Original Article

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Pathology Section

Serum Prostate Specific Antigen and Mast Cells in Distinguishing Benign Prostatic Hyperplasia from Prostatic Carcinoma: Is there a Correlation?

RAJENDRA PRASAD MUKHERJEE[1], DHRUBAJYOTI MAULIK[2], SOUMYA KUNDU[3], APARUP DHUA[4], PRIYA RANJAN CHATTOPADHYAY[5]

ABSTRACT

Introduction: Benign Hyperplasia of the Prostate (BHP) and prostate cancer comprise about 90% of all diseases of the prostate gland. An increase in serum Prostate Specific Antigen (PSA) is an indicator of underlying hyperplasia, inflammation, or cancer. Mast cells are found in both inflamed and tumour tissue.

Aim: To find the correlation of mast cell count with age, weight of prostate, and serum PSA level, and thereby distinguishing between the benign or inflammatory prostatic enlargement against prostatic carcinoma.

Materials and Methods: This cross-sectional observational study was conducted over a period of 18 months from November 2013 to April 2015 in a tertiary care hospital in West Bengal, India. Patients coming for treatment of enlarged prostate were included in this study as a convenience sample. Their age in years, weight of the gland by ultrasonography, serum PSA level, and mast cell count were recorded for analysis. The data between benign and malignant lesions were compared by the Mann-Whitney U test and the Spearman correlation coefficient was calculated to find correlation among the continuous variables. Chi-square test was done to compare categorical data. Microsoft Excel 2010 (Microsoft Inc, USA) and International Business Machines (IBM) Statistical Package for the Social Sciences (SPSS) Statistics 20.0 (IBM, New York, USA) software were used for conducting the statistical tests.

Results: A total of 48 males with a median age of 63.5 years were studied. The weight of the prostate gland, serum PSA, and mast cell count were significantly higher in carcinoma of the gland. The weight of prostate gland (r_s= 0.34, p-value= 0.02) and serum PSA (r_s= 0.61, p-value <0.0001) was significantly positively correlated with mast cell count in overall sample. The PSA (p-value <0.001) significantly contributed to predicting the mast cells in linear regression.

Conclusion: The serum level of PSA and mast cells were higher in carcinoma of the prostate. Higher prostate gland size and PSA would have higher mast cell infiltration. This study showed a correlation of serum PSA level with mast cell density, which may be used as an additional tool in distinguishing BHP versus prostatic carcinoma. Further studies are needed to find a more generalisable regression equation.

Keywords: Hypertrophy, Prostatic neoplasms, Inflammation

INTRODUCTION

Enlargement of the prostate gland is frequently found in elderly males occurring approximately at 65 years of age. Benign hyperplasia or cancer can cause the enlargement that cause several symptoms due to either pressuring nearby structures or metastasis from the cancerous tissue. Across the globe, millions of men are dying due to prostate cancer [1]. The highest incidence is reported in developed countries. The reason may be the higher awareness among the population and screening tests. In India, the incidence of prostate cancers is not available due to inconsistent data collection, storage, and sharing across the states. However, from the current knowledge of available studies, it has been found that the incidence is lower than that of western countries [2]. However, the cases are increasing day by day. The available population-based cancer registries of different Indian cities reported that Indian metropolitan cities are among the areas reporting the high prostate cancer incidence [3].

The normal and cancerous prostatic epithelium both can secrete a significant quantity of PSA. The majority of its secretion is into seminal fluid, where it breaks down the gel that forms after ejaculation. In healthy conditions, a very little amount of PSA is released into the bloodstream. However, in prostatic diseases, a greater amount of PSA is released into the bloodstream. As a result, PSA is a widely-used blood marker for BHP and prostate cancer [4,5]. The inability to discriminate between BHP and prostate cancer limits PSA as a screening tool for cancer. However, resource-limited settings still use it as a screening tool to decide if biopsy is to be done [6].

Lymphocytes, neutrophils, macrophages, and mast cells are among the cells that infiltrate the site of inflammation and frequently accompany neoplastic growth. Inflammation acts as a line of defence against tumours, and inflammatory infiltrates in patients with tumours may improve their prognoses. The development of many cancer is controlled in part by the mast cells [7]. Although mast cells are well-acknowledged for allergic reactions and anaphylaxis, now it is found that they are multifunctional effectors' cells of the innate and adaptive immune systems. Mast cells also may be considered as potential independent prognostic indicators in prostate cancer. As prostate cancer is a multifocal and diverse disease higher number of screening, diagnostic tests, and prognostic factors may help to improve the management of the patient [8].

With this background, the study was taken up as an additional tool for triaging the patients with prostate enlargement in a resource limited setting where Immunohistochemistry (IHC) markers are not readily available. This study aimed to find correlation of mast cell count with age, weight of prostate, and serum PSA level, and thereby distinguishing between the benign or inflammatory prostatic enlargement against prostatic carcinoma.

MATERIALS AND METHODS

This was a cross-sectional, observational study conducted in a tertiary care teaching hospital in West Bengal, India. The study was conducted in the Department of Pathology and General Surgery from November 2013 to April 2015. This study was carried out after obtaining approval from the Institutional Ethics Committee (IEC) of Bankura Sammilani Medical College and Hospital, West Bengal, India (IEC No. PR-HC/6-119/87(53) Dated 09/01/2014).

Inclusion criteria: All the research participants were adults (completed age >18 years) who were capable of providing consent for participation in the study. The patients were approached for possible inclusion in the study after explaining the study procedure, risk, benefit, and autonomy for participation. The briefing was done in the local language (i.e., Bengali or Bangla). The patients, who were interested to participate voluntarily, were recruited for the study after taking written informed consent.

Exclusion criteria: Patients with prostatitis, acute retention of urine, biopsy proven prostatic sarcoma, and transitional cell carcinoma were excluded from the study.

Sample and recruitment: A convenience sample for this hospital-based study with predetermined inclusion and exclusion criteria was taken.

Study variables and measurement: The age of the patient was recorded in completed years as declared by the patient. The gross weight of the prostate gland was measured from the transrectal ultrasonography by a single expert radiologist for all the patients. This was done to avoid any interobserver variation in the measurement. A blood sample of 5 mL was collected after 12-hour fasting from the antecubital vein after maintaining aseptic precaution. The blood sample was immediately transferred to the central laboratory for testing PSA level. The measurement was done by an automated chemiluminescence system. The pathological specimen, obtained from either biopsy or tissue after radical prostatectomy, was further processed in the Department of Pathology for observation. The tissue specimen was prepared for histopathological examination. The fixative was dehydrated passing the tissue through ascending grades of alcohol. Then the alcohol was replaced by Xylene. The tissue was then impregnated with paraffin and the sections were cut-off 5 µm thickness with a research-grade microtome. Then Haematoxylin and Eosin (H&E) staining was done for diagnostic observation. Toluidine blue staining was used for the identification of mast cells. In this staining, the mast cell stains red-purple, and the background is stained blue.

STATISTICAL ANALYSIS

The data were first checked for their distribution by the Shapiro-Wilk test. The distributions of all the variables were not following a normal distribution. Hence, the data were presented in median and quartiles {first quartile (Q1)-third quartile (Q3)}. The data between benign and malignant lesions were compared by the Mann-Whitney U test and the Spearman correlation coefficient was calculated to find correlation among the continuous variables. Chi-square test was carried out to compare categorical data. For linear regression, the mast cell count was considered as the outcome variable and age, size of the gland, and PSA level as predictor variables. For the entire statistical tests, a p-value <0.05 was considered as statistically significant. Microsoft Excel 2010 (Microsoft Inc, USA) and IBM SPSS Statistics 20.0 (IBM, New York, USA) software were used for conducting the statistical tests. The p-value <0.05 was considered to be statistically significant.

RESULTS

A total of 48 male patients were enrolled in the study with a median age of 63.5 years. Among the patients, 36 (75%) were diagnosed as having BHP, 8 (16.67%) with adenocarcinoma, and 4 (8.33%) with Prostatic Intraepithelial Neoplasia (PIN), $\chi^2 = 38$, p<0.0001.

Among the patients, 22 (45.93%) underwent open prostatectomy and 26 (54.17%) underwent Transurethral Resection of the Prostate (TURP). The age, weight of the prostate, serum PSA level, and mast cell number per high power field are shown in [Table/Fig-1].

Variable	Overall (n=48)	Benign prostatic hyperplasia (n=36)	Prostate cancer (n=12)	p-value
	Median (first quartile-third quartile)			
Age (years)	63.5 (55-70.75)	64 (56.25-72)	59.5 (54.25-65)	0.21
Weight of prostate (gm)	64.5 (53-80.75)	57 (50.25-72.75)	85.5 (74-98.75)	<0.0001
Serum PSA (ng/mL)	14 (9-22.75)	11 (8.25-15.75)	42.5 (25.25-51)	<0.0001
Mast cell/ high power field (number)	7 (5-11.5)	6 (4-7.75)	28 (23.5-31.75)	<0.0001

[Table/Fig-1]: Age, weight of prostate, serum Prostate-Specific Antigen (PSA), and mast cell in overall sample and patients with BHP and malignant lesion.
*Statistically significant p-value of Mann-Whitney U test; PSA: Prostate-specific antigen

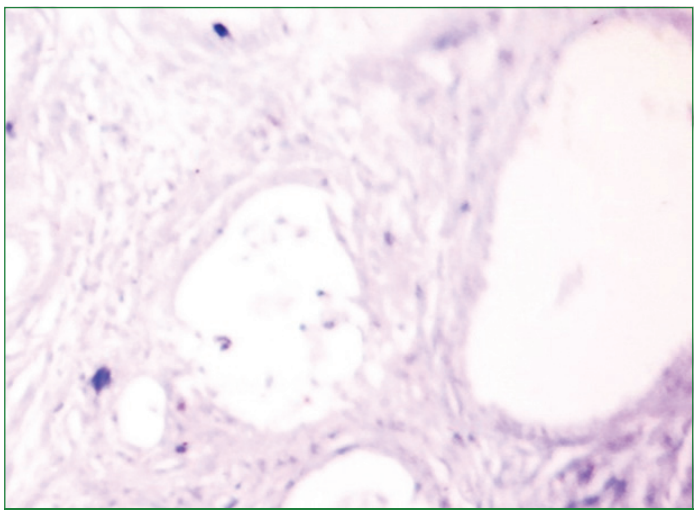
There was no difference in the age of the patients in the BHP and malignant groups (p-value=0.21). However, the weight of the prostate gland, serum PSA, and mast cells per high power field was significantly higher (all p-value <0.0001) in prostatic carcinoma.

In overall sample, the weight of the prostate gland (r_s=0.34, p-value=0.02) and PSA (r_s=0.61, p-value <0.0001) showed a significant positive correlation with mast cells number per high power field. However, when analysed group-wise, there was no significant correlation of mast cells with age, the weight of the prostate, and PSA in patients with BHP. There was a negative correlation between mast cells density and PSA (r_s=-0.69, p-value=0.01) [Table/Fig-2].

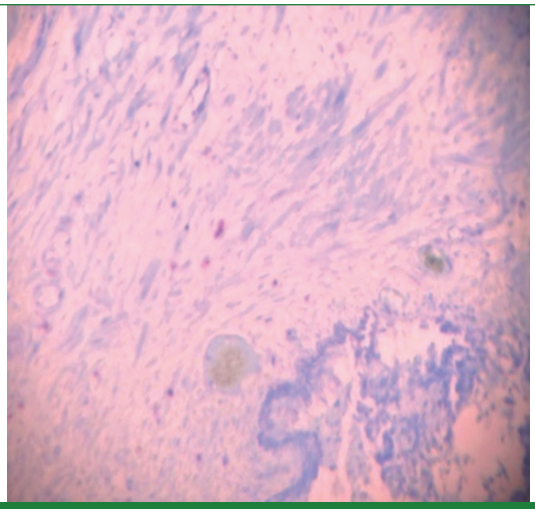
Sample	Age (years)	Weight (gm)	PSA (ng/mL)
	r_s (95% CI), p-value		
Overall (n=48)	-0.09 (-0.37 to 0.21), 0.53	0.34 (0.049 to 0.57), 0.02*	0.61 (0.38 to 0.76), <0.0001*
BHP (n=36)	0.08 (-0.27 to 0.41), 0.65	-0.14 (-0.46 to 0.2), 0.4	0.25 (-0.09 to 0.54), 0.14
Prostate cancer (n=12)	-0.12 (-0.66 to 0.49), 0.68	-0.18 (-0.69 to 0.46), 0.57	-0.69 (-0.91 to -0.18), 0.01*

[Table/Fig-2]: Spearman correlation of mast cell count per high power field with age, weight of prostate, and serum PSA level.
r_s: Spearman correlation coefficient; CI: Confidence interval (lower bound-higher bound);
*Statistically significant p-value of Spearman correlation coefficient

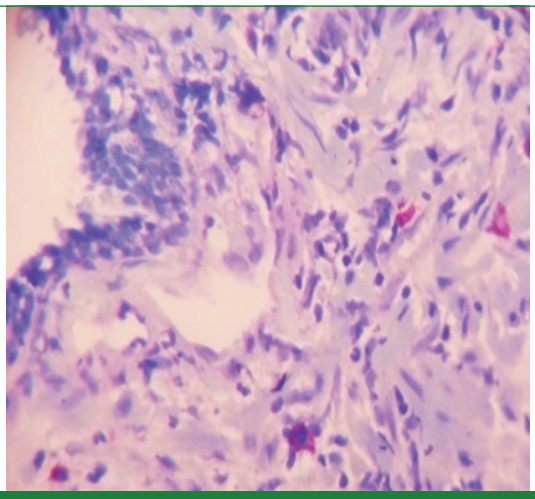
The toluidine blue special stain depicting mast cells are shown in a case of BHP [Table/Fig-3], Prostatic adenocarcinoma [Table/Fig-4] and PIN [Table/Fig-5].



[Table/Fig-3]: Histopathologic picture of benign hyperplasia of prostate (toluidine blue stain 10X) showing mast cells.



[Table/Fig-4]: Histopathologic picture of adenocarcinoma of prostate (toluidine blue stain 10X) showing increased mast cells.



[Table/Fig-5]: Histopathologic picture of Prostatic Intraepithelial Neoplasia (PIN) (toluidine blue stain 10X) showing mast cells.

In the overall sample, when multiple linear regression was run considering mast cell as outcome variable and age, the weight of prostate, and PSA as predictor variables, the model successfully predicted the number of mast cell numbers from age (years), weight of the prostate (gm), and PSA (ng/mL) R=0.71, R_2=0.504, F (3,44)=14.88, p-value <0.001. However, individually, only PSA statistically significantly contributed to the prediction (p-value <0.001).

DISCUSSION

The patients presented with the symptoms and signs of prostatic disease need to be subjected to clinical examination and various radiological and biochemical tests to reach a diagnosis. Histopathological examination of prostate gland may be done for diagnostic purpose as in needle biopsy or as evaluation of TURP and radical prostatectomy specimen. It is an important exercise to predict a prostatic lesion as benign or malignant preoperatively, to optimise the management of the patient.

In order to find the difference in gland size, PSA, and mast cell infiltration in BHP and prostatic cancer, present study found that the weight of the gland measured by transrectal ultrasonography, serum PSA, and infiltrated mast cell per high power field was significantly higher in malignant lesions when compared to benign lesions [Table/Fig-1].

It has been reported that genetic, hormonal, and inflammatory mechanisms are driving factors for both BHP and prostate cancer. However, a causal relationship between these diseases has not been established [9]. According to a meta-analysis of observational studies done by Dai X et al., BHP is associated with a higher risk of prostate cancer and they observed that associated risk seems to be much larger in Asians than in Caucasians [10]. Therefore, the conundrum remains unsolved till now. Yamashiro JR et al., showed in their review article that the majority of the literature suggests that the progression of BHP to cancer is higher in small size glands [11].

In the present study, however, the size of the gland was found to be larger in prostatic adenocarcinoma [Table/Fig-1]. The underlying reason for this finding may lie in the fact that the diagnosed cases of BHP and malignancy were taken and progression over time was not considered.

Men with smaller prostates have higher-grade tumours and more advanced diseases. Hence, in cancer, prostate size may be a significant prognostic factor that should be assessed [12,13]. With an increment of age, the serum PSA increases. Evidence has indicated that prostate volume is a powerful predictor of BPH-related outcomes, including the development of symptoms and the need for BHP-related surgery [14]. Hence the detection of gland size remains a significant prognostic factor. It was found that the digital rectal examination underestimates the size of the prostate. Hence, transrectal ultrasonography is suggested [15].

The PSA level has been classically used for a screening test to detect either BHP or cancer. Both conditions increase the level [16]. In the present study, the cancer patients were found to be having a higher level of PSA [Table/Fig-1]. The obvious reason may be the higher prostate gland size in present study.

In a study done in Nairobi, there was significant overlap of PSA level between BHP and prostatic adenocarcinoma patients [17]. Hence, PSA as a single is not reliable to distinguish between the above two conditions and should always be used with other tests. Cancer cells undergo both genetic and behavioural changes as it progresses, and these changes are influenced in part by the tumour microenvironment. According to histopathological analysis, prostate cancer is associated with a variety of immune cell infiltrates. The mast cell is one among them that infiltrates frequently [18]. When compared to BPH [Table/Fig-3], present study found that mast cell infiltration is higher in the case of adenocarcinoma (both intra- and peritumoural) [Table/Fig-4] and PIN [Table/Fig-5]. After radical prostatectomy, a high extratumoural mast cell count is linked to biochemical recurrence and metastatic growth [19]. Hence, the mast cell count may be considered for further treatment planning.

In the current study, the overall sample (including all the benign and malignant patients), the weight of the prostate gland and PSA level showed a positive correlation with mast cells [Table/Fig-2]. This indicates a possible both-way relationship. An increase in weight or PSA may increase the mast cell infiltration or a higher mast cell infiltration may show higher gland weight and PSA level in patients. A previous study by Nonomura N et al., from Japan has shown that the mast cell number is positively correlated well with the clinical stage of prostate cancer. However, serum PSA level did not correlate significantly with mast cell count in a study of prostate carcinoma needle biopsy [20].

Categorising the patients according to BPH and malignancy, a significant negative correlation was found in the present study between mast cell counts with the PSA in the malignant group [Table/Fig-2]. This was supported partially by the study conducted by Vani D et al., [21]. However, the result of the present study should be interpreted with caution as only a small sample (n=8) was in the malignant group.

When the linear regression analysis was conducted, it was found that the age of the patient, weight of the prostate gland, and serum PSA level can predict the number of mast cell infiltration in the tissue. Although the model successfully predicted the mast cells from the mentioned predictor variables, individually only the PSA was significantly contributing to the prediction model [Table/Fig-2]. Thus,

from the present study a correlation pattern of serum PSA level with mast cell density was seen to emerge, which may be used as an additional tool in distinguishing BHP versus prostatic carcinoma.

In future, a study with a larger sample may provide further support to find a generalisable regression equation.

Limitation(s)

This study had several limitations. The study was conducted in a single tertiary care hospital in one Indian state. The sample was a convenience sample taken from the hospital. Being a non probability sample, the result may not be generalisable. A further study is needed to validate the finding from multiple centres across different Indian states for a more generalisable result.

CONCLUSION(S)

When compared to the benign lesion, the malignant growth of the prostate gland is associated with higher gland weight, higher levels of serum PSA, and higher infiltration of mast cells in the tumour tissue. It was concluded from this study that a correlation of serum PSA level with mast cell density was seen to emerge, which may be used as an additional tool in distinguishing BHP versus prostatic carcinoma. A further large-scale study is needed to find a more generalisable regression equation to find mast cell infiltration levels from PSA.

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PARTICULARS OF CONTRIBUTORS:
1. Ex Postgraduate Trainee, Department of Pathology, Bankura Sammilani Medical College and Hospital, Bankura, West Bengal, India.
2. Associate Professor, Department of Surgery, Bankura Sammilani Medical College and Hospital, Bankura, West Bengal, India.
3. Assistant Professor, Department of Pathology, Midnapore Medical college and Hospital, Midnapore, West Bengal, India.
4. Associate Professor, Department of Respiratory Medicine, College of Medicine and Sagore Datta Hospital, Kamarhati, Kolkata, West Bengal, India.
5. Associate Professor, Department of Pathology, Midnapore Medical College and Hospital, Midnapore, West Bengal, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Aparup Dhua,
Katjuridanga (Saratpally), P.O-Kenduadihi, Pin-722102, Bankura, West Bengal, India.
E-mail: docaparup@gmail.com

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