ROLE OF IMMUNOHISTOCHEMICAL MARKERS IN DIFFERENTIAL DIAGNOSIS OF PROSTATIC ADENOCARCINOMA AND ITS MIMIMICKERS

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CERTIFICATE

This is to certify that this dissertation titled **"ROLE OF IMMUNOHISTOCHEMICAL MARKERS IN DIFFERENTIAL DIAGNOSIS OF PROSTATIC ADENOCARCINOMA AND ITS MIMICKERS"** is a bonafide work done by **Dr. P. RAMYA** in partial fulfilment of the requirement for M.D., (Branch III) in Pathology examination of the Tamil Nadu Dr. M.G.R Medical University to be held in April 2012.

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I, Dr. P. Ramya, solemnly declare that this dissertation titled **" ROLE OF IMMUNOHISTOCHEMICAL MARKERS IN DIFFERENTIAL DIAGNOSIS OF PROSTATIC ADENOCARCINOMA AND ITS MIMICKERS"** is the bonafide work done by me under the expert guidance and supervision of **Prof. Dr. P.KARKUZHALI, M.D.,** Professor, Institute of Pathology and Electron Microscopy, Madras Medical College, Chennai – 3. This dissertation is submitted to the Tamil Nadu Dr. M.G.R Medical University towards partial fulfilment of requirement for the award of M.D., Degree (Branch III) in Pathology. This has not been submitted by me for the award of any degree or diploma from any other university.

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ABBREVIATIONS

TZ	:	Transition Zone
PZ	:	Peripheral Zone
PSA	:	Prostate Specific Antigen
PIN	:	Prostatic Intraepithelial Neoplasia
LG PIN	:	Low Grade Prostatic Intraepithelial Neoplasia
HG PIN	:	High Grade Prostatic Intraepithelial Neoplasia
VACURG	:	Veterans Administration Co-operative Urological Research Group
AAH	:	Atypical Adenomatous Hyperplasia
PCA	:	Prostatic carcinoma
ASAP	:	Atypical Small acinar Proliferation
TURP	:	Trans Urethral Resection of Prostate
CCCH	:	Clear Cell Cribriform Hyperplasia
IHC	:	Immuno Histo Chemistry
PAS	:	Periodic Acid Schiff
NA	:	Nephrogenic Adenoma
AMACR	:	Alpha Methyl Acyl COA Racemase
PSAP	:	Prostate Specific Acid Phosphatase
TRUS	:	Trans Rectal Ultra Sound
BPH	:	Benign Prostatic Hyperplasia
BCH	:	Basal Cell Hyperplasia
HMWCK	:	High Molecular Weight Cytokeratin
SAP	:	Sclerosing Adenosis Prostate
SRCP	:	Signet Ring Carcinoma prostate
XGP	:	Xantho granulomatous Prostatitis

CONTENTS

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.

A valuable method of classifying benign mimickers is in relationship to major growth patterns depicted in the Gleason diagram. The four major patterns are small gland, large gland fused gland, and solid. Most of the mimickers fit in the small gland type and common ones giving rise to false positive diagnosis are small acinar atrophy, post atrophic 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. At the other end, poorly differentiated adenocarcinoma of the prostate may be difficult to distinguish from inflammatory infiltrates, metastatic carcinoma and TCC involving the prostate and can lead to false negative cancer interpretation.

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 with the cautious use of immunohistochemistry will guide to a correct diagnosis and avoid a false-positive and false negative cancer interpretation.

AIMS AND OBJECTIVES OF THE STUDY

1. To define, list and study the clinical and histopathological features of mimics of prostatic adenocarcinoma.

2. To differentiate histopathologically between mimics and adenocarcinoma.

3. To define the role of immunohistochemical markers in differential diagnosis of adenocarcinoma and its mimics.

REVIEW OF LITERATURE

ANATOMY

The prostate is a sex related gland that belongs to male reproductive system, having the size of walnut and weighs up to 20 g. It is situated around the upper part of the urethra and lies with its superior surface (the base) immediately below the urinary bladder and its inferior surface (the apex) above the pelvic musculofascial floor. A thin layer of connective tissue surrounds the prostate. The Denonviler's fascia seperates its posterior surface from the rectum. The prostate is anteriorly fixed to the pubic bone with the help of puboprostatic ligaments and held in the dorsal vein plexus between these structures[1,2,3].

Mc Neal described the zonal anatomy of the prostate which includes the peripheral, transition and central zone representing approximately 65%, 10%and 25% respectively of the normal organ volume. This zonal anatomy is important is prostate pathology. Most of the cancers develop in the Peripheral zone (PZ) and benign hyperplasia mainly develops in the transition zone (TZ) of the prostate gland (Mc Neal 1988)

HISTOLOGY

The prostate is composed of fibromuscular stroma and 30-50 glands that empty its contents into the prostatic urethra. Two cell layers form the branching duct acinar system, the luminal columnar secretory

cells and the basal cells[2,3,4].The architectural structure and polarity of the glandular cells are important for diagnosing and grading prostatic carcinoma.

The prostate does not have a well-defined capsule [5], but the most peripheral layer of the fibromuscular stroma bordering on periprostatic fat, forms a pseudocapsule. The organ borders become very intricate at the base of the prostate, particularly at the junction with seminal vesicles, while in other areas prostatic glands reach the edge of the prostate without a distinct capsule, leading to difficulties in the assessment of extra prostatic extension.

The prostate is supplied by branches from the inferior vesical, internal pudendal artery and middle rectal arteries. It drains into internal vesical and internal iliac veins. Lymphatics from the prostate drain chiefly into internal iliac, sacral and obturator nodes. The prostate has an abundant nerve supply from the inferior hypogastric plexus [6].

PHYSIOLOGY

The prostate gland secretes a milky, alkaline fluid into the urethra during ejaculation. The prostate fluid is a semen component and represents one half to two thirds of ejaculate volume. It is slightly acidic (pH6.5) and contains several secretory products like acid phosphate, citrate, zinc, carbohydrates, soluble proteins, electrolytes, hormones,

lipids and growth factors [7]. Among them is prostate-specific antigen (PSA), which proved to be of paramount importance for diagnosing prostatic adenocarcinoma. PSA is a glycoprotein that has been recognized as a kallikerin like protease and its main role is to keep the semen liquid [8].

Although prostate specific antigen is specific for prostatic epithelium, it is not a prostate cancer specific as it can be found elevated in many of the benign conditions that may affect the gland as well as in malignant lesions[9]. In addition some authors found correlation between patient's age and PSA level[10]. Kamal B, Ali G,Taha S. conducted a study in saudhi men and found that the PSA level increases with age and the mean values of total PSA were 0.87 for men in 40-49 years, 1.36 for men in 50-59 years, 1.81 for men in 60-69 years, 2.32 for men in 70-79 years and 2.36 for men in 80-89 years.

PSA is the now commonest initial assessment method used in the early detection and follow up of the prostate cancer. However its ability to distinguish among benign and malignant lesions is particularly poor in the intermediate range of 4.1and 10ng/ml.

ADENOCARCINOMA OF THE PROSTATE

Prostate cancer is the most common cancer in men accounting for 33% of all malignant tumours in men and accounts for 9% of cancer death. Excluding skin cancer, prostate cancer is the most commonly

diagnosed cancer among men in the US and the second most common cause of cancer related death among men[11].

Age is the most important risk factor for prostate cancer. The incidence rate increases in men until about age 70 and decline thereafter[11,12]. Carcinoma may arise in any zone of the prostate but the relative distribution is different in each zone: 68% of the carcinoma occur in the peripheral zone, 24% arise in the transition zone and 8% develops in the central zone[13].

DIAGNOSIS OF MINIMAL ADENOCRCINOMA IN PROSTATE NEEDLE BIOPSY[14].

Algaba et al defined the criteria for the diagnosis of minimal prostatic adenocarcinoma[15].

MAJOR CRITERIA

- Architectural: Infiltrative small glands or cribriform glands too large or irregular to signify high grade PIN.
- Absence of basal cell layer
- Nuclear and nucleolar enlargement.

MINOR CRITERIA

- Intraluminal wispy blue mucin
- Pink amorphous secretions

- Mitosis
- Intraluminal crystalloids
- Adjoining high-grade PIN
- Amphophilic cytoplasm.
- Nuclear hyperchromasia.

No single criterion, not even one of the major diagnostic criteria, is by itself diagnosis of malignancy. Rather consideration of the constellation of findings assist in arriving at a specific diagnosis.

DIFFERENTIAL DIAGNOSIS AND MIMICS OF ADENOCARCINOMA OF PROSTATE

A PATTERN BASED APPROACH TO DIFFERENTIAL DIAGNOSIS

The utility of the famous Gleason diagram extends beyond its role as a Grading tool [16]. Dr Donald F Gleason and members of the veteran's administration Cooperative urological Research group.[17] (VACURG) devised grading system of adenocarcinoma in 1960s and 1970s.

From 1960 to 1975 the VACURG examined roughly about 5000 prostate cancer patients in prospective randomized clinical trials. One of

the major strength of the Gleason grading system is that it was tested in this large population, with long term follow-up[17].

In the Gleason diagram, there are nine patterns which are clumped into four major architectural categories for discussion of differential diagnosis[18]

Major growth patterns of adenocarcinoma

Growth pattern	Gleason pattrrn	Descriptions
1. Small gland	1, 2, 3A, 3B	Tiny, small , medium separate acini
2. Large gland	3A, 3C, 5A.	Simple, papillary, cribriform.
3. Fused gland	4A, 4B	Coalescing acini, amphophilic or clear. (Hypernephroid)
4. Solid	5B	Sheets, cords, single cells.

The leading pattern of adenocarcinoma is small glandular pattern. Most of the benign mimickers come in the differential diagnosis of small gland adenocarcinoma.

PROSTATIC INTRAEPITHELIAL NEOPLASIA

In 1986 Mc Neal & Bostwick, studied 100 specimens of prostatic adenocarcinoma and 100 benign prostates obtained at autopsy. They noticed foci of PIN in 82 prostates with carcinoma and 43 benign prostates. It provided strong support regarding the status of PIN as a precursor lesion.

CRITERIA FOR PROSTATIC INTRA EPITHELIAL NEOPLASIA

	FEATURES	**LOW GRADE PIN**	**HIGH GRADE PIN**
A.	Architectural features	Epithelial cell crowding with irregular spacing	similar to low grade,more crowding and stratification
B.	cytological features		
	Nuclei	Enlarged with considerable size variation	Enlarged with some size and shape variation
	Chromatin	Normal	Increased in density and clumping
	Nucleoli	Rarely prominent	Large and prominent, sometimes multiple
C.	Associated features		
	Basal cell layer	Intact	May show disruption
	Basement membrane	Intact	Intact

CLASSIICATION OF BENIGN MIMICKERS OF ADENOCARCINOMA

HISTOANATOMIC STRUCTURES

- Seminal vesicle/ejaculatory duct
- Cowper's gland
- Paraganglion
- Verumontanum mucosal glands (hyperplasia)
- Mesonephric gland remanants

ATROPHY

- Simple (Lobular)
- Sclerotic
- Cystic
- Linear
- Post atrophic hyperplasia (partial atrophy)

INFLAMMATION

- Usual prostatitis with preservation artefacts
- Granulomatous prostatitis, non specific
- Xantho granulomatous prostatitis (xanthoma)
- Malakoplakia.

REACTIVE ATYPIA

- Inflammatory
- Ischemic
- Radiation

METAPLASIA

- Mucinous
- Nephrogenic (adenoma)

PROSTATIC HYPERPLASIA

- Basal cell hyperplasia
- Benign nodular hyperplasia, small gland pattern
- (clear cell) cribriform hyperplasia
- Sclerosing adenosis
- Atypical adenomatous hyperplasia.

BENIGN MIMICKERS IN RELATION TO MAJOR GROWTH PATTERNS OF PROSTSTIC ADENOCARCINOMA

Small gland pattern

- Seminal vesicle
- Cowper's gland
- Atrophy
- Post atrophic hyperplasia
- Reactive atypia
- Mucinous metaplasia
- Nephrogenic metaplasia
- Basal cell hyperplasia
- Benign nodular hyperplasia
- Sclerosing adenosis
- Verumontanum mucosal gland hyperplasia
- Mesonephric gland hyperplasia
- Atypical adenomatous hyperplasia.

Large gland pattern

- Clear cell cribriform hyperplasia
- Reactive atypia

Fused gland pattern

- Paraganglioma
- Xanthogranulomatous inflammation
- Malakoplakia

Solid pattern

- Usual prostatitis with crush artefact
- Idiopathic granulomatous prostatitis
- Signet ring like changes in stromal cells and lymphocytes

As already stated nearly all benign mimickers come in the differential diagnosis of small gland pattern.

SEMINAL VESICLE

Seminal vesicle tissue possibly present in transurethral resection specimens or in needle biopsies, generally unexpectedly. Sometimes they are specifically sampled.

Jensen KM, Sonneland P. reviewed histologic specimens from 123 consecutive patients undergoing transurethral resection of prostate for the existence of seminal vesicle tissue. The incidence was 23%.[19]

Arias-stella J, Takano-Manon J reviewed 264 prostatic needle biopsy specimen for the presence of seminal vesicle. The incidence was 15%.[20] They also described atypia in seminal vesicle epithelium in old age.

ATROPHY

In 1936, Moore et al[21], studied 678 prostate gland specimens and published a detailed account of the histological features of the normal gland and involutional prostate gland . He suggested atrophy as a physiological and age related phenomenon. He also described the presence of luminal acidophilic secretions in atrophy. Atrophy of prostate is a general process characteristically but not exclusively seen in older patients. In young adults it is usually admixed among areas of nodular hyperplasia.[22]

The term proliferative inflammatory atrophy was introduced by De Marzo et al. [23] to designate discrete foci of proliferative glandular epithelium which exhibits morphologic appearance of simple atrophy or post atrophic hyperplasia which occurs in association with inflammation. De Marzo et al.[23] and Putzi suggested that post inflammatory atrophy may

indeed give rise to carcinoma directly or indirectly via development into HG-PIN.

But Athense Billis, Luis A Magna[24] studied 100 prostate specimens from men older than 40 years and found that post inflammatory atrophy does not seem to be associated with histological carcinoma or LG-PIN.

POST ATROPHIC HYPERPLASIA

In 1936 Moore[25] illustrated and published post atrophic hyperplasia, although he did not make any special reference to it in the text. This was followed by Totten et al in 1953, but they referred to this process as lobular hyperplasia. The term post atrophic hyperplasia and post sclerotic hyperplasia were coined by Frank et al in 1954, who proposed this lesion as a precursor to prostatic adenocarcinoma. But later studies failed to establish such relationship between post atrophic hyperplasia and prostatic adenocarcinoma.

In 1999 Mahul B.Amin, Phenoze Tamboli, Muralivarma and John R.Srigley[26] studied 56 needle biopsy specimens to ascertain the morphologic spectrum of post atrophic hyperplasia. Age of the patient ranged from 49 to 85 years. Selection of cases were restricted to those containing foci of small acinar proliferation atleast some of which are suspicious of carcinoma. In this study prevalance of post atrophic

hyperplasia presenting as small acinar proliferation in consecutive biopsy specimen was 3.6%.

ATYPICAL ADENOMATOUS HYPERPLASIA (ADENOSIS)

Atypical adenomatous hyperplasia is one more common mimicker of prostatic adenocarcinoma recognised on both biopsy and transurethral resectates. In 1986 Mc Neal[27] referred atypical adenomatous hyperplasia (AAH) as a possible premalignant proliferation, most probably of carcinoma arising in the transition zone. In 2000, Kien, T.Mare et al. [28] reviewed 533 and 499 TURP specimens before and after the introduction of PSA screening respectively. They suggested the possibility of association of atypical adenomatous hyperplasia with low grade carcinoma developing from transitional zone and association of PIN with carcinomas arising in non-transitional zone.

Atypical adenomatous hyperplasia has been projected as a precursor of prostatic adenocarcinoma of the transitional zone for the following reasons.

i. Age peak that precedes that of PCa.

ii. Increased incidence in association with PCa.

iii. Topographic relationship with small acinar PCa.

iv. Increased size of nucleus.

iv. A proliferative index similar to that of small acinar PCa.

v. Occasional cases with genetic alterations.

The term ‘adenosis’ was suggested to replace atypical adenomatous hyperplasia. This has not been accepted and ‘atypical’ has been retained to indicate the unusual pattern of small acinar formations that characterize AAH.

Currently, the term atypical adenomatous hyperplasia is replaced by “Atypical small acinar proliferation” (ASAP).

Previously the data were insufficient to conclude atypical adenomatous hyperplasia as a premalignant lesion. In 2005 Courtenay K.Moore et al. in their study of 1,188 cases selected 105 cases of which 33 had HGPIN and 72 had ASAP. They applied an extended biopsy scheme over the patients diagnosed with high grade PIN and atypical small acinar proliferation. According to that study in the first repeat biopsy, only 1 of 22 (4.5%) men with previous HG PIN had cancer while 19 of 53 (36%) with a history of ASAP were found to have cancer. In the second repeat biopsy, none of the 11 men previously diagnosed with HG PIN had cancer. But 3 of 19 (16%) men with ASAP had cancer.

Hence, they recommended that high-grade PIN does not warrant a repeat biopsy and atypical small acinar proliferation continues to be

associated with a high risk of cancer and requires atleast one repeat biopsy using extended biopsy scheme.

Ahmet Midi, Tulay Tecimer, Suhayala Bozkurt[29] reviewed 105 radical prostatectomy specimens and defined new histologic criteria to differentiate AAH from prostatic adenocarcinoma grade 1and 2. They assesed 18 anatomical and structural parameters and immunohistochemistry with 34βE12-basal cell marker. They concluded the lack of basal cells in adenocarcinoma and their occasional presence in AAH is the most important diagnostic criterion.

BASAL CELL HYPERPLASIA.

Basal cell hyperplasia was fairly a common lesion in hyperplastic prostates being examined by Young R.H. et al.[30] in his studies. Basal cell hyperplasia is seen in the transition zone typically as a part of the continuum of benign nodular hyperplasia. Recently it has been recognised that basal cell hyperplasia might also involve the peripheral zone.

Phatarapon Thorson, et al[31] studied the existence of basal cell hyperplasia in the peripheral zone of the prostate. They reviewed series of 500 consecutive needle biopsies and 26 radical prostatectomy specimens. The incidence of BCH in needle biopsy tissue was 10.2%. Usual basal cell hyperplasia was noticed in 8.2% of the 500 cases and

atypical basal cell hyperplasia was 2.0%. 84% cases of basal cell hyperplasia was associated with lymphocytic infiltration. 23% of whole prostate glands showed basal cell hyperplasia in peripheral zone.

Basal cell hyperplasia is easily separated from adenocarcinoma in majority of the cases, particularly in transurethral resectate and open prostatectomy specimens. The nodular architecture, presence of ordinary nodular hyperplasia, lack of pleomorphism and absence of prominent nucleoli assist in separating this condition from carcinoma. However it may be difficult in small biopsies. In such cases the recognition of uniform cytological and nuclear features along with staining for high molecular weight keratin(34βE12) serve to seprate this condition from adenocarcinoma.

CLEAR CELL CRIBRIFORM HYPERPLASIA

Clear cell cribriform hyperplasia of the prostste is a rare form of hyperplasia found in BPH. It was recognised in 1980 by world health organisation. Gleason described the same lesion as florid benign papillary cribriform hyperplasia in 1985. The clear cells of CCCH show strong immunoreactivity with prostate specific antigen and prostatic acid posphatase. Cribriform hyperplasia is a mimicker of both prostatic intra epithelial neoplasia and cribriform adenocarcinoma. The difference relies mainly on the identification of nodularity in the low power, cellular stroma, existence of basal cells and absence of cytologic atypia.

SCLEROSING ADENOSIS

Sclerosing adenosis is a prostatic lesion which has been first reported by Chen A Schiff in 1983 as adenomatoid tumor of prostate due to its morphologic resemblance to adenomatoid tumor. Young and Clement introduced the term sclerosing adenosis in 1987 on the basis of histologic resemblance to sclerosing adenosis of the breast.

In 1991 Sakomoto et al.[32] analyzed 263 specimens of prostate, found 5 cases of sclerosing adenosis with incidence of 1.9% which was found to be localised to the transition zone.

Rafael J.Luque et al.[33] described histological features of sclerosing adenosis of the prostate. They found a combination of histologic (mainly myxoid cellular stroma and double layering of acinar cells) and immunohistochemical features demonstrating a continuous basal cell layer with myoepithelial differentiation to be diagnostic.

MUCINOUS METAPLASIA

Mucinous metaplasia was studied by Frank et al.[34] in 1964. About 155 prostate glands were studied in which whole organ sections were stained for mucin. They described the presence of PAS and alcian blue positive goblet cells within the transitional epithelium of prostatic urethra and proximal prostatic ducts.

Dikman and Toker et al.[35] in 1973 noted the presence of seromucinous glands in prostatic stroma. They concluded that the lesion was an ectopia of minor salivary glands.

In 1993 David J. Grignon and Frances P.O Malley[36] noted tall columnar mucin secreting cells in 12 cases of benign prostatic hyperplasia out of 1700 cases in a three year study and stained histochemically for mucicarmine, alcian blue and periodic acid schiff. They documented the presence of acid mucin in the luminae of basal cell hyperplasia, post atrophic hyperplasia and also in some glands involved with transitional cell metaplasia. The presence of acidic mucin in secretory cells in benign lesions indicates the nonspecificity of this finding in the diagnosis of malignancy.

MESONEPHRIC GLAND HYPERPLASIA

Remnants of mesonephric glands are rarely identified in prostatic specimens. In a series of 700 transurethral resectates, 0.6% had mesonephric remnants[37]. Occasionally they may go through hyperplasia and possibly confused with adenocarcinoma. Two cases of mesonephric gland hyperplasia is identified by Gikas et al. in transurethral resection specimens that were diagnosed as adenocarcinoma and led to unnecessary radical prostatectomy[38] in one case. Immunohistochemistry is helpful in such cases. The mesonephric glands stains negatively for PSA, PAP and

stain positively for HMWCK in contrary to adenocarcinoma which lacks basal cells.

VERUMONTANUM MUCOSAL GLAND HYPERPLASIA

Verumontanum mucosal gland hyperplasia is generally incidentally discovered in radical prostatectomy specimens[39]. The incidence was found to be 14% in one series containing 30 radical prostatectomy specimens. This process is hardly seen in needle biopsy specimens[40]. It is characterized by uniform round glands which are closely packed, containing numerous corpora amylacea.

Basal cells are typically identified and there is no nuclear features of malignancy. Specifically, prominent nucleoli are not seen.The existence of lipofuscin pigment in the cytoplasm of glandular cells is also an important diagnostic clue.

The prominent basal cells and corpora amylacea, the absence of nuclear atypia and suburethral location helps in differentiating from adenocarcinoma.

NEPHROGENIC METAPLASIA (ADENOMA)

The nephrogenic adenoma (NA), a lesion of suspected renal tubular origin, is seen in different sites within the urinary system which includes the renal pelvis, ureters, urinary bladder (common location), and

prostatic urethra. It is mistaken for prostatic adenocarcinoma especially when it is located in the prostatic urethra. Histologically papillary structures, small, or dilated tubules lined by cuboidal, columnar or hobnail eosinophilic cells are characteristically seen. Lesions containing small tubules are the one which commonly leads to confusion with prostatic adenocarcinoma. This is further complicated by frequent negative staining reaction with basal cell markers, positive for AMACR, PSA and/or PAP by IHC. PAX2 and/or PAX8 are newly described specific markers for NA and is useful in arriving at the correct diagnosis[42].

REACTIVE ATYPIA OF LARGE GLANDS

In the situation of concurrent inflammation, ischemia and radiation[43] medium to large sized glands may show reactive atypia which may lead to distortion of the glands and nuclear atypia that can cause confusion with prostatic intraepithelial neoplasia (PIN) and Gleasons large gland patterns of adenocarcinoma. The nuclei of reactive atypia may appear hyperchromatic but exhibits degenerative changes. In some cases prominent nucleoli is seen causing more confusion with adenocarcinoma.

The features which are most helpful in differentiating reactive atypia from malignancy are the detection of the associated findings such

as inflammation, infarction or radiation and the existence of the basal cell compartment confirmed by the 34βE12 stain.

MALAKOPLAKIA

Malakoplakia of the prostate gland is featured by diffuse sheets of histiocytic infiltration, admixed with lymphocytes, plasma cells and neutrophils[44,45]. The von-Hanseman histiocytes which is predominantly seen in the early stage of malakoplakia may mimic carcinoma.

The most useful features to distinguish malakoplakia from malignancy are lack of acinar differentiation , presence of inflammatory cells and typical Michaelis–Gutmann bodies. In difficult cases immunohistochemistry is needed which is characterised by the presence of CD68 and lack of cytokeratins and prostatic epithelial makers.

XANTHOMA

Prostatic xanthoma is another benign mimicking lesion of high-grade prostatic adenocarcinoma or hormonally treated prostatic cancer. Chuang, Ai-Ying; Epstein, Jonathan I. studied the cases from 1995 to 2006, at The Johns Hopkin Hospital, USA[46]. Xanthoma was noted on needle biopsy in 25 cases with 2 cases observed on TURP specimens, The cells of xanthoma had uniform, benign-nuclei, inconspicuous nucleoli and abundant foamy cytoplasm. No mitotic figures were identified. Focal areas of necrosis was seen in 1 case. The predominant

pattern observed is the well circumscribed solid nodular pattern (17cases). Ten cases showed a pattern of cords and individual cells infiltrating the stroma, further simulating high-grade prostate carcinoma. A mixture of these two patterns is observed in two cases. IHC is done in 19 cases which had sufficient tissue. CD68 was strongly positive in 18 cases (94.7%) and CAM5.2 was positive in none of the cases (0%). 2of 17 (11.8%) cases 1of 15 (6.7%), and 1 out of 12 (8.3%) cases were positive for, prostate-specific acid phosphatase prostate-specific antigen, and [alpha]-methylacyl-CoA racemase, respectively.

Meticulous morphological examination and proper use of CD 68 and CAM5.2 immunohistochemical stains are benificial in the diagnosis of prostatic xanthoma, chiefly in complicated cases with an infiltrative pattern.

Familiarity with the differential diagnosis of prostatic adenocarcinoma is important in the situation of diagnosing minimal adenocarcinoma in small biopsy samples. It is essential to be aware of those conditions which may lead to false-positive cancer diagnosis and the role of various immunohistichemical markers in arriving correct diagnosis.

BENIGN MIMICKERS OF ADENOCARCINOMA: USEFUL IMMUNO

HISTO CHEMICAL MARKERS

- **Cytokeratins(general)**

  AE1/AE3, CAM 5.2, MAK6

- **Basal cell markers**

  34βE12, CK5/6, p63

- **Secretory cell marker**

  Prostate-specific antigen (PSA),

  Prostatic acid phosphatase (PAP),

  CD57

- **Neuroendocrine markers**

  Chromogranin, synaptophysin

- **Lymphohistiocytic markers**

  Leukocyte common antigen, CD56, CD68

- **Other markers**

a-Methylacyl-CoA racemase (P504S).

Basal Cell–Associated Markers

In invasive prostate carcinoma, the basal cell layer is absent, so a complete absence of staining in basal cell– associated markers is supportive of malignant diagnosis. Under hematoxylin-eosin (H&E) microscopy, basal cells may be mimicked by prostatic stromal cells juxtaposed to the glandular-basement membrane, by endothelial cells of blood vessels closely situated to acini, and by tangentially sectioned neoplastic cells. Basal cell–associated markers highlight basal cells present in benign prostate glands and related benign, but architecturally atypical proliferations.

High- Molecular- Weight Cytokeratin 34βE12.

Highmolecular-weight cytokeratin (HMWCK) 34βE12 is a cytoplasmic marker that highlights intermediate cytokeratin (CK) filaments in basal cells and is specific for basal cells in the prostate. The monoclonal antibody clone 34βE12 (also known as CK903), which targets CK1, CK5, CK10, and CK14, is the time-honored basal cell marker used since 1985[47]. Although extended formalin fixation may affect 34βE12 antigenicity, it can usually be restored with appropriate antigen-retrieval techniques. This was the first prostatic marker available for the differential diagnosis of cancer versus atypical benign glands.

CK 5/6.

Another HMWCK is CK5/6. The overall sensitivity, specificity and diagnostic utility of CK5/6 in prostate needle biopsies are similar to 34βE12.

p63

This antibody targets the nuclear protein p63 which is homologous to the *TP53* tumor suppressor gene and has been proven to selectively stain the basal cell nuclei[50]. P63 is comparable to HMWCK in sensitivity and specificity in needle biopsies, but they have better sensitivity than 34βE12 in transurethral resection specimens. This difference in staining may be related to alterations in antigenicity of basal cells in benign prostatic hyperplasia.

p63 immunostaining provides greater specificity because of its nuclear localization than the cytoplasmic staining of HMCK markers which may have greater potential for nonspecific reaction.

Recommended Interpretation Guidelines.

If basal cell-layer–associated makers alone are used, the diagnosis of carcinoma is made on a negative immunoreaction and therefore, appropriate external and internal positive and negative controls must be used while interpreting the stain. Before evaluation of the

immunohistochemical slide, all morphologically atypical glands must be identified in H&E sections and the corresponding glands in the suspicious focus should be completely negative by immunohistochemistry. The consistency of the staining reaction should be confirmed in a second section on the same slide, if available.

Potential Diagnostic Pitfalls.

Pitfalls in staining with basal cell–associated markers may be due to false negativity in benign mimics or false positivity in carcinoma. False negative staining in scattered, obviously benign glands is observed in 5% to 23% of cases. Staining may be weak-reactive to nonreactive in some benign proliferations that mimic cancer such as in up to 23% of glandular atrophy, up to 50% of atypical adenomatous hyperplasia (AAH;adenosis) and 23% of post–atrophic hyperplasia.

Completely negative staining can occur in non prostatic mimickers of carcinoma such as in 44% to 75% of nephrogenic adenoma and 66% of mesonephric glandular hyperplasia.

There are rare scenarios in which prostate carcinoma may show immunoreactivity with basal cell markers, for instance, entrapped benign gland within carcinoma, cancerization of benign glands, intraductal cancer growth, ductal carcinoma of prostate and high-grade prostatic carcinoma (especially at metastatic sites).

Epithelial Markers

The cocktail of AE1 and AE3 detects acidic (CK10, CK14–16, and CK19) and basic (CK1–CK6 and CK8) cytokeratins and is the most universally used epithelial marker. Cytokeratin AE1/AE3 is useful in the differential diagnosisof nonspecific granulomatous prostatitis, xanthoma cells versus high-grade prostate cancer with an infiltrative individual cell pattern. Cytokeratin AE1/AE3 is also helpful in diagnosing small cell proliferations involving the prostate (differential diagnosis for small cell carcinoma, lymphoma, and rhabdomyosarcoma).

In the post treatment setting CK AE1/AE3is superior to PSA in highlighting individual atrophic prostate cancer cells[52] because PSA can be suppressed by therapy and is, therefore, not detectable immunohistochemically following treatment.

Prostate Lineage–Specific Markers

Within the prostate gland, PSA and prostate-specific acid phosphatase (PSAP) are used to confirm the prostatic acinar cell origin and are useful in ruling out nonprostatic carcinoma mimics such as seminal vesicle/ejaculatory duct, hyperplastic mesonephric glands, nephrogenic adenoma, Cowper glands, and paraganglionic tissue.[53]

Another recent immunohistochemical marker for this purpose is prostate-specific membrane antigen, but there are few studies to date with this antibody[54].

Another use of PSA and PSAP is in the diagnosis of unusual variants of prostate carcinoma (ie, ductal, mucinous, and signet ring carcinoma), which stain positive for PSA and PSAP versus secondary tumors involving the prostate (such as bladder or colonic adenocarcinomas) which are typically negative.

Potential Diagnostic Pitfalls.

In poorly differentiated prostate carcinoma, Prostate-specific antigen expression can be weak and focal. The polyclonal PSA antibody when compared to monoclonal antibody may show occasional reactivity in up to 32% of normal, seminal vesicles. Another condition which shows PSA and PSAP positivity is nephrogenic adenoma.

Prostate Cancer–Associated Marker AMACR (P504S)

The *P504S* gene was identified by combination of complementary DNA subtraction and high-throughput microarray to be over expressed selectively by malignant, but not by benign, prostatic glands[55,56]. The subsequent studies from radical prostatectomies, transurethral resection of prostate and needle biopsy specimens confirmed the selective immunoreactivity in malignant, but not in benign glands.

The prostate carcinoma–associated AMACR, if used in combination with basal cell markers has superior diagnostic value .The positive staining of AMACR complements the lack of basal cell–associated staining in prostate carcinoma and thus safeguards from false negativity associated with basal cell–related markers

Currently, an antibody cocktail of AMACR and basal cell markers is available and is an efficient diagnostic tool as suggested by many studies. α-Methylacyl coA racemase is seen in 75% to 95% of prostate carcinomas in diagnostic material staining observed across the spectrum of Gleason 5 to 10 carcinoma.

Recommended Interpretation Guidelines.

To be interpreted as positive for carcinoma, AMACR should be circumferential, strong and cytoplasmic, with a granular quality .To be found positive, the staining of malignant glands must be stronger than adjacent benign acinar glands. Interpretation must always be in conjunction with H&E morphology and preferably, with a basal cell stain. If there is a lot of background staining throughout the biopsy, staining should not be interpreted.

Potential Diagnostic Pitfalls.

Positive AMACR staining does not always indicate carcinoma, and negative staining does not rule out carcinoma. False negative immunoreactivity to AMACR may be seen in 5% to 25% of typical prostate carcinomas. It also varies with specific patterns of prostate

carcinoma and can be negative in 30% of atrophic carcinoma, 32% to 38% of foamy gland carcinoma and 23% to 30% of pseudo hyperplastic carcinoma variants. Expression can be substantially diminished or completely lost in up to 29% of prostate carcinoma following hormonal therapy.[57]

Conversely, reactivity with AMACR is seen in relatively higher proportions of premalignant proliferations. 56% to 100% of high-grade prostatic intraepithelial neoplasia and 18% of AAH showed positive AMACR staining reaction in one study. Gladell P. Paner, Daniel J. Observed a range close to50%

Occasionally, reactivity with AMACR can be seen in benign entities, such as in 35% to 58% of nephrogenic adenoma and 2% to 36% of typical benign glands and also in some secondary tumors involving the prostate such as urothelial carcinoma and colonic adenocarcinoma.

The application of basal cell–associated markers, prostate cancer associated marker AMACR, and prostate lineage–specific markers PSA and PSAP provide significant, objective evidence in confirming whether glandular lesions are benign or malignant and whether they are of prostatic origin.

Although these markers provide invaluable ancillary diagnostic assistance, the myriad differential diagnostic considerations and overlapping staining reactions mean that the final diagnosis must reflect the context and be correlated with the original H&E-derived diagnosis.

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 90 cases and open prostatectomy in 5 cases. The age group of the patients ranged from 33-90 yrs.

Transurethral resection had been done to the patients who came to the urology outpatient department with complaints of urinary obstruction. If the patient had been clinically suspected of having carcinoma prostate by digital rectal examination, they were screened for prostatic specific antigen (PSA) levels in the serum. Patients with elevated PSA levels in the serum or clinically suspicious patients or both have been selected for trucut needle biopsy. Only few patients underwent transrectal ultra sound (TRUS) guided biopsy.

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 10 gram 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. Microphotographs were taken. IHC stains were done wherever found necessary.

PROCEDURE OF HAEMATOXYLIN AND EOSIN STAIN:

- Dewax the sections, hydrate through graded alcohols to water.
- Remove fixation pigments if necessary.
- Stain in haematoxylin for 5 minutes.
- Wash well in running tap water until sections become `blue' for 5 minutes.

- Differentiate in 1 percent acid alcohol for 2-4 sec.
- Wash well in running tap water until sections are again `blue' for 15 to 20 minutes.
- Stain in eosin for one minute.
- Wash in tap water for 5 minutes.
- Dry and mount the slide.

CASES OF CLEAR CELL METAPLASIA ARE STAINED WITH PERIODIC ACID-SCHIFF.

METHOD:

1. Dewax sections and bring to distilled water.
2. Treat with periodic acid for 5 minutes.
3. Wash well with several changes of distilled water.
4. Cover with Schiff's solution for 15 minutes.
5. Wash in running tap water 5-10 minutes.
6. Stain nuclei with Harris Hematoxylin. Differentiate as appropriate in acid alcohol and blueing in tap water for 5 minutes.
7. Wash in water.
8. Rinse in absolute alcohol.
9. Clear in Xylene and mount with DPX.

IMMUNOHISTOCHEMISTRY

Cases for IHC were selected after viewing the H &E sections. Slides were coated with chrome alum, and subjected to Antigen Retrival using the Microwave technique with Citrate buffer solution. Slides were then treated by HRP (Horse radish peroxidase) polymer technique.

HRP POLYMER TECHNIQUE

The coated slides were taken through the following steps.

1. Treatment with peroxidase block for incubation of endogenous peroxidase in the tissue for 20 minutes, washed in PBS buffer for 5 mts.

2. Applications of power block O - to block non specific antigen antibody reactions for 20 minutes. The excess power block was blot dried.

3. Applications of Primary antibody – Murine antibodies for 60 minutes. Washed in PBS buffer for 5 minutes.

4. Application of super enhancer for 30 minutes which increased the sensitivity of antigen -antibody reaction thereby enhancing the final reaction product.

5. Application of SS label – Secondary antibody from goat with the tagged horse radish peroxidase enzyme for 30 minutes. Washed in TRIS buffer.

6. Application of DAB (Diamino benzidine) Chromogen for 5 minutes –which was cleared by the enzyme to give the colored product at antigen sites. Washed in distilled water for 5 minutes.

7. The slides were then counter stained with hematoxylin . Slides were air dried and mounted with DPX (Dibutylphalate Xylene).

The following IHC markers were done.

HMWCK (34βE12), CK 5/6, Prostate specific antigen (PSA), vimentin and CD68.

OBSERVATION AND RESULTS

Out of 504 cases analysed, 409 were TURP specimens, 90 were trucut needle biopsies and 5 were open prostatectomy specimens.

DISTRIBUTION OF CASES IN RELATION TO SURGICAL BIOPSY SPECIMENS

TABLE - 1

Surgical biopsy specimens	Total No. Of cases	Percentage
Transurethral resection of prostate	409	81.15
Trucut needle biopsy	90	17.86
Open prostatectomy	5	0.99

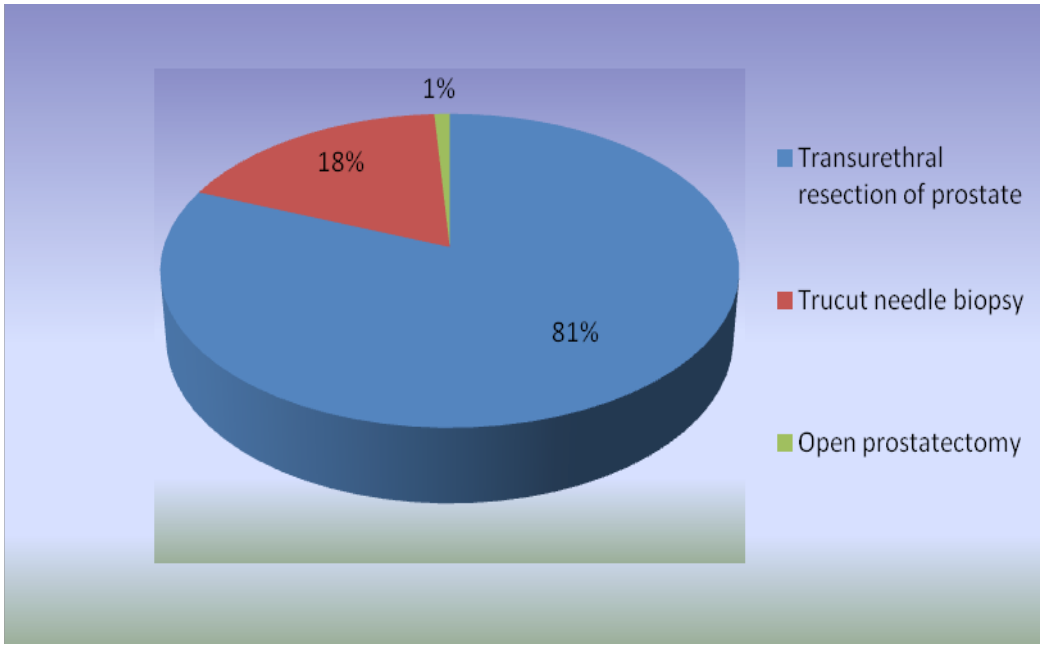

Chart-1: Distribution of cases in relation to surgical biopsy specimen

DISTRIBUTION OF CASES BASED ON HPE DIAGNOSIS

TABLE - 2

Lesions	Total no. of cases	TURP	Trucut biopsy	Open prostatectomy
BPH	448 (89%)	397(97%)	47(52%)	4 (80%)
Adenocarcinoma	44(9%)	9(2%)	34(37%)	1(20%)
Unsatisfactory specimen	12(2%)	3(1%)	3(1%)	---

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. This includes inadequate tissue, poorly preserved specimens and biopsy from non representative sites. (Table 2)

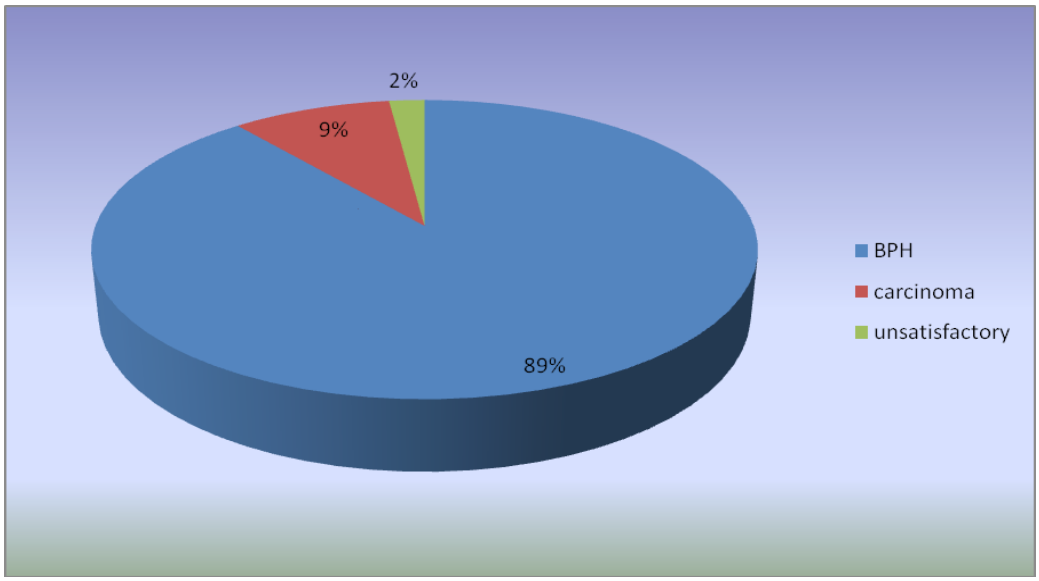

Chart-2: Distribuion of cases in relation to HPE diagnosis

DISTRIBUTION OF CASES IN RELATION TO AGE.

TABLE - 3

Age group	No.of cases	Percentage
31-40	6	1.21%
41-50	32	6.5%
51-60	130	26.4%
61-70	202	41.05%
71-80	106	21.54%
81-90	16	3.25%

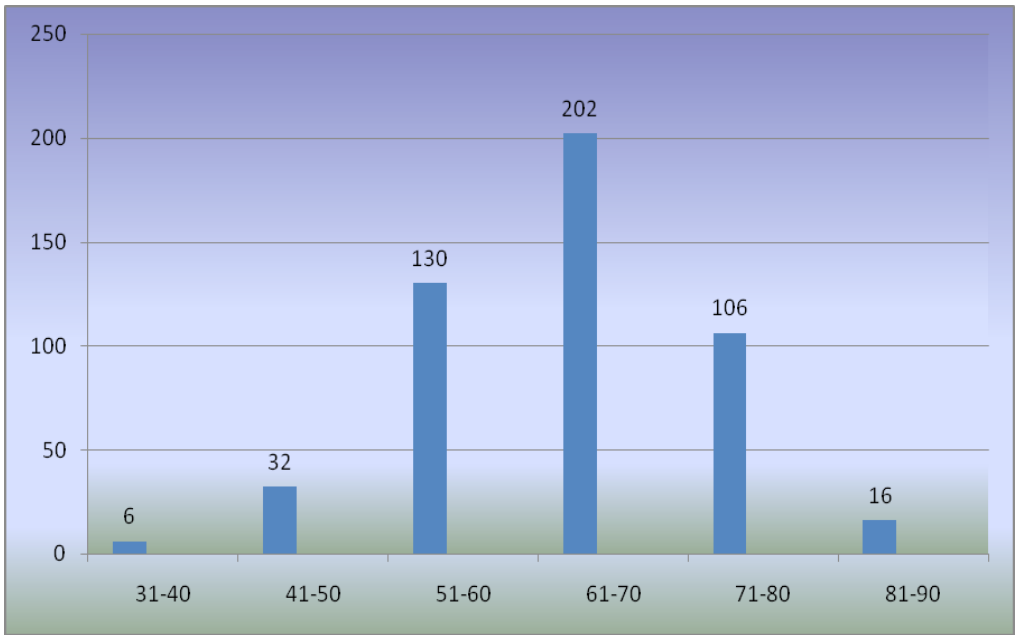

Chart-3: Distribution of cases in relation to age

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%).

DISTRIBUTION OF MIMICKERS:

TABLE - 4

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

DISTRIBTION OF IDENTIFIED BENIGN MIMICKERS:

TABLE - 5

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.Sclerosing adenosis		4	3.8
5.Stromal clear cell metaplasia		14	13.2
6.Xantho granulomatous prostatitis		4	3.8

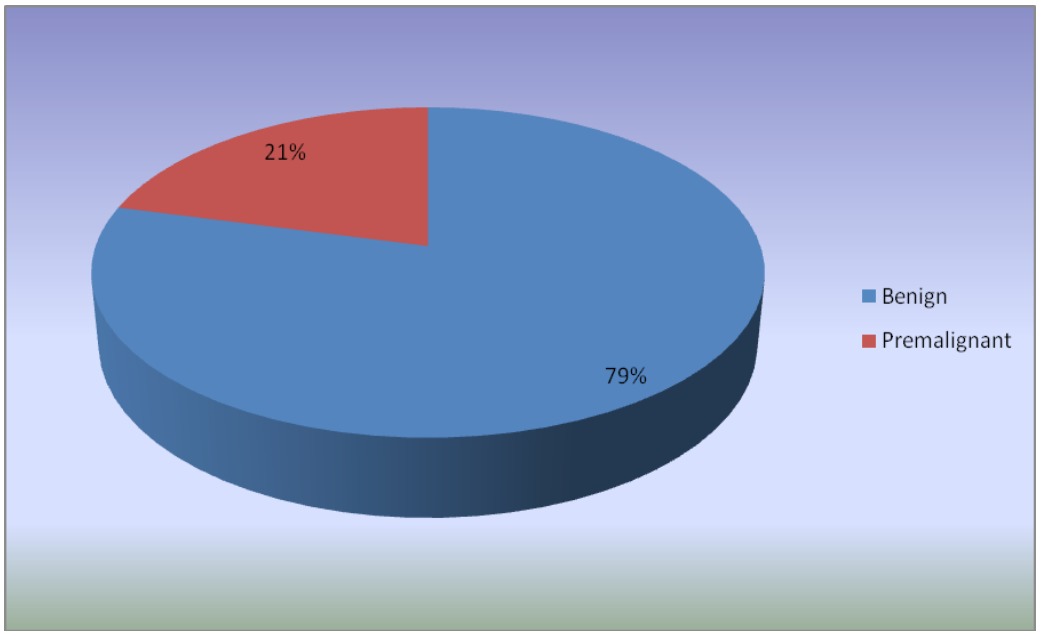

Chart-4: Distribution of mimickers

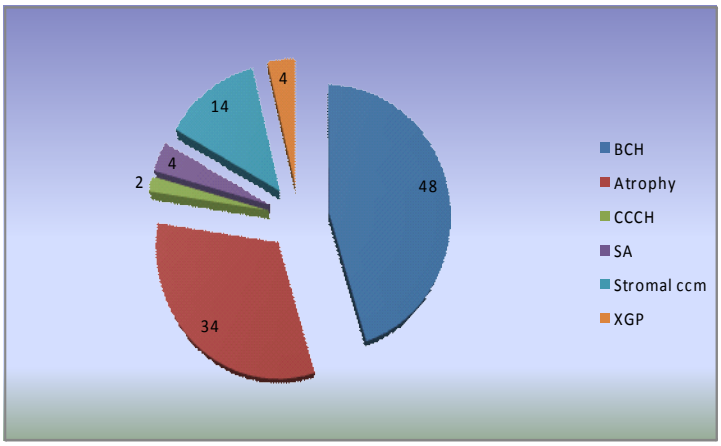

Chart-5: Distribution of benign mimickers

Among benign mimickers BCH was the commonest (45%) followed by atrophy (32%).

Totally 48 foci of basal cell hyperplasia were found in the 504 surgically 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.Out of 48 foci 47 were seen in association with benign prostatic hyperplasia and one was seen in the backdrop of adenocarcinoma.

TYPES OF BASAL CELL HYPERPLASIA:

TABLE - 6

Types	No. Of cases	Percntage
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.

PREMALIGNANT MIMICKERS :

TABLE - 7

Premalignant mimicker	No. Of cases	Percentage
AAH/ASAP	22	78.6
PIN	6	21.4

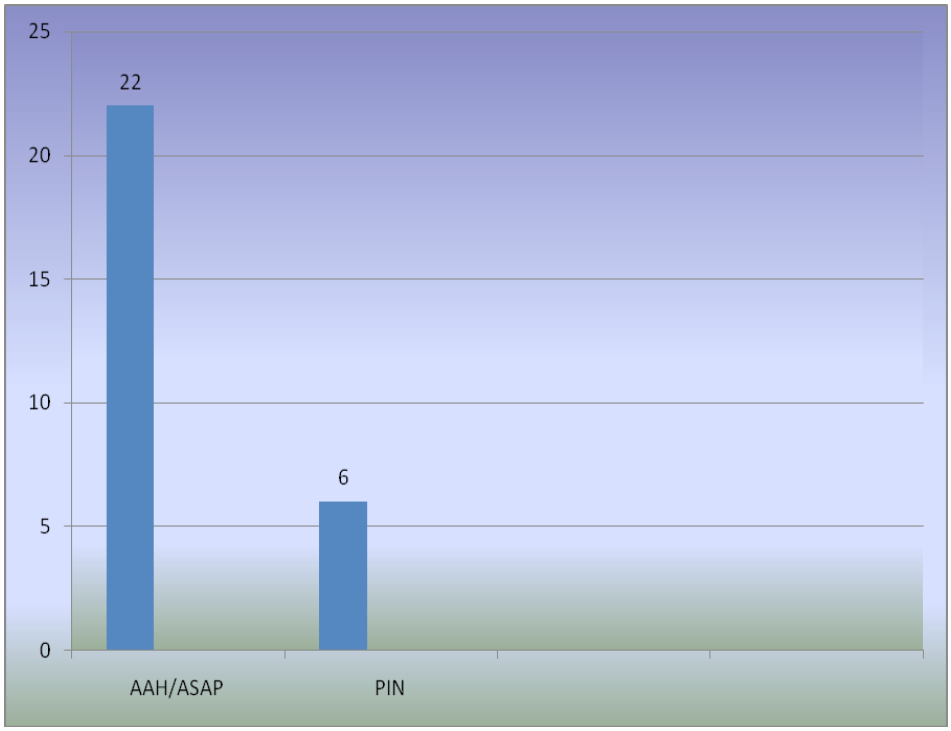

Chart-6: Identified premalignant lesions

ASSOCIATED CONDITIONS IN PREMALIGNANT MIMICKERS

TABLE - 8

HPE Diagnosis	Premalignant lesions	
	AAH/ASAP	PIN
BPH	20 (4.46%)	5 (1.11%)
Adenocarcinoma	2 (4.54%)	1(2.27%)

ASSOCIATED CONDITIONS IN MIMICKERS

TABLE - 9

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

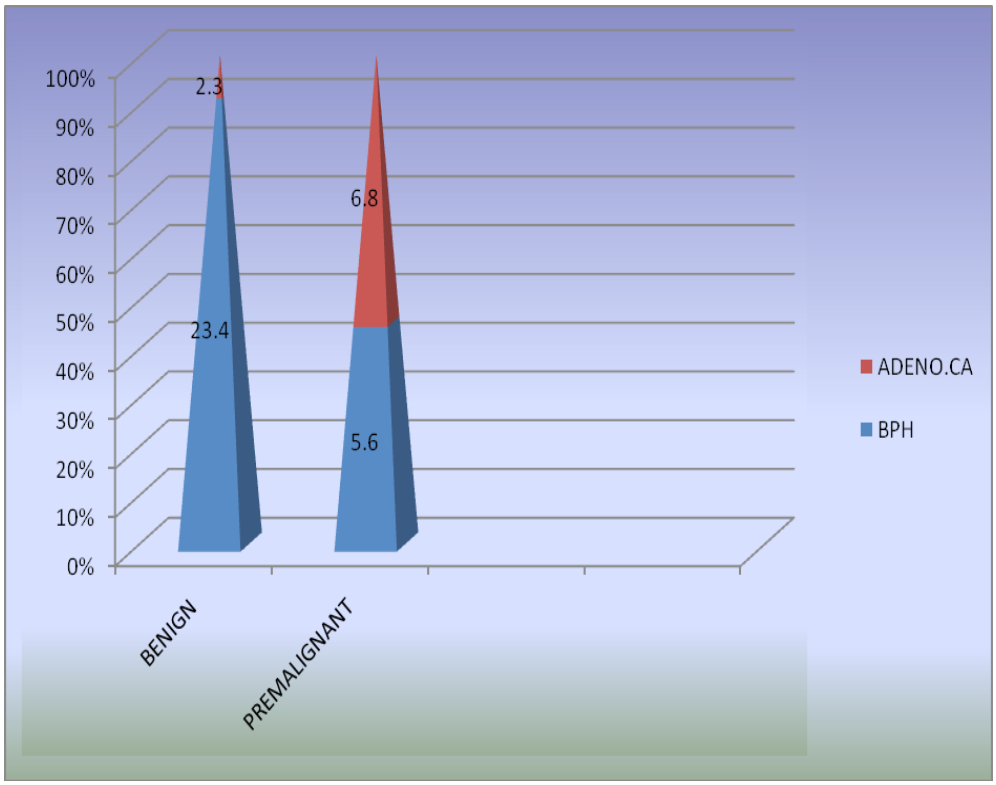

Chart-7: Associated conditions in mimickers

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 wer seen in association with adenocarcinoma.

IHC IN EACH GROUP OF BENIGN MIMICKERS:

TABLE - 10

Mimicker	total no.of cases	IHC Done	34βE12		CK5/6		Vimentin		CD68		PSA	
			total	+ve	total	+ve	total	+ve	total	+ve	total	+ve
BCH	48	12	12	12	12	12	-		-		-	
SAA	10	10	10	9	10	9	-		-		-	
CCCH	2	2	2	2	2	2	-		-		-	
Stromal CCM	14	14	14	14	14	-	14	11	14	1	2	2
XGP	4	4	4	4	4	4	4	2	4	2	-	-
SA	4	4	4	4	4	4	-		-		-	

Immunohistochemical staining with 34βE12 and CK5/6 was done in 46 cases of benign mimickers. Out of which 45 showed continuous staining of the basal cell layer. A single case of small acinar atrophy showed absence of basal layer. Staining with vimentin and CD 68 was done in 18 cases. Out of which 13 were positive for vimentin and 3 were positive for CD68.The remaining two cases which were negative for both vimentin and CD68 were further stained with PSA and the clear cells showed positive reaction with PSA.

IHC IN PREMALIGNANT MIMICKERS

Mimicker	Total no.of.case	IHC done	34BE12 & CK 5/6			PSA +ve
			Continuous	discontinuous	negative	
ASAP	22	16	1	14	1	15
PIN	6	6	3	3	-	6

In 28 cases of premalignant mimickers IHC was done in 22 cases which includes 16 cases of ASAP and 6 cases of PIN. Out of 16 ASAP cases 14 cases showed discontinuous staining pattern of basal cells, continuous staining pattern was observed in one case and one case showed no staining of basal cells. In 6 PIN cases, continuous staining of basal cells was seen in 3 cases and another 3 cases showed discontinuous staining pattern. Out of 22 cases stained with PSA except for one case all other showed positive staining reaction.

DISCUSSION

Prostatic carcinoma and benign prostatic hyperplasia are the two principal conditions to involve the prostate. They account for more than 90% of all prostatic disease.

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.

They do not have specific clinical manifestations and most encountered during examination of prostatic samples from patients in whom the clinical diagnosis is BPH. The distinction between PCA and benign conditions is traditionally made on purely morphologic grounds, but is often problematical. As a result, immunohistochemical methods have been introduced in the differential diagnosis of these conditions.[58,59.]

Preservation of the prostate gland's two-cell-layer structure (inner glandular epithelium and outer basal cells) is a reliable criterion for benign glandular proliferation. Because the two-cell-layer structure in benign proliferative lesions is often not discernible on purely morphologic grounds in hematoxylin and eosin-stained (H&E) sections,

differential diagnosis could benefit from detection of outer basal cells by immunohistochemical methods that employ 34βE12, directed against high molecular weight cytokeratin, as the primary antibody[60,61]. Several investigators have recently reported the usefulness of this method.[62,63.]

Out of 504cases analyzed in our study benign prostatic hyperplasia were found in 448 (89%) patients, prostatic adenocarcinoma in 44 (9%) patients and 12 (2%) specimens turned out to be inadequate samples for making a diagnosis. The patients were in the age group ranging from 33to 90 years.

Totally 134 mimickers were identified. Out of these lesions benign mimickers were 106 and premalignant mimickers were 28. Benign mimickers were almost always witnessed in association with benign prostatic hyperplasia, whereas premalignant lesions are commonly seen in association with adenocarcinoma rather than BPH.

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.[64] 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 is

6.66%. 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[66] 26% of cases of basal cell hyperplasia were misdiagnosed as adenocarcinoma .

In our study 12 cases of atypical BCH with prominent nucleoli was identified. Many entities come into the differential diagnosis of basal cell hyperplasia containing prominent nucleoli. The features help to discriminate basal cell hyperplasia with prominent nucleoli from high grade prostatic intraepithelial neoplasia, includes the nodular architecture, the presence of atypical basal cells beneath benign secretory nuclei, solid nests, smaller glands absence of PSA immunoreactivity in the atypical basal cells and the evidence of high molecular weight cytokeratin immunoreactivity.

We confirmed the existence of basal cells in all of our cases of atypical basal cell hyperplasia, with the help of 34βE12 and CK5/6 immunohistochemical staining. We had one case of cribriform basal cell hyperplasia. Cribriform basal cell hyperplasia may be misdiagnosed as cribriform pattern of PIN or carcinoma. However the bland nature of basaloid cells in high power magnifications help in diagnosis.

Other prostatic basal cell proliferative conditions that should be in differential diagnostic checklist comprise basal cell adenoma, basal cell carcinoma, adenoid basal cell tumor, adenoid cystic-like tumor and adenoid cystic carcinoma, and. Use of proliferative markers such as bcl-2 and Ki-67 immunomarkers can help to distinguish basal cell hyperplasia from the basaloid carcinomas that rarely occurs in the prostate[67] .

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 .[68]

ATROPHY

Mahul B. Amin et al.[69] stated that the most commonly encountered pattern simulating the microacinar architecture of carcinoma is atrophy. A less common glandular pattern that forms one part of the spectrum of atrophy is postatrophic hyperplasia, a lesion that has attained a renewed attention in the recent past in the literature.

Recently, Herawi et al.[70] showed that partial atrophy is one of the common benign lesion which mimics adenocarcinoma in needle biopsy specimens in a consultation service at an academic institution.

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.

In our study 10 cases of small acinar atrophy were identified, stains for high molecular weight keratin (34βE12) and CK5/6 are utilized to highlight the basal cells. Out of 10 cases 9 showed presence of intact basal cell layer and one case was negative suggesting malignant nature of the glands and it was further stained with PSA to confirm.

But studies shows that complete negativity for basal cell markers in atrophic glands can be seen upto 23% of cases. Less number of basal cells in individual glands also leads to disrupted staining pattern.[70] Additionally atrophic glands may also stain positive with AMACR (p504S), a prostate cancer specific antigen.

Therefore, one must use caution when interpreting AMACR and basal cell stains in small foci of atrophic glands in needle biopsy specimens. It is essential to compare AMACR immunostaining with that of adjacent benign glands in conjunction with recognition of histologic features of partial atrophy.

Based on previous studies and the present study, partial atrophy resembles adenocarcinoma in the following ways:

1. crowded, sometimes disordered architecture, often with individual appearing cells because of tangential sections of angulated glands.
2. Pale glands with more cytoplasm than in complete atrophy
3. Occasional larger nuclei and more prominent nucleoli than in benign glands
4. Patchy basal cells with focal absence of basal cells on sections; and
5. Perineural indentation (pseudo–nerve invasion).
6. Negative basal cell staining and positive AMACR staining in some cases.

SCLEROSING ADENOSIS

In this study 4 cases of sclerosing adenosis were identified with an incidence of 1%. Sakamoto et al.[71] reviewed sections of prostate from 263 patients and found 5 cases of sclerosing adenosis, with an incidence of 1.9%.

Sclerosing adenosis is largely restricted to transition zone and is incidental finding in TURP and prostatectomy specimens. Its occurrence

in needle biopsy is extremely rare. In our study all the 4 cases are seen in TURP specimen.

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 adenosis prostate.[66]

Microscopically, the lesion can be partially well circumscribed, and the margins resemble an infiltrative lesion, but the stroma is distinctive; usually it is cellular and myxoid with no smooth muscle cells present. Other features of diagnostic importance include the finding of a double cell population of clear secretory and amphophilic basal cells, sometimes presenting as fusiform cells infiltrating the stroma. Nucleoli are readily identifiable in foci of SAP, but not in the size and extent of prostatic carcinoma. In most cases, applying these criteria is enough to arrive at the diagnosis of SAP.

Pathologic diagnosis can be confirmed by using a panel of immunohistochemical markers, which includes high-molecular-weight cytokeratin, muscle-specific actin and S100 protein. The characteristic expression of high-molecular-weight cytokeratin is diagnostic and demonstrates the presence of an intact basal layer in the acini and in fusiform cells infiltrating the stroma as solid nests and cords. 4 cases identified in this study are subjected to staining with high-molecular-

weight cytokeratin and they demonstrated the presence of an intact basal layer in the acini.

CLEAR CELL CRIBRIFORM HYPERPLASIA

Benign nodular hyperplasia sometimes shows areas of prominent cribriform glands. It is characterized by complex papillary cribriform hyperplasia of clear cells involving the acini of BPH. This lesion usually has a nodular appearance in low power with intervening cellular stroma.

The cells comprising the central cribriform areas are cuboidal to columnar cells with uniform nuclei and clear cytoplasm. They lack nuclear atypia and nucleomegaly. Basal cells are significantly seen around the periphery. CCCH should not be mistaken for a carcinoma or paraneoplastic condition of the prostate with a papillary cribriform pattern. The key to the diagnosis of CCCH is the combination of bland cytological features and architectural uniformity in H&E sections and presence of basal cells highlighted by HMWCK stains.

Two cases of CCCH is noted in our study and the existence of basal cells is confirmed by 34βE12 staining.

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 to

identify 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.[72]

Degeneration of lymphocytes and stromal cells can give rise to a signet ring- like morphology.[73,74.] 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, immunohistochemical stains can be used to verify the cell's nonepithelial nature.

Signet ring cell carcinoma is a very rare entity in prostate. It is seen more frequently as a minor component of a high grade adenocarcinoma. SRPC in its pure form is extremely rare. The diagnosis is made when there are at least 25% of typical cells[75,76].

In this study 14 cases are identified as stromal clear cell metaplasia in H&E sections. Immunohistochemical study using basal cell marker HMWCK, mesenchymal marker vimentin and histiocytic marker CD68 and PSA was performed to confirm the origin of clear cells and to rule out malignancy. Out of 14 cases 11 cases reacted with vimentin confirming the H&E diagnosis of stromal origin. 1 case turned out to be of histiocytic origin showing positive staining for CD68. Other 2 cases

which were negative for both vimentin and CD68 were stained with PSA, showed positivity suggesting their 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[77] finding and abnormally elevated serum PSA levels[78].

Xanthomatous histiocytes usually have small nuclei with inconspicuous nucleoli and are admixed with other inflammatory cells. Only foam cells is seen in some instances which can lead to significant diagnostic confusion. Hypernephroid 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.

In our study, out of 4 cases initially labelled as xanthogranulomatous prostatitis , 2 cases retained their initial diagnosis

after IHC in which the clear cells have taken CD68.The clear cells in the other 2 cases stained positive for vimentin and not stained with CD68 suggesting their origin from stromal cells.

PREMALIGNANT LESIONS.

Atypical adenomatous hyperplasia/atypical small acinar proliferation is a generally well defined lesion characterised by proliferation of small glands in the prostate. The incidence is reported as 1.6- 36.9%. They are most commonly spotted in the transition zone.

The importance of ASAP lies in its potential for being misinterpreted as adenocarcinoma and various benign mimics such as simple lobular atrophy, post atrophic hyperplasia, sclerosing atrophy, basal cell hyperplasia and verumontanum mucosal gland hyperplasia .

The low-power architecture is indicative of Gleason patterns 1 and 2 adenocarcinoma. Individual glands are packed close together but not fused. They exhibit some discrepancy in size and shape and are lined by cuboidal to columnar cells having moderate to abundant clear cytoplasm. Basal cells are noted at least focally.

They have irregular and somewhat serrated luminal borders in contrast to the rigid borders present in small acinar carcinoma. The lumens are empty but may contain corpora amylacea sometimes . A fibroblastic stromal response is identified in some instances which can be

mistaken for sclerosing adenosis. Nucleolar size is invariably smaller in atypical adenomatous hyperplasia than adenocarcinoma. This is identified as a transition between normal prostate epithelium and well differentiated adenocarcinoma usually seen in the transitional zone.

Similar to high-grade PIN, ASAP holds a significant predictive value for cancer in repeat biopsy specimens. In studies published between 1997 and 2001, the reported incidence of prostate cancer in repeat biopsy specimens following a diagnosis of ASAP ranged from 34% to 60%.[79,80]

There are two potential reasons for performing immunohistochemistry in the ASAP setting: to obtain further evidence of carcinoma, and to rule out potential mimics. The key immunostains for this scenario are basal cell associated markers and AMACR used separately or in a cocktail. In our study totally 22 cases of ASAP is identified and IHC was done in 16 cases. Among these 16 cases 14 showed discontinuity in basal cell layer when stained with HMWCK antibody supporting the original H&E diagnosis. One case showed absence of basal cell layer completely suggesting malignancy. The cells of proliferating glands in one case stained continuosly with HMWCK and was negative for PSA suggesting basal cell hyperplasia, a common benign mimicker of ASAP. Although immunohistochemistry provides discriminatory staining patterns between benign and malignant

conditions, the final interpretation must be morphologic, using appropriate staining with internal and external controls.

PROSTATIC INTRAEPITHELIAL NEOPLASIA

Prostatic intraepithelial neoplasia is defined as architecturally benign ducts and acini lined by abnormal secretory cells with changes similar to those in cancer, but at least a focally present basal cell layer. This basal cell layer should be demonstrable by basal cell immunostaining.

Initially PIN was classified into three grades (Grades 1, 2 and 3) and later on replaced by two grade system (low grade and high grade). Currently the term PIN refers only to High grade PIN. HGPIN as an isolated finding is found in 2.7% to 14.2% of needle biopsies in one study. There are four major patterns of high-grade PIN: tufting, , cribiform, micropapillary and flat[81]. 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 different patterns of HG-PIN carries no clinical or prognostic significance and their detection appears to be only of diagnostic value. The differential diagnosis of PIN are lobular atrophy, atypical basal cell hyperplasia, postatrophic hyperplasia, cribriform hyperplasia , and changes associated with radiation , infarction, and prostatitis. 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 abluminal which is seen in PIN.

PIN is often overdiagnosed as adenocarcinoma. A review of transurethral resection specimens in the Mayo Clinic between 1960 and 1970 showed that PIN was often diagnosed as adenocarcinoma[82]. Immunohistochemistry with antibodies 34βE12 (high molecular weight keratin) and p63 may be used to demonstrate the presence of basal cells, recognizing that PIN has an intact or fragmented basal layer whereas cancer cells do not .

According to the study of Junqi Qian and David G Bostwick , basal cell layer interruption is evident in 56% of high-grade PIN, and is more common in acini next to carcinoma than in acini at distant site. Similar to the above study, our study also showed basal cell layer disruption in 3 out of 6 cases which is 50%.

Thus, immunohistochemical 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.[83] However, recent reports have noted that the percentage of ambiguous cases can be reduced significantly, by 68%,[84] or from 5.1 to 1.0 %[85] by addition of this marker.

The main importance of recognizing PIN is based on its strong association with prostatic carcinoma. PIN has a high predictive value as a marker for adenocarcinoma, and its detection in biopsy specimens of the prostate demands further search for concurrent invasive carcinoma.

The predominant uses of immunohistochemical staining in the prostate are distinction of prostate cancer from its benign mimics, distinction from urothelial carcinoma, and identification of metastatic prostate cancer. For the first purpose, prostate cancer diagnosis, the dominant ancillary immunostain is high-molecular weight keratin clone 34βE12, serving to document the absence of a basal cell layer. Keratin 5/6 is an equivalent alternative.

SUMMARY AND CONCLUSION

- Among all the surgical specimens received for the study period for two years, the most common were TURP specimens (81.15%) with benign prostatic hyperplasia (89%) constituting the commonest histological category. Adenocarcinoma were found in (9.7%) of the cases. Most of the adenocarcinomas were diagnosed in needle biopsy specimen.

- About more than 90% of the prostatic lesions studied were found in sixth to eighth decade.

- 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.

- Staining with basal cell markers 34βE12 and CK 5/6 showed retention of intact basal cell layer in most of the benign condition. Discontinuos staining pattern was observed in atypical small acinar proliferation and in HGPIN. No difference in staining pattern or intensity is seen between 34βE12 and CK5/6 .Either of the marker can be used.

- Immunohistochemical staining with PSA, vimentin and CD 68 helped to identify the origin of clear cells i.e whether epithelial, stromal or histiocytic origin and helps to rule out malignancy especially the clear cell variety.

- In summary IHC plays an important role in diagnosis of prostate cancer. It helps to differentiate malignant glands from benign lesions especially for morphologically equivocal glandular proliferations in small biopsy.

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MASTER CHART

S.NO	HPE NO.	AGE	CLINICAL DIAGNOSIS	SPECIMEN TYPE	HPE DIAGNOSIS	IHC				
						HMWCK STAINING PATTERN	CK 5/6 STAINING PATTERN	VIMENTIN	CD 68	PSA
1.	3897/09	50	BPH	TURP	simple atrophy	-	-	-	-	-
2.	4473/09	70	BPH	TURP	simple atrophy	-	-	-	-	-
3.	5477/09	70	BPH	TURP	partial BCH	-	-	-	-	-
4.	5900/09	56	BPH	TURP	simple atrophy	-	-	-	-	-
5.	5939/09	57	BPH	TURP	ASAP	-	-	-	-	-
6.	7025/09	70	BPH	TURP	simple atrophy	-	-	-	-	-
7.	7025/09	70	BPH	TURP	complete BCH	-	-	-	-	-
8.	7160/09	50	Carcinoma	TRUS BIOPSY	simple atrophy	-	-	-	-	-
9.	7302/09	63	BPH	TURP	partial BCH	-	-	-	-	-
10.	7775/09	70	BPH	TURP	complete BCH	-	-	-	-	-
11.	7866/09	75	BPH	TURP	simple atrophy	-	-	-	-	-
12.	7935/09	55	BPH	TURP	cystic atrophy	-	-	-	-	-
13.	8174/09	51	BPH	TURP	complete BCH	-	-	-	-	-
14.	8245/09	65	Carcinoma	TRUS BIOPSY	simple atrophy	-	-	-	-	-
15.	49/10	62	BPH	TURP	partial BCH	-	-	-	-	-
16.	51/10	70	BPH	TURP	cystic atrophy	-	-	-	-	-
17.	88/10	70	BPH	TURP	SAA	continuos	continuous	-	-	-
18.	194/10	60	BPH	TURP	Partial BCH	-	-	-	-	-

S.NO	HPE NO.	AGE	CLINICAL DIAGNOSIS	SPECIMEN TYPE	HPE DIAGNOSIS	IHC				
						HMWCK STAINING PATTERN	CK 5/6 STAINING PATTERN	VIMENTIN	CD 68	PSA
19.	550/10	81	Carcinoma	TRUCUT BIOPSY	simple atrophy	-	-	-	-	-
20.	631/10	50	BPH	TURP	partial BCH	-	-	-	-	-
21.	835/10	75	BPH	TURP	partial BCH	-	-	-	-	-
22.	998/10	60	Carcinoma	TURP	simple atrophy	-	-	-	-	-
23.	1044/10	65	Carcinoma	TURP	simple atrophy	-	-	-	-	-
24.	1052/10	45	BPH	TURP	cystic atrophy	-	-	-	-	-
25.	1218/10	84	Carcinoma	TRUCUT BIOPSY	PIN	discontinuous	discontinuous	-	-	positive
26.	1334/10	56	BPH	TURP	simple atrophy	-	-	-	-	-
27.	1575/10	65	BPH	TURP	PIN	continuous	continuous	-	-	positive
28.	1794/10	74	BPH	TRUCUT BIOPSY	partial BCH					
29.	1841/10	70	Carcinoma	TRUCUT BIOPSY	simple atrophy	-	-	-	-	-
30.	2447/10	60	BPH	TURP	partial BCH	-	-	-	-	-
31.	2528/10	**70**	BPH	TURP	Cystic atrophy	-	-	-	-	-
32.	2630/10	73	BPH	TURP	CCCH	continuous	continuous			
33.	3043/10	63	BPH	TURP	atypical BCH	continuous	continuous	-	-	-
34.	3043/10	63	BPH	TURP	XGP	continuous	continuous	positive	negative	negative
35.	3117/10	64	Carcinoma	TRUCUT BIOPSY	atypical BCH	continuous	continuous	-	-	-
36.	3117/10	64	Carcinoma	TRUCUT BIOPSY	ASAP	discontinuous	discontinuous	-	-	positive

S.NO	HPE NO.	AGE	CLINICAL DIAGNOSIS	SPECIMEN TYPE	HPE DIAGNOSIS	IHC				
						HMWCK STAINING PATTERN	CK 5/6 STAINING PATTERN	VIMENTIN	CD 68	PSA
37.	3164/10	61	BPH	TURP	ASAP	discontinuous	discontinuous	-	-	positive
38.	3340/10	65	BPH	TURP	SAA	continuous	continuous	-	-	positive
39.	3350/10	58	BPH	TURP	partial BCH	continuous	continuous	-	-	-
40.	3477/10	57	BPH	TURP	ASAP	discontinuous	discontinuous	-	-	positive
41.	3526/10	70	BPH	TURP	partial BCH	-	-	-	-	-
42.	3670/10	60	BPH	TURP	Atypical BCH	continuous	continuous	-	--	-
43.	3672/10	70	BPH	TURP	Atypical BCH	continuous	continuous	-	-	-
44.	3862/10	75	BPH	TURP	sclerosing adenosis	continuous	continuous	-	-	-
45.	3757/1o	65	BPH	TURP	SAA	continuous	continuous	-	-	-
46.	3875/10	65	BPH	TURP	PIN	discontinuous	discontinuous	-	-	positive
47.	3969/10	60	BPH	TURP	partial BCH	-	-	-	-	-
48.	4151/10	64	BPH	TURP	Atypical BCH	continuous	continuous	-	-	-
49.	4453/10	67	BPH	TURP	Cribriform BCH	-	-	-	-	-
50.	4537/10	58	Carcinoma	Prostatectomy	cystic atrophy	-	-	-	-	-
51.	4773/10	75	BPH	TURP	stromal CCM	continuous	continuous	positive	negative	negative
52.	4848/10	70	carcinoma	TURP	partial BCH	-	-	-	-	-

S.NO	HPE NO.	AGE	CLINICAL DIAGNOSIS	SPECIMEN TYPE	HPE DIAGNOSIS	IHC				
						HMWCK STAINING PATTERN	CK 5/6 STAINING PATTERN	VIMENTIN	CD 68	PSA
53.	4851/10	60	BPH	TURP	ASAP	discontinuous	discontinuous	-	-	positive
54.	4877/10	52	BPH	TURP	stromal CCM	continuous	continuous	positive	negative	negative
55.	4881/10	75	BPH	TURP	stromal CCM	continuous	continuous	positive	negative	negative
56.	4951/10	51	BPH	TURP	partial BCH	-	-	-	-	-
57.	4953/10	57	BPH	TURP	partial BCH	-	-	-	-	-
58.	4967/10	65	BPH	TURP	SAA	continuous	continuous	-	-	-
59.	4968/10	62	BPH	TURP	atypical BCH	continuous	continuous	-	-	-
60.	4968/10	62	BPH	TURP	stromal CCM	continuous	continuous	positive	negative	negative
61.	4974/10	70	BPH	TURP	XGP	continuous	continuous	positive	negative	negative
62.	4976/10	65	BPH	TURP	stromal CCM	continuous	continuous	positive	negative	negative
63.	5018/10	60	BPH	TURP	stromal CCM	continuous	continuous	positive	negative	negative
64.	5141/10	65	BPH	TURP	partial BCH	-	-	-	-	-
65.	5142/10	60	BPH	TURP	XGP	continuous	continuous	negative	positive	negative
66.	5346/10	70	BPH	TURP	stromal CCM	continuous	continuous	positive	negative	negative
67.	5346/10	70	BPH	TURP	sclerosing adenosis	continuous	continuous	-	-	-
68.	5539/10	50	Carcinoma	biopsy	partial BCH	-	-	-	-	-
69.	5577/10	70	BPH	TURP	stromal CCM	continuous	continuous	positive	negative	negative

S.NO	HPE NO.	AGE	CLINICAL DIAGNOSIS	SPECIMEN TYPE	HPE DIAGNOSIS	IHC				
						HMWCK STAINING PATTERN	CK 5/6 STAINING PATTERN	VIMENTIN	CD 68	PSA
70.	5626/10	50	BPH	TURP	atypical BCH	continuous	continuous	-	-	-
71.	5669/10	60	BPH	TURP	XGP	continuous	continuous	negative	positive	negative
72.	5669/10	60	BPH	TURP	sclerosing adenosis	continuous	continuous	-	-	-
73.	5672/10	72	BPH	TURP	simple atrophy					
74.	5757/10	70	BPH	TURP	sclerosing adenosis	continuous	continuous	-	-	-
75.	5757/10	70	BPH	TURP	ASAP	discontinuous	discontinuos	-	-	-
76.	5899/10	65	BPH	TURP	ASAP	discontinuous	discontinuous	-	-	positive
77.	5959/10	55	BPH	TURP	atypical BCH	continuous	continuous	-	-	-
78.	5969/10	62	BPH	TURP	complete BCH	-	-	-	-	-
79.	6134/10	72	Carcinoma	TRUCUT BIOPSY	complete BCH					
80.	6722/10	64	Carcinoma	TURP	partial BCH	-	-	-	-	-
81.	6812/10	69	carcinoma	biopsy	SAA	continuous	continuous	-	--	-
82.	6854/10	60	BPH	TURP	PIN	continuous	continuous	-	-	positive
83.	6929/10	80	BPH	TURP	CCCH	continuous	continuous	-	-	-
84.	6931/10	80	BPH	TURP	complete BCH	-	-	-	-	-
85.	7107/10	62	BPH	TURP	complete BCH	-	-	-	-	-

S.NO	HPE NO.	AGE	CLINICAL DIAGNOSIS	SPECIMEN TYPE	HPE DIAGNOSIS	IHC				
						HMWCK STAINING PATTERN	CK 5/6 STAINING PATTERN	VIMENTIN	CD 68	PSA
86.	7464/10	75	BPH	TURP	ASAP	-	-	-	-	-
87.	7647/10	62	BPH	TURP	cystic atrophy	-	-	-	-	-
88.	7717/10	60	BPH	TURP	PIN	discontinuous	discotinuous	-	-	positive
89.	7717/10	60	BPH	TURP	SAA	continuous	continuous	-	-	positive
90.	7717/10	60	BPH	TURP	stromal CCM	continuous	continuous	negative	negative	positive
91.	8157/10	64	BPH	TURP	ASAP	-	-	-	-	-
92.	8469/10	65	carcinoma	trucut biopsy	ASAP	-	-	-	-	
93.	8540/10	66	BPH	TURP	ASAP	discontinuos	discontinuous	-	-	-
94.	8547/10	65	BPH	TURP	partial BCH	-	-	-	-	-
95.	8647/10	65	BPH	TURP	atypical BCH	continuous	continuous	-	-	-
96.	8647/10	65	BPH	TURP	ASAP	discontinuous	discontinuos	-	-	positive
97.	8988/10	60	BPH	TURP	SAA	continuous	continuous	-	-	-
98.	9008/10	83	BPH	TURP	simple atrophy					
99.	9115/10	67	BPH	TURP	ASAP	-	-	-	-	-
100.	9130/10	57	BPH	TURP	partial BCH	-	-	-	-	-
101.	9231/10	45	BPH	TURP	SAA	continuous	continuous	-	-	-
102.	9231/10	45	BPH	TURP	atypical BCH	continuous	continuous	-	-	-

S.NO	HPE NO.	AGE	CLINICAL DIAGNOSIS	SPECIMEN TYPE	HPE DIAGNOSIS	IHC				
						HMWCK STAINING PATTERN	CK 5/6 STAINING PATTERN	VIMENTIN	CD 68	PSA
103.	9231/10	45	BPH	TURP	ASAP	discontinuous	discontinuous	-	-	positive
104.	9232/10	83	BPH	prostatectomy	PIN	continuous	continuous	-	-	positive
105.	9253/10	40	BPH	TURP	complete BCH	-	-	-	-	-
106.	9338/10	57	BPH	TURP	complete BCH	-	-	-	-	-
107.	9505/10	75	BPH	TURP	cystic atrophy	-	-	-	-	-
108.	9507/10	60	Carcinoma	TRUS biopsy	ASAP	discontinuous	discontinuous	-	-	positive
109.	65/11	65	BPH	TURP	partial BCH	-	-	-	-	-
110.	155/11	60	Carcinoma	TURP	SAA	continuous	continuous	-	-	-
111.	273/11	65	Carcinoma	TRUS biopsy	ASAP	discontinuous	discontinuous	-	-	positive
112.	331/11	70	BPH	TURP	stromal CCM	continuous	continuous	positive	negative	negative
113.	382/11	75	Carcinoma	TRUS BIOPSY	ASAP	discontinuous	discontinuous	-	-	positive
114.	392/11	47	BPH	TURP	atypical BCH	continuous	continuous	-	-	-
115.	476/11	67	BPH	TURP	ASAP	discontinuous	discontinuous	-	-	positive
116.	582/11	75	Carcinoma	TRUS biopsy	ASAP	discontinuous	discontinuos	--	-	-
117.	1155/11	62	BPH	TURP	partial BCH	-	-	-	-	-
118.	1409/11	60	BPH	TURP	cystic atrophy	-	-	-	-	-
119.	1566/11	70	BPH	TURP	partial BCH	-	-	-	-	-

S.NO	HPE NO.	AGE	CLINICAL DIAGNOSIS	SPECIMEN TYPE	HPE DIAGNOSIS	IHC				
						HMWCK STAINING PATTERN	CK 5/6 STAINING PATTERN	VIMENTIN	CD 68	PSA
120.	1566/11	70	BPH	TURP	stromal CCM	continuous	continuous	negative	negative	positive
121.	1615/11	72	BPH	TURP	ASAP	continuous	continuous	-	-	negative
122.	1675/11	60	BPH	TURP	stromal CCM	continuous	continuous	positive	positive	negative
123.	1712/11	60	BPH	TURP	partial BCH	-	-	-	-	-
124.	1924/11	85	BPH	TURP	simple atrophy	-	-	-	-	-
125.	2104/11	72	BPH	TURP	cyst.atrophy	-	-	-	-	-
126.	2802/11	74	BPH	TURP	partial BCH	-	-	-	-	-
127.	3027/11	68	BPH	TURP	ASAP	discontinuous	discontinuous	-	-	positive
128.	3307/11	66	BPH	TURP	partial BCH	-	-	-	-	-
129.	3463/11	68	carcinoma	biopsy	partial BCH	-	-	-	-	-
130.	3692/11	63	BPH	TURP	SAA	continuous	continuous	-	-	
131.	3692/11	63	BPH	TURP	stromal CCM	continuous	continuous	negative	negative	positive
132.	4061/11	53	BPH	TURP	stromal CCM	continuous	continuous	positive	negative	negative
133.	4061/11	53	BPH	TURP	SAA	continuous	continuous	-	-	-
134.	4298/11	65	Carcinoma	TRUCUT biopsy	ASAP	discontinuous	discontinuous	-	--	positive

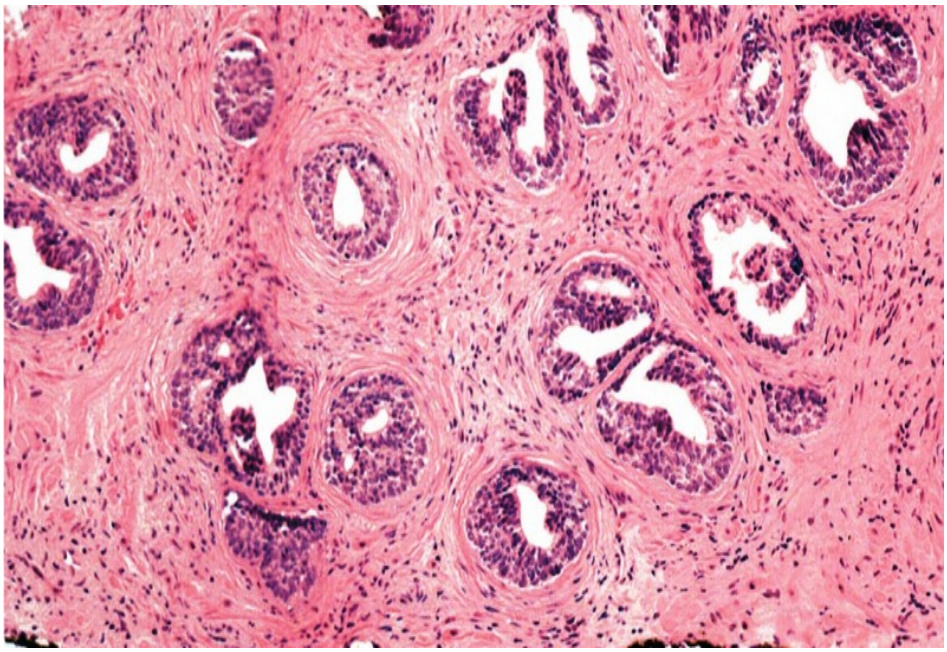

Figure-1 Basal cell hyperplasia (H&E X100x)

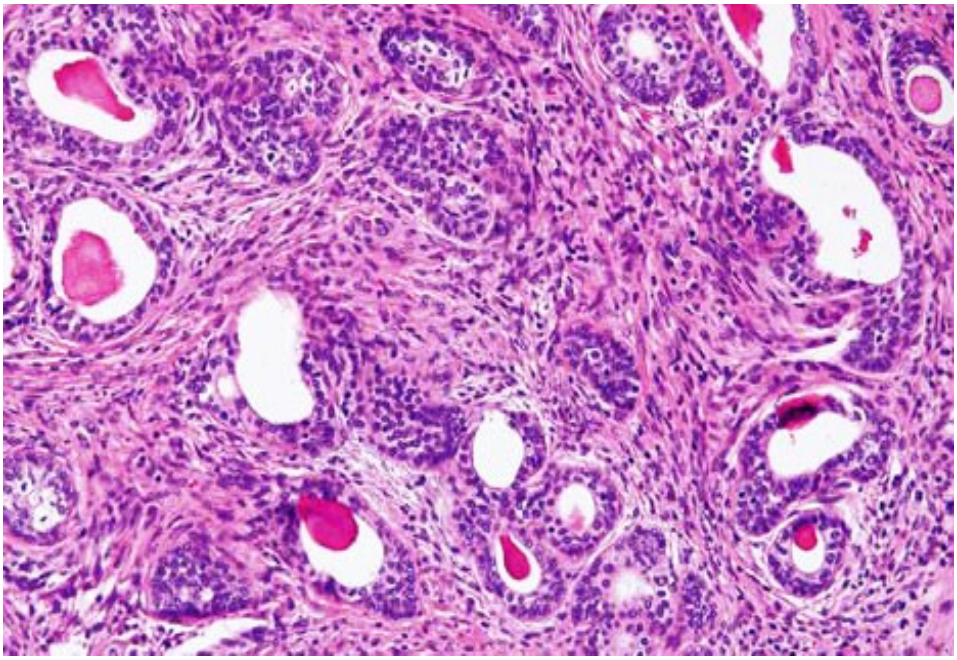

Figure-2 Basal cell hyperplasia (H&EX100x)

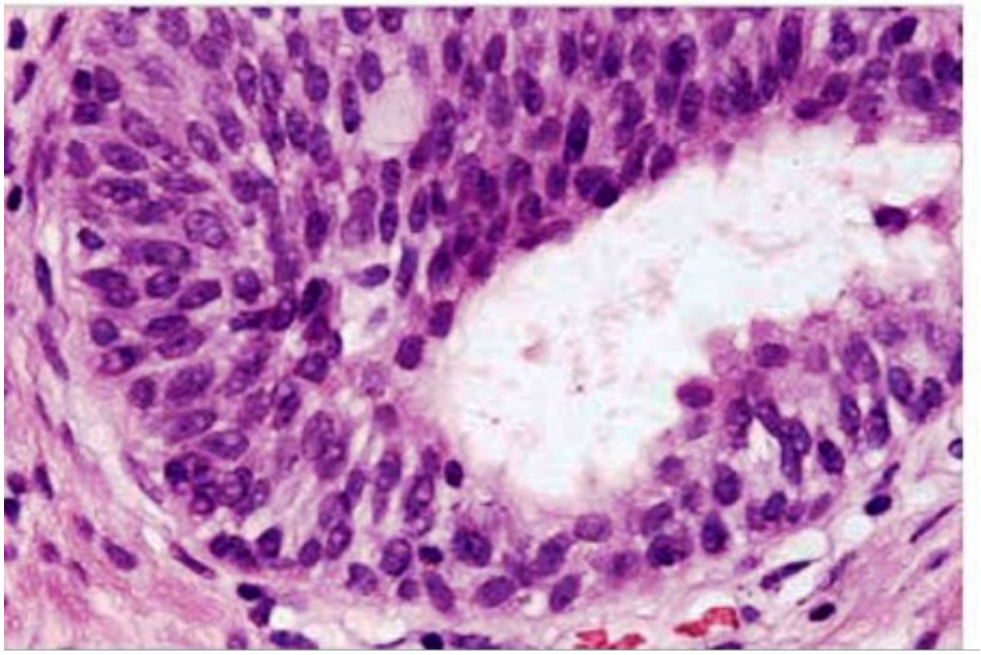

Figure-7. Atypical Basal cell hyperplasia (H&Ex400)

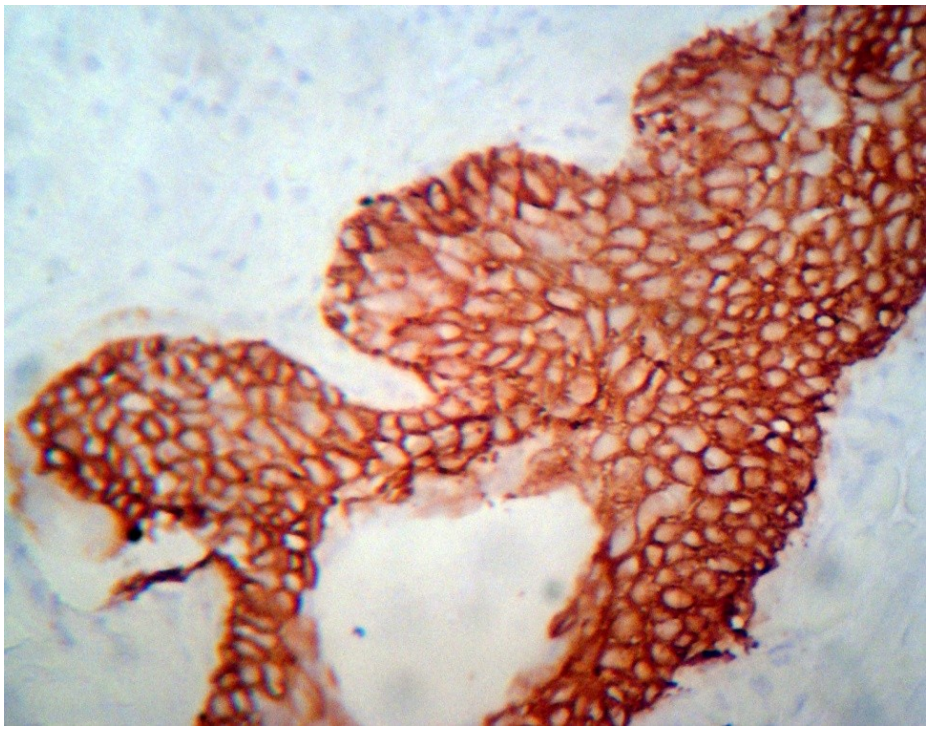

Figure-8. Atypical basal cell hyperplasia-HMWCK stain

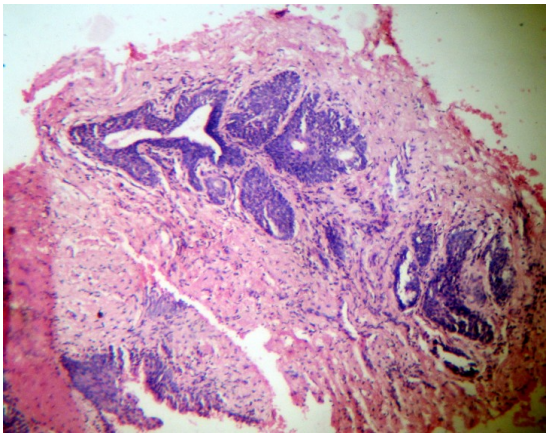

Figure-3 Basal cellhyperplasia (H&Ex100)

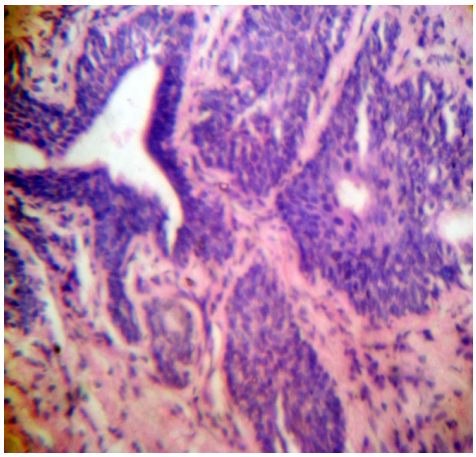

Figure-4 Basal cell hyperplasia (H&Ex400)

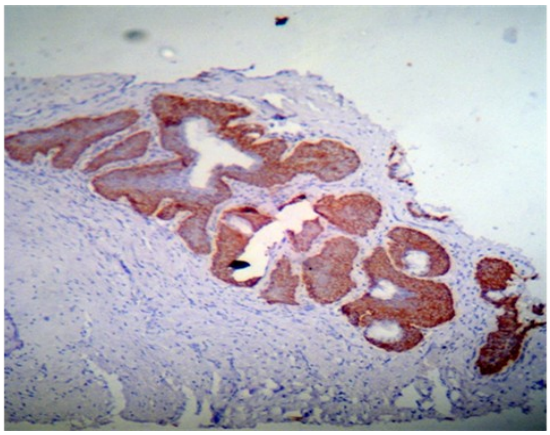

Figure-5: BCH-HMWCK Stain (100x)

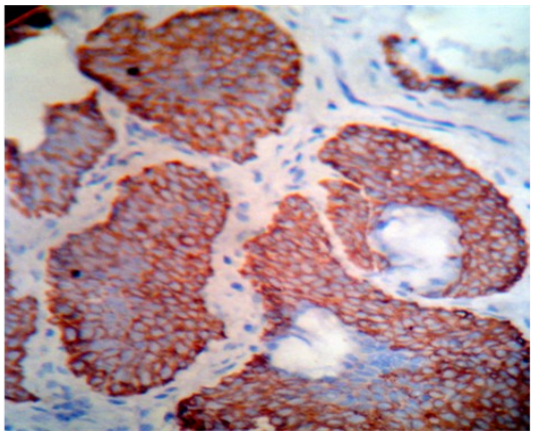

Figure-6 BCH CK5/6 Stain(400x)

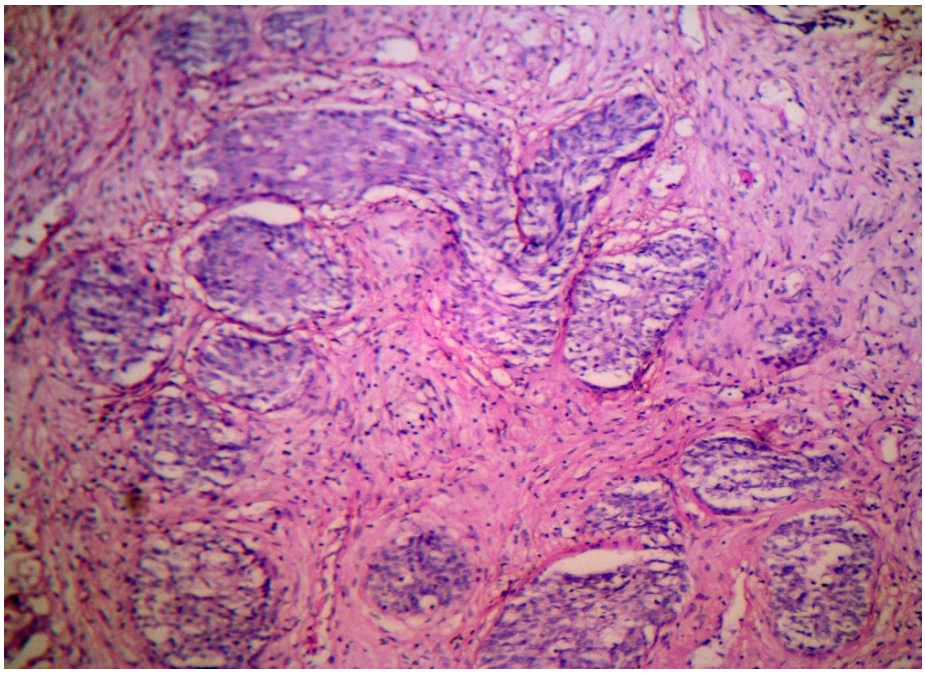

Figure-9 Squamous metaplasia (H&EX100x)

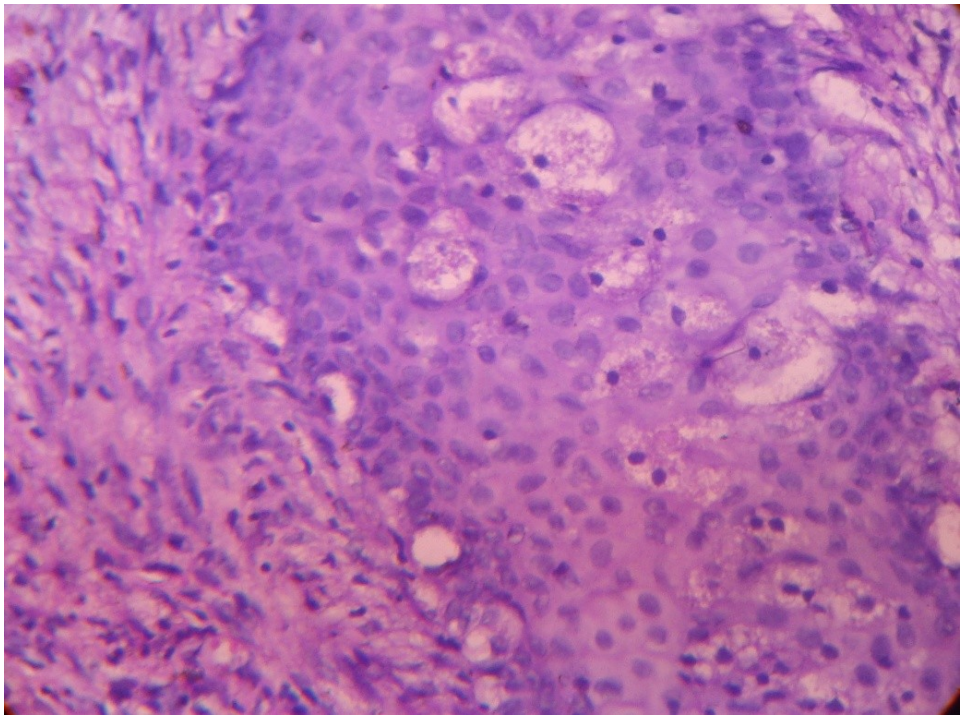

Figure-10 Squamous metaplasia (H&E X400x)

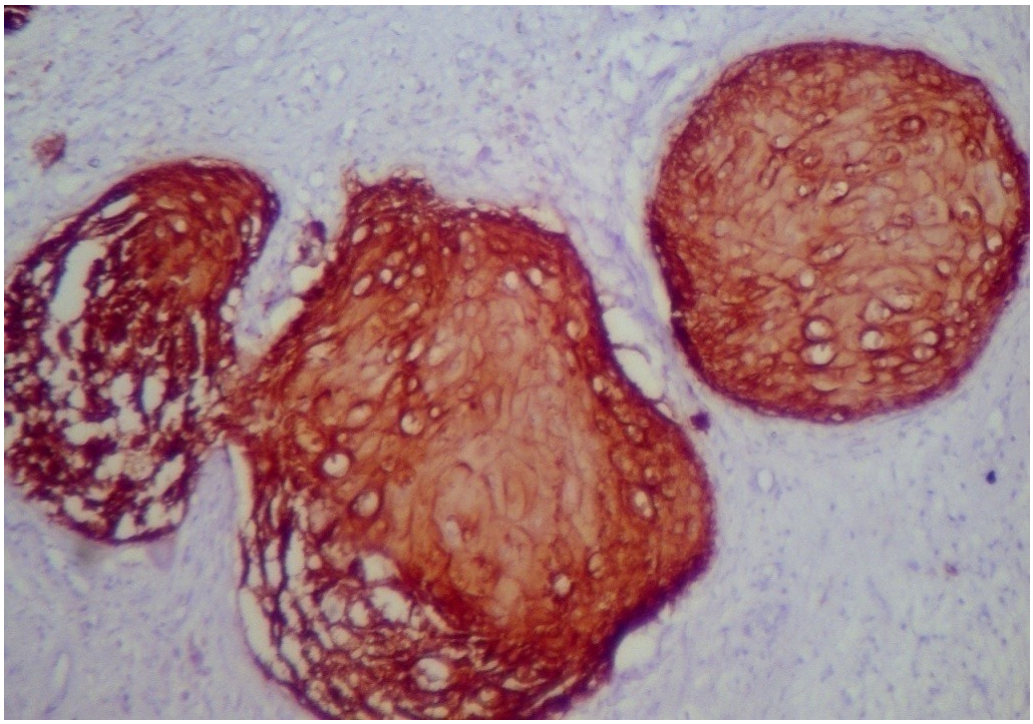

Figure-11 Squamous metaplasia- HMWCK stain

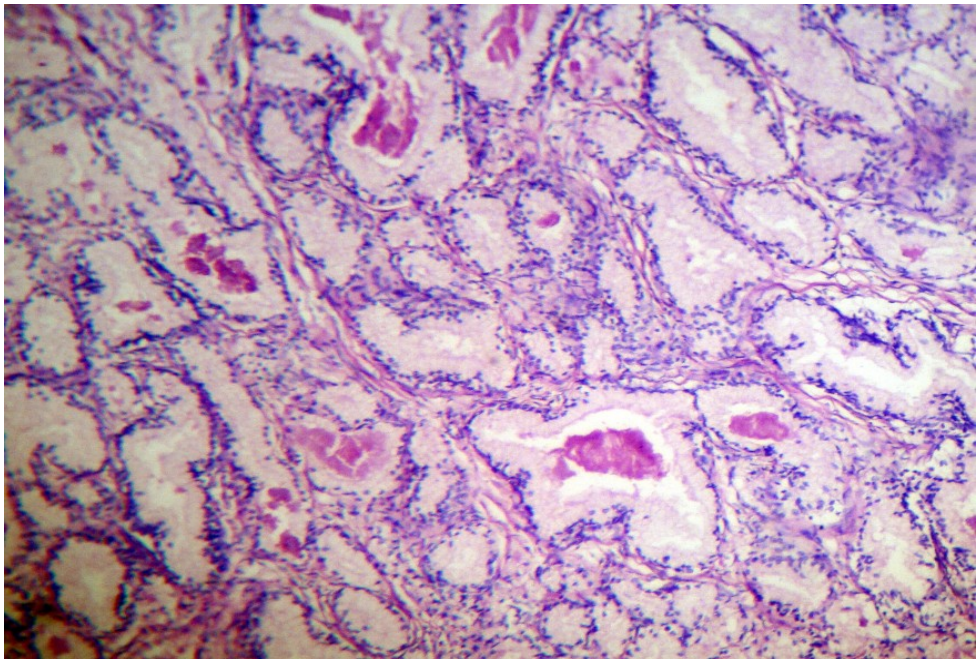

Figure-12 Clear call hyperplasia (H&EX100x)

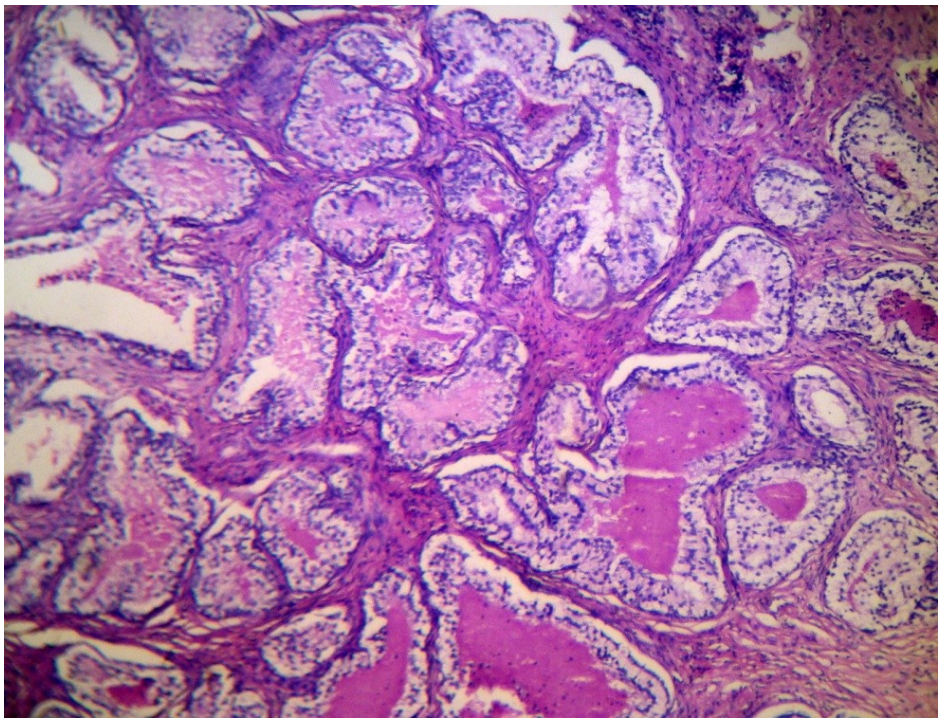

Figure-13 Clear cell hyperplasia (H&Ex100x)

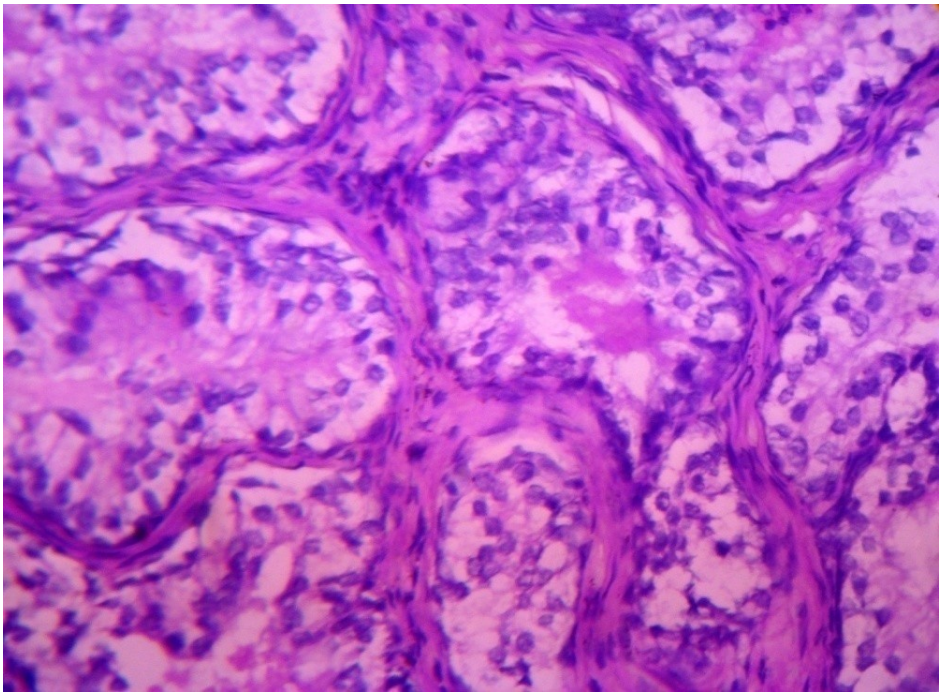

Figure- 14 clear cell cribriform hyperplasia (H&EX400x)

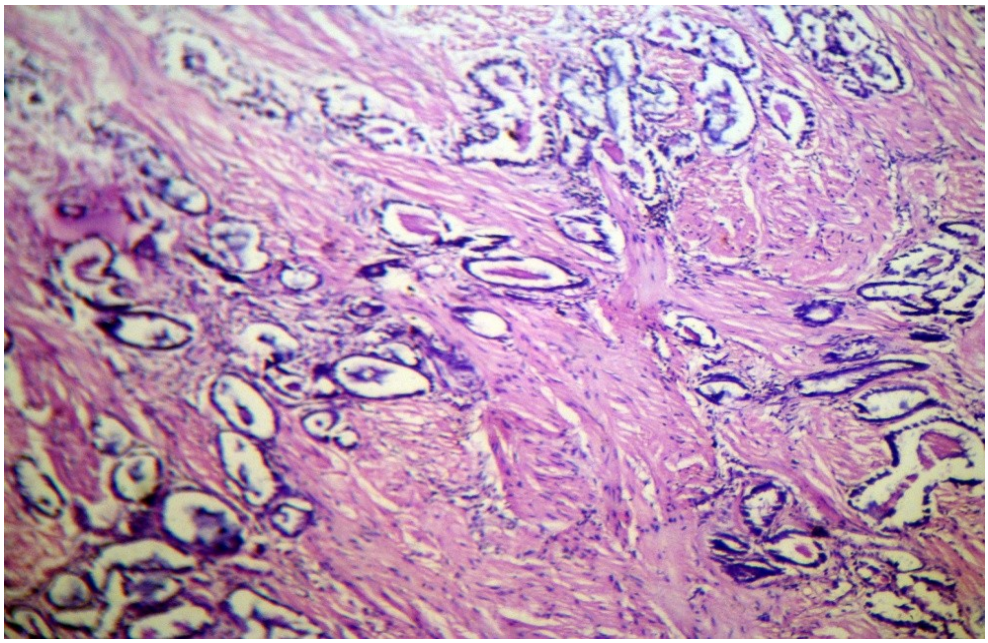

Figure-15 Simple atrophy (H&EX100x)

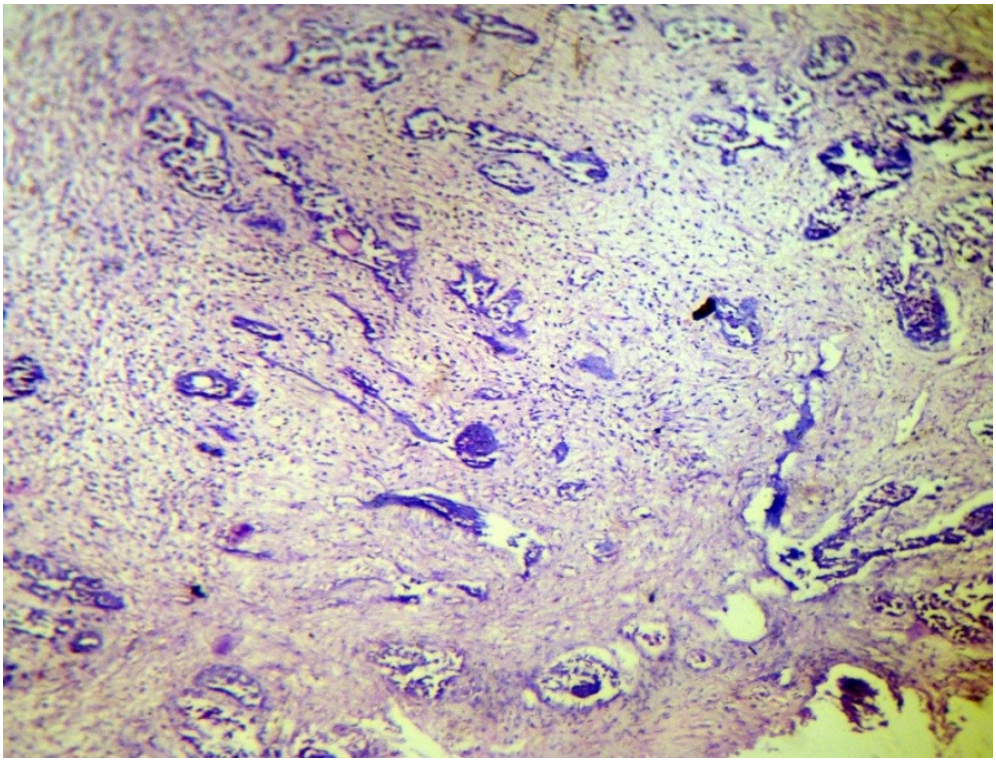

Figure-16: Small acinar atiophy (H&EX100x)

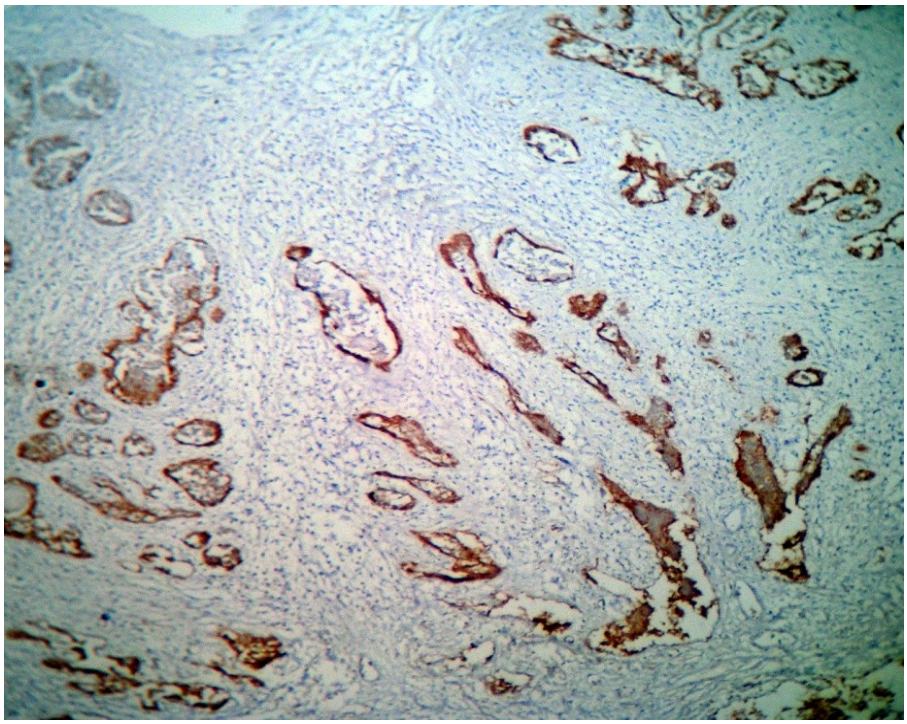

Figure-17 : Small acinar atrophy-HMWCKstain

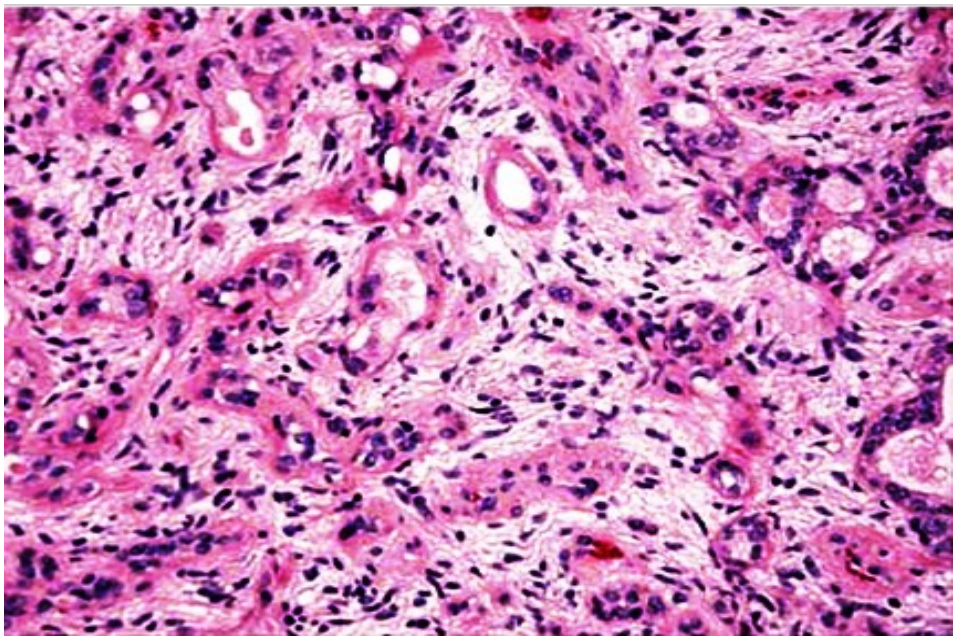

Figure-18 : Sclerosing adenosis (H&EX100x)

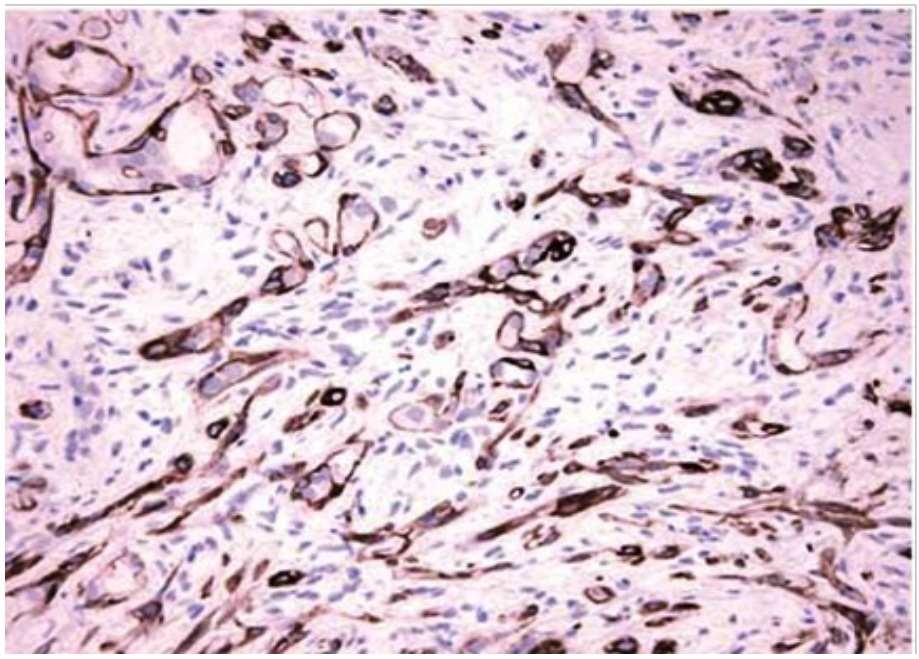

Figure-19: Sclerosing adenosis- HMWCK stain

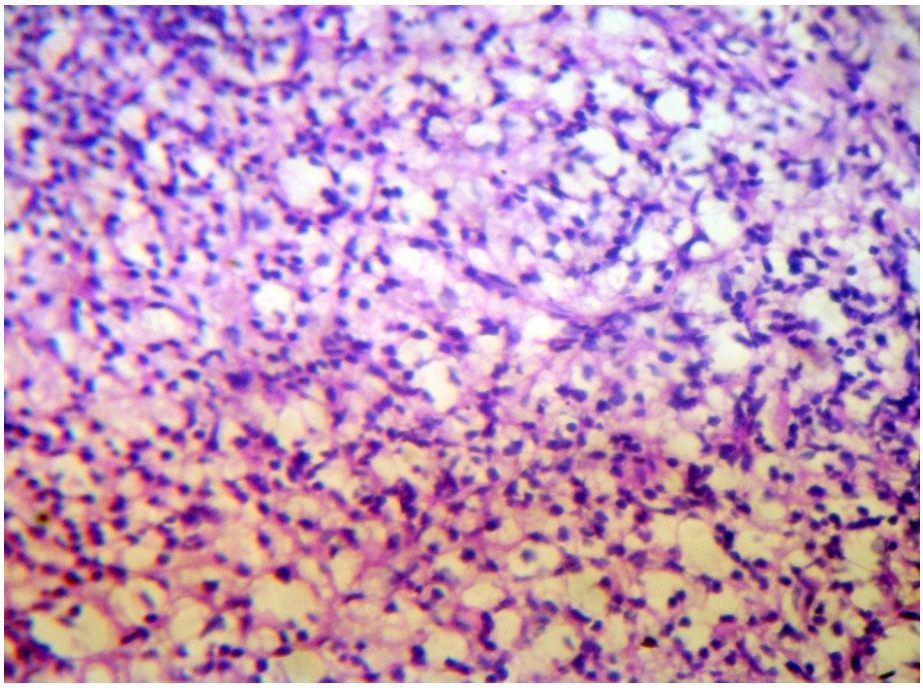

Figure-20: Stromal clear cells (H&E x100x)

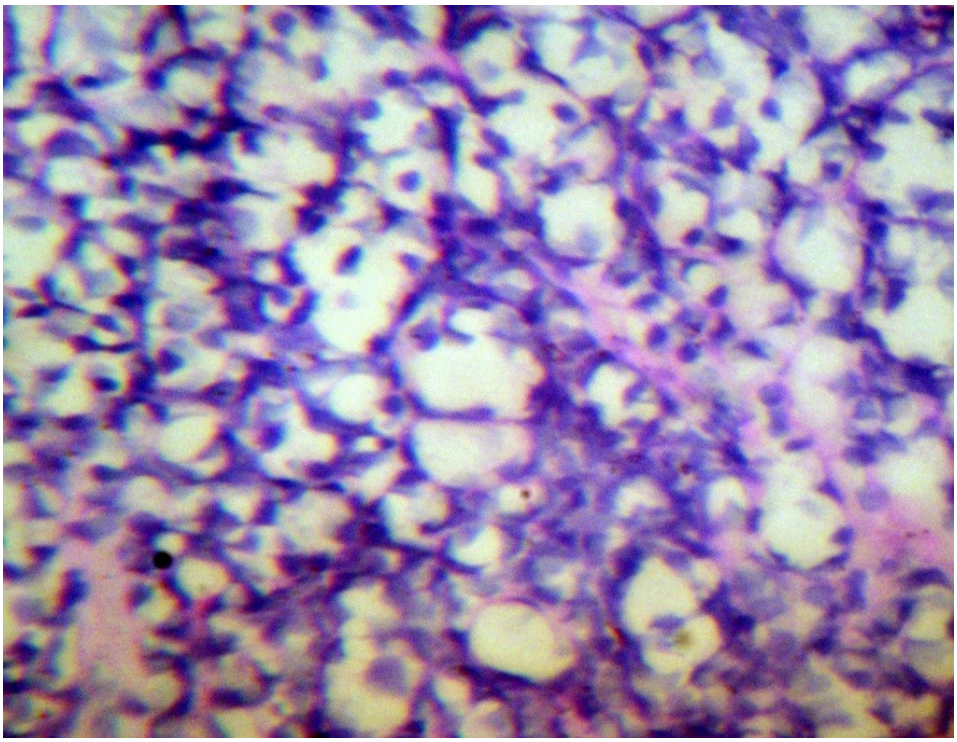

Figure-21: Stromal clear cells (H&EX400x)

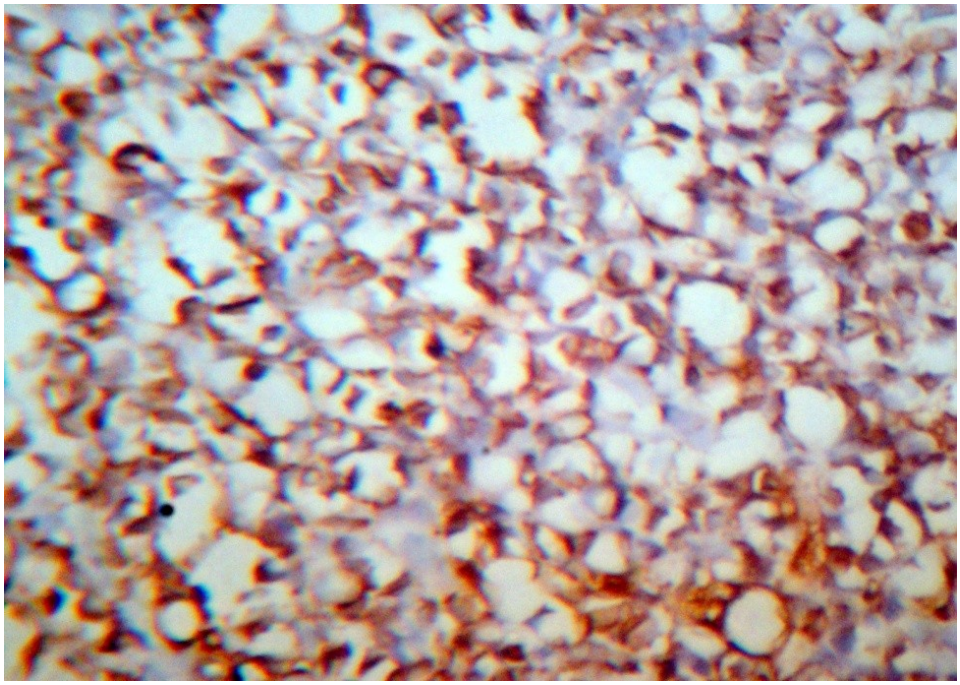

Figure-22: Stromal clear cells –vimentin positive

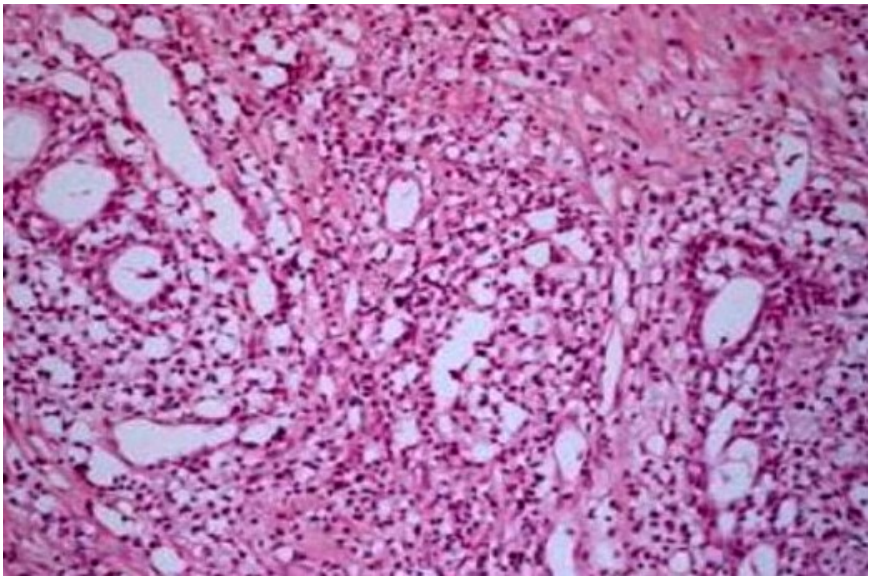

Figure-23.Xanthoma-(H&Ex 100x)

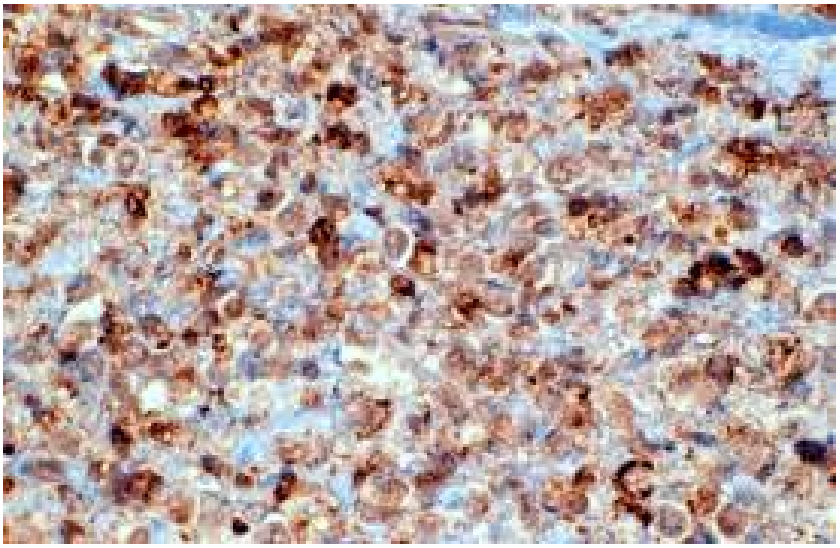

Figure-24. Xanthoma :CD68 stain

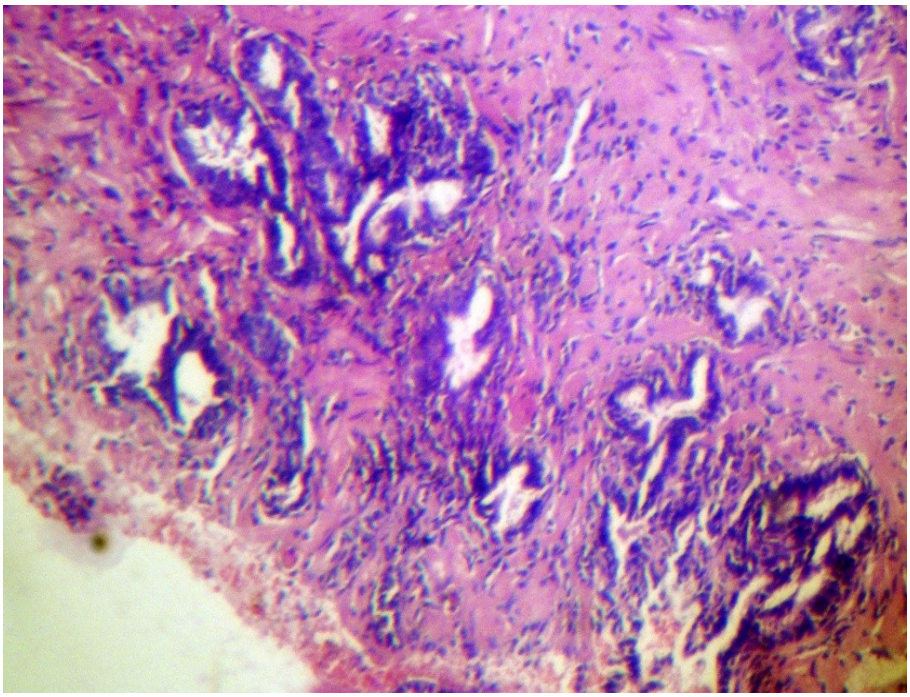

Figure-25: Atypical small acinar proliferation(H&EX100x)

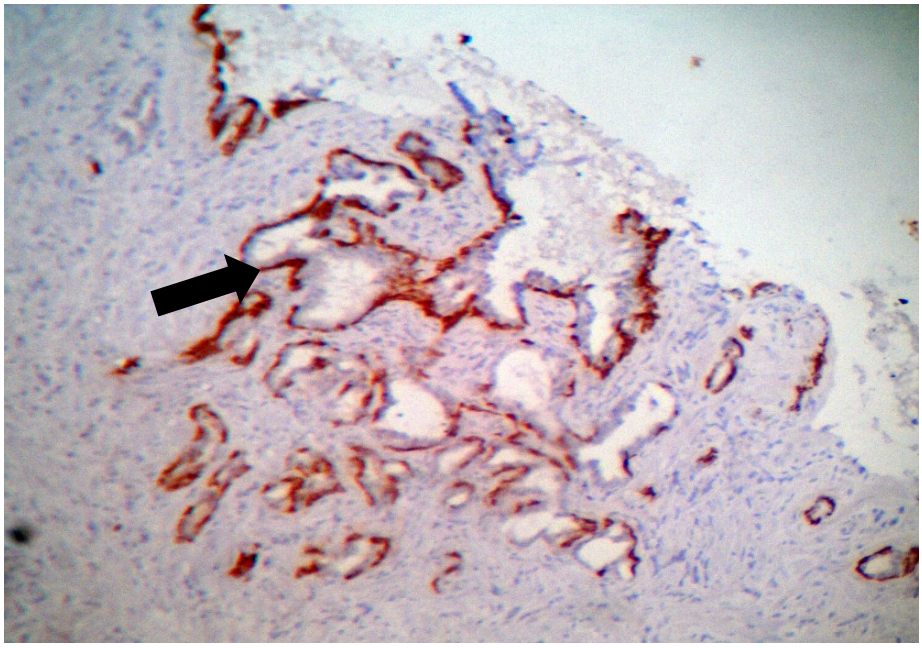

Figure-26: Atypical Small acinar Proliferation

HMWCK stain-Discontinuous lining of basal cell layer

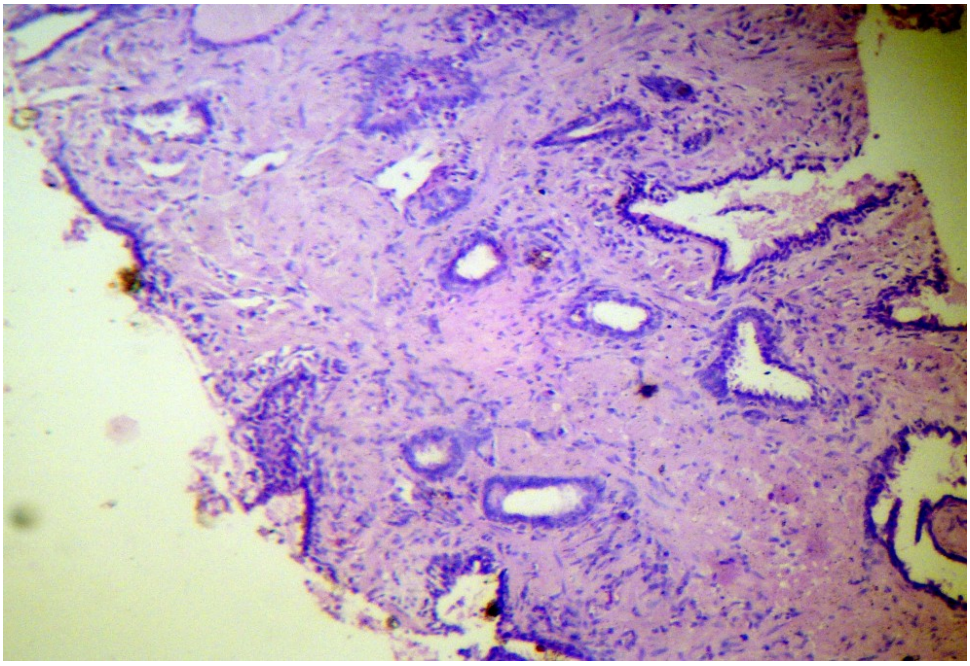

Figure-27. Atypical small acinar proliferation.(H&EX100x)

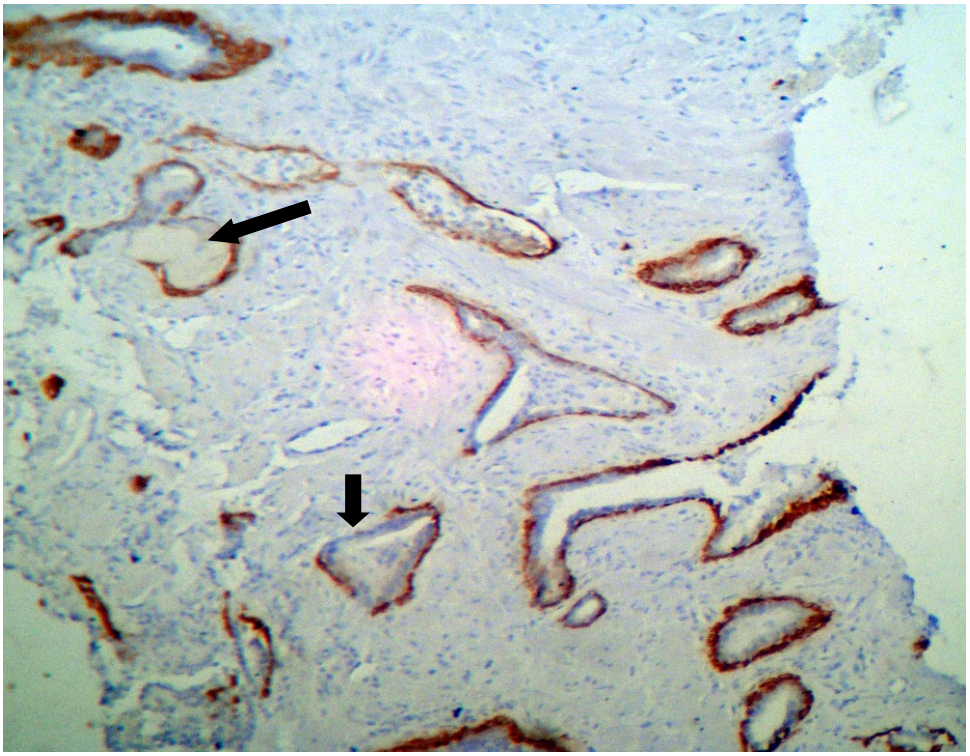

Figure-28. Atypical Small acinar Proliferation

CK 5/6 stain-Discontinuous lining of basal cell layer

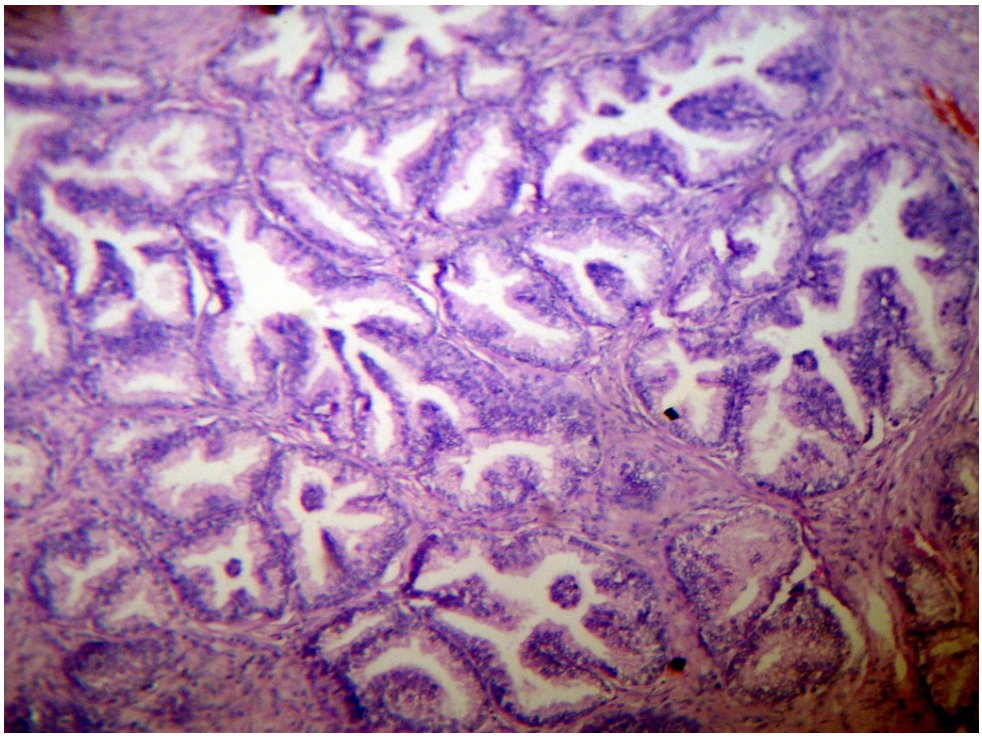

Figure-29 :Prostatic intraepithelial neoplasia –Tufting pattern.

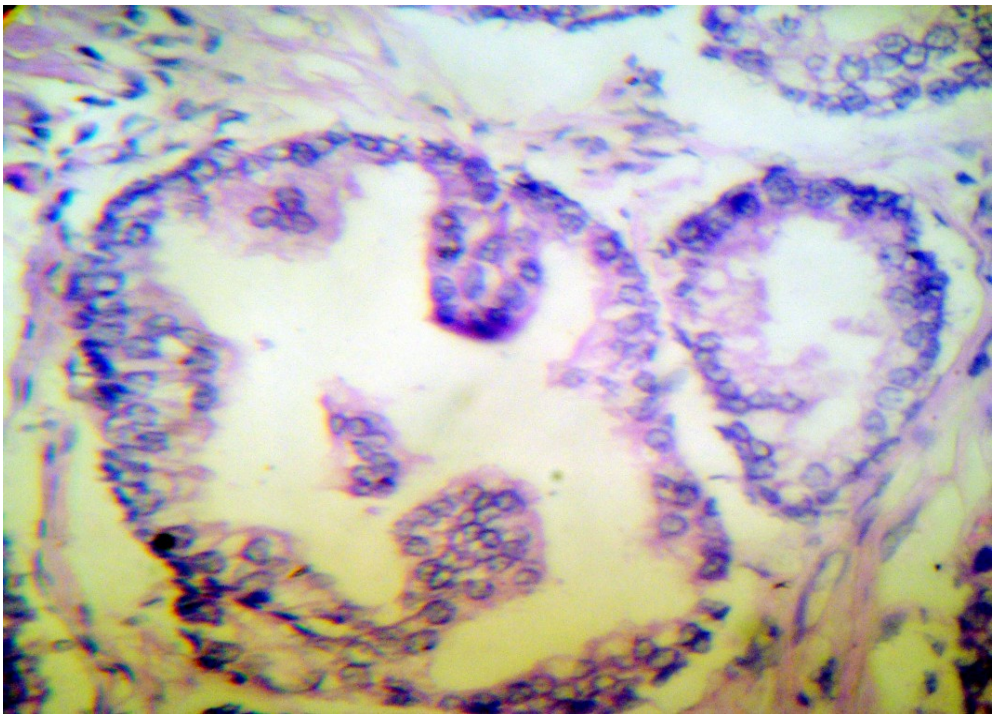

Figure-30 : PIN –Tufting pattern. (H&EX400x

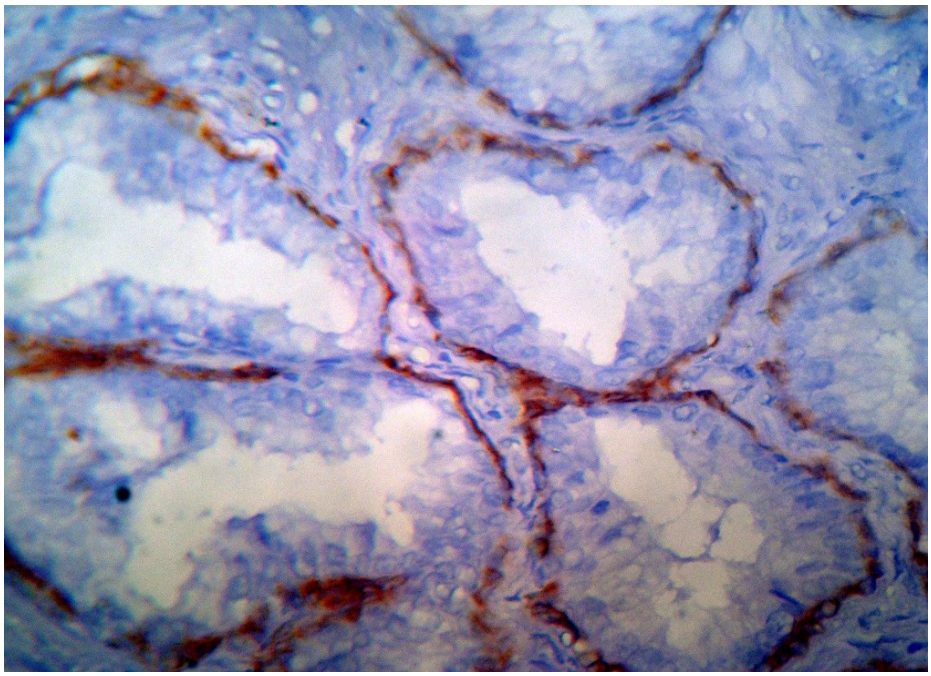

Figure-31: PIN-HMWCK stain,continuous staining of basal cells

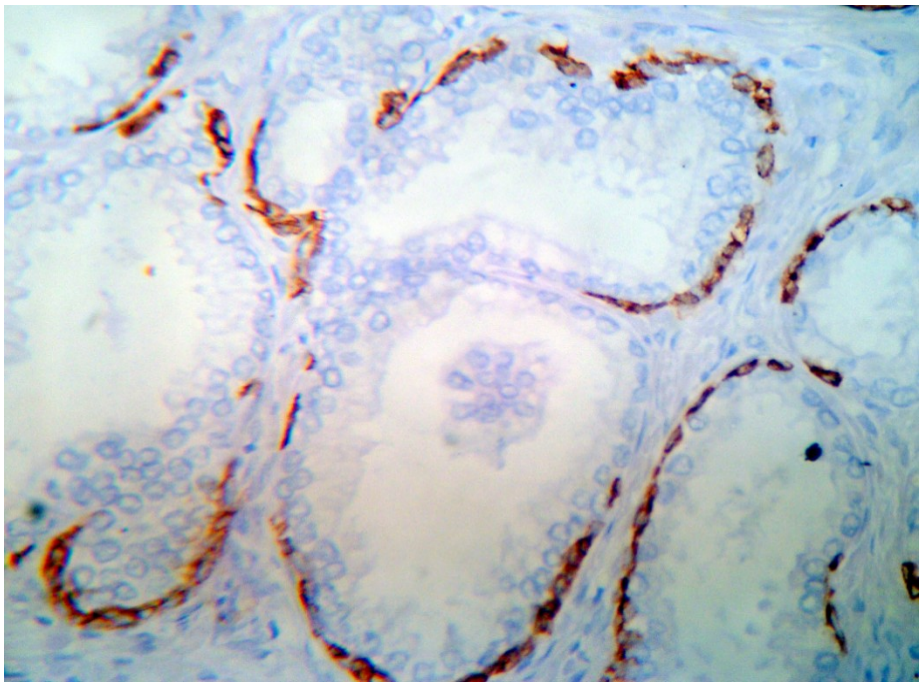

Figure-32: PIN –Discontinuous staining of basal cells (HMWCK)

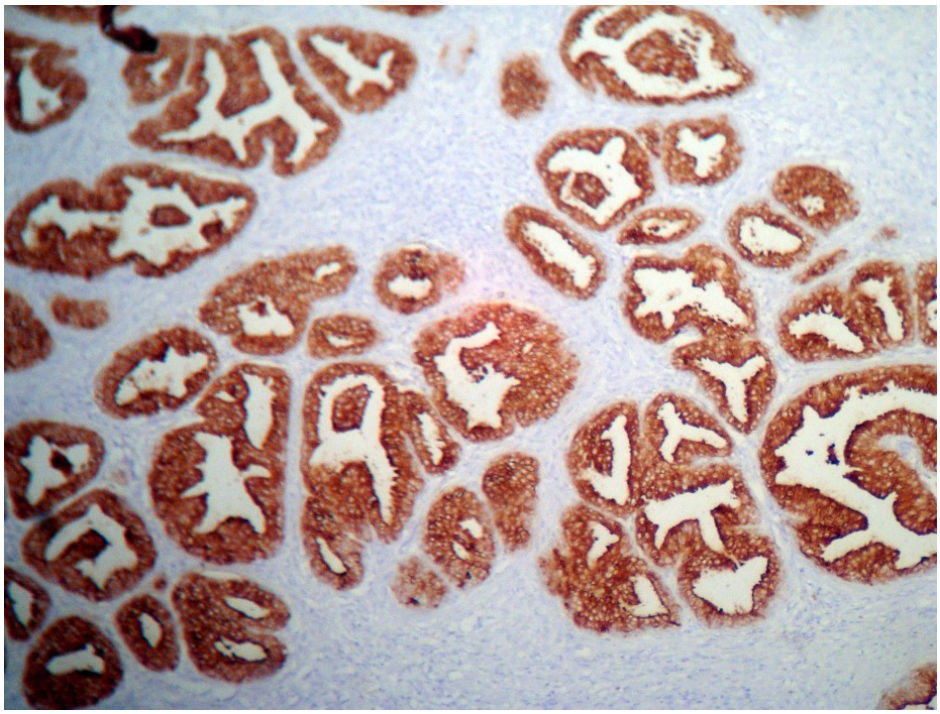

Figure-33: Prostatic intraepithelial neoplasia-PSA stain

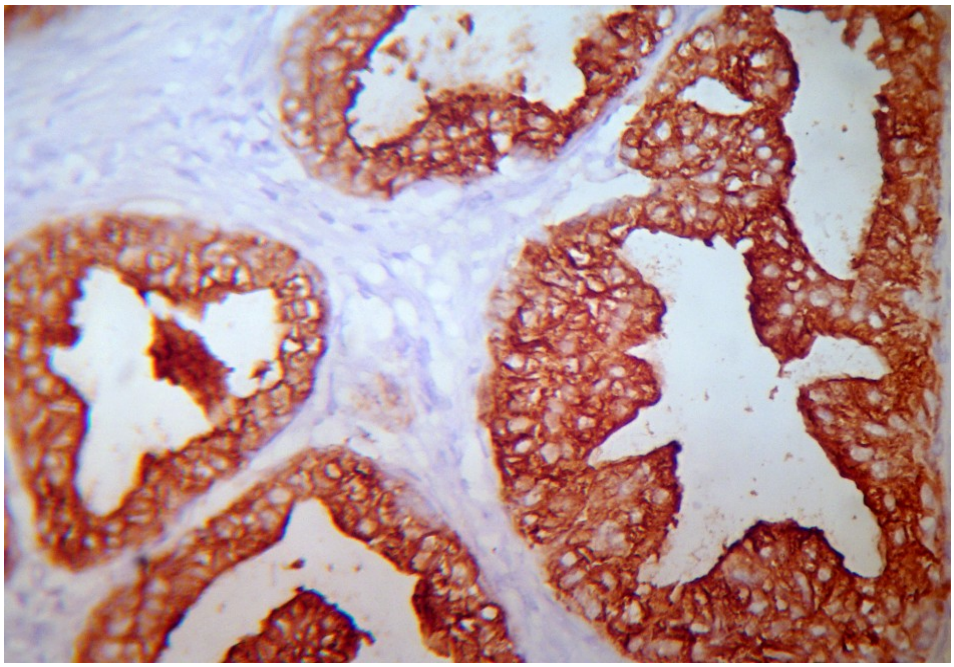

Figure-34 : Prostatic intraepithelial neoplasia-PSA stain(400x)

ABSTRACT

BACKGROUND: Prostatic cancer is the most common cancer in men and is the third leading cause of cancer death in men in USA. Early detection of cancer is very important and PSA serves as a useful tool for screening the patients. The diagnosis is however established by needle biopsy samples and occasionally in TURP and other resected specimens. They are various benign lesions which may mimic adenocarcinoma and they are basal cell hyperplasia, atrophy, adenosis, atypical adenomatous hyperplasia and verumontanum mucosal gland hyperplasia. Also normal structures such as seminal vesicle and ejaculatory ducts may show focal atypia and may be confused with adenocarcinoma. Premalignant lesions such as low grade and high grade PIN also have to be differentiated from adenocarcinoma. They may pose diagnostic dilemmas in small biopsies, so that the application of IHC markers could be of use in distinguishing between non-neoplastic, preneoplastic and neoplastic lesions.

AIMS: To study the histopathological features of mimics of prostatic adenocarcinoma, to differentiate histopathologically between mimics and adenocarcinoma and to define the role of immunohistochemical markers in differential diagnosis of adenocarcinoma and its mimics.

MATERIALS AND METHODS: Clinical data are collected from patients consulted in department of urology and surgery for prostate lesions during the

period of July 2009 to June 2011. The tissues are processed and histological features are studied. Various benign and premalignant mimickers are identified and IHC markers, particularly basal cell markers 34βE12and CK5/6, vimentin, CD68 and PSA are applied in difficult cases to differentiate from malignancy and to identify the origin of clear cells present in the stroma.

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. Premalignant lesions are commonly seen in association with adenocarcinoma. Retention of intact basal cell layer is seen in almost all benign lesions and discontinuous basal layer is observed in 3/6 PIN cases and in 14/16. atypical small acinar proliferation cases. Complete loss of basal cells is observed in 2/16 cases of ASAP. Origin of clear cells are confirmed using IHC markers. Out of 18 cases with clear cells, 13 cases stained positive for vimentin, 3 cases are positive for PSA and 2 cases are positive for CD68.

CONCLUSION: Basal cell layer of prostate gland is retained in most of the benign lesions. It is lost focally in PIN and in ASAP. Immunohistochemical markers are particularly useful in differentiating malignant glands from benign lesions especially for morphologically equivocal glandular proliferations in small biopsy and to identify the origin of clear cells and helps to rule out malignancy especially the clear cell variety.

KEY WORDS: Prostate, Adenocarcinoma, Mimickers, Benign.