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HISTOMORPHOLOGIC CORRELATION OF PSA LEVELS IN BENIGN, PREMALIGNANT & MALIGNANT LESIONS OF PROSTATE

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ABSTRACT

Background: Due to the widespread use of serum PSA (Prostate specific antigen)as a mass screening test for prostate cancer there has been an ever increasing number of prostate needle biopsies and hence the need to give an accurate diagnosis despite the limitations. Present study was aimed to study histomorphologic correlation of PSA levels in benign, premalignant & malignant lesions of prostate. **Material and Methods:** Present study was single-center, cross sectional study, conducted in prostate biopsies/transurethral resection of prostate (TURP) specimens/prostatectomies received. The PSA level in serum is estimated and correlated with histopathological diagnosis. **Results:** In present study, 31 cases of various prostatic lesions were studied. Common lesions were prostatic adenocarcinoma (32.5 %) & benign prostatic hyperplasia (32.5 %) followed by high grade prostatic intraepithelial neoplasia (22.5 %), atypical small acinar proliferation (7.5 %) & atypical adenomatous hyperplasia (5 %). As per histopathology reports, majority lesions were premalignant (35 %), followed by benign & malignant lesions (32.5 % each). Raised age specific PSA levels were noted in 27 cases (67. 5%). PSA is not a specific marker for Prostatic malignancy, as four cases out thirteen cases of BPH showed abnormal PSA levels. PSA level was raised in all the prostatic adenocarcinoma cases. Ten cases out of fourteen premalignant cases showed raised PSA There was statistically significance is established between age specific PSA levels and Histopathology reports. There was significant difference in PSA levels between Benign and malignant lesions (p value<0.05). There was significant difference in PSA levels between malignant and premalignant lesions (p value<0.05). There was no significant difference in PSA levels between Benign and premalignant lesions (p value<0.05). **Conclusion:** PSA is not a specific marker for prostate malignancy, it can be increased in the premalignant and benign condition too like BPH with inflammation.

KEYWORDS: Prostatic adenocarcinoma, Prostate specific antigen, Prostate malignancy, Histology.

INTRODUCTION

Cancer of the prostate is typically a disease over age 50. It increases from 20% in their 50s to approximately 70% in between the ages of 70 and 80 years. Adenocarcinoma of prostate is the most common form of cancer in men, accounting for 29% of cancer in the united states in 2012.[1]

The diagnosis of prostatic cancer (PC) is based on a combination of architectural, cytological and ancillary features rather than any single diagnostic feature none of which is absolutely sensitive and specific. Accurate tissue diagnosis can be very challenging due to the presence of either a small focus of cancer or due to the presence of many benign mimickers of malignancy like adenosis, sclerosing adenosis, atrophy, partial atrophy, basal cell hyperplasia, clear cell cribriform hyperplasia, post atrophic hyperplasia, nephrogenic adenoma, mesonephric hyperplasia, radiation atypia, seminal vesicle and cowpers glands.[2]

Due to the widespread use of serum PSA (Prostate specific antigen) as a mass screening test for prostate cancer there has been an ever increasing number of prostate needle biopsies and hence the need to give an accurate diagnosis despite the limitations. PSA is a protein which is found exclusively in prostatic tissue.[3,4] Although, increased PSA levels have been found to be

closely associated with prostate cancer, there can be different reasons for an elevated PSA level, including benign prostatic hyperplasia, prostatitis, prostatic trauma, and prostatic infarction.[5] Approximately 40-50% of patients with limited cancer had moderately advanced or advanced carcinoma on final radical Prostatectomy.[2] Present study was aimed to study histomorphologic correlation of PSA levels in benign, premalignant & malignant lesions of prostate.

MATERIAL AND METHODS

Present study was single-center, cross sectional study, conducted in department of Pathology, Bangalore Medical College, Bengaluru, India. Study duration was of 2 years (November 2016 to May 2018). Study approval was obtained from institutional ethical committee.

Study was conducted in prostate biopsies/transurethral resection of prostate (TURP) specimens/prostatectomies received from the Department of Urology, Bangalore Medical College. Inadequate biopsy material, follow-up cases, post therapeutic and recurrent tumours were excluded from the present study.

Demographic, clinical diagnosis & laboratory investigations were collected & entered in a pre-designed proforma. The PSA levels were estimated in our Department of Biochemistry, Total serum PSA levels estimation was done with Lisa plus micro-plate ELISA reader/Architect I 1000. The PSA level in serum is estimated and correlated with histopathological diagnosis.

All the specimens obtained were fixed in buffered neutral formalin for a period of 12-24 hrs and then the entire specimen was submitted for processing. The weight of the specimen was noted and the findings were recorded as per the format. The entire bits were submitted for processing. For light microscopy one slide from each block was routinely stained with H&E to arrive at a diagnosis. Slides were air dried, clear in xylene and then mounted. (Haemotoxylin and Eosin :Nuclei –blue to black. Cytoplasm and other substances – pink.) After preparing coated slides the paraffin sections were taken into the slide. Immunohistochemistry staining procedure were done for HMWCK and AMACR.

Data was collected and compiled using Microsoft Excel, analysed using SPSS 23.0 version. Frequency, percentage, means and standard deviations (SD) was calculated for the continuous variables, while ratios and proportions were calculated for the categorical variables. Difference of proportions between qualitative variables were tested using chi- square test or Fisher exact test as applicable. P value less than 0.5 was considered as statistically significant.

RESULTS

In present study, 31 cases of various prostatic lesions were studied. Prostatic lesion was seen in the age group of >40yrs with peak incidence from age 71-80 years (42.5 %). Sixteen were core biopsy specimens, twenty four was from TURP specimen. Premalignant and Malignant lesions were seen in both the TURP and core biopsy specimens.

Table 1: General characteristics.

Age groups (in years)	No. of patients	Percentage
≥ 40	1	2.5
51 - 60	6	15
61 - 70	11	27.5
71 - 80	17	42.5
81 - 90	4	10
>90	1	2.5
type of specimen Core biopsy	16	40.0
TURP	24	60.0

In present study, common lesions were prostatic adenocarcinoma (32.5 %) & benign prostatic hyperplasia (32.5 %) followed by high grade prostatic intraepithelial neoplasia (22.5 %), atypical small acinar proliferation (7.5 %) & atypical adenomatous hyperplasia (5 %).

Table 2: Histopathology reports.

Histopathology reports	No. of patients	Percentage
Prostatic adenocarcinoma	13	32.5
Benign prostatic hyperplasia	13	32.5
High grade prostatic intraepithelial neoplasia	9	22.5
Atypical small acinar proliferation	3	7.5
Atypical adenomatous hyperplasia	2	5

As per histopathology reports, majority lesions were premalignant (35 %), followed by benign & malignant lesions (32.5 % each).

Table 3: Benign, premalignant & malignant lesions.

Histopathology reports	No. of patients	Percentage
Benign	13	32.5
Malignant	13	32.5
Premalignant	14	35

AMACR was negative in all the BPH cases. 92.3% of malignant cases showed strong positivity with AMACR.

Table 4: IHC staining pattern of AMACR in correlation with Histopathology Report.

HPR	AMACR Negative	Mild	Moderate	Strong	Total
Benign	13 (100 %)	0	0	0	13
Premalignant	1 (7.14 %)	9 (94.2%)	4 (28.5%)	0	14
Malignant	0	0	1 (7.69%)	12 (92.3%)	13
Total	14 (35 %)	9 (22.5%)	5 (12.5%)	12 (30 %)	40

HMWCK is negative in all malignant cases. All benign cases showed continuous positivity for HMWCK.

Table 5: IHC staining pattern of HMWCK in correlation with Histopathology Report.

HPR	HMWCK Continous positivity	Negative	Patchy positivity	Total
Benign	13 (100 %)	0	0	13
Premalignant	1 (7.14 %)	2 (14.4%)	11 (78.5%)	14
Malignant	0	13 (100 %)	0	13
Total	14 (35 %)	15 (37.5%)	11 (27.5%)	40

Raised age specific PSA levels were noted in 27 cases (67. 5%).

Table 6: Distribution of age specific PSA levels.

Age specific PSA	No. of patients	Percentage
Normal	13	32.5
Raised	27	67.5

PSA is not a specific marker for Prostatic malignancy, as four cases out thirteen cases of BPH showed abnormal PSA levels. PSA level was raised in all the prostatic adenocarcinoma cases. Ten cases out of fourteen premalignant cases showed raised PSA. By using chisquare test with p value<0.05, there is statistically significance is established between age specific PSA levels and Histopathology reports.

Table 7: Age Specific PSA levels and Histopathology Report.

HPR	Age specific Normal	PSA Raised	Total
Benign	9 (69.2%)	4 (30.8%)	13
Premalignant	4 (28.5%)	10 (71.5%)	14
Malignant	0	13 (100 %)	13
Total	13	27	40

Chisquare=6.53, p<0.03

By using independent sample t-test, there was significant difference in PSA levels between Benign and malignant lesions (p value<0.05).

Table 8: Mean PSA levels between Benign and Malignant group.

HPR	N	Mean	Std. Deviation	t	p
PSA Benign (ng/ml)	13	5.2546	5.94131	6.2	0.001
Malignant	13	71.7677	38.20655		

By using independent sample t-test, there was significant difference in PSA levels between malignant and premalignant lesions (p value<0.05).

Table 9: Mean PSA levels between Premalignant and Malignant group.

HPR	N	Mean	Std. Deviation	T p
PSA (ng/ml) Malignant 1	13	71.7677	38.20655	4.5 0.001
Premalignant	14	16.4214	24.31040	

By using independent sample t-test, there was no significant difference in PSA levels between Benign and premalignant lesions (p value<0.05).

Table 10: Mean PSA levels between Benign and Pre- Malignant group.

HPR	N	Mean	Std. Deviation	T p
PSA(ng/ml) Benign	13	5.2546	5.94131	1.6 0.12 NS
Premalignant	14	16.4214	24.31040	

DISCUSSION

Prostate-specific antigen (PSA) is synthesized in the ductal epithelium and prostatic acini. It is found in normal, hyperplastic, and malignant prostate tissue.[6] PSA is secreted into the lumina of the prostatic ducts to become a component of the seminal plasma. It reaches the serum by diffusion from the luminal cells through the epithelial basement membrane and stroma where it can pass through the capillary basement membranes. PSA is a serine protease of the human glandular kallikrein family.

In present study ,out of forty cases, thirteen were BPH, three were atypical small acinar proliferation, two were atypical adenomatous hyperplasia , nine were high grade intraepithelial neoplasia, thirteen were prostatic adenocarcinoma. IHC was done using HMWCK and AMACR markers in the all this cases.

Under diagnosis of a small focus of prostatic adenocarcinoma might delay early treatment and cause severe adverse consequences for patients. Benign glands contain basal cells, which are absent in cancerous glands and hence the use of basal cell markers (HMWCK 34βE12, p63, CK5/6) to label the basal cells when faced with an morphologically difficult cases of prostatic lesion. More recently a positive marker for prostate carcinoma, α-methyl acyl CoA racemase (AMACR) has been reported to have sensitivity ranging from 82-100%.[2] Hence the use of AMACR and HMWCK done in this study to differentiate between benign and malignant cases in morphologically difficult cases of prostatic cancers.

In our study BPH was seen in the age group of 55-85yrs of age. In a study done by M Koteshwari et al.[7] 90.7% showed the BPH cases. Our study did not correlate with the above study, because the number of samples used in above study are more.

In a study conducted by Ingle et al.,[8] 100% of BPH cases showed normal PSA levels.[111] Another study conducted by Bedarshi Banerjee et al.,[9] 41.9% of BPH cases showed normal PSA levels. In our study, we had thirteen cases of BPH, four cases had raised PSA and rest nine cases had normal PSA levels. The four cases which had raised PSA showed features of prostatitis.

In our study all the 13 cases of BPH, showed continuous positivity for HMWCK. HMWCK positivity in BPH is correlated with Deepika Jain et al.,[11] Uma Samundeeswari et al,[11] & K kumarseran et al.,[2] In our study of 13 cases of BPH, the glands were negative for the AMACR immunostaining. The percentage of negativity was 100%. It is comparable with studies by K kumarseran et al.,[2] & Deepika Jain et al.,[10] E.Lakshmi. Bai et al.,[12]

AMACR negativity in BPH is correlated with Deepika Jain et al.,[10] E Lakshmi Bai et al.,[12] & K Kumarseran et al.,[2] In present study, among premalignant lesion raised PSA was noted in 71.5 % cases, while Shilpha k Patel et al.,[13] & M. Koteshwari et al.,[7] noted raised PSA levels in 66.5 % & 50 % cases of premalignant lesion respectively.

In the study conducted by Shilpa K Patel et al.,[14] there were 28 malignant cases of prostate, out of which 27 cases showed increased PSA levels, 1 case of adenosquamous carcinoma showed lowest PSA level(0.006ng/ml). Our study gave the same results as that of study done by Varsha S Kant et al.,[14]

As large screening trials have demonstrated clinically significant cancers in men with serum PSA levels of 2.5 to 4.0 ng/mL, some experts have proposed lowering the PSA cut off to 2.5 ng/mL to improve the early detection of cancer in younger men.[6] Serum PSA levels are not diagnostic of prostate cancer is that benign prostate tissue also produces serum PSA. Other factors such as prostatitis, infarct, instrumentation of the prostate, and ejaculation also increase serum PSA levels.[15] Finasteride, used to treat benign prostatic hyperplasia and hair loss, lowers serum PSA levels on average by approximately 50%.[16]

The increase in serum PSA depends on differentiation of tumour cells. Gleason score and grade grouping are most powerful predictors of biological behaviour and influential factors used in determining treatment. PSA, when combined with Gleason score and clinical stage, improves the prediction of pathological stage for prostatic carcinoma.[17]

CONCLUSION

Prostatic adenocarcinoma is most common type of prostatic carcinoma. PSA is not a specific marker for prostate malignancy, it can be increased in the premalignant and benign condition too like BPH with inflammation. All the cases diagnosed adenocarcinoma on histology, had raised PSA levels, showed positivity with AMACR and was negative with HMWCK staining. Histology still remains gold standard in diagnosis of prostatic malignancy.

Conflict of interest

None to declare.

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Nil.

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