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A Study of Benign and Premalignant Mimickers of Prostatic Adenocarcinoma

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ABSTRACT

Introduction: The Pathologist's familiarity of the vast collection of benign mimickers is important in the systematic approach to the diagnosis of prostatic adenocarcinoma. Awareness of these patterns on light microscopy coupled will guide to a correct diagnosis and avoid a false-positive and false negative cancer interpretation. Aims; To study the histopathological features of mimics of prostatic adenocarcinoma, to differentiate histopathologically between mimics and adenocarcinoma. M**ethods:** This study is done in institute of pathology, madras medical college, Chennai during the period of July 2012 to June 2014. The H&E slides from prostatic samples are viewed and various benign and premalignant mimickers are identified. **Results:** Out of 492 cases analysed 134 mimickers were identified. Benign mimickers are commonly found (79%) than premalignant mimickers (21%).Among benign lesions basal cell hyperplasia is the commonest followed by atrophy. **Conclusion:** Premalignant lesions are commonly seen in association with adenocarcinoma.

Keywords: Adenocarcinoma, Mimickers, prostate.

INTRODUCTION

The diagnosis of prostatic adenocarcinoma particularly when present in small amounts, is often challenging. Before making a diagnosis of carcinoma it is prudent for the pathologist to consider the various benign entities that can mimic prostatic adenocarcinoma. Most of the mimickers fit in the small gland type and common ones giving rise to false positive diagnosis are small acinar atrophy, postatrophic hyperplasia, atypical adenomatous hyperplasia and seminal vesicle.

Other normal structures like cowper's gland verumontanum mucosal glands, paraganglionic tissue and mesonephric glands can be confused with adenocarcinoma. Also metaplastic and hyperplastic processes in the prostate may possibly be confused with adenocarcinoma. Moreover, inflammatory processes like granulomatous prostatitis, Xanthoma, and malakoplakia may replicate high-grade adenocarcinoma, clear cell adernocarcinoma in particular.

Atypical adenomatous hyperplasia (adenosis), a alleged precursor of adenocarcinoma has similar features with low grade adenocarcinoma and might cause problems in differential diagnosis in needle biopsy setting.

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MATERIALS AND METHODS

An analysis of 504 cases of surgically resected prostatic specimens referred from urology department from July 2009 to June 2011 for a two year period, has been carried out in Institute of Pathology, Madras Medical College, Chennai. The histological material were derived from biopsy specimens of transurethral resection of prostate in 409 cases, trucut needle biopsy in 90cases and open prostatectomy in 5 cases. The age group of the patients ranged from 33-90 yrs. As a routine, all prostatic specimens were fixed in 10% formalin.

The total amount of prostatic chips received per each case varied grossly. But in general, we received 15 to 30 gm of prostatic chips for each case of TURP specimen. If the total amount of resected prostatic chips could be included in four histological sections it was examined in its entirety. Excess tissue was sampled at the rate of one histological section per 10gram of resected tissue. In most of the trucut biopsy specimens, we received only a bit of soft tissue measuring 0.5 to 1 cm and serial sections were taken from this. As a routine, 5 to 8 histological sections were taken from open prostatectomy specimens: 2 to 3 sections from the right and left lobe and one to two sections from the middle lobe. All these histological sections were stained with Haematoxylin & Eosin (H&E) stain and examined. In each benign prostatic hyperplasia and adenocarcinoma case diagnosed, the evaluation was

done for the presence of mimickers of adenocarcinoma, inflammatory aspects, presence of focal acinar atrophy, metaplastic lesions, hyperplastic lesions and premalignant lesions.

RESULTS

Out of 504 cases analysed, 409 were TURP specimens, 90 were trucut needle biopsies and 5 were open prostatectomy specimens. In total about 448 cases of BPH and 44 cases of adenocarcinoma have been diagnosed in this two years period. 12 cases turned to be unsatisfactory specimen. Out of 492 cases that had been reported, majority (41%) of cases occurred in the age group of 61-70.Totally 134 mimickers were identified with benign lesions being the commonest (79%) and premalignant lesions mimicking adenocarcinoma were (21%). [Table 1] Among benign mimickers BCH was the commonest (45%) followed by atrophy (32%). [Table 2] Totally 48 foci of basal cell hyperplasia were found in the 504surgically resected specimens (9.52%). 26 were partial basal cell hyperplasia, 9 were complete basal cell hyperplasia, 1 was cribriform BCH and 12 were atypical basal cell hyperplasia [Table 3]. Out of 48 foci 47 were seen in association with benign prostatic hyperplasia and one was seen in the backdrop of adenocarcinoma.

Table 1: Distribution of Mimikers

Total	Benign	Malignant
134	106 (79%)	28 (21%)

Table 2: Distribtion of Identified Benign Mimickers

Mimickers		No.of cases	Percentage
1. Basal cell hyperplasia		48	45.3
2. Atrophy	Simple & cystic	24	22.6
	Small acinar	10	9.43
3. Clear cell cribriform hyperplasia		2	1.9
4. Sclerosingadenosis		4	3.8
5. Stromal clear cell metaplasia		14	13.2
6. Xantho granulomatous prostatitis		4	3.8

Table 3: Types of Basal Cell Hyperplasia

Total	No.of cases	Percentage
Partial (Glandular)	26	54
Complete (Solid)	9	19
Cribriform	1	2
Atypical (with prominent nucleoli)	12	25

Premalignant Lesions

Atypical small acinar proliferation and PIN are the two premalignant mimickers identified in this study. Both of these lesions were commonly seen in association with adenocarcinoma rather than BPH. [Table 4]. Out of 106 benign mimickers identified 105 were seen in association with benign prostatic hyperplasia and only one case was seen in the setting of adenocarcinoma. Premalignant mimickers are found in both BPH and in adenocarcinoma but majority were seen in association with adenocarcinoma [Table 5].

Table 4: Premalignant Mimickers

Premalignant Mimickers	No.of cases	Percentage
AAH/ASAP	22	78.6
PIN	6	21.4

Table 5: Associated conditions in Mimickers

		BPH	Adenocarcinoma
Mimickers	Benign(106)	105 (23.4%)	1 (2.3%)
	Premalignant (28)	25 (5.6%)	3 (6.8%)

DISCUSSION

In general, the morphological diagnosis of prostatic lesions, particularly separating benign from malignant lesions is relatively straightforward. However there are several benign proliferations and normal histoanatomic structures of the prostate, which exhibit a small glandular pattern with or without cytological atypia, and they can be mistaken for malignancy if one is not aware of the morphologic nuances. Basal cell hyperplasia: Basal cell hyperplasia is the commonest benign lesion identified (9.52%) in our study. Majority of them are seen in TURP specimens and only 6 cases are noticed in needle biopsy specimens. Phatarapon Thorson et al.[1] studied the occurence of basal cell hyperplasia in peripheral zone using 500 consecutive needle biopsy specimen and found the incidence to be 10.2%. In our study 90 trucut needle biopsies were examined and BCH were found in 6 cases which is6.66%. This finding has diagnostic value because basal cell hyperplasia, especially atypical basal cell hyperplasia, can simulate high-grade prostatic intraepithelial neoplasia and adenocarcinoma particularly in needle biopsy specimen 65. In one study 26% of cases of basal cell hyperplasia were misdiagnosed as adenocarcinoma.[2] In our study 12 cases of atypical BCH with prominent nucleoli was identified. There is no proof till date to suggest that basal cell hyperplasia, with or without nucleoli, is a precursor lesion for high-grade prostatic intraepithelial neoplasia or carcinoma.[3] Atrophy :In our study totally 34 atrophic foci were identified of which simple and cystic atrophy contributed to 24 cases and remaining 10 cases were small acinar atrophy/ partial atrophy.

Regardless of the architectural subtype the cytological features of atrophy are similar. The cells are small, dark and shrunken. They had increasd nuclear cytoplasmic ratios but had regular nuclear membrane without any identifiable chromatin abnormalities. Double layering of cells is regularly

seen but in some cases it was difficult to appreciate due to marked atrophy of secretory cells. Sclerosing adenosis: In this study 4 cases of sclerosing adenosis were identified with an incidence of 1%. Sakamoto et al.[4] reviewed sections of prostate from 263 patients and found 5 cases of sclerosing adenosis, with an incidence of 1.9%. The diagnostic difficulties of sclerosing adenosis of prostate have been recognized, and a recent series on over diagnosis of prostatic adenocarcinoma showed that 2% of stage T1a prostatic carcinomas were in fact cases of sclerosing adenosi s prostate.[5] Stromal clear cell metaplasia: Clear cells in the stroma of prostate can be of stromal origin, histiocytic origin or may be malignant signet ring cells. It is important to58identify the origin of the clear cells, because it can cause confusion with the foamy gland variant of prostatic adenocarcinoma or, if occuring as individual cells, with grade 5 adenocarcinoma or signet ring cell carcinoma which is a rare variant and has worst prognosis.[6] Degeneration of lymphocytes and stromal cells can give rise to a signet ring- like morphology.[7,8] When the change is prominent, the pattern can simulate high-grade adenocarcinoma containing individual signet ring cells. One should be aware of this possibility and not to over interpret such cells as malignant. In difficult cases, immune-histochemical stains can be used to verify the cell's non epithelial nature. Xanthoma: Xanthoma of prostate is a rare condition characterised by collection of lipid-laden macrophages in the prostate. Besides being a histologic mimicker of carcinoma, It is also a clinical mimicker because it is often associated with unusual digital rectal examination finding and abnormally elevated serum PSA levels.[9,10] Xanthomatous histiocytes usually have small nuclei within conspicuous nucleoli and are admixed with other inflammatory cells. Only foam cells is seen in some instances which can lead to significant diagnostic confusion. Hyper nephroid carcinomas which has foam cells similar to that of xanthomatous cell sometimes do not have the typical malignant nuclear features complicating the problem further. The presence of other inflammatory cells assist in diagnosis. IHC for cytokeratin AMACR and CD68 is often required to solve problematic cases. Xanthomas are CD68 positive and cytokeratin, AMACR and PSA negative. Atypical small acinar proliferation.: The importance of ASAP lies in its potential for being misinterpreted as adenocarcinoma and various benign mimics such a ssimple lobular atrophy, post atrophic hyperplasia, sclerosing atrophy, basal cell hyperplasia and verumontanum mucosal gland hyperplasia. Similar to high-grade PIN, ASAP holds a significant predictive value for cancer in repeat biopsy specimens. In studies published between1997 and 2001, the reported incidence of prostate cancer in repeat biopsy specimens following a diagnosis of ASAP ranged from 34% to 60%.[11,12] PIN.: There are four major patterns of high-grade PIN: tufting, cribiform, micropapillary and flat.[13] The most common pattern is tufting pattern observed in 97% of cases, although most cases show multiple patterns. In our study all the 6 cases of PIN had tufting pattern. The most common mimic of HGPIN is atypical basal cell hyperplasia. In atypical basal cell hyperplasia, cells are stratified and have prominent nucleoli, but they are basally located rather than a biluminal which is seen in PIN. PIN is often overdiagnosed as adenocarcinoma. Thus, immune-histochemical stains for antikeratin 34βE12 may demonstrate the existence of basal cells in a small focus of atypical glands, serving to confirm the diagnosis. This antibody can be used effectively if one carefully interprets the findings in combination with the light microscopic features.[14] However, recent reports have noted that the percentage of ambiguous cases can be reduced significantly, by68%,[15] or from 5.1 to 1.0 % by addition of this marker.[16]

CONCLUSION

Benign mimickers were commonly identified (59%) than premalignant mimickers. Benign mimickers are almost 100% seen in specimens of benign prostatic hyperplasia.• Among the benign mimicking lesions basal cell hyperplasia was the commonest followed by atrophy. ASAP is the commonest premalignant lesion identified. Histomorphology was sufficient to diagnose most cases. Difficulties were faced in differentiating atypical small acinar proliferation, PIN, and small acinar atrophy from adenocarcinoma and in determining the origin of clear cells present in the stroma and epithelium and their benign vs malignant nature.

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