Rarity of carcinoma of the prostate in Yemeni patients

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Introduction
Prostate cancer is the most commonly diagnosed non-skin cancer in most Western countries (1) in the USA it is the second leading cause of deaths following lung cancer (2).

In the United States some 180,400 men were diagnosed with prostate cancer in the year 2000 alone, and 31,900 men died from the disease during the same year (3). In fact prostate cancer is the most commonly diagnosed malignancy in the USA (3). In the UK there are 19,000 new cases diagnosed each year and 10,000 deaths (4).

Despite the substantial morbidity and mortality, the etiology of the prostate cancer is unknown. The only established risk factors are age, race and family history of prostate cancer (5).

The most striking epidemiological observation regarding prostate cancer is the very large differences in incidence rate among racial/ethnic groupings despite the current belief that the prevalence of microscopic (latent) prostate tumours in most populations is similar (6). The large disparity in the incidence between (Western and Asian men is striking (about 40 folds); this observation remains one of the most intriguing etiologic clues for prostate cancer (5).

Patients and Material
In a quick review of 360 cases of prostatomegaly presentations admitted to Al Gamhoriah Teaching Hospital, in Aden, Yemen, from 1995 - 1997, Adenomyectomy and histo-pathological examination was carried out for all of them.

Results:
Between 1995 -1997, 360 new cases of prostatomegaly were operated in the urology unit at Al -Ghamhoriah Teaching Hospital. Only 9 cases of prostatic biopsies were diagnosed as Adenocarcinoma of the prostate at the age of 60-70 years and 20 cases of squamous cell carcinoma in the same age group. The remaining cases were benign prostatic hyperplasia (BPH).

Pathology of BPH
Benign enlargement of the prostate (benign prostatic hyperplasia (BPH), nodular hyperplasia or adenofibromyomatous hyperplasia (AFH) consists of overgrowth of the epithelium and fibro-muscular tissue of the transition zone and periurethral area. Lower urinary tract symptoms (LUTS) are caused by interference with muscular sphincteric function and obstruction of urine flow through the prostatic urethra. There is a positive but weak correlation between the amount of hyperplastic tissue and clinical symptoms.

The normal adult prostate contains about 50% stroma, 30% acinar lumens and 20% epithelium, according to morphometric studies. Development of BPH includes three pathological stages- nodule formation, diffuse enlargement of the transition zone and periurethral tissue, and enlargement of nodules. In men under 70 years of age, diffuse enlargement predominates, probably as the result of androgenic and other hormonal stimulation.
BPH usually involves the transition zone, but occasionally nodules arise from the periurethral tissue at the bladder neck. Protrusion of bladder neck nodules into the bladder lumen is referred to as median lobe hyperplasia. Rarely, hyperplastic nodules are present in the peripheral zone. Microscopically, BPH is invariably nodular, composed of varying proportions of epithelium, fibrous connective tissue and smooth muscle. There are five types of nodules, including adenomyofibromatous (most common), fibromuscular, muscular (uncommon), fibroadenomatous and stromal. In practice, pathologists do not subclassify BPH histologically because of the wide variation in composition. Common associated findings include chronic inflammation, acinar atrophy and luminal corpora amylacea and microcalculi.

The diagnosis of BPH is often used by pathologists in reporting the findings in needle biopsy specimens when only normal benign peripheral zone tissue is present. The transition zone is infrequently sampled by needle biopsy unless the urologist specifically targets this area or there is massive BPH that compresses the peripheral zone. The presence of at least part of a nodule is required for the diagnosis of BPH. Vascular insufficiency probably accounts for infarction of BPH nodules, seen in up to 20% of resected cases. The center of the nodule undergoes haemorrhagic necrosis, often with reactive changes in the residual epithelium at the periphery, including squamous metaplasia and Transitional Cell Metaplasia. BPH sometimes protrudes from the transition zone into the peripheral zone, creating a palpable abnormality that may be clinically or radiographically mistaken for denocarcinoma. Rarely, fibroadenomatous nodules may originate in the peripheral zone that is spatially distinct from the transition zone. These nodules are present in about 2% of radical prostatectomies with cancer, and are of unknown aetiology. Possible explanations include embryonic reawakening, similar to that proposed for transition zone BPH, parasitic nodules from the transition zone extending into the peripheral zone, and implantation of transition zone extending into the peripheral zone during embryogenesis. There is no apparent relationship between peripheral zone BPH nodules and cancer.

The clinical importance of the ratio of epithelium and stroma is that men with symptomatic BPH have a significantly higher proportion of stroma than men with asymptomatic BPH. It is likely that the predominant component of the BPH nodule determines the response to therapy. Smooth muscle-predominant nodules would respond to alpha-blockers, epithelial nodules to androgen-deprivation therapy (LHRH agonists, steroid antiandrogens and 5 alpha-reductase inhibitors), and fibrous nodule to surgery. There is a wide morphological spectrum of epithelial and stromal hyperplasia. Awareness of these variants is important to avoid misinterpretation as adenocarcinoma.

Atrophy is a common microscopic finding, consisting of small distorted glands with flattened epithelium, hyperchromatic nuclei and stromal fibrosis. At low magnification, atrophy may be confused with Adenocarcinoma owing to the prominent acinar architectural distortion. At high magnification, atrophy usually lacks nuclear and nuclear enlargement, except in cases of Postatrophic Hyperplasia (PAH).

PAH consists of a microscopic lobular cluster of five to 15 small acini with distorted contours reminiscent of atrophy. One or more larger dilated acini are usually present within these small round to oval clusters, and the small acini appear to bud off the dilated acinus, imparting a lobular appearance to the lesion. The small acini are lined by a layer of cuboidal secretory cells with mildly enlarged nuclei with an increased nucleus-to-cytoplasmic ratio when compared with adjacent benign epithelial cells. The nuclei contain finely granular chromatin, and nucleoli are usually small, although mildly enlarged nucleoli are focally present in 39%
of cases. The cytoplasm is often basophilic or finely granular to clear, and luminal apocrine like blebs are present in 33% of cases. Luminal mucin is occasionally present in PAH. Corpora amylacea are present in 75% of cases of PAH but crystalloids are rare, if ever, any.

The basal cell layer is usually present in PAH but often inconspicuous by routine light microscopy. Basal cell hyperplasia is rarely seen in foci of PAH. Stomal changes are always present in PAH, ranging from smooth muscle atrophy to dense sclerosis with compression of acini.

PAB is distinguished from carcinoma by its characteristic lobular architecture, intact or fragmented basal cell layer, inconspicuous or mildly enlarged nucleoli, and adjacent acinar atrophy with stromal fibrosis or smooth muscle atrophy. Low-grade adenocarcinoma is the most important differential diagnostic consideration with PAB. PAB usually has a lobular pattern on low power, similar to Gleason pattern 2 and 3 Adenocarcinoma. Stromal hyperplasia with atypia consists of stromal nodules in the setting of BPH with increased cellularity and nuclear atypia. There are three patterns of benign basal cell hyperplasia: Typical basal cell hyperplasia, Atypical basal cell hyperplasia, and basal cell adenoma. Basal cell hyperplasia consists of a proliferation of basal cells, two or more cells in thickness, at the periphery of prostatic acini. These basal cells are enlarged, ovoid or round, and plump (epitheliod), with large pale ovoid nuclei, finely reticular chromatin and a moderate amount of cytoplasm. Nucleoli are usually inconspicuous except in atypical basal cell hyperplasia. It is rarely associated with atypical adenomatous hyperplasia. Atypical basal cell hyperplasia is identical to basal cell hyperplasia except for the presence of large prominent nucleoli. The nucleoli are round to oval and lightly eosinophilic. There is chronic inflammation in the majority of cases, suggesting that nucleolomegaly is a reflection of reactive atypia. Basal cell adenoma consists of a large round, usually solitary, circumscribed nodule of acini with basal cell hyperplasia in the setting of BPH. These cells are plump, with large nuclei, scant cytoplasm and usually inconspicuous nucleoli, although large prominent nucleoli are rarely observed. Many cells are cuboidal or "epitheloid", particularly near the centre of the cell nests, and some contain clear cytoplasm.. Prominent calcific debris is often present within acinar lumens. Multiple basal cell adenomas are referred to as basal cell adenomatosis. Basal cell adenoma invariably arises in association with BPH, and appears to be variant.

IMMUNOHISTOCHEMICAL FINDINGS

Basal cell hyperplasia (typical and atypical) displays intense cytoplasmic immunoreactivity in virtually all of the cells with high-molecular-weight keratin 34BE 12. Immunoreactivity for prostate-specific antigen (PSA), prostatic acid phosphatase (PAP), chromogranin, S-100 protein, and neuron-specific enolase is present in rare basal cells in the majority of cases. 

ROLE OF BASAL CELLS

Basal cells may act as "reserve" cells that are capable of dividing and replenishing the prostatic epithelium, including the ability to differentiate into other cell types such as secretory cells. Basal cells and secretory cells retain the ability to divide; transition forms have rarely been identified. Basal cells apparently retain the ability to undergo metaplasia, including squamous differentiation in the setting of prostatic infarction and myoepithelial differentiation in the setting of sclerosing adenosis. Epidermal growth factor receptors have been identified in basal cells but not in secretory cells, suggesting that these cells play a part in growth regulation.
ATYPICAL ADENOMATOUS HYPERPLASIA (AAH):
AAH- is a localized proliferation of small acini within the prostate that may be mistaken for carcinoma. AAH varies in incidence from 19.6% (TURP specimens) to 24% (autopsy series in 20-40-year-old men). It can be found throughout the prostate, but is usually present near the apex and in the transition zone and periurethral area. AAH is distinguished from well-differentiated carcinoma by the following:

1) Inconspicuous nucleoli; 2) infrequent crystalloids; 3) fragmented basal cell layer, as seen with basal-cell-specific antikeratin antibodies.

IMMUNOHISTOCHEMISTRY OF AAH:
Immunohistochemistry is often useful in the diagnosis of AAH. The basal cell layer is characteristically discontinuous and fragmented in AAH, but absent in cancer, a feature that can be demonstrated in routine formalin-fixed sections with basal cell-specific antikeratin (high-molecular-weight keratin antibodies 34BE12).

Sclerosing adenosis
Sclerosing adenosis of the prostate, originally described as adenomatoid or pseudoadenomatoid tumour, consists of a benign circumscribed proliferation of small acini set in a dense spindle cell stroma. Sclerosing adenosis can be distinguished from adenocarcinoma by the following: its distinctive fibroelastic stroma, which is rarely seen in carcinoma; benign cytology, with epithelial cells and stromal cells that lack the prominent nucleomegaly and nucleolomegaly usually seen in prostatic carcinoma; hyalinized periacinar stroma, occasionally seen in sclerosing adenosis; intact basal cell layer; frequent association with BPH; and nophenotype of\u2013protein and actin immunoreactivity.

Table 1 The relative frequency of different pathological types of prostate lesions:

<table>
<thead>
<tr>
<th>Type</th>
<th>No</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>BPH</td>
<td>331</td>
<td>91.9</td>
</tr>
<tr>
<td>Adeno Ca</td>
<td>9</td>
<td>2.5</td>
</tr>
<tr>
<td>Sq.Cell Ca</td>
<td>20</td>
<td>5.6</td>
</tr>
<tr>
<td>Total</td>
<td>360</td>
<td>100</td>
</tr>
</tbody>
</table>

Table 2 Difference in mean age among different pathological types of prostatic lesions:

<table>
<thead>
<tr>
<th>Type</th>
<th>Mean age</th>
</tr>
</thead>
<tbody>
<tr>
<td>BPH</td>
<td>45-59</td>
</tr>
<tr>
<td>Adeno Ca</td>
<td>60-70</td>
</tr>
<tr>
<td>SQCCa</td>
<td>6070</td>
</tr>
</tbody>
</table>

Discussions:
Depending on the exposure and its effect on particular stage of the prostate Cancer, natural history, some changes in exposures in population may result in a rapid change in incidence while the effect of exposures may take long time to become evident. There is a large variation in prostate cancer incidence rate between racial\'ethnic groups in the United States. It is highest among African Americans, intermediate among Caucasian-Americans and Hispanic-Americans, and lowest among Asian - Americans. These epidemiological data provide support for a major genetic component to prostate cancer risk. Androgens play an important role in normal and abnormal prostate development. Both testosterone and dihydrotestosterone, have been shown to induce prostate adenocarcinoma in experimental rats model. The hypothesis that dietary fat increase the risk of prostate cancer grew out of early ecologic studies that shared a positive correlation between prostate cancer mortality and per capita intake of fat, meat and milk in international comparisons. The relation between meat consumption and prostate cancer is inconstant, but there are several possibilities:
1- Red meat is a major source of zinc, which
is essential for testosterone synthesis and may have other deleterious effect on prostate (8).

2- Diet high in meat and other animal products may be relatively deficient in certain anti carcinogenic constituents (8).

3- Meat cooking at high temperature can result in the formation of heterocyclic amines, a potent carcinogen in animals (8). Fruits are unlikely to substantially influence prostate cancer risk, while vegetables and their associated phytochemicals may have anti-prostate cancer properties (9). A subclass of phytochemicals which has estrogen-like activities (phytoestrogen) has received a great deal of attention in recent years; these phytoestrogens may prevent prostate cancer because of a dose dependent reduction in serum 1 7B estradiol and testosterone level (10).

A polyphenolic compound, known as catechine in Green tea and theaflavin and thearubigens which are oxidized and condensed products of catechine in Black tea, have an antioxidant properties and have been shown to inhibit the activities of transcription factor AP-1, NF kB and synthesis of a nitric oxide. All these factors could affect the development of cancer (11). Tea polyphenols have also been demonstrated to inhibit cell transformation, cancer cell growth and related signal transduction pathways as well as induce apoptosis of cancer cell. (11)

Tea consumption is one of the important traditional habits in Yemen, and in certain regions like Hadhramout, people may consume more than 15 cups of tea. The Moderate Alcohol consumption, up to about three drinks per day, does not appear to influence prostate cancer risk; however heavy consumption of about seven to more drinks per day may be associated with an excess risk for this disease. (12)

Religion in Yemen prohibits Alcohol drinking, and more than 70% of the population are non drinkers of alcohol. The relation between smoking and cancer is established but its role in prostate cancer is not clear. Smoking may hasten the course of prostate cancer, such that prostate cancer in smokers follows a more aggressive path than in non smokers. Smoking has been shown to affect the immune system. It is unclear how these changes in immune function play a role in disease onset and progression (13). The role of the prostate cancer with sexual history and particularly, sexually transmitted diseases have been suggested by case control investigation, but these relations are not firmly established. Although it is not possible to entirely rule out the role of human papilloma virus or other known sexually transmitted infection in prostate cancer (14).

The physical activity may play a role in preventing and decreasing the risk of prostate cancer, and this may modulate by decreasing the level of testosterone. Obesity may adversely affect the prostate cancer risk via its influence on insulin like growth factor -I and its binding protein (15). Studies of the incidence and mortality of prostate cancer in various countries suggest that changeable environmental elements are important in its etiology (1). Prostate cancer risk is much lower in the people of southeast Asia compared with Americans (11). Prostate cancer incidence and mortality rate vary widely according to geography and race, with more than 90 fold differences in incidence between highest and lowest (13). The worlds highest prostate cancer incidence is among African American and lowest prostate cancer incidence rate are reported in Asian countries (13). Yemeni people have nearly similar life style like those of other Asian countries, so they have similar low incidence of prostate cancer. Bilharzias is an endemic disease in our country. Urinary bladder, lower end of ureter and seminal vesicles are most commonly affected by the disease because they have rich blood supply (16). The percentage distribution of eggs of S. Haematobium among the endopelvic organs are: 900/0 in urinary bladder ,80% in seminal vesicles and 19% in prostate. Furthermore the intensity of eggs deposition in the tissue bear similar correlation. In quantitative postmortem study, Smith et al noted the mean egg count of 431 3/g of tissue in urinary bladder, 19,929 in seminal vesicle and 8058 in the prostate(16). There was a significant
correlation between eggs burden and the histological severity of tissue reaction (16). In our study 20 cases of prostatic carcinoma were squamous cell carcinoma, representing 60/0 of total adenomyectomy and 69% of prostatic cancer. These are related to bilharzial fibrous prostate.

References
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