Immunohistochemical expression of cyclooxygenaSe-2 (Cox-2) in benign prostatic hyperplasia and prostatic adenocarcinoma

THESIS

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Abstract

The study of oncogenes, tumor suppressor genes and other growth regulatory cellular components have advanced rapidly during the last few years. Markers of these genes and their protein products are already clinically useful for a number of human neoplasmes**,**

diagnosis of prostate cancer is usually readily made on morphological grounds by use of traditional histological parameters, including architecture, nuclear features, and the presence or absence of a basal cell layer. However, in morphologically equivocal cases the histopathologist may have to resort to the use of immunohistochemistry to resolve the differential diagnosis.

Key Words :

Prostatic adenocarcinoma - Immunohistochemical expression of cyclooxygenaSe-2 .

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INTRODUCTION

The main three pathologic processes that affect the prostate gland with sufficient frequency are inflammation, benign nodular enlargement and tumours. Of these three, the benign nodular enlargement is by far the most common, followed by prostatic carcinoma ***(Cotran et al., 1999).***

Carcinoma of the prostate is the most common internal malignancy in different parts of the world including the united states and is responsive for 10% of cancer deaths in this population ***(Boring, 1994).*** However, it is not that common in Egypt and Arab World where it is preceded by other common types of cancer ***(Hattab and Nouh, 1998).***

As regards the diagnostic techniques of prostatic carcinoma, two immunocytochemical markers in routinely processed material with polyclonal or monoclonal antisera are used. They are prostate specific antigen (P.S.A) and prostatic acid phosphatase (P.A.P). prostatic carcinoma cells are also positive for low molecular weight keratin, leu7, EMA, CEA and cathepsin D ***(Bovenberg et al., 1993 and Catalona et al., 1998).***

Molecular biological parameters are needed as new tumour markers. The study of oncogenes, tumor suppressor genes and other growth regulatory cellular components have advanced rapidly during the last few years. Markers of these genes and their protein products are already clinically useful for a number of human neoplasmes ***(Bishop, 1991).***

The identification of an enzyme catalyzing fatty oxidation as a rate limiting step in the progress from normal cell growth through hyperplasia or to neoplasia has opened up a whole new field of cancer search ***(Bottone et al., 2004*)**.

Cox-1 and COX-2 are isoforms of an enzyme which catalyze the first stage in the oxidations of arachidonic acid to prostaglandins and other ecosanoids ***(Kawamori et al., 2003).***

Aberrant or increased expression of cyclooxygenase (COX-2) has been implicated in the pathogenesis of many diseases including carcinogenesis ***(Gupta et al., 2000).*** A recent report has indicated a selective COX-2 inhibitor resulted in increased apoptosis and down regulated Bcl-2 exprewsion in androgen sensitive human prosuatic cancer cell ***(Tanji et al., 2000).***

COX-2 has been shown to be overexpressed in several human cancers including prostauik0adeîocarcinoma ***(Lee et al., 2001).***

AIM OF THE WORK

The aim of the present study is to:

- Assess the expression of COX-2 in benign prostatic hyperplasia, PIN and prostatic adenocarcinoma.
- Evaluation of its role in tumor development of the prostate.
- To correlate its expression with the type of the lesion and tumor grade.

A Historical View of Prostate Diseases

The first description of prostate anatomy dated back to 300 B.C. when Herophilus (a physician in the newly founded city of Alexandria) described the prostate as the prostate glandulosae and the prostatae cirsoides. However, the first scientific description of the pathophysiology of prostatic enlargement is attributed to Jean Riolanus in 1649 who pointed out that obstruction causes thickening of bladder wall and difficulty in emptying the bladder. A landmark in understanding the anatomy and pathophysiology of prostate gland was found in the studies of Moragagni in 1769. john Hunter, the famous pathologist, made several important observations in 1786, a chief of which was the effect of castration on the rat prostate both prepubertal and postpubertal. It was not until the 20th century that surgeons began to realize that carcinoma of the prostate (producing symptoms of urinary obstruction indistinguishable from those of benign prostatic hyperplasia) is a far more common problem than previously recognized ***(Lawson, 1993).***

Robinson et al., in (1939),and Gutman et al., in (1936) , made the observation that prostate cancers and men with metastatic prostate cancers had high serum levels of acid phosphatase. Their work was the foundation of the clinical utility of acid phosphatase and prostate-specific antigen (PSA) for the presence of cancer prostate **.**

Huggins and Hodges, in (1941) reported that androgen withdrawal by orchidectomy or by the administration of large doses of estrogen causes prostate cancer to regress and the phosphatase level to normalize in a majority of cases. This was the base for the many new modalities of hormonal manipulations nowadays ***(Lawson, 1993).***

Benign Prostatic Hyperplasia.

Benign prostatic hyperplasia (BPH) is the usual name applied to a common benign disorder of the prostate that, when extensive, results in varying degrees of urinary obstruction, sometimes, requiring surgical intervention. BPH is characterized by hyperplasia of prostatic stromal and epithelial cells resulting in the formation of large, fairly discrete nodules in the periurethral region of the prostate. When sufficiently large, the nodules compress and narrow the urethral canal causing partial or sometimes virtually complete obstruction of the urethra ***(Steers and Zorn, 1995).***

Epidemiology :

The normal adult prostate plateaus at a weight of about 20 grams at age 30 then this weight remains stable until approximately age of 50 when a process of growth is initiated again. Incidence rates show a positive statistical relation between the incidence of BPH and the advance of age. This is demonstrated by the studies of ***Berry et al., (1984)*** who found clinical evidence of BPH in almost 90% of autopsied men at the age of 80 – 90 years. Also ***Glynn et al., (1985)*** found that the incidence of BPH is 59.2/1000 persons at 70-87 age group while ***Arrighi et al., in 1990,*** found that 159/1000 persons at the age of 80-84 years suffer from BPH.

Howeve ***Fay (1983), Watanabe et al., (1984) and Sidney et al., (1991),*** ,studies showed low incidence of BPH in the Asian race than whites and African-American who show similar incidence rate ,however , difference is not statistically significant. In ***1992, Morrison*** found that

Jewish men had an estimated 2.2-2.6 fold higher rate for prostatectomy related to BPH than non-Jewish men.

Barry, (1993),suggested that regular milk consumption and decreased intake of green and yellow vegetables regularly may be associated with BPH. However, this may be explained by the high socioeconomic status among patients in this study **.**

Smoking was thought to be negatively correlated with BPH ***(Morrison, 1978).*** However, failure to demonstrate a dose-response relationship in a case-control study casts doubts on these observation ***(Morrison, 1992).***

Glynn et al., in 1985, found that a lower body mass index was marginally negatively associated with a clinical diagnosis of BPH. Similar results were obtained by ***Sidney et al., in 1991.*** however, both studies pointed out to the fact that lower sensitivity is met with during examination of heavier individuals.

Araki et al., in 1983, found that several factors were marginally (and perhaps coincidentally) associated with BPH. These were first nocturnal emission before age 20, taking longer than 10 minutes to complete one act of sexual intercourse and no history of sexual impotence lasting more than 1 month.

The occurrence of BPH has been positively associated with diabetes and hypertension ***(Bourke and Griffin, 1966 and Roberts, 1966)*** and negatively associated with liver cirrhosis ***(Bennett et al., 1950 and Strumpf and Wilens, 1953***). On the other hand, the evidence of an

inverse relationship between cirrhosis and BPH (particularly epithelial compared to stromal hyperplasia) is relatively strong. This might be due to the hyperestrogenic state in these patients that retard the process of epithelial hyperplasia ***(Frea et al., 1987).***

Pathology of Benign Prostatic Hyperplasia

Grossly:

At autopsy, the average weight of a prostatic gland affected by nodular hyperplasia is 33 gm ± 16 gm. Specimens obtained weigh 100 gm on average, but on rare occasions weights of over 800 gm have been recorded ***(Price et al., 1990).***

Grossly, variously sized nodules with a gray to yellow colour and a granular appearance are seen projecting above the cut surface. A cross section of an entire gland with early involovement clearly shows that nodular hyperplasia usually begins in the "inner" gland, i.e, in the portion around the urethra and specifically where the ejaculatory ducts enter the urethra, which is also referred to as the periurethral or transition zone ***(Oyen et al., 1993).***

In most instances the nodules congregate on both sides of the urethra compressing it into a slit-like orifice resulting in so-called lateral lobe hyperplasia. With increased growth, the periphery of the organ is pushed aside and compressed. In only about 5% a focal lesion of nodular hyperplasia will be found in the peripheral zone of the organ ***(Van de Vorrde et al., 1995).***

When the entire affected prostate is available for pathological examination, the nodules usually are fairly identified. They vary in colour