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Role of Neutral Mucin in Differentiating Prostatic Adenocarcinoma from Nodular Hyperplasia of Prostate

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Abstract: ***Background:*** Prostatic enlargement is a significant cause of morbidity in men, and distinguishing between prostatic adenocarcinoma and benign prostatic conditions remains challenging. ***Objective:*** This study aims to assess the role of neutral mucin in distinguishing prostatic adenocarcinoma from benign prostatic nodular hyperplasia. ***Methods*:** This cross-sectional study was conducted from March 2018 to February 2020 in the Department of Pathology at Rajshahi Medical College and Bangabandhu Sheikh Mujib Medical University (BSMMU). A total of 60 prostate tissue specimens, including 30 diagnosed cases of nodular hyperplasia and 30 of prostatic adenocarcinoma, were included. The specimens were processed with Hematoxylin and Eosin staining, followed by Periodic Acid Schiff (PAS) staining to detect neutral mucin. Positive or negative staining was recorded. Statistical analysis was performed using SPSS version 20. ***Results:*** Of the 30 prostatic adenocarcinoma cases, neutral mucin was detected in 6 (20%) cases and absent in 24 (80%). In contrast, among the 30 cases of nodular hyperplasia, neutral mucin was present in 27 (90%) cases and absent in 3 (10%). The sensitivity of PAS stain for detecting prostatic adenocarcinoma was 80%, and its specificity for nodular hyperplasia was 90%. The accuracy of PAS stain in distinguishing adenocarcinoma from benign nodular hyperplasia was 85%. ***Conclusions:*** The PAS stain is a reliable histochemical marker for differentiating prostatic adenocarcinoma from nodular hyperplasia.

Keywords: Neutral mucin, Periodic Acid Schiff (PAS), Prostatic adenocarcinoma, Nodular hyperplasia of prostate.

Original Research Article

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Article at a glance:

Study Purpose: *To contribute the extend of existing knowledge and to search the new findings.*
Key findings: *Among the cases of nodular hyperplasia PAS stain showed positivity in 90% cases but in case of prostatic adenocarcinoma it was positive in only 20% cases. There was a statistical difference in staining between these two groups indicated by $p<0.05$.*
Newer findings: *The sensitivity and specificity of PAS stain was higher in this study than previous study.*
Abbreviations: PAS *– Periodic Acid-Schiff,* ***SPSS*** *– Statistical Package for Social Sciences,* ***H&E*** *– Hematoxylin and Eosin,* ***CA*** *– Cancer,* ***BPH*** *– Benign Prostatic Hyperplasia.*

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INTRODUCTION

Nodular hyperplasia of Prostate and Prostatic adenocarcinoma (BPH) are the two most common conditions that involve the prostate and account for more than 90% of all prostatic diseases.[1] Nodular hyperplasia is a very common disorder in elderly men[2] and its clinical incidence is only 8% during the fourth decade, but it reaches 50% in the fifth decade and 75% in the eighth decade.[3] It has been estimated that about half of all men aged 80 years and over will have lower urinary tract symptoms associated with bladder outlet obstruction (BOO) due to nodular hyperplasia.[4] It results from hyperplasia of prostatic stromal and epithelial cells[5] and typically affects the submucous group of glands in the transitional zone.[6] Nodular hyperplasia of prostate is an androgen-dependent disorder and occurs only in individuals with intact testes.[7]

Carcinoma of the prostate is the most common malignant tumor in male over the age of 65 years[6] and almost all are adenocarcinomas.[4] It accounts for more than 25% of all Malignant lesions in male and is regarded as the second leading cause of death after lung carcinomas in the United States.[1] In Bangladesh the prevalence of prostate cancer among all cancers is 2.3% (Cancer Control in Bangladesh, 2013). It has a remarkably wide range of clinical behaviors, from incidentally discovered clinically insignificant cancers to very aggressive lethal forms.[5] Prostatic carcinoma is typically a disease of men older than age 50 years and its incidence increases from 20% in men in their 50s to approximately 70% in men between the ages of 70 and 80 years.[5] Carcinoma of prostate tends to arise within the peripheral zone of the gland[4] and hormonal factors play a role in their development.[3] The diagnosis of prostate cancer is based on a combination of architectural and cytological features.[7] Though the majority of prostatic adenocarcinomas are not difficult to diagnose; however, problem areas do exist.[1] An accurate diagnosis can be challenging because the separation of well-differentiated adenocarcinoma from the vast number of benign or atypical small-gland proliferations is not easy.[1] Moreover the threshold for recognizing extremely small foci of cancer in needle biopsy specimens is difficult.[1]

Mucin stain may be an adjunctive aid in the diagnosis of adenocarcinoma of the prostate. Neutral mucin is predominantly seen in benign cases but absent in malignant tumours.[8] For these characteristic features, Neutral mucin have a diagnostic value in differentiating benign and malignant prostatic lesions.[7] Pariodic Acid Schiff (PAS) stain is used to identify neutral mucin in tissue sections.[9] Bastola and Talwar[7] stated that neutral mucin has a role in the diagnosis of prostatic adenocarcinoma. In Bangladesh, the diagnosis of prostatic adenocarcinoma is a difficult task in surgical pathology. A reliable marker is needed which is specific, cost effective and can be used in institutions with limited resources. So, the aim of the study is to find out the role of this type of mucin histochemistry in differentiating benign and malignant tumors of prostate which will help more precisely in the diagnosis of prostate cancer.

MATERIAL AND METHODS

The present study was a descriptive type of cross-sectional study and was conducted in the Department of Pathology, Rajshahi Medical College and in the Department of Pathology, BSMMU. The study was aimed at finding the diagnostic role of neutral mucin in differentiating prostatic adenocarcinoma from the nodular hyperplasia of prostate and it was detected by Periodic Acid Schiff (PAS) stain. A total 60 samples of histopathologically diagnosed prostatic lesions were included in the study group among which 30 cases were prostatic adenocarcinoma and another 30 cases were nodular hyperplasia of prostate. The specimens were obtained by Trans-urethral Resection of Prostate (TURP) and needle biopsy.

The tissues were fixed in 10% formaldehyde solution and embedded in paraffin block to make the histopathological slides. Routine Hematoxylin and Eosin stains were done in the Department of Pathology, Rajshahi Medical College. Sections were studied under light microscope and classified into benign and malignant lesions microscopically. Associated prostatic tissue changes such as tumor invasion, prostatitis and others were also analyzed. Periodic Acid Schiff (PAS) stain was done in Department of Pathology, BSMMU to demonstrate the presence or absence of neutral mucin. In most of the benign cases the glandular acinar cells showed magenta color indicating the presence of neutral mucin. Few malignant cases showed these positive results but maximum was negative. Statistical analyses were carried out by using the Statistical package for Social Sciences (SPSS) version 20 for Windows. Chi-square tests were used to analyze categorical variables. Results having p-values <0.05 were considered statistically significant.

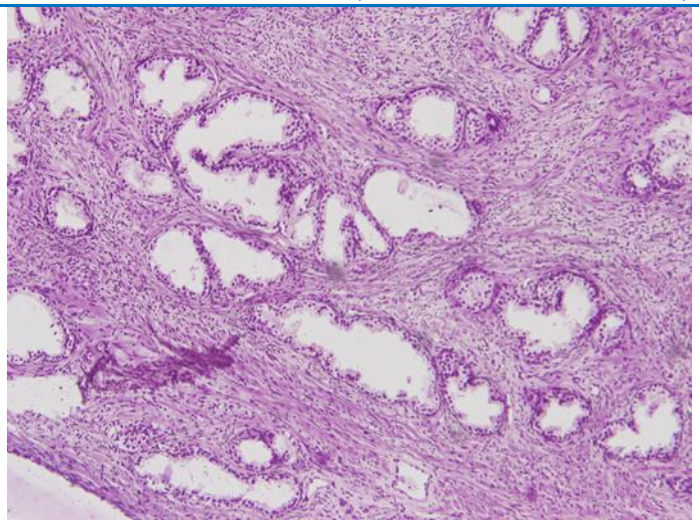

Figure 1: Photomicrograph showing Nodular Hyperplasia of prostate (H &E X 100) (Case no. 12)

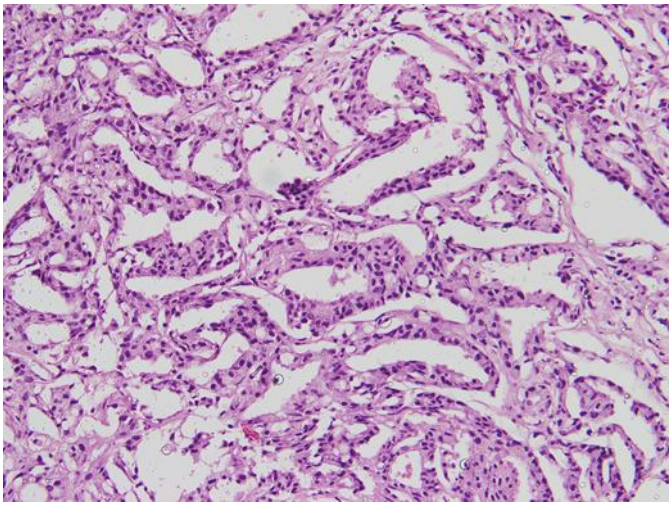

Figure 2: Photomicrograph showing Prostatic Adenocarcinoma with Gleason score of 4+4= 8. (H & E X 400) (Case no. 54)

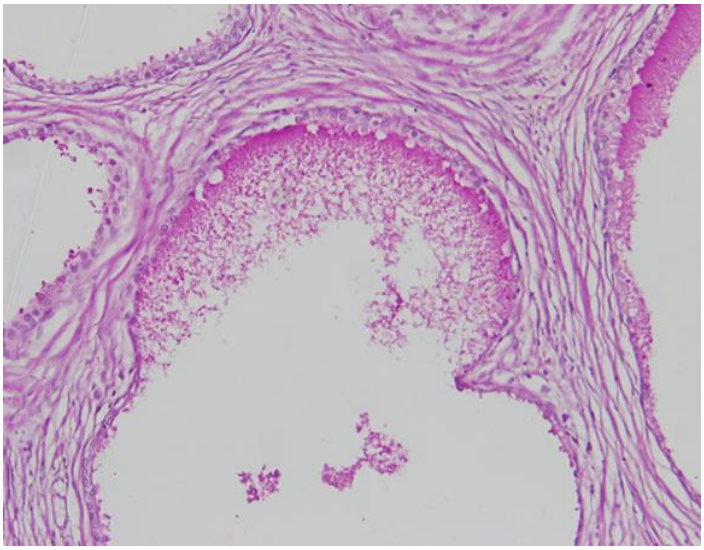

Figure 3: Photomicrograph showing PAS stain of Nodular Hyperplasia of Prostate characterized by magenta color (arrows) of acinar cell cytoplasm (PAS X 400) (Cases no. 20)

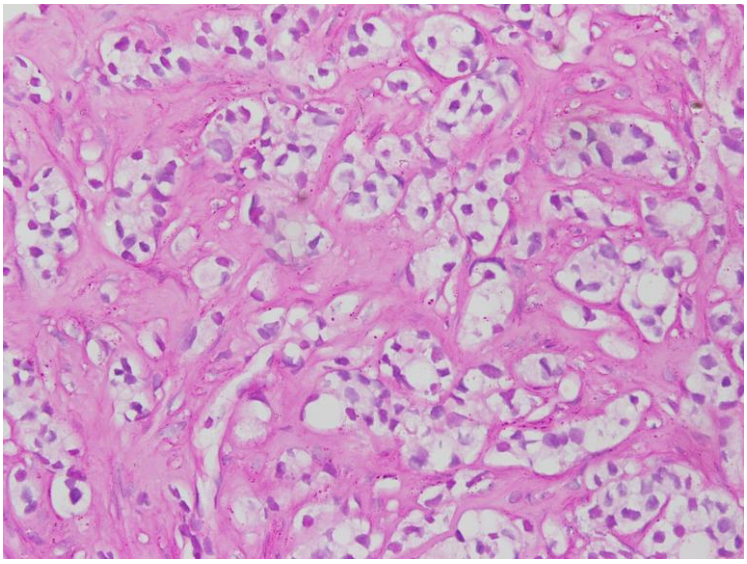

Figure 4: Photomicrograph showing absence of PAS staining in Prostatic Adenocarcinoma (Gleason score, 4+5=9) (PAS X 400) (Case no. 47).

RESULTS

A total 60 cases of patients with prostatic lesions were studied during the period of two years. 30 patients had prostatic adenocarcinoma and another 30 patients had nodular hyperplasia of prostate which were diagnosed by histopathological examination (Table 1). Table 2 shows the distribution of patients by their presenting symptoms. The predominant symptom was difficulty in starting and stopping urine stream (75%) followed by nocturia (70%), dysuria (55%), urinary hesitancy (55%), increased frequency (53%), urgency of micturition (50%), weight loss (50%), backache (44%) and hematuria (40%). The less common symptoms were retention of urine (33%) and overflow of urine (30%).

Table 1: Distribution of the patients by their histopathological findings (n= 60)

Histopathological Diagnosis	Frequency	Percentage
Prostatic Adenocarcinoma	30	50%
Nodular Hyperplasia	30	50%
Total	60	100%

Table 2: Distribution of patients by their presenting symptoms (n= 60)

Presenting symptoms	Frequency	Percentage
Increased frequency of micturation	32	53.0
Urgency of micturation	30	50.0
Urinary hesitancy	33	55.0
Retention of urine	20	33.0
Nocturia	42	70.0
Difficulty in starting and stopping urine stream	45	75.0
Overflow urine	18	30.0
Dysuria	33	55.0
Hematuria	24	40.0
Backache	27	44.0
Weight loss	30	50.0

Table 3 shows the comparison of the Periodic Acid Schiff (PAS) stain between prostatic adenocarcinoma and nodular hyperplasia. It is seen that among the total 30(100%) cases of adenocarcinoma, 24(80%) showed negative staining for PAS and 6(20%) cases showed positive staining. Among the 30(100%) cases of nodular hyperplasia only 3(10%) showed negative staining for PAS and 27(90%) showed positive staining. There was a statistically significant difference in PAS staining between these two study groups (p< 0.05). Table 4 shows the sensitivity, specificity, positive predictive value, negaetive predictive value and diagnostic accuracy of Periodic Acid Schiff (PAS) stain as a diagnostic test.

Table 3: Comparison of PAS stain between adenocarcinoma and nodular hyperplasia (n= 60)

	Periodic Acid Schiff (PAS) stain					p-value
	Adenocarcinoma		Nodular Hyperplasia			
	Frequency	%	Frequency	%	Total	
Negative	24	80	3	10	27	<0.05
Positive	6	20	24	90	33	
Total	30	100	30	100	60	

Data were analyzed using **Chi-square (χ^2) Test.**

Table 3 shows the comparison of the Periodic Acid Schiff (PAS) stain between prostatic adenocarcinoma and nodular hyperplasia. It is seen that among the total 30(100%) cases of adenocarcinoma, 24(80%) showed negative staining for PAS and 6(20%) cases showed positive staining. Among the 30(100%) cases of nodular hyperplasia only 3(10%) showed negative staining for PAS and 27(90%) showed positive staining. There was a statistically significant difference in PAS staining between these two study groups (p< 0.05). Table 4 shows the sensitivity, specificity, positive predictive value, negaetive predictive value and diagnostic accuracy of Periodic Acid Schiff (PAS) stain as a diagnostic test.

Table 4: Summary of Sensivity, Specificity, Positive Predictive Value, Negative Predictive Value and Diagnostic Accuracy of PAS stain for Prostatic Adenocarcinoma

PAS	Adeno-Carcinoma	Nodular Hyperplasia	Total
Negative	24 (TP)	3 (FP)	27
Positive	6 (FN)	27 (TN)	33
Total	30	30	60

TP= True Positive, FP= False Positive, TN= True Negative, FN= False Negative

Test	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	Diagnostic Accuracy
PAS	80%	90%	88.9%	81.9%	85%

DISCUSSION

The neutral mucin is predominantly seen in nodular hyperplasia of prostate in contrast to malignant prostatic glands where it is produced in a much lesser extent.10 Periodic Acid Schiff (PAS) stain was used in this study to detect the neutral mucin and the result showed a higher level of positivity in nodular hyperplasia of prostate. Among the 30 cases of histopathologically diagnosed prostatic adenocarcinoma 24 (80.0%) were negative for PAS stain and 6 (20.0%) were positive. On the other hand, nodular hyperplasia which produce neutral mucin in increased level, shows PAS positivity in 27 (90.0%) of total 30 cases. PAS negativity was seen in rest of the 3 (10.0%) cases of nodular hyperplasia which may be due to faulty technique or poor preservation of tissue. There was a statistically significant difference in the staining of PAS between adenocarcinoma and nodular hyperplasia, indicated by p< 0.05. This

finding is similar to the study done by Bastola and Talwar7 who conducted a research to evaluate the role of mucin histochemistry on benign and malignant prostatic lesions. They found the absence of neutral mucin in prostatic carcinoma and showed that the PAS technique can be used as a negative histochemical marker for the diagnosis of prostatic adenocarcinoma. In their study the P value for PAS negativity in malignancy was 0.00068 which was statistically significant ($p< 0.05$). The result of our study is also similar to a study done by Mathur et al[9] where they found that the neutral mucin is less frequently seen in carcinoma cases (36%) as compared to nodular hyperplasia of prostate (93.3%). Another study was conducted by Khanna A et al[8] at the Jawaharlal Nehru Medical College, Sawangi, Wardha, Maharastra, India. The study was done on 176 prostatomegaly specimens to assess the role of PAS stain in differentiating benign and malignant prostatic lesions but in this case the result was less significant. The PAS staining was positive in 89.82% of nodular hyperplasia cases but it was also positive in 66.67% of prostatic carcinoma that decreased the sensitivity of PAS technique in favor of malignancy.

Among the 30 cases of prostatic adenocarcinoma, 6 (20%) cases were positive for neutral mucin; a finding which was also observed by Manoj PA et al.[10] They stated that the neutral mucin can reappear in late stage of carcinoma. Hadi NI et al.[11] stated that the presence of neutral mucin in carcinoma may be due to the reversion of malignant clone to an embryonic state. So, in this study the presence of neutral mucin in adenocarcinoma may be due to the reshuffling of neoplastic clone to an embryonic state but it should be confirmed by genetic analysis using specialized molecular techniques.

For testing the accuracy of Periodic Acid Schiff (PAS) stain as a diagnostic test in differentiating the prostatic adenocarcinoma from nodular hyperplasia of prostate the standard formula of sensitivity, specificity, positive predictive value and negative predictive value were used and the results were 80%, 90%, 88.9%, and 81.9% respectively. The overall diagnostic accuracy of PAS was 85.0%. The result was almost similar to Bastola and Talwar[7] who demonstrated 84.4% diagnostic accuracy of PAS in the detection of prostatic adenocarcinoma. In this study the result shows 80.0% sensitivity of PAS technique which was quite higher than the result of Bastola and Talwar7 where a sensitivity of 55.0% was observed in case of PAS technique. So, in our study we found that the neutral mucin which is detected by Periodic Acid Schiff (PAS) stain can give a satisfactory result in differentiating benign and malignant prostatic lesions and it can be used in the diagnosis of prostatic adenocarcinoma.

CONCLUSION

From the findings of the study, it can decide that neutral mucin has a beneficial role in the diagnosis of prostate cancer. So, its detection by Periodic Acid Schiff (PAS) stain can be used as a diagnostic tool for early detection of prostatic adenocarcinoma in institutions where limited facilities are available.

Declarations

I, hereby, declare that the submitted Research Paper is my original work and no part of it has been published anywhere else in the past.

Ethical approval

Ethical clearance for the study was taken from the Instutional Review Board and concerned authority, Rajshahi Medical College & Hospital.

Conflict of interest: None declared.

Consent: Informed written consent was taken from each patient or patient's attendants.

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