NON-NEOPLASTIC LESIONS INCLUDING CANCER MIMICS IN BENIGN PROSTATIC HYPERPLASIA

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ABSTRACT

BACKGROUND

Transurethral resection of prostate and prostatic biopsies are very common specimens in surgical pathology. Prostatic biopsies are done in cases where there is clinical suspicion of malignancy. These specimens have to be thoroughly examined to avoid false negative diagnosis of adenocarcinoma prostate. Morphological lesions in benign nodular hyperplasia that mimic adenocarcinoma prostate can be broadly divided into those that mimic low-grade adenocarcinoma (Gleason grade ≤ 3) and those that mimic high-grade tumours. Non-neoplastic lesions which are to be distinguished from adenocarcinoma prostate are atrophy including partial atrophy, atypical adenomatous hyperplasia (adenosis), crowded benign glands, sclerosing adenosis, radiation atypia in benign glands, basal cell hyperplasia, clear cell hyperplasia, cribriform hyperplasia, non-specific granulomatous prostatitis, dense inflammation and malakoplakia, signet ring-like change in non-epithelial cells, prostatic xanthoma and paraganglia.

The aims of this study is to evaluate the spectrum of histomorphological lesions in benign nodular hyperplasia and to review the histomorphological features in cancer mimickers and how to distinguish them from adenocarcinoma prostate.

The objective of this study is to evaluate and review the different cancer mimickers in benign nodular hyperplasia.

MATERIALS AND METHODS

It is a descriptive study from Jan. 2012 to Dec. 2014; 221 cases were identified in this period. All these cases were reviewed and incidence of various non-neoplastic lesions was evaluated. Statistical analysis was performed using SPSS 10.0 for Windows student version (SPSS Inc., 233 South Wacker Drive, 11th Floor, Chicago, IL 60606-6412).

RESULTS

Age of the patients ranged from 38 to 103 years. Common clinical presentation was obstructive symptoms (71.1%) and irritative symptoms (28.9%). Of the total 221 specimens, 203 were TURP specimens and 18 were open prostatectomy specimens. Incidence of various lesions was glandulostromal hyperplasia: 97.3%, stromal hyperplasia: 2.71%, corpora amylacea: 68%, cystically dilated glands: 92%, acute prostatitis: 1.2%, chronic prostatitis: 18.6%, papillary infoldings: 53.2%, proteinaceous material: 13.54%, infarct: 22%, gland necrosis: 4.22%, calcification: 0.82%, squamous metaplasia: 6%, transitional metaplasia: 2.9%, basal cell hyperplasia: 4.5%, cribriform hyperplasia: 0.45%, atrophy: 6%, post-atrophic hyperplasia: 25%, partial atrophy: 0.5%, atypical adenomatous hyperplasia: 8% of cases, crowded benign glands: 96%, sclerosing adenosis: 1.5% and reactive epithelial atypia: 22%.

CONCLUSION

Histomorphological lesions in the differential diagnosis of adenocarcinoma prostate are atrophy including partial atrophy, atypical adenomatous hyperplasia, basal cell hyperplasia, cribriform hyperplasia and crowded benign glands. These lesions mimic adenocarcinoma prostate (Gleason grade < 3).

KEYWORDS

Benign Prostatic Hyperplasia, Cancer Mimickers, Adenocarcinoma and Histomorphological.


BACKGROUND

Benign prostatic hyperplasia is an extremely common disorder in elderly men that affects more than 70% of men by 60 years of age. It is characterised by proliferation of prostatic epithelial and stromal cells resulting in enlargement of prostate.1 The incidence of benign prostatic hyperplasia increases with age. It is seen in 20% of men by 40 years of age, 70% of men by age 60 years and 90% of men by age 80 years.2

There is no direct correlation between histologic changes and appearance of clinical symptoms. Benign prostatic hyperplasia usually affects periurethral region of prostate resulting in the formation of large, discrete nodules. These nodules compress the urethra and patient presents with
lower urinary tract symptoms. Only 50% of those who have microscopic evidence of hyperplasia have clinically detectable enlargement of prostate and only 50% of those who have clinical evidence of prostate enlargement develop clinical symptoms (LUTS). These patients present with symptoms of increased urinary frequency, nocturia, difficulty in starting and stopping the streams of urine, overflow dribbling, dysuria and acute urinary retention. Mild cases of benign prostatic hyperplasia are treated without medical or surgical therapy. Moderate to severe cases recalcitrant to medical therapy are treated with surgical therapy. Transurethral resection of prostate is gold standard for surgical therapy of benign prostatic hyperplasia. Transurethral resection of prostate and prostatic biopsies are very common specimens in surgical pathology. Prostatic biopsies are done in cases where there is clinical suspicion of malignancy. There is huge burden of these patients on health care system and as a result hundreds of crores of money is used for the treatment of benign prostatic hyperplasia. This load is increasing in developing countries like India where life expectancy is increasing because of improving economic conditions and improving health care facilities, the number of people more than 60 years of age are increasing, thereby increasing the number of people with benign prostatic hyperplasia. Carcinoma prostate is the most common cancer in men and occurs in this age group only. Transurethral resection specimens have to be thoroughly examined to avoid false negative diagnosis of adenocarcinoma prostate. Morphological lesions in benign nodular hyperplasia that mimic adenocarcinoma can be broadly divided into those that mimic low-grade adenocarcinoma (Gleason grade ≤ 3) and those that mimic high-grade tumours. Morphological classification of these lesions seen in routine haematoxylin and eosin stained sections is shown in table given below.

### Table 1. Morphological Lesions in the Differential Diagnosis of Adenocarcinoma Prostate including Cancers Mimicked

<table>
<thead>
<tr>
<th>Architectural Pattern</th>
<th>Non-Neoplastic Prostate Lesions</th>
<th>Types of Prostate Carcinoma Mimicked</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small gland pattern</td>
<td>Lesions of prostatic epithelial origin Atrophy including partial atrophy Atypical adenomatous hyperplasia (adenosis) Crowded, benign glands Sclerosing adenosis Radiation atypia in benign glands Basal cell hyperplasia</td>
<td>Gleason pattern ≤ 3 Atrophic PCa</td>
</tr>
<tr>
<td>Large and cribriform gland patterns</td>
<td>Basal cell hyperplasia Clear cell cribriform hyperplasia Medium-to-large sized hyperplastic glands Reactive epithelial atypia</td>
<td>Cribriform Gleason patterns 3, 4 and 5 Ductal adenocarcinoma Pseudo-hyperplastic</td>
</tr>
<tr>
<td>Solid and non-glandular patterns</td>
<td>Non-specific granulomatous prostatitis, dense inflammation and</td>
<td>Gleason patterns 4 and 5 Foamy gland</td>
</tr>
</tbody>
</table>

PCa, Prostatic adenocarcinoma

Therefore, we planned this study to evaluate the spectrum of non-neoplastic lesions, especially cancer mimics in these specimens.

**MATERIALS AND METHODS**

It is a descriptive study. All cases of benign prostatic hyperplasia signed out in the Department of Pathology from January 2012 to Dec. 2014 were retrieved from surgical pathology files and consult files of Govt. Medical College, Jammu. In total, 221 cases were identified over a period of three years. Haematoxylin and eosin stained sections of 5 µm thickness were re-examined in all cases to evaluate the following histologic features: Glandulostromal proliferation-stromal or glandular predominance, corpora amylacea, cystically dilated glands, papillary infoldings, lymphoctic collections/infiltration, homogenous eosinophilic material, gland necrosis, acute prostatitis, chronic prostatitis, non-specific granulomatous prostatitis, malakoplakia, prostate xanthoma, atrophy, post-atrophic hyperplasia, atypical adenomatous hyperplasia [AAH] (adenosis), Crowded benign glands, sclerosing adenosis and radiation atypia in benign glands. Hyperplastic glands, reactive epithelial atypia, squamous metaplasia, transitional metaplasia, basal cell hyperplasia and cribriform hyperplasia. Clinical features and follow-up data was obtained from consult files and referring surgeons. Statistical analysis was performed using SPSS 10.0 for Windows student version (SPSS Inc., 233 South Wacker Drive, 11th Floor, Chicago, IL 60606-6412).

**RESULTS**

Age of the patients ranged from 38 to 103 years and most patients were in 6th and 7th decade of life. The common clinical presentation was obstructive symptoms (71.1%) and irritative symptoms (28.9%). Common clinical symptoms were hesitancy followed by poor urine flow and increased frequency of urination. Of the total 221 specimens, 203 were TURP specimens and 18 were open prostatectomy specimens. All cases included in the study had glandulostromal hyperplasia and only 6 (2.71%) cases showed predominantly stromal pattern. Corpora amylacea was present in 68% of cases. Cystically dilated glands were present in 92% of cases. Acute and chronic prostatitis was observed in 1.2% and 18.6% of cases respectively. Papillary infoldings was seen in 53.2% of cases and Proteinaceous material in 13.5% of cases. Infarct and gland necrosis was seen in 22% and 4.22% of cases respectively. Calcification in only 0.82% of cases. Among metaplasias squamous and transitional metaplasia was seen in 6% and 2.5% of cases.
Basal cell hyperplasia was seen in 4.5% of cases and cribriform hyperplasia in 0.45% of cases. The incidence of atrophy was seen in 6%, post-atrophic hyperplasia in 2% and that of partial atrophy was seen in 0.5%. Atypical adenomatous hyperplasia was seen in 8% of cases. Crowded benign glands was very frequent finding (96%). Sclerosing adenosis was identified in 1.5% of cases. Reactive epithelial atypia was seen in 22% of cases. Xanthoma prostate or granulomatous prostatitis was not identified in any case.
processes. Florid basal cell hyperplasia and atypical basal cell hyperplasia are its other variants. Basal cell hyperplasia should be distinguished from basal cell carcinoma. Basal cell carcinoma is characterised by extensive infiltration between normal prostate glands, extension out of prostate, perineural invasion and necrosis. MIB-1 labelling index is usually below 5% in basal cell hyperplasia, whereas in basal cell carcinoma it is very high. Bel-2 can also help in this distinction. Bel-2 is not expressed in basal cell hyperplasia. 

Cribiform hyperplasia was seen in 0.45% of cases, which is comparable with that reported in the literature. Cribiform hyperplasia is usually seen in transition zone and is part of benign nodular epithelial hyperplasia. It has a nodular appearance and intervening cellular stroma is also seen. It is characterised by a crowded proliferation of complex glands having round lumina and clear cytoplasm. The cells lining the cribiform hyperplasia are cuboidal to low columnar with uniform round nuclei, clear cytoplasm and inconspicuous nucleoli. Basal cells are present. Cribiform hyperplasia is to be distinguished from cribiform prostatic adenocarcinoma. This distinction is made on the low power nodularity, cellular stroma, presence of basal cells and lack of cytological atypia. Atypical adenomatous hyperplasia (AHH) was seen in 8% of the cases. The incidence is comparable with the literature, i.e. 1.5% - 19.6%. Atypical adenomatous hyperplasia is characterised by a nodular proliferation of closely packed small glands that often merge with larger more complex glands. It is a common mimic of prostatic adenocarcinoma on both needle biopsy and transurethral resection specimen. Sometimes there is a prominent perinodular distribution of the abnormal glands. On microscopic examination, these lesions resemble prostatic adenocarcinoma grade 1 and 2. Sometimes the acini show more extensive crowding and nonlobular distribution termed diffuse adenosis. Immunohistochemistry reveals positivity for PSA and PAP, up to 18% of cases express AMACR. Immunohistochemistry reveals these lesions are negative for basal cells in about half of glands (10% - 90%). Distinguishing features between atypical adenomatous hyperplasia and adenocarcinoma are given in Table 2.

### Table 2

<table>
<thead>
<tr>
<th>Atypical Adenomatous Hyperplasia (Adenosis)</th>
<th>Prostate Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lobular</td>
<td>Haphazard growth pattern</td>
</tr>
<tr>
<td>Small glands share features</td>
<td>Small glands differ from adjacent benign glands</td>
</tr>
<tr>
<td>with admixed larger glands</td>
<td>Pale-clear cytoplasm</td>
</tr>
<tr>
<td>Pale-clear cytoplasm</td>
<td>Amphilophic cytoplasm</td>
</tr>
<tr>
<td>Medium-sized nucleoli</td>
<td>Occasionally large nucleoli</td>
</tr>
<tr>
<td>Blue mucinous secretions are rare</td>
<td>Blue mucinous secretions are common</td>
</tr>
<tr>
<td>Basal cells present</td>
<td>Basal cells absent</td>
</tr>
<tr>
<td>Corpora amylacea are common</td>
<td>Corpora amylacea are rare</td>
</tr>
</tbody>
</table>

Atrophy includes simple atrophy, post-atrophic hyperplasia and partial atrophy. These patterns are often mixed. Simple atrophy may show cyst formation. Proliferative atrophy and proliferative inflammatory atrophy are optional terms. Simple atrophy and post-atrophic hyperplasia do not generally pose a diagnostic problem. Immunohistochemistry for basal cells is helpful in difficult cases. Partial atrophy also show lobular architecture, but this is not always as it can also show diffuse and disorganised growth pattern. The
glands in partial atrophy do not show atrophic, basophilic appearance, instead glands have pale scant cytoplasm. The features seen in partial atrophy that create problem to distinguish it from prostatic adenocarcinoma are crowded and sometimes disorganised pattern of growth, relative high nuclear to cytoplasmic ratio with slightly enlarged nuclei, straight luminal borders in some glands, presence of visible yet small nuclei, negativity of some of the glands for basal cell markers and positivity of some glands for alphamethylacyl coenzyme A racemase (AMACR). Atrophic adenocarcinoma also exists; partial atrophy differs from atrophic adenocarcinoma, in that adenocarcinoma have more infiltrative pattern where the cancer glands infiltrate as isolated glands in between benign glands. There is associated atrophic adenocarcinoma, prominent cytological atypia and negative immunohistological stains for basal cells.

CONCLUSION
Histomorphological lesions in the differential diagnosis of adenocarcinoma prostate are atrophy including partial atrophy, atypical adenomatous hyperplasia, basal cell hyperplasia, cribriform hyperplasia and crowded benign glands. These lesions mimic low-grade adenocarcinoma prostate (Gleason grade ˂ 3). Immunohistochemistry for basal cell markers (34 beta E12, p63), prostatic adenocarcinoma (AMACR) and prostate lineage specific markers (PSA and PAP) provide significant objective evidence whether the lesion is benign or malignant. Immunohistochemistry show overlapping staining reactions in many of these lesions, so final diagnosis has to be on morphological context and to be correlated with the original H and E derived diagnosis.

REFERENCES


