Cyclo-oxygenase-2(COX-2) expression in renal cell carcinoma:Histopathological and Immunohistochemical study

Thesis

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Submitted By

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ABSTRACT

Renal cell carcinoma accounts for approximately 3% of adult malignancies and 90-95% of neoplasms arising from the kidney. Renal cell carcinoma has a male-to-female preponderance of 1.6:1 and it commonly occurs in the fourth to sixth decades of life, but the disease has been reported in younger people who belong to family clusters **(Sachdeva et el., 2008).**

Cyclooxygenase -2 catalyses the synthesis of prostaglandins from arachidonic acid. There is ample evidence to suggest an important role for COX-2 in cancer formation **(Hashimoto et al., 2003)**.

Retrospective study including retrieval of formalin fixed paraffin embedded tissue sections from archival blocks of thirty cases of renal cell carcinoma were collected from the Department of Pathology-Cairo University and private laboratories in the period from May 2005 up to February 2007.

This thesis consisted of introduction, aim of work, review of literature, material and methods used, results illustrated by images, discussion of results, conclusions, recommendations and list of references, together with a summary in English and another in Arabic.

Immunohistochemical staining of COX-2 (Cyclooxygenase-2) was done using the streptavidin-biotin technique.This work reveals that COX-2 is positive in almost all cases of renal cell carcinoma (29/30) and negative in only one case. An association was found between COX-2 expression and some clinicopathological features, including tumor size, and tumor

grade while there were no relationship between COX-2 expression and age, sex of patient and histological type and stage of tumor.

Key words: COX-2, Renal cell carcinoma.

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INTRODUCTION

Renal cell carcinoma is the most frequently occurring solid lesion within the kidney and comprises different RCC types with specific histopathological and genetic characteristics. There is a 1.5:1predominance of men over women, with peak incidence occurring between 60 and 70 years of age **(Ljungberg et al., 2007).**

Risk factors for renal-cell carcinoma include smoking, obesity, and hypertension, as well as acquired cystic kidney disease associated with end-stage renal disease. The classic presentation of renal-cell carcinoma includes the triad of flank pain, hematuria, and a palpable abdominal mass. Few patients present in this manner. Other common presenting features may be nonspecific, such as fatigue, weight loss, or anemia **(Chow et al., 2000).**

Many renal masses remain asymptomatic and non-palpable until late in the natural course of the disease. More than 50% of RCCs are detected incidentally using non-invasive imaging for the evaluation of a variety of non-specific symptom complexes **(Novick et al., 2002).**

The tissue of origin for renal cell carcinoma is the proximal renal tubular epithelium. Renal cancer occurs in both a sporadic (nonhereditary) and a hereditary form, and both forms are associated with structural alterations of the short arm of chromosome 3 (3p) **(Sachdeva et al., 2008).**

A quarter of the patients present with advanced disease, including locally invasive or metastatic renal-cell carcinoma. Moreover, a third of the patients who undergo resection of localized disease will have a recurrence. Median survival for patients with metastatic disease is about 13 months.

Thus, there is a great need for more effective surgical and medical therapies **(Herbert et al., 2005).**

Cyclooxygenase 2(COX-2) is an inflammation-associated enzyme involved in the pathogenesis of many solid tumors **(Ladetto et al., 2005).**

Elevated tumor (COX-2) expression is associated with increased angiogenesis, tumor invasion and promotion of tumor cell resistance to apoptosis **(Krysan et al., 2003).**

COX-2 is a key enzyme in the production of prostaglandins and thromboxanes from free arachidonic acid. Increasing evidence suggests that COX-2 plays a role in tumorigenesis. COX-2 is over-expressed in many tumors, including non-small cell lung cancer (NSCLC) ,adenocarcinoma of colon and renal cell carcinoma **(Liu et al., 2007).**

In human RCC tissues the levels of COX-2 expression were correlated with tumour grade and pathological stage. Expression of COX-2 was higher in the granular cell subtype than in the clear cell subtype of RCC. Immunoelectron microscopy revealed that COX-2 was expressed in the nuclear membrane, rough endoplasmic reticulum, Golgi complex and mitochondrial membrane of RCC cells. COX-2 overexpression within these intracellular organelles in RCC may be associated with renal cell carcinogenesis and COX-2 may be a useful biomarker in RCC **(Hashimoto et al., 2003).**

AIM OF THE WORK

To assess COX-2 expression in renal cell carcinoma and its relation to various clinicopathological features.

RENAL CELL CARCINOMA

Epidemiology of renal cell carcinoma

Clinically, the most common renal neoplasm is renal cell carcinoma. For nearly a century some thought that it was derived from adrenal rests, and the name hypernephroma still persists. Another frequently seen synonym is renal adenocarcinoma **(Herbert et al., 2005).**

Renal cell carcinoma was regarded as a single entity with a wide variety of gross and histologic appearances and a highly variable clinical course. Renal cell carcinoma is recognized as a family of cancers derived from the epithelium of the renal tubules, but has distinct morphological features resulting from different genetic abnormalities **(Ljungberg et al., 2007).**

In renal cell carcinoma the male-to-female ratios range between 1.5:1 and 2:1, and the average age at diagnosis is 60-64 years. However, 7% of sporadic renal cell carcinoma is diagnosed in patients younger than 40 years, and rare cases have been reported in patients aged 14-18 years **(Cohen et al., 2009).**

Some reports have been made of familial clustering of renal cell carcinoma outside recognized hereditary syndromes such as von Hippel-Lindau disease, but it is not clear whether these represent hereditary renal cell carcinoma, shared exposure to carcinogens, or coincidence **(Levinson et al., 1990).**

Etiology and Pathogenesis

A number of environmental and genetic factors have been studied as possible causes for renal cell carcinoma.

- Smoking is a major risk factor, accounting for as much as 30% of renal cell carcinoma **(La Vecchia et al., 1990).**
- Obesity, especially in women, is also important and up to 25% of the cases are attributed to this risk factor **(Maclure & Willell, 1990).**
- Long-term phenacetin and acetaminophen use and exposure to cadmium and petroleum products **(McLaughlin et al., 1985).**
- Industrial chemicals are also risk factors. The excess risk from exposure to gasoline is highest after a latent period of about 30 years **(Partanen et al., 1991).**
- Kidney stones are also risk factor **(Maclure and Willett., 1990).**
- Hypertension may be associated with increased incidence of renal cell carcinoma **(Lipworth et al., 2006).**
- There is an increased incidence of acquired cystic disease of the kidney in patients undergoing long-term renal dialysis; this predisposes to renal cell cancer **(Ramon et al.,2004).**
- Von Hippel-Lindau disease (VHL) is an inherited disease associated with renal cell carcinoma **(Sachdeva et el., 2008).**

Further reduction in cigarette smoking, and a decrease in the rates of obesity and hypertension would likely moderate the increasing incidence of renal cell cancer **(Lipworth et al., 2006).**

Clinical Features

Many renal masses remain asymptomatic and non-palpable until late in the natural course of the disease.More than 50% of RCCs are detected incidentally using non-invasive imaging for the evaluation of a variety of non-specific symptom complexes **(Ljungberg et al., 2007**).

Most common presentations are hematuria (40%) ,flank pain (40%) and palpable mass in the flank or abdomen (25%).Other signs and symptoms are weight loss (33%),fever (20%), hypertension (20%), hypercalcemia (5%), night sweats and malaise **(Sachdeva et el., 2008).**

Paraneoplastic syndromes are found in around 30% of patients with symptomatic RCC. The most common of these are: hypertension, cachexia, weight loss, pyrexia, neuromyopathy, amyloidosis, elevated erythrocyte sedimentation rate, anaemia, abnormal liver function, hypercalcaemia and polycythaemia **(Cohen et al., 2009).**

Diagnosis

Plain radiographic findings are nonspecific, and images may demonstrate a large, soft-tissue mass in the renal area with displacement of the fat planes. Renal tumors are most accurately and consistently detected with some type of radiographic procedure. Calcification occurs in 1 to 15 percent of lesions and is usually localized to non-peripheral portions of the mass.