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Limited Use of AMACAR And 34βE12 in Prostate Biopsy Lead To Misdiagnosis in Significant Numbers Due To Presence of Mimickers of Prostatic Adenocarcinoma: Observations in a Tertiary Care Centre

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ABSTRACT

The pathologist's awareness of the vast array of benign mimickers of prostate carcinoma is important in the systematic approach for the diagnosis of prostatic Adenocarcinoma especially when dealing with limited sampling in thin core needle biopsies / Trans urethral resection of prostate (TURP). In the present study with an aim to evaluate both diagnostic miss and over diagnosis of carcinoma prostate, we re-evaluated all TURP specimens and prostate biopsies of previous two consecutive years systematically using an algorithm complimented with Immunohistochemistry (IHC). Algorithm based review of TURP chips and prostatic biopsies were done followed by IHC for 34βE12 and AMACAR. We found that over diagnosis and diagnostic miss was seen in around 12% of biopsies. There were very interesting cases; in which even on following the algorithm malignancy was missed; only IHC results were consistent with malignant diagnosis. We found only two cases in carcinoma category which were over diagnosed. The lessons learned through this work was that in spite of just observation, an algorithm should be followed and all suspected cases should be further subjected to IHC confirmation to be doubly sure before signing off the report.

Keywords: Rhinoliths; foreign bodies; nasal cavity

INTRODUCTION:

Prostate cancer is a major health problem among elderly men. In 2008, as part of GLOBOCAN series published by the International Agency for Research on Cancer (182 countries from worldwide), prostate cancer was the second most common cancer diagnosed among men worldwide and the fifth most common cancer overall. [1]

In a study conducted in 2009, cancer of the prostate was found to be the third most frequently diagnosed cancer among men in Delhi accounting for about 6.3% of all malignancies. [2] Prostate cancer can be picked up early due to widespread use of various screening tools that is, digital rectal examination (DRE), evaluation of a serological marker i.e. prostate-specific antigen (PSA), radiological assessment by trans-rectal ultrasonography (TRUS) and histopathological examination of ultrasound guided core needle biopsies.

Correct interpretation of core biopsies is essential for making this screening tool effective. The majority of prostate adenocarcinoma are not difficult to diagnose; however, certain problematic areas exist: first, is the separation of well-differentiated adenocarcinoma from the vast number of benign or atypical small

glands proliferations; Second, is the threshold for recognizing extremely small foci of cancer in needle biopsies; and finally, at the extreme of the histological spectrum based on the morphology, a very poorly differentiated adenocarcinoma of the prostate may be difficult to distinguish from inflammatory infiltrates in the stroma, metastatic carcinoma, and urothelial carcinoma involving the prostate. The present study was done to identify the histopathological spectrum of mimickers of prostatic malignancy and hence distinguish between the mimickers and prostatic adenocarcinoma histomorphologically and immunohistochemically. Clinical and co-relation with serum PSA levels was also made.

MATERIAL AND METHODS

This is an observational retrospective and prospective study in which 49 cases reported as prostatic carcinoma and 64 cases reported as benign prostatic hyperplasia in the previous two years were included in the study and also the new cases were worked up as they were received.

The clinical data of the cases was recorded from the clinical datasheets including age, total S. PSA) levels (all values in ng/ml), type of biopsy specimen- a) transurethral resection of prostate (TURP), b) needle biopsy or c) Radical prostatectomy.

Follow up data of the patients was retrieved by telephone calls to the patients and the current status of the patient was noted (Alive, Deteriorating or Dead with the time of death). Figure 1 and 2 demonstrate the brief layout of the study.

2.1 Morphological examination:
Hematoxylin and Eosin (H&E) stained slides and blocks were retrieved from the records and were reviewed systematically for the features shown in Table 1. Cases thus found to harbour the potential mimicker were subjected to Immunohistochemical (IHC) staining using poly L-lysine coated slides with the following markers.

- A-methylacyl-CoA racemase (AMACR *Flex Mono RxH AMACR, Clone 13H4,RTU (DAKO AS/AS+)*) (P504S; DAKO™, Denmark)
- 34βE12 (HMWCK) (also called CK34βE12 and keratin 903 (CK903; DAKO™, Denmark))
- Prostate-specific antigen (PSA; DAKO™, Denmark)

2.2 IHC Interpretation:
Glands having cytoplasmic AMACR expression (Moderate to strong intensity in more than one third of gland outline) and loss of 34βE12 (more than two third of glandular outline) were considered to be positive for malignancy on IHC.

RESULTS AND DISCUSSION

Of the 113 specimens, 51 (45.13%) were biopsy specimens and 62 (54.87%) specimens were TURP. Of the 113 specimens, 49 (43.36%) were reported as prostatic carcinoma (Adenocarcinoma) and 64 (56.64%) as Benign Prostatic Hyperplasia.

After reviewing the slides microscopically it was found that out of 64 cases, 3 cases were under diagnosed as BPH, but were adenocarcinoma, so were included them in the adenocarcinoma group for further evaluation. Thus, the study was therefore done for BPH in 61 cases and for Adenocarcinoma in 52 cases. Age of patients suffering from adenocarcinoma ranged from 44 and 85 years, mean age was 66.02±9.46 years while age of patients diagnosed as BPH ranged between 34 and 93 years with a mean age of 65.28±11.16 years.

PSA level of patients diagnosed as adenocarcinoma ranged between 0.08 to 1709, with a median value of 44.96 and mean value of 151.54±315.97ng/ml while for patients diagnosed as BPH, PSA levels ranged between 0.1 to 45.3 with a median value of 6.10 and mean value of 6.85±7.31ng/ml. A statistically significant difference in PSA levels of patients diagnosed as adenocarcinoma and BPH was observed (p=0.003).

The PSA levels for the mimickers identified in our study ranges from 3.9 to 14.3, with a mean of 8.1 and median of 7.7. This raised PSA level with the diagnosis of BPH can be explained by a foci of adenocarcinoma missed during the diagnosis.

Skeletal muscle (80%) was the most common normal structure found on histopathological examination of slides, followed by verumontanum gland (11.67%), rectal mucosa (6.67%) and seminal vesicle (1.67%).

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69 foci were identified as morphological alterations. 16 foci of hyperplasia could be easily separated by morphological examination alone, whereas 53 foci were extremely confusing for rendering a correct diagnosis. Most common potential mimicker was atrophy (71.70%), second was adenosis (24.53%) and least common mimicker was inflammation (3.77%).

Immunohistochemical staining was performed in all 28 cases identified as potential mimickers for further confirmation of diagnosis. Table 2, shows the expression of diagnostic immunohistochemical markers AMACR and 34βE12 in cases selected as potential mimickers. Thus after immunohistochemical examination 16 cases out of 28 (57.14%) were positive for 34βE12 with negative staining for AMACR. Twelve cases (42.86%) were positive for AMACR; whereas 2 cases were also positive for 34βE12 (7.14% positive for both) suggesting focal positivity of AMACR can be seen in few benign lesions.

Only 10 cases (35.71%) were positive for AMACR with loss of 34βE12 expression. So we concluded that 10 out of 28 cases selected turned out to be malignant after immunohistochemical examination, whereas, 18 cases (64.29%) were benign. Atrophy was found in 5 (17.86%), adenosis in 4 (14.29%) and inflammation in 1 (3.57%) of the 28 cases. Figure 3 shows microscopic and IHC images of 34βE12 and AMACAR of few cases which displayed atrophy, inflammation, small glands and hyperplastic glands respectively. On IHC these cases displayed loss of 34βE12 with expression of AMACAR.

Of the 48 cases diagnosed as Adenocarcinoma, Gleason's score ranged from 6 to 10. Mean score was found to be 8.04±1.071 and median score was found to be 8.0. We found that patients with mean Gleason's score > 8.7 had grave clinical outcomes.

Among 113 patients PSA co-relation with clinical follow up was available for 44 patients. 13 patients died due to disease on follow up, their mean PSA level of 223.95ng/mL, patients with deteriorating health (4 out of 44) had a mean PSA of 123.68 ng/mL. Whereas, the patients with mean PSA levels 10.79ng/mL were alive and healthy. Thus, a significant association between PSA levels and clinical outcome was observed (p=0.013). Higher the PSA levels at the time of diagnosis, higher were the risk of disease progression and higher prostate cancer death rates. Mean survival time ranged from 9.625±0.53 to 15.50±0.50 months and median survival time ranged from 10 to 15 months in different groups. Statistical difference in survival among different groups was not significant.

Out of the 113 cases retrieved in our study, 61 cases diagnosed as BPH were examined histomorphologically for identification of missed potential mimickers of prostatic malignancy.

Pretreatment baseline PSA and rate of PSA change are proven prognostic factors in prostatic cancers [17, 18] Our results showed similar findings. We found on follow-up that 52.63% (10/19) and 21.05% (4/19) patients with PSA levels >10.0ng/mL died and deteriorated. Thus, higher pretreatment baseline PSA levels are a poor predictor of disease progression.

148 foci of various histological structures were identified in a TURP or needle biopsy specimens. The skeletal muscle from the pelvic floor anchors prostate gland thus the muscle fibres are present at the anterior and anterolateral aspects from apex to base.[14] Thus, skeletal muscle (80.00%) was the most common normal structure found out of normal structures identified. Second most common was verumontanum gland (11.67%), followed by rectal mucosa (6.67%) and seminal vesicle (1.67%). Gagucas RJ et al (1995) [6] found 14% of prostates contained foci of verumontanum glandular hyperplasia (VMGH). Tissue fragments derived from seminal vesicles and ejaculatory ducts were also observed during examination of TURP or prostatic needle biopsy specimens, with a reported frequency of 3% to 23% reported in two studies by Tsuang MT[15] (6/185 cases) and Jensen KM [16] (28/123 cases) respectively. We also found, distorted rectal mucosa which when compressed with prostatic tissue can mimic Adenocarcinoma. [16] These normal occurrences in prostatic biopsy should be carefully evaluated. A hurried interpretation and interpretation by an inexperienced pathologist may lead to over diagnosis of adenocarcinoma.

Nineteen metaplastic foci were identified, 17 (89.47%) foci of transitional metaplasia and one (5.26%) each of mucinous and squamous metaplasia were seen.

By careful observation alone the normal structures and metaplastic foci can be easily recognized by

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routine histopathology. They also lack the basic characters of malignancy i.e., nuclear atypia, nucleomegaly and prominent nucleoli.

In further evaluation the normal structures and metaplastic foci were not characterized as mimickers. Thus, 69 foci of morphological alterations were identified in our study with 16 foci of hyperplasia and 53 foci of potential mimickers which were further evaluated for confirmation.

Out of 61 cases diagnosed as BPH, we recognized 53 foci of Potential mimickers in 28 cases. The most common potential mimicker identified in our study is Atrophy, with 38 foci (71.70%), second being Adenosis, 13 foci (24.53%) and Inflammation with 2 foci was third (3.77%).

54 selected lesions from 44 TURP specimens were evaluated by Bostwick DG et al in 1993 [5] and 3 patterns of glandular proliferation were observed, all arising in association with nodular hyperplasia having 38 foci of atypical adenomatous hyperplasia (AAH), 8 foci of atypical small acinar proliferation of uncertain significance, and 8 foci of well-differentiated carcinoma. Herawi et al in 2005 [9] selected a total of 567 separate suspected atypical foci from 345 patients. The most common mimicker identified by them by IHC (on 281 cases) was partial atrophy (203 of 567; 35.8%) and crowded benign glands, or adenosis, was the second most common mimicker (146 of 567; 25.7%).

To solve this diagnostic dilemma use of IHC is mandatory.

Weak and focal AMACAR expression may be seen in benign cases; [7] moreover AMACAR expression complimented by loss of 34βE12 is seen in malignancy. [8-10] Careful examination and knowledge of interpretation of IHC also plays a pivotal role in diagnosis. [11, 12]

AMACR was undetectable in the majority of Atypical adenomatous hyperplasia (33 of 40, 82.5%) and was focally expressed in only four of 40 (10.0%).

Both under diagnosis of a small focus of adenocarcinoma or over diagnosis of a benign mimicker as malignant is a possibility. In our study 10 cases, out of 61 (16.39%) were under diagnosed as BPH, but were found to be malignant by immunohistochemical technique, whereas 2 cases, out of 52 (3.85%) were over diagnosed as malignancy by routine histopathology, however they turned out to be benign on using AMACR and 34βE12 immunostaining. Thus, possibility of under diagnosis of malignancy is more as compared to over diagnosis of a benign focus.

According to large western studies overall false-negative prostate biopsies (biopsies previously classified as benign but containing prostate adenocarcinoma or atypical small acinar proliferation (ASAP)) were estimated to be 2.4%: 1.1% for prostate cancer and 1.3% for ASAP. [4] According to our data this number is larger, a total of 12 histological mimickers (10.62%) were identified out of 113 cases.

Wrong clinical as well as histopathological diagnosis can lead to incorrect therapeutic interventions. Ten patients with a missed diagnosis of malignancy could not receive the treatment for malignancy thus leading to a shorter survival, whereas 2 patients underwent unnecessary bilateral orchidectomy with its side effects.

So according to our algorithmic approach based on the above observation to minimise incorrect diagnosis and identification of potential mimickers in prostatic biopsies, a comment on normal identifiable structures and metaplasia should be made first. This ensures they are looked upon and are not missed. Next any atrophic focus and compact glandular structures should be subjected to further IHC confirmation even though no morphologic evidence of malignancy is thought of. This approach defiantly benefits and we are saved from superfluous or incorrect interpretation.

CONCLUSION

Incorrect diagnosis can lead to unfortunate consequences for the patients. The analysis of these small foci of prostate cancer is diagnostically challenging, so to prevent both under diagnosis and over diagnosis, thorough knowledge of the various mimickers on routine microscopy along with the judicious use of IHC should be mandatory to arrive at a confident and correct diagnosis thus averting a false-positive or false-negative interpretation. Prostatic biopsies with small glandular proliferations or with foci of glandular atrophy in clinical setting of mildly raised PSA levels should be subjected to IHC

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confirmation of malignancy by 34βE12 and AMACAR before signing off it as benign on morphological examination alone.

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