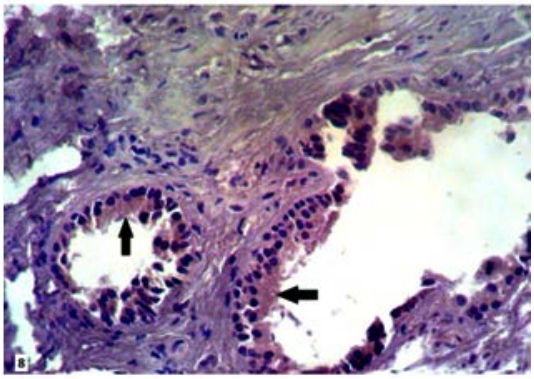

Fig. 8. Immunohistochemical expression of CD133 in NPCA sample show 1+ staining (weak membranous staining) of CD133 (black arrows). X400

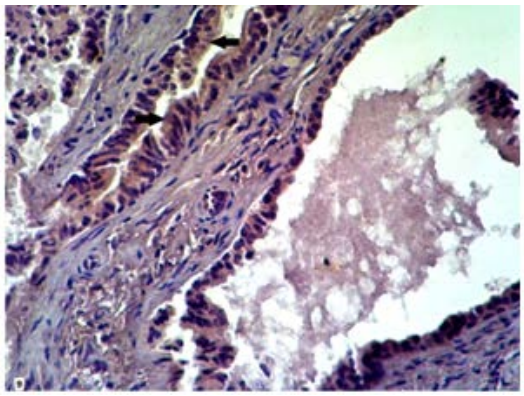

Fig. 9. Immunohistochemical expression of CD133 in NPCA sample show 2+ staining (moderate membranous and cytoplasmic staining) of CD133 (black arrows). X400

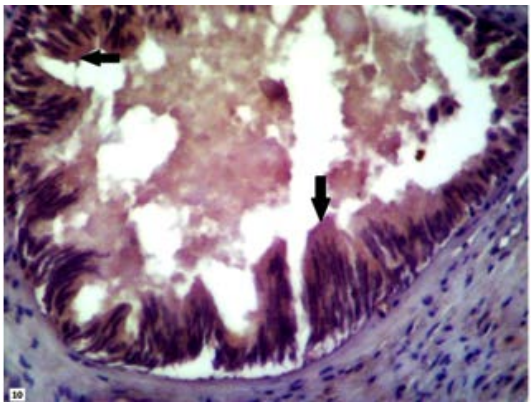

Fig. 10. Immunohistochemical expression of CD133 in NPCA sample show 3+ staining (strong membranous &cytoplamic staining) of CD133 (black arrows). X400

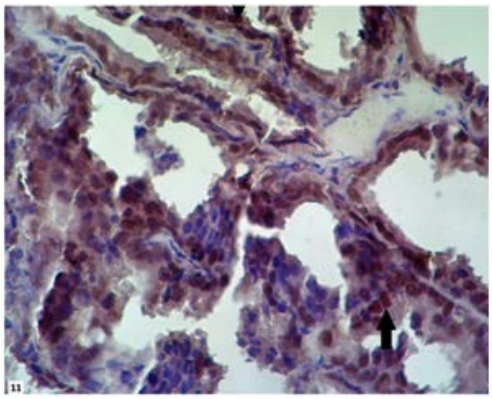

Fig. 11. Immunohistochemical expression of CD133 in NPCA sample show 2+ staining (moderate membranous &cytoplamic staining) of CD133 with nuclear involvement (black arrows). X400

CD133 was found to be expressed in normal epithelial tissues of different organs such as the hematopoietic system[21], the prostate[22], the pancreas[23], and the kidney[24].

Also CD133 is expressed in the benign epithelial conditions such as BPH[18] and other benign conditions like benign tumors of skin with apocrine differentiation[19]. In addition to the expression CD133 in malignant conditions like breast cancer[25], colorectal carcinoma[26], bladder carcinoma[27] and prostatic cancer[18].

Moreover, antibodies against CD133 have been designed for the separation and identification of a putative populace of tumor initiating cells or cancer stem cells (CSCs) in many of human carcinomas[28,29], and in malignant melanoma[30]. In glioma, the amplified number of CD133 positive cancer cells, in addition to the existence of clusters of these cells, has been suggested as a main prognostic factor, autonomous of other featuressuch as tumor grade[31]. On the other hand, other readings, using altered and novel anti-CD133 clones, have proposed that the appearance of CD133 is not restricted to stem and progenitor cells[32,33]and appears to be expressed in adult epithelial tissue cells of mouse and human[34,35].

According to our results, all samples of both BPH and NPCA groups are CD133 positive and no negative expression were obtained in both groups. The explanations for these positivity is that: CD133 is a stem cell marker of normal, benign and malignant epithelial cells[12], but the intensity of CD133 expression was different in both groups. In BPH group; 44% of samples showed strong positivity, on the other hand, 56% of samples in NPCA group expressed CD133 weakly. The reason for this different positive intensity of expression is associated to differential attraction of the diverse antibodies to different glycosylated types of CD133. So the glycosylation may altered depending on the stage of cellular differentiation[19], or it can be changed during the path of malignant transformation[36]. The other reason for over expression of CD133 in BPH samples is correlated to presence of inflammatory cell populations in BPH samples[17], which may be accompanying with the hyperplastic changes[37] and so the intensity of staining is stronger than normal tissue around cancer in NPCA group which appeared low as explained by other researchers[17]. In contrast, Miyazawa *et al.*,[18] suggested that there were no clear reason for the different staining intensity between benign and cancer patients.

CD133 was latelyestablished to undergo differential glycosylation in colon

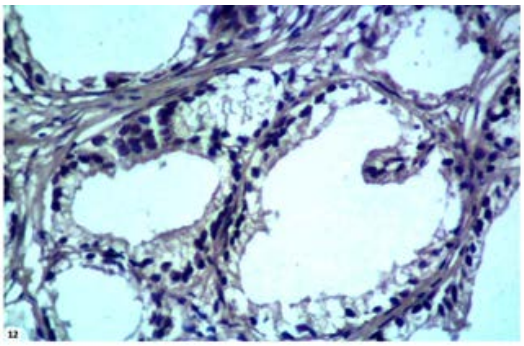

Fig. 12. Negative immunohistochemical expression of CD166 in BPH sample. X400

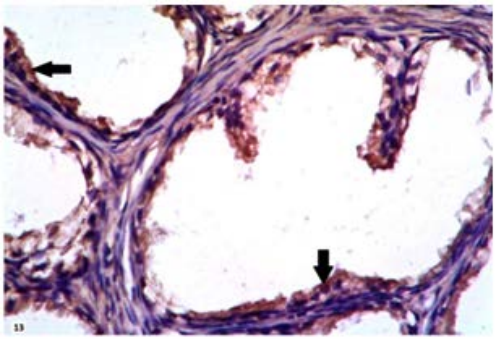

Fig. 13. Immunohistochemical expression of CD166 in BPH sample show 1+ staining (weak membranous staining) of CD166 (black arrows). X400

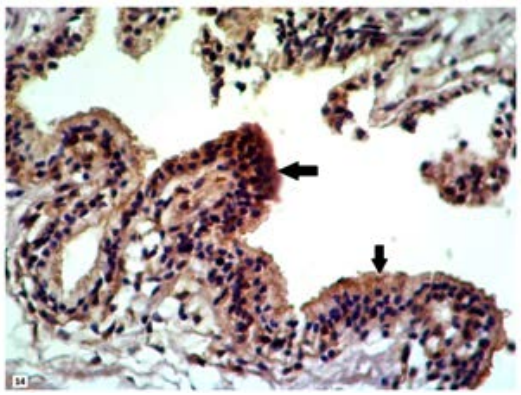

Fig. 14. Immunohistochemical expression of CD166 in BPH sample show 2+ staining (moderate membranous staining) of CD166 (black arrows). X400

CSCs as paralleled with differentiated cancer cells[38]. This occurrencewouldclarify some conflictingexplanations that have been described when the CD133 protein and mRNA expression designs were linked[39]. As newlysuggested by Kemper *et al.*, differential glycosylation of the extracellular domain of CD133 can armor the epitope from recognition by IHC using the antibody CD133[38].

CD133 was considered as a marker of tumor initiating cells in many cancers[25], one of these cancers is the prostatic carcinoma. Based on these information, the tumor cells were allocated in to CD133+ and CD133- cells, that CD133+ cells showed stem like features[26], while CD133- cells did not. According to these data, the great number of CD133+ tumor cells is related with early lymph node metastasis, advanced cancer stages and poorly differentiated tumors[40,41] and so exhibited resistance to management and poor survival[26]. Conversely, other researchers clarified that the tumorigenic potential did not exist in the CD133+ stem cells but was constantlydetected in the CD133-populace[42]. These factsestablished that benign basal cells contain cells of origin of prostate cancer and recommended that proliferative CD133- basal cells are more vulnerable to tumorigenesisif compared to CD133+ stem cells[43]. Tumorigenic potential did not arise from positive CD133 stem cells; but might be appeared in the negative CD133 populace[44]. Certainly, The resistance of CD133 positive cells to chemotherapy were more than CD133 negative cells in glioma and hepatocellular cancer, proposing CD133 as a probable marker of cancer stem

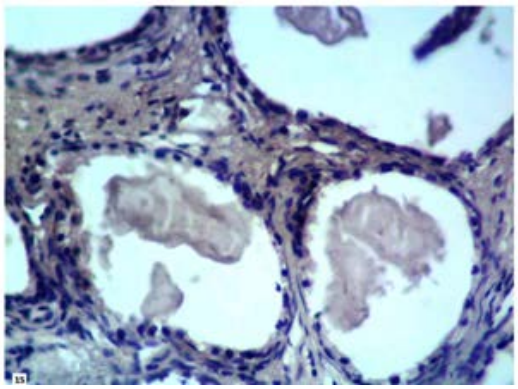

Fig. 15. Negative immunohistochemical expression of CD166 in NPCA sample. X400

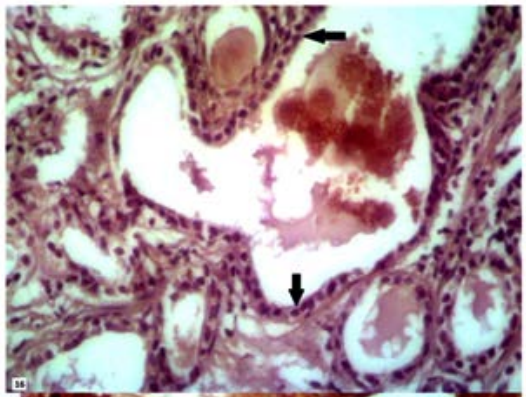

Fig. 16. Immunohistochemical expression of CD166 in NPCA sample show 1+ staining (weak membranous staining) of CD166 (black arrows). X400

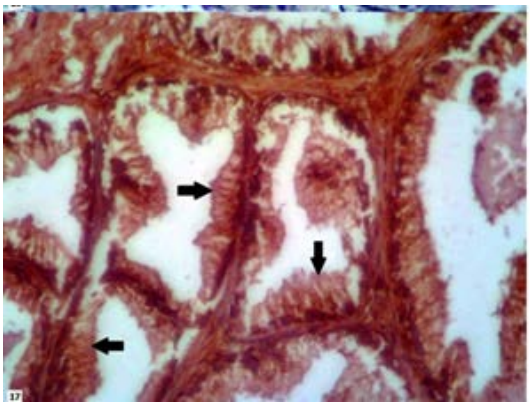

Fig. 17. Immunohistochemical expression of CD166 in NPCA sample show 2+ staining (moderate membranous & cytoplasmic staining) of CD166 (black arrows). X400

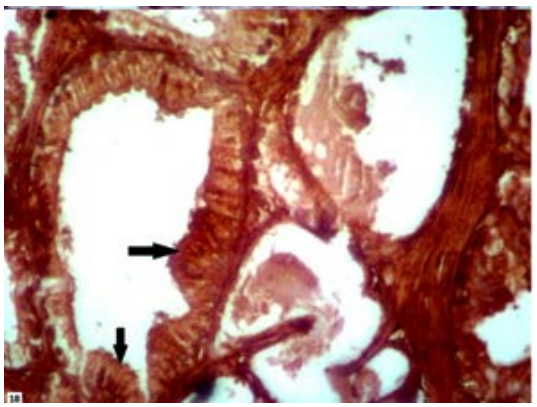

Fig. 18. Immunohistochemical expression of CD166 in NPCA sample show 3+ staining (strong membranous & cytoplasmic staining) of CD166 (black arrows). X400

cells[45,46]. It has been displayed that prostate tumor derived CD133 positive cells are displayingself-renewaland widespread proliferationirrespective of the tumor grade[16]. These conclusionsconfronted the existingacceptance that normal stem cells and cells of origin of cancer are the similar cell type(s)[42]. Thorough studies need to be performed to learn more about the role of CD133 in PCa origination.

Other researchers found that the significance of CD133 expression may be attenuated by using it with other stem cell markers to confirm the presence of stem cell like activity in prostatic epithelial cells[20].

Expression of CD166 in BPH and NPCA groups

Our results showed that the percentage of CD166 expression in the NPCA group was higher than BPH group with statistical significance. Additionally, the strong intensity of CD166 staining was appeared in the NPCA group samples, were 48% of samples expressed3+ level of intensity which was statistically significant as compared to BPH group with weak intensity (1+) for 48% of samples. As a result, statistically significant higher total score obtained in NPCA group as compared to BPH group. These results are agreed with the findings of other researchers[47,48].

CD166 expression is commonly existing in most epithelial tissues and related carcinomas[49]. It is important in tumor development and invasion[50]. The molecular activity of CD166 is controlled through shedding of its extracellular domain[51].

CD166 has been mentioned in few revisions as a significant potential biomarker for prostatic carcinoma[9], although it is functionally and clinically connected to many other cancers in the body[48,52].

According to Kristiansen *et al.*[47]; CD166 was usually expressed in normal prostatic epithelia which showed a mainly membranous and weak cytoplasmic staining of secretory cells with no staining of basal cells and stromal appearance was not detected, the staining was commonly homogenous which conclude the cell adhesive criteria of CD166 molecule. It involves both the stem cells and progenitor populations which is a likely function for CD166 to preserve the reliability of the stem cell niche by preserving the epithelial microenvironment[49]. CD166 is commonlyelaborate in morphogenesis of tubular structures, regardless of endothelial or epithelial source. This mechanism would clarify the low CD166 appearance in normal prostatic glands, which illustrate a very low level of proliferation[47]. CD166 also appeared in the hyperplastic glands with weak intensity[47].

CD166 is a tumor initiating and cancer stem cell markers[48] and it is up regulated in prostatic carcinoma[53], give the reason that when addition of CD166;augmented sphere forming activity in prostatic tumor cell lines and in human prostatic cancer specially castration resistant prostatic cancer (CRPC) samples[43]. Consequently, CD166 may enhance both human prostate tissue stem/progenitor cells and (CRPC) cells[9]. Prostate stem/progenitor cells function in glandular development and preservation;they may be marks for tumor initiation, so classification of these cells may be of therapeutic value[54]. Cells from detached tissues that form spheres *in vitro* often characterize stem/progenitor cells. A subclass of human prostate cells that custom spheres are accomplished for self-renewal and tissue regeneration[55].

Normal human prostate comprises three dissimilarsorts of cells, that is luminal secretory, basal and neuroendocrine cells. Subsequently, human prostate cancer is described by loss of basal cells and growth of luminal cells, numerous animal models suggest that luminal specific progenitors are the causes of initiating prostate cancer[56]. Though, using the tissue regeneration methodology, basal cells have verified to be veryeffective oncogenic targets for human prostate cancer initiation[57,58]. Remarkably, Choi *et al.*confirmed that adult murine prostate basal and luminal cells are self-sustained lineages that both of them canassist as oncogenic targets for prostate cancer initiation[59].

In our results, this up regulation ad strong expression of CD166 in the normal tissue around prostatic cancer was obtained and this can be explained on the finding of Jones *et al.*that considered this normal tissue as a field cancerization zone because of the molecular alterations of the cells in the normal tissue adjacent to cancer and so express CD166 strongly and give the idea of presence of tumor initiating cancer stem-like cell in this tissue or even they are a cancer stem cells[60]. The explanations for this field effect was described by many researchers as that tumor tissue and adjacent normal tissue[61], both of them exhibited significant up regulation of proliferation related genes including transcription

factors[62], signal transducers and growth regulators and proposed that normal appearing prostate tissue can experience genetic modifications in response to or inexpectation of morphologic cancer[63,64]. This is an important prognostic feature which determine the suggestion of increased CD166 appearance with human prostate cancer metastasis and CRPC growth. Furthermore, CD166-high expressing subpopulation involves prostate stem/progenitor and cancer initiating cells[9].

However, Kristiansen *et al.*, 2003 showed that CD166 is over expressed in low grade tumor but is down regulated in high grade tumor, This difference might be clarified by altered biological characters of CD166 in cell adhesion of different cancers[65], another explanation for this difference of CD166 expression was that glandular (low-grade) carcinomas precise CD166 at higher levels, perhapsreplicating ongoing growth and tubulesdevelopment, however high-grade cancersincreasingly wildness tubulesgrowth in favor of cribriform, solid, or single-cell invasion designs[47]. Other reasons included CD166 mRNA up regulation in low grade prostate cancer and progressive loss in high-grade lesions may be of important implication[66].

So CD166 have a very important prognostic effects on prostatic carcinoma treatment and follow up. CD166 has also been recommended to show a seriouspart in numerous human carcinomas and play as a potential therapeutic target for cancer initiating cells[67], and may be for a proper surface marker for upcoming targeted drug delivery[68]. Also can be applied to examine the efficiency of CD166 - mediated drug delivery to prostate cancer initiating cells *in vivo*, particularly during CRPC expansion[9].

The weak expression of CD166 in 48% of samples of BPH may be of significant importance in determining whether there were a tumor initiating cancer stem-like cell or cancer stem cell in the hyperplastic tissue, Jiao *et al.*[9]supposed that CD166 was focally appeared in the benign adult prostate, CD166 mightaugment sphere-forming capability of benign primary human prostate cells *in vitro* and encourage the formation of tubule-like organizations*in vivo*. But,Weichert*etal.*[14] hypothesized that over expression of CD166 is a prematureoccurrence in malignant cell alteration in colon carcinogenesis, as it was established in all adenomas of the colon, which was reflected to be precursor lesions. According to these findings, further information and more molecular investigations may be needed to confirm these findings. In addition, in murine models, CD166 was upregulated in prostates after castration[9]. These records specified that the amounts of stem cells in primary tumors or the patient circulation can be applied to recognize patients likely to experience a relapse and for whom very aggressive management is required.

IHC Expression of CD133and CD166 in BPH and NPCA groups

CD133 is a cell membrane marker[44], but also expressed in the cytoplasm of the cells[69].Our resultsshowed both cell membrane and cytoplasmic appearance of CD133 in both BPH and CA group of samples and this is agreed with the findings of Huwait*et al.*[44]. In addition to membranous and cytoplasmic expressions of CD133, nuclear involvement also appeared in the nuclei of prostatic cells in BPH and normal tissue around cancer in the NPCA group. These results are similar to the findings of many researchersin breast cancer[12], lung cancer[69], hepatocellular carcinoma[70] and colorectal cancer[71] respectively. The explanation of this nuclear expression is controversial. Cantile*et al.* and Huang *et al.*[12,69]hypothesized that nuclear localization of CD133 may be asign of poor prognosis in breast cancer and lung cancer, as they recognized that surface molecules, when travelling into the nucleus, can act as transcriptional regulators by interfering with molecular paths directly linked to the proliferation and differentiation of cancer cells. In contrast, Chen *et al.* and Lee *et al.*[70,71] hypothesized that cytoplasmic CD133 appearance was associated with poor prognosis, while nuclear CD133 appearance was considerablyassociated with positive prognosis. No previous study explained the nuclear expression of CD133 in BPH, but we must take this nuclear expression of CD133 in some of BPH cases on considerations that it might give us a hint for any transformation and cancer development risk, since some researchers demonstrated a telomerase activity in BPH might change and therefore would obtain similar characters like those of normal looking cells around tumor and cancer cells and so the possibility of developing cancer is present and follow up is needed[72]. So,

further studies are needed for examining CD133 expression role in the development and progress of prostate carcinoma and its appropriateness as a prognostic biomarker[73].

CD166 is a membranous marker also and cytoplasmic expression is appeared in our results and agreed with others[14,50]. But some researchers hypothesized that membranous expression of CD166 is suggestive of poor survival of colorectal cancer[14]. So, further prognostic and therapeutic stratification may be achieved according to CD166 localization.

CONCLUSIONS

This study provided suggestion that:

1. Over expression of CD166 in normal tissue around prostatic carcinoma than benign tissue in BPH.
2. Over expression of CD133 in benign tissue of BPH cases than normal tissue around prostatic carcinoma.
3. Increasing age is one of important common reasons of both BPH and prostatic carcinoma in addition to other epidemiological causes.
4. Possibility of changing in histology of benign tissue to malignant is still query and need more advanced investigation on molecular level, but follow up of suggestive BPH cases must take into consideration.
5. CD166 is a stem cell marker for tumor tumorigenicity, while the positive expression of CD133 is not of value for cancer initiation.

ACKNOWLEDGEMENTS

This work was not supported by research grants.

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