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HISTOPATHOLOGICAL STUDY OF PROSTATIC LESIONS AND ASSESSEMENT WITH AGNOR INDEX

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ABSTRACT

Interpretation of prostatic biopsies has been a continuous problem for practicing pathologist. This current study aims at the analysis of histopathological features of various non neoplastic and neoplastic lesions of the prostate including the grading of malignant lesions and evaluation of role of AgNOR index in different benign, premalignant and malignant lesions of prostate. One hundred and eight transurethral resection of prostate specimens were studied with haematoxylin and eosin and AgNOR staining. Benign prostatic hyperplasia was the most common lesion affecting the prostate in elderly. High grade prostatic intra epithelial neoplasia had strong association with prostatic carcinoma. Among the malignant lesions of the prostate, primary prostatic adenocarcinoma was the commonest. According to Gleason Grading system higher grades were more commonly observed as the predominant pattern. Mean AgNOR counts were higher in malignant lesions when compared with the benign lesions.

KEYWORDS: **Benign prostatic hyperplasia, Prostatic adenocarcinoma, AgNOR**

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INTRODUCTION

Prostatic diseases, benign and malignant are collectively responsible for significant morbidity and mortality in men throughout the world. Only three pathologic processes affect the prostate gland with sufficient frequency to merit discussion namely inflammation, benign prostatic hyperplasia (BPH) and tumors. Benign prostatic hyperplasia (BPH) is common in elderly men and It is characterized by nodular proliferation of both glandular and stromal components.. Prostate cancer is now the sixth most common cancer in the world. Prostatic adenocarcinoma is the second most common cause of cancer mortality in men next to lung cancer. Prostatic cancers are diagnosed by fine needle aspiration cytology, needle biopsies, transurethral resection of prostate (TURP) and prostatectomy. Various types of difficulties have been encountered while diagnosing and typing prostatic carcinoma and premalignant lesions especially in TURP chips where there is loss of orientation and coagulation of tissue during cauterization. Prostatic lesions on routine haematoxylin & eosin staining sometimes cause diagnostic difficulties in identifyingpremalignant and malignant conditionsAn important diagnostic criterion in the differentiation is the loss of basal cell layer in adenocarcinoma and its presence in the benign lesions. Several immunohistochemical markers have been used to stain the basal cells of prostate like High molecular weight cytokeratin (HMWCK), p63 etc. Proliferative markers like silver staining nucleolar organizer regions (AgNOR), proliferating cell nuclear antigen (PCNA) are of great help in differentiating benign premalignant and malignant lesions. This current study aims at analysis of histopathological features of various non neoplastic and neoplastic lesions of the prostate including the grading of malignant lesions and evaluation of role of proliferative markers in different benign, premalignant and malignant lesions of prostate. Histological typing, grading and staging of prostatic carcinoma are vital in planning the treatment strategies and predicting the survival rate.

MATERIALS AND METHODS

This present study is a prospective study undertaken in the department of pathology, Madurai Medical College, Madurai, during the period of May 2009 to July 2011. This study was conducted on 108 prostatic specimens of which 56 specimens were from Government Rajaji Hospital, Madurai and 52 were from Madurai Kidney centre, Madurai. All the 108 specimens received were Trans Urethral Resection of Prostate (TURP) specimens ranging in volume from 1 to 10 grams. These were fixed in 10% neutral buffered formalin for 12 hours. After adequate fixation, the specimens were submitted for processing until four cassettes were filled. Tissue processing was done with automated tissue processor and sections were made manually with microtome of thickness 2-4 microns. Staining was done with routine haematoxylin and eosin and examined under light microscope. Silver staining of nucleolar organizer region (AgNOR) method of Smith and Crocker was done for all the cases taken for study excluding the cases of Leiomyosarcoma of prostate and contiguous spread of rectal adenocarcinoma to prostate. All the slides were examined under 100X oil immersion objective with 10X eye piece. One hundred lesional nuclei of epithelial cells were taken at random for the counting procedure. Careful focusing allowed the nucleolar organizer regions (NOR) to be visualized as black dots arranged both in clusters and clumps and as individual “satellites” within the cell nucleolus. The NOR dots were counted per nuclei and an average count was noted.

RESULTS

Benign prostatic hyperplasia was the most common type of lesion – 96 cases (88.89%), followed by malignant lesion – 10 cases (9.26%) and inflammatory lesions – 2 cases (1.85%). The incidences of various prostatic lesions are illustrated in Graph1. Among the 98

benign lesions, youngest case reported was 41 years old and oldest was 81 years. The mean age group for benign lesions was 63.44. Among the 10 malignant lesions, youngest case reported was 50 years old and oldest was 77 years. The mean age group for malignant lesions was 63.90. Two cases (1.85%) showed features of granulomatous prostatitis. (Figure 1). Out of all the prostatic lesions studied, Nodular hyperplasia constituted the bulk of the lesions [88.89 % (96 cases)]. Foci of low grade PIN were identified in12 cases (11.11%). Foci of High grade PIN was identified in three cases (2.78%). Among the three cases one was BPH and other two were adenocarcinoma. (Figure 2) In our prospective study, malignant lesions constituted the second most common pathology of prostate. This study included a total of 10 cases of malignant lesions of prostate. Adenocarcinoma was the most common [7.41% (8 cases)] type of primary carcinoma encountered. Others were Leiomyosarcoma of prostate invading the bladder [1 case (0.93%)] and the Rectal adenocarcinoma invading the prostate [1 case (0.93%)]. All the cases of primary prostatic carcinoma were graded using Gleason scoring system. Primary grade was assigned to dominant pattern and secondary grade to second dominant pattern and then the two numeric scores were added to obtain combined Gleason score. In tumors with one pattern of arrangement, the number was doubled. (Table 1) (Figure 3, 4, 5) Mean AgNOR count was higher in malignant lesions when compared to benign lesions. (Figure 6, 7, 8), (Table 2. One way Analysis Of Variance test was used to assess the statistical difference between benign, premalignant and malignant lesions. The differences in the mean value between benign and pre malignant lesions were statistically significant. (P = < 0.001). The differences in the mean value between benign and malignant lesions were statistically significant. (P = < 0.001).

Graph 1
Incidence of various prostatic lesions

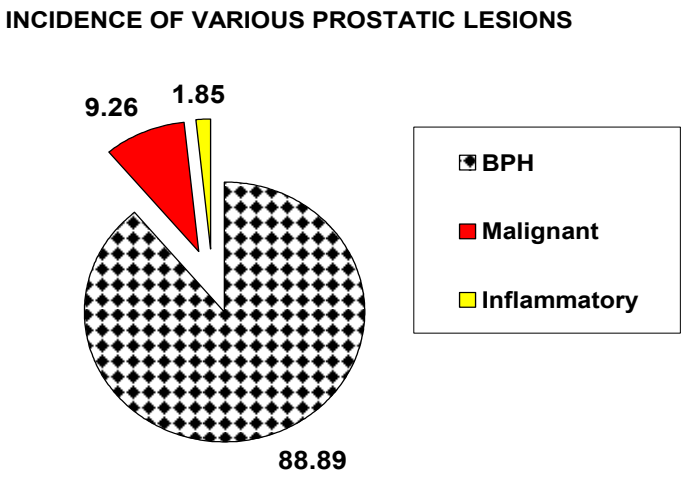

Table 1
Gleason's grading for adenocarcinoma

S.NO	PATH NO	HPE DIAGNOSIS	GLEASON'S GRADE	GLEASON'S SCORE	AgNOR count
1	3667/09	Adenocarcinoma	3+3	6	5.1
2	3909/09	Adenocarcinoma	2+2	4	4.5
3	2674/10	Adenocarcinoma	3+4	7	5.5
4	36/09	Adenocarcinoma	1+2	3	4
5	50/09	Adenocarcinoma	1+4	5	4.5
6	78/10	Adenocarcinoma	3+2	5	4.8
7	25/11	Adenocarcinoma	2+3	5	4.9
8	46/11	Adenocarcinoma	3+4	7	5.2

Table - 2
The mean AgNOR count in various prostatic lesions

Lesions	No of cases	Mean AgNOR count
Granulomatous prostatitis	2	1.9
BPH with or without prostatitis	83	1.43
BPH with LGPIN	11	2.08
BPH with HGPIN	1	3.9
Adenocarcinoma	8	4.81

Table 3
Comparison of mean AgNOR count in various studies

Studies	BPH	PIN	Prostatic adenocarcinoma
Sakr, W. A[13]	1.836	3.129	4.737
Asim Kumar Manna[11]	1.3	4.7	4.91
Present study	1.44	2.23	4.81

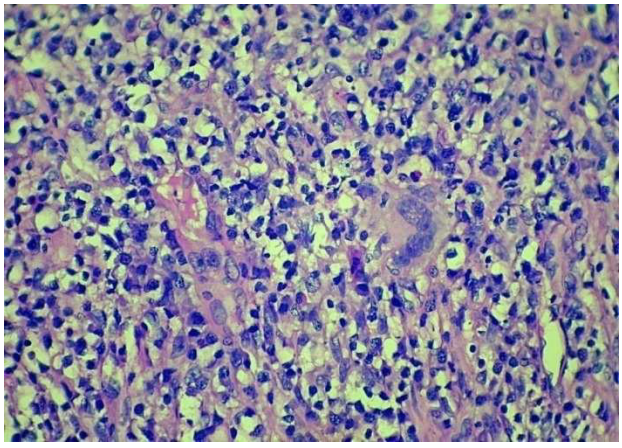

Figure 1
Nonspecific granulomatous prostatitis showing foamy histiocytes and multinucleated giant cells (H & E 400X) (21/10).

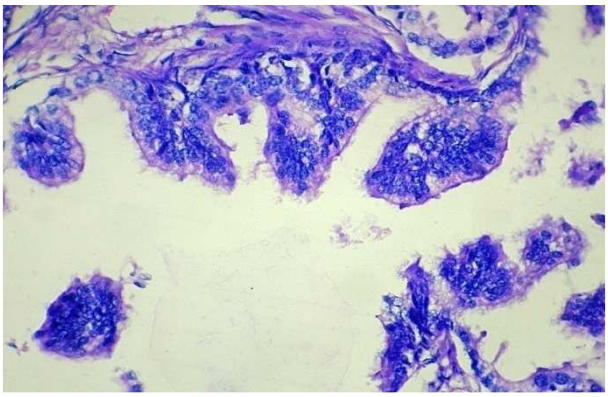

Figure 2

Foci of High grade PIN showing epithelial cell crowding and stratification in tufting pattern with enlarged nuclei and prominent nucleoli. (H&E 400X)

Figure 3

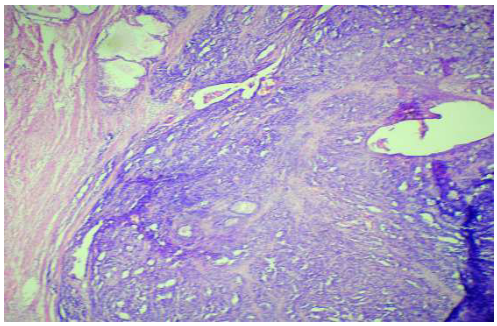

Figure 4

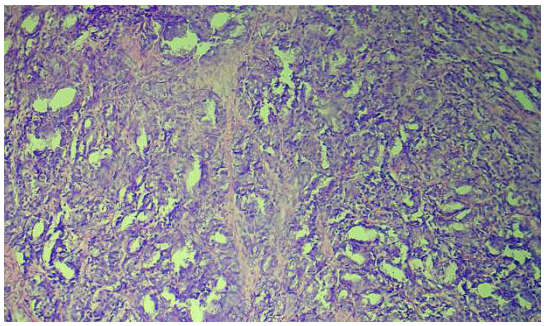

Figure 5

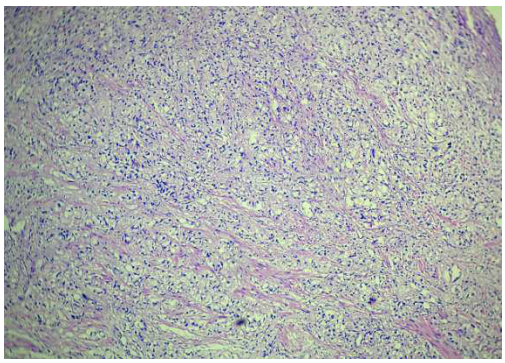

Figure 3: Prostatic adenocarcinoma Gleason's pattern 2 –loosely packed single glands with irregular edges. (H&E 100X) (78/10), Figure 4: Prostatic adenocarcinoma Gleason's pattern 3 – scattered single glands. (H&E 100X) (78/10), Figure 5: Prostatic adenocarcinoma Gleason's pattern 4 – fused infiltrating glandular pattern. (H&E 100X) (2674/10)

Figure 6

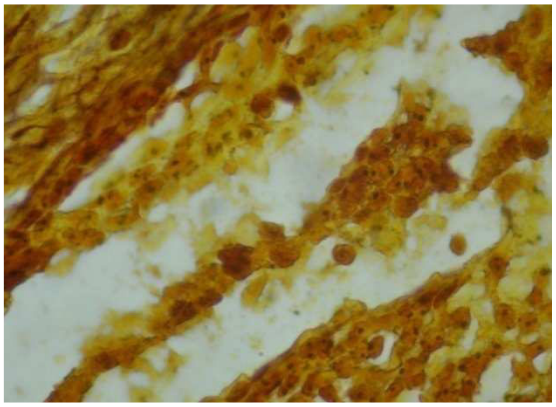

Figure 7

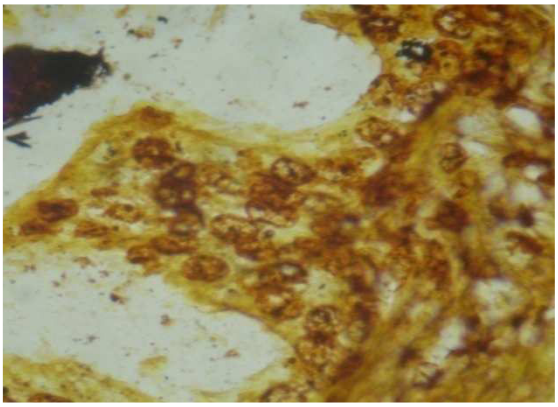

Figure 8

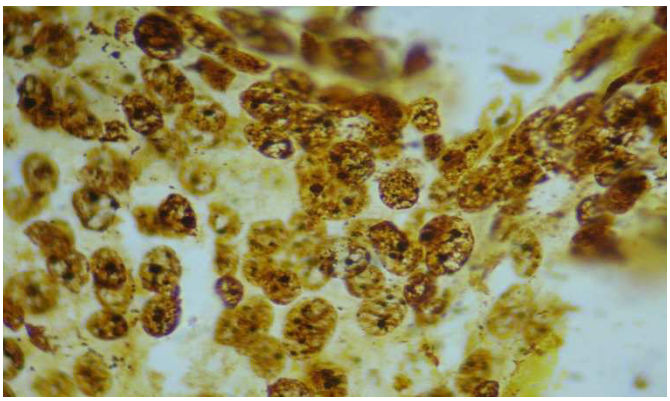

Figure 6: BPH showing occasional AgNOR dots per nuclei. (AgNOR stain 1000X) (2116/10), Figure 7: High grade PIN showing two to three AgNOR dots per nuclei. (AgNOR stain 1000X) (103/10), Figure 8: Prostatic adenocarcinoma showing numerous AgNOR dots per nuclei. (AgNOR stain 1000X) (2674/10)

DISCUSSION

The incidence of BPH increases with age. BPH is seen in 20% of the men at 40 years of age, a figure that increases to 70% by age of 60 and to 90% by age of 80. In the present study 108 cases of TURP specimen were examined. Benign prostatic hyperplasia was seen in 96 cases. Highest incidence of nodular hyperplasia was noted in the 7th decade[1]. In a classic paper by Berry et al[2], the prevalence of BPH ranged from 8% for men in their 30s to 88% for men over 80s. In another classic paper Issac and Coffey[3] compared the prevalence of BPH by age in autopsy studies from various countries. This study demonstrated relatively similar prevalence of BPH across a spectrum of countries and ethnicities. In our study also the incidence of BPH increases with age reaching maximum in 7th decade. The decline in the number of cases beyond the age of 80 years may reflect the average life span of people in our country. Prostatic Intra Epithelial Neoplasia (PIN) has high predictive value as a marker for adenocarcinoma. This is particularly true for high grade PIN; if this lesion is identified; close surveillance and follow up biopsy are indicated. The frequency of HGPIN in transurethral resection of the prostate specimens is between 2.3% and 4.2 %[4]. The present study was comparable well with the above study, stating 2.78% prevalence of HGPIN in all TURP

specimens. The frequency of HGPIN in prostates involved with cancer is significantly increased when compared with the cancer free prostates. The incidence of high grade PIN is low in our study because all the specimens were TURP which does not have enough material compared to whole prostate specimen examined in other studies. In a study by Pacelli A and Bostwick DG[5] the incidence of high grade PIN in TURP specimens without carcinoma was 2.8%. The incidence of PIN in prostatic malignancy, as quoted in the literature, varies from 33% to 100%, depending on the nature of specimen.[6,7] . In our study, we_observed high grade PIN in 25% of the carcinomas.

In this study, malignant lesions account for 9.26% (10 cases) of cases. Among the malignant lesions incidence of primary prostatic adenocarcinoma is high [8cases (80%)]. Prostate cancer is now the sixth most common cancer in the world. The prevalence of prostatic adenocarcinoma in this study is 7.41% (8 cases). All these cases were incidental adenocarcinoma which were identified in transurethral resection of the prostate (TURP) done for BPH. According to WHO study, when TURP is done without clinical suspicion of cancer, prostate cancer is incidentally detected in approximately 8- 10% of the specimens[8], which is in correlation with our study. The risk of prostate cancer rises very steeply with age. Worldwide, about three-quarters of all cases occur in men aged 65 or more[8.] In our study also maximum numbers of cases were found in the age group of 60-69 years[1]. Gleason scoring system is the most widely used and officially recommended system for scoring prostatic adenocarcinoma[9,10] . Gleason score correlates with prognosis after radical prostatectomy and with outcome following radiotherapy. Gleason grade on biopsy can influence mode of treatment. We applied Gleason grading system for all adenocarcinoma (Table2) Tumor differentiation and proliferative activity are important predictors of biological behavior. While routine histological evaluation is fairly adequate to assess differentiation, tumor proliferative activity is difficult to measure. Silver staining for nucleolar organizer regions (AgNORs) is reported to be helpful for assessing tumor proliferation. AgNOR value is significantly higher in Prostatic carcinoma than BPH &PIN. It is also significantly higher in PIN than BPH. The mean AgNOR value is higher in adenocarcinoma with high gleason score than the lower gleason score. (Table2) Our study showed identical results with the study done by Asim Kumar Manna et al[11]. Kawase[12] found AgNOR counts were higher in carcinoma (4.2+/- 1.57) than in benign lesions (1.9 +/- 0.24). Wael A sakr[13] found that AgNOR study is helpful in assessing tumor proliferation (Table 3).

CONCLUSION

We conclude that mean AgNOR counts are significantly higher in adenocarcinoma when compared to benign and premalignant lesions and correlated with histological grade of the tumor. The proliferative markers have a significant role in the diagnosis of prostatic lesions especially which fall in the premalignant category and create difficulty in the diagnosis by routine histopathological study.

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