Pathology of bladder cancer in Egypt; a current study.

Thesis

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Abstract

Bladder cancer is one of the most common malignancies in Egypt, however its percentage has been reduced over last years but it's still high representing about 11.7% of cancers in contrast to the percentage found in Europe and USA, where it's about 6.6%.

Pathological types also differ between that found in Egypt and western countries; where in these countries transitional cell carcinoma is considered the most presenting type representing more than 90%. In Egypt, for decades, squamous cell carcinoma was considered the most prevalent type by more than 70%, this was attributed to widespread of bilharziasis which is considered a highly risk factor for squamous cell carcinoma, however this percentage is greatly reduced now after mass treatment of bilharziasis by oral antibilharzial drugs since 1977, which lead to marked decrease of squamous cell carcinoma and increase of transitional cell carcinoma.

Key Words:

Carcinoma in situ - National Cancer Institute.
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List of abbreviations

AJCC : American Joint Committee of Cancer.
Cis  : Carcinoma in situ.
ISUP : International Society of Urological Pathology.
NCI  : National Cancer Institute.
SCC  : Squamous Cell Carcinoma.
TCC  : Transitional Cell Carcinoma.
TNM  : Tumour,Node,Metastasis.
TUR-BT: Transurethral Resection of Bladder Tumour.
UC   : Urothelial carcinoma.
UICC : Union for International Cancer Control.
WHO  : World Health Organization.
Introduction

Bladder carcinoma is the most common malignancy of the urinary tract. It is considered one of the predominant malignancies all over the world. In Europe, in 2006, an estimated 104,400 incident cases of bladder cancer were diagnosed. This represents 6.6% of the total cancers in men and 2.1% in women (Ferlay et al, 2007). In the United States, approximately 71,000 individuals develop bladder cancer each year, and 14,000 die from the disease (Jemal et al, 2010).

In Egypt, bladder cancer incidence is much higher than reported in western countries. The high frequency of bladder cancer was confirmed by early reports of the National Cancer Institute (NCI) registry (1977) in which that tumor contributed 27.6% of all cancers in Egypt (El-Sebai, 1977). In a recent study of the NCI (2007) there is a decline of bladder cancer incidence in Egypt compared to other cancers, reaching about 11.7% (Gouda et al, 2007).

For decades, squamous cell carcinoma was considered the most common pathological type of cancer bladder in Egypt unlike that found in western countries in which transitional cell carcinoma predominates. For example in 1970, squamous cell carcinoma was 76.6% since it arises on top of squamous metaplasia resulting from chronic bilharzial cystitis (El-Bolkainy et al, 1981), but this percentage has changed greatly over the years, so that, in the NCI study in 2007, transitional cell carcinoma predominated over squamous cell carcinoma (65.8% versus 28.4%) (Gouda et al, 2007).
This means that there is a change in the various histopathological patterns of bladder cancer in Egypt to a distribution that is more in line with the rest of the world.
Aim of the work

The aim of our work is to document the pathologic types of bladder carcinoma currently encountered here, the relative frequency of different pathological types of bladder cancer and the changes in the pattern of carcinoma over years, in the form of increase frequency of types and decrease of others.

Bilharzial infection, which is will established in Egypt, will be mentioned in the study according to presence of bilharzial ova in the specimens, with comparison to other studies done before.
Epidemiology of cancer bladder

More than 12 million new cases of cancer occur annually worldwide. Of those 5.4 million occur in developed countries and 6.7 million in developing countries (Ferlay et al, 2004; Garcia et al, 2007).

Bladder cancer is the fourth most common cancer in males after prostate, lung & colorectal cancers accounting for 6.6% of all cancer cases (Ferlay et al, 2007). In women, it is the ninth most common cancer, accounting for 2.4% of all cancers (Ferlay et al, 2007). Approximately over 350,000 new bladder cancer cases occurred worldwide annually (Ferlay et al, 2007). In Europe, in 2006, an estimated 104,400 incident cases of bladder cancer were diagnosed. This represents 6.6% of the total cancers in men and 2.1% in women (Ferlay et al, 2007). In the United States, approximately 71,000 individuals develop bladder cancer each year, and 14,000 die from the disease (Jemal et al, 2010).

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The mean age of bladder cancer cases in Egypt was 56.24 ± 11 (El-Bolkainy et al, 2005). This age is less than reported in the literature for
other parts of the world; Lynch and Cohen (1995) reported that the median ages at diagnosis for urothelial carcinoma is 69 years in males and 71 years in females (Lynch, Cohen, 1995).
Pathology of cancer bladder

Normal Bladder Urothelium

The wall of the bladder consists of four layers (figure 1):

1- Urothelium — The urothelium is the innermost epithelial lining of the bladder. The urothelium is the site of origin for urothelial carcinomas.

2- Lamina propria — The lamina propria is separated from the urothelium by a thin basement membrane that is composed of abundant connective tissue containing vascular and neuronal structures. Fascicles of smooth muscle can be found within the superficial lamina propria, either isolated or forming complete or incomplete muscularis mucosae.

3- Muscularis propria — The muscularis propria (detrusor muscle) surrounds the lamina propria and consists of thick, irregularly arranged muscle bundles. In small biopsies, fascicles of muscle in the lamina propria may be confused with the larger smooth muscle bundles of the muscularis propria, potentially resulting in an error in tumor staging. Adipose tissue also can be present within the lamina propria and/or muscularis propria. The presence of invasive tumor in fat thus is not always indicative of extravesical extension.

4- Advenitia or serosa — The muscularis propria is separated from the surrounding tissues by a serosal layer (Ro et al, 1987; Epestein et al, 1998).
Figure 1: Normal bladder wall.

**Epithelial Hyperplasia and Metaplasia:**

The term *epithelial hyperplasia* is used to describe an increase in the number of cell layers without nuclear or architectural abnormalities.

Urothelial *metaplasia* refers to the bladder lining, often in focal areas, demonstrating a nontransitional epithelial appearance, usually with epidermoid (squamous metaplasia) or glandular (adenomatous metaplasia) development.

*Von Brunn's nests* are islands of benign-appearing urothelium situated in the lamina propria (figure 2).
**Cystitis cystica** (figure 3), is von Brunn's nests in which urothelium in the center of the nest has undergone eosinophilic liquefaction.
Cystitis glandularis (figure 4), is similar to cystitis cystica except that the transitional cells have undergone glandular metaplasia (Mostofi et al, 1973; Epstein et al, 1998).

Urothelial Dysplasia (Preneoplastic Proliferative Abnormalities):

Atypical hyperplasia is similar to epithelial hyperplasia, except that there are also nuclear abnormalities and partial derangement of the umbrella cell layer. The World Health Organization (WHO) and the International Society of Urological Pathology (ISUP) developed a consensus classification of urothelial neoplasms, including flat intraepithelial lesions (Epstein et al, 1998).

The term dysplasia (figure 5), denotes epithelial changes that are intermediate between normal urothelium and carcinoma in situ (severe
dysplasia). Dysplastic cells have large, round, notched, basally situated nuclei that do not exhibit the normal epithelial polarity (Epstein et al, 1998).

![Figure 5: Dysplasia.](image)

**Inverted Papilloma** (figure 6):

An *inverted papilloma* is a benign proliferative lesion associated with chronic inflammation or bladder outlet obstruction. Papillary fronds project into the fibrovascular stroma of the bladder rather than into the bladder lumen. The lesion is usually covered by a thin layer of normal urothelium. Inverted papillomas may contain an area of cystitis cystica or squamous metaplasia.

Mainly, because the overlying epithelium is normal, inverted papillomas appear as small raised nodules rather than as papillary or frondlike tumors on endoscopic inspection (Mostofi et al, 1973; Epstein et al, 1998).
Vesical Leukoplakia:

*Leukoplakia* is characterized by squamous metaplasia with marked keratinization, downward growth of rete pegs (acanthosis), cellular atypia, and dysplasia. It is believed to be a response of the normal urothelium to noxious stimuli and is generally considered a premalignant lesion that may progress to SCC in up to 20% of patients *(Epstein et al, 1998)*.

Pseudosarcoma (Postoperative Spindle Cell Nodule):

*Postoperative spindle cell nodule* is a rare lesion resembling a sarcoma of the bladder. It consists of reactive proliferation of spindle cells occurring several months after a lower urinary tract procedure or infection *(Huang et al, 1990)*.
Carcinoma in Situ

CIS is a flat lesion in which the surface epithelium contains cells that are cytologically malignant. CIS is synonymous with high-grade intraurothelial neoplasia (Mostofi et al, 1973).

De novo (primary) CIS accounts for less than 1 to 3 percent of urothelial neoplasms. Areas of CIS are also identified in 45 to 65 percent of patients with invasive UCs. Patients with primary CIS are typically in their 40s or 50s, and may be asymptomatic or have dysuria, frequency, urgency, or hematuria. Multifocal involvement of the urinary tract with CIS is common and may be synchronous or metachronous. Endoscopically, CIS is characterized by irregularly hyperemic mucosa (figure 7) (Mostofi et al, 1973; Epstein et al, 1998).

Severe cytologic atypia is required to diagnose CIS. The degree of nuclear anaplasia is identical to high-grade papillary UC, although a spectrum of severity may exist. There may be complete loss of polarity, marked crowding, and pleomorphism. The nuclei are enlarged, frequently hyperchromatic, and have coarse or condensed chromatin. Most nuclei in CIS are approximately four to five times the size of adjacent stromal lymphocytes. Large nucleoli may be present. Mitoses are common, may be atypical, and can extend into the upper cell layers. (figure 8)
The neoplastic changes may or may not involve the entire thickness of the epithelial layer. Different cytologic and architectural patterns are recognized in CIS. These include lesions characterized by pleomorphic large