

THE PATHOBIOLOGY OF BILHARZIA-ASSOCIATED BLADDER CANCER

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Summary

Urinary bilharziasis is endemic throughout most of Africa, and the Middle East especially in Egypt. The highest incidence of bilharzia-associated bladder cancer (BABC) comes from Egypt. At the National Cancer Institute (NCI, Cairo), which is a specialized center in this disease the BABC presents with distinctive clinicopathologic features quite different from that reported from Europe and North America. However, time trend analysis showed a change in such pattern. WHO classification is used for its subtyping. The major differences in the clinico-pathologic features observed between the Western type of bladder cancer and the BABC in Egypt may probably reflect underlying alternate tumor biology and carcinogenic pathways. From the pathogenic perspective, TCC occurring in Western industrial nations has been associated with cigarette smoking and exposure to aniline dyes, while bladder cancer in Egypt is associated with chronic bladder infection and schistosoma hematobium infestation. All such factors convey a direct carcinogenic insult to the urothelium, yet through variable mechanisms. BABC showed a special biologic pattern as revealed by different chromosomal alterations as well as genetic profile when compared to the Western pattern of bladder cancer. A proposed sequence of chromosomal aberrations in BABC is described. A high association between human papilloma virus (HPV) and BABC has been reported from Egypt with a possible viral-bilharzial association. HPV was higher in bilharzial cases than non-bilharzial ones. The study also revealed concordance between HPV and p53 of cases.

1. Introduction

Bilharziasis, also known as schistosomiasis, is a parasitic disease that dates back to antiquity. The ancient Egyptians, through settling and cultivating the Nile valley, were among the first to contract the disease. Thus, the main symptom hematuria was mentioned in Egyptian papyri (1500-1800 B.C.), and schistosome eggs were identified in Egyptian mummies through paleopathologic studies. In 1852, Theodor Bilharz, a German pathologist working in Cairo, discovered the worms in the portal circulation and was the first to describe the pathology of the disease. Ferguson in 1911 was the first to report on the high frequency of bladder cancer in Egypt and to suggest an etiologic relation with urinary bilharziasis, a fact which is now generally accepted.

Urinary bilharziasis is endemic throughout most of Africa, the Middle East, Madagascar, Reunion, Mauritius and India. In Africa, a high frequency is reported in countries along river Nile such as Egypt and Sudan, as well as, countries around lake Victoria as Kenya and Uganda. The disease is also prevalent in the west of the continent (Gold Coast and Senegal) and the eastern side of the continent below the Equator (Mozambique, Zambia and New Guinea). In the Middle East, it occurs in Iraq, Iran, Syria, Saudi Arabia and Yemen.

Schistosomiasis tends to reach its highest prevalence and severity where agriculture depends on irrigation such as in Egypt. In this situation, the irrigation and drainage canals provide a favorable environment for the snail intermediate host and a large number of people are infected repeatedly through contact with water all the year around. The geographic coincidence of bladder cancer and endemic bilharziasis is remarkable, with reported high frequency of bladder cancer in the above mentioned countries.

The highest incidence of bilharzia-associated bladder cancer (BABC) comes from Egypt (1). At the National Cancer Institute (NCI, Cairo), which is a specialized center in this disease, bladder cancer constituted 30.3% of all cancers, 40.6% of male cancers and 14.3% of female cancers. Conversely, in general hospitals, such as Cairo University Hospitals, a lower general frequency of 10.2% was reported. In a private pathology series, it was also the most common tumor encountered (20.6%), constituting 31.7% of male cancers and 5% of female cancers.

The BABC presents with distinctive clinicopathologic features quite different from that reported from Europe and North America (2). Thus, it affects patients at a much younger age (mean: 46.4 years) who present by cystitis rather than hematuria. The tumors are commonly nodular and usually arise from the upper vesical hemisphere. There is a high frequency (59%) of squamous cell carcinoma. Finally, the majority of tumors present at an advanced stage (95.3% of tumors > T1), hence radical cystectomy is the main line of treatment.

2. Precursor Lesions

The urothelium is a multipotential unstable epithelium, hence the multiple tumor types which may arise from it. A recently updated WHO classification (Table 1) is applicable to the BABC (6).

3. Classification

Carcinoma in situ
Transitional cell Carcinoma
Transitional neoplasm of low malignant potential
Papillary transitional carcinoma
Invasive transitional carcinoma
Transitional carcinoma variants

Squamous cell carcinoma
Conventional type
Verrucous type
Verrucoid type

Adenocarcinoma
Mucinous type
Enteric type

Undifferentiated carcinoma

Table 1. The updated WHO histologic classification of bladder carcinoma

3.1 Transitional Cell Carcinoma

In the BABC, transitional cell carcinoma contributed about 25% of cases in large series collected over several years (2), but there has been an increase in its relative frequency in recent years (Table 2). Three histologic subtypes and 10 rare variants are recognized.

3.2 Papillary Transitional Neoplasm of Low Malignant Potential

This type is a papillary noninvasive tumor (Ta) which resembles a papilloma but with epithelial thickening exceeding the normal 6 layers. Histologically, it shows preserved normal cell polarity with intact umbrella cells and intact basement membrane, no cellular atypia, and infrequent mitosis restricted to basal cell layer. Rarely it may show a prominent endophytic or inverted pattern. Such tumors were previously classified as grade I transitional carcinoma in the 1973 WHO classification. However, long-term follow up studies have confirmed its rather benign nature. They frequently recur locally and rarely progress to muscle invasion, and hence are considered favorable tumors of borderline malignancy or very low malignant potential.

3.3 Papillary Transitional Carcinoma

This refers to papillary tumors, which are composed partially, or entirely of malignant transitional epithelium. This type may be invasive or noninvasive. It is usually exophytic in pattern, rarely endophytic. Histologically, it shows both architectural disorder, as well as, cellular atypia of variable degree. They are graded either on a scale of three (I, II, III) as recommended by WHO, or a scale of two (low and high grades), in such case the high grade includes WHO grade II and III.

3.4 Invasive Transitional Carcinoma

This describes a nonpapillary urothelial carcinoma that invades the bladder wall, hence an aggressive behavior is expected. Such invasive property may complicate a papillary tumor, or may arise de novo. Also, these tumors are graded either on a scale of 3, or a scale of 2 (low and high grades). For therapeutic and prognostic implications, it is important to describe the pattern of invasion at tumor margin, namely: expansile with broad-front or tentacular growth, as well as, the depth of invasion, namely: infiltration of lamina propria (focal or extensive) or muscularis propria. In BABC, The majority of tumors are invasive and 86% are high grade (2).

3.5 Squamous Cell Carcinoma

The high frequency of squamous cell carcinoma is one of the main distinctive features of carcinoma in the bilharzial bladder and has been noted for a long time in different reports from Egypt, A relative frequency of 59% was recently reported from the Urology and Nephrology Center of Mansoura. (2). This contrasts sharply with the relative infrequency of true squamous cell carcinoma in the Western world, which varied between 3% and 7% (7). The predominance of squamous cell carcinoma in bilharzial series is probably related to squamous metaplasia and dysplasia which are relatively common in chronic bilharzial cystitis that are frequently associated (65%) with this type of carcinoma (3). Histologically, squamous cell carcinoma is composed of one cell type exhibiting squamous differentiation throughout the tumor. Malignant squamous cells may exhibit one or more of the following

features according to their grade: eosinophilic cytoplasm, sharp cell borders, intercellular bridges, and concentric cellular formations of cell nests (squamous pearls). In bilharzial series, one half of cases are grade 1 or low grade with numerous cell nests and only slight nuclear anaplasia.

Verrucous carcinoma is an unusual variant of squamous carcinomas in the bilharzial bladder contributing 4.6% of squamous carcinoma or 3.4% of all types of bilharzial bladder carcinoma (8). Verrucous carcinomas are divided into pure form which is exceptionally rare, and verrucous carcinoma associated with an invasive component (verruroid carcinoma) which is more common. The former is a tumor of low malignant potential, but the latter will rather behave as conventional squamous cell carcinoma. Histologically, the tumor is a well differentiated, hyperkeratotic squamous cell carcinoma with elongated surface projections and down growths of club-shaped finger-like processes. The deeply advancing margin has a pushing rather than infiltrating border, where the cells are arranged in large bulbous masses of cohesive squamous cells.

The decline in the prevalence of bilharziasis in Egypt during the past two decades was associated with significant changes in the pathology of bladder carcinoma. This was confirmed by a time trend analysis study which demonstrated a significant decrease in bilharzia eggs in tissues, a decline in the relative frequency of squamous carcinoma and an increase of transitional carcinoma (Table 2).

3.6 Adenocarcinoma

Primary adenocarcinoma arises on top of cystitis glandularis, and is a rare tumor in western literature with a reported incidence of about 2%. This tumor type is more frequently encountered in areas where bilharziasis is endemic with a reported frequency variable between 6% (9) and 11% (2).

In a series of 185 patients of bilharzia-associated primary adenocarcinoma, (10) 32% were non-mucin producing enteric type, 54% with interstitial mucin production, 10% with intraluminal mucin and 4% with intracellular mucin or signet ring type.

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Bibliography

El-Bolkainy, M.N. Topographic Pathology of Cancer, NCI Cairo, First edition, (2000) pp.58-62. (This book describes the pathology of different systems)

Ghoneim, M.A., EL-Mekresh. M.M., El-Baz, M.a., El-Attar, I.A. and Ashamallah, A. Radical cystectomy for

carcinoma of the bladder: critical evaluation of the results of 1,026 cases. *J.Urol.*, (1997). 158:399. (This article studies the prognostic clinico-pathologic factors of bilharzia-associated bladder cancer in Egypt)

Khafagy, M.M., El-Bolkainy, M.N. and Monsour, M.A. Carcinoma of the bilharzial urinary bladder, a study of the associated mucosal lesion in 86 cases. *Cancer* (1972). 50:150-159. (This article studies the different mucosal changes in bilharzial bladder)

Cheng L., Cheville I.C., Neumann R.M. Bostwick D.G. Flat intraepithelial lesions of the urinary bladder cancer, (2000) 88:625-631. (This article describes the early lesions of bladder carcinogenesis)

Cheng L. Cheville, J.C., Neumann, R.M. and Bostwick, D.G., Natural history of urothelial dysplasia of bladder *Am. J. Surg. Pathol.* (1999) 23:443, (This article studies the natural history of precancerous lesions in bladder)

Mostofi, F.K., Davis, C.J. and Sesterhenn I.A. WHO Histologic Typing of Urinary Bladder Tumours. Second Edition, Springer-Verlag, Berlin (1999). (This book is a landmark for the classification of bladder tumors)

Mostofi, F.K.: Pathology of malignant tumors of urinary bladder, in the *Biology and Clinical Management of Bladder Cancer* E.H. Cooper and R.E. Williams (Eds), Blackwell Scientific, Oxford, (1975). (This chapter in a book deals with the pathology and clinical picture of cancer bladder)

El-Sebai, I., Sherif, M., El-Bolkainy, M.N., Mansour, M.A. and Ghoneim, M.A. Verrucous squamous carcinoma of the bladder. *Urology*, (1974) 4:407-410. (This article introduced a new subtype of squamous carcinoma, present mostly in association of bilharziasis in Egypt)

El-Bolkainy, M.N., Mokhtar, N.M., Ghoneim, M.A. and Hussein, M.H. The impact of schistosomiasis on the pathology of bladder carcinoma. *Cancer*, (1981). 48:2643-2648. (This historical article compares the bilharzial versus non-bilharzial bladder cancer)

El-Mekresh, M.M., El-Baz., Abol-Enein, H., and Ghoneim, M.A. Primary adenocarcinoma of the urinary bladder: a report of 185 cases. *Brit. J. Urol.*, (1998) 82:206-212. (This article describes a rather uncommon types of bladder cancer)

El-Bolkainy M.N., Chu E.W., Ghoneim M.A., Ibrahim A.S. Cytologic detection of bladder cancer in a rural Egyptian population infested with schistosomiasis. *Acta Cytol.*, (1982). 23:303-310. (This work compiles data from screening program done in Egypt for the early detection of bladder cancer)

Khaked H, Abdel-Salam I, Abdel-Gawad M, et al. Evaluation of the BTA Tests for the detection of bilharzial related bladder cancer: The Cairo experience. *Eyr Urol* (2001) 39:91-94. (This paper studies the level of BTA in different types of bladder cancer)

Grossman H, Amancio D, Ellard J, Leibert M, Khaled H. Expression of bladder cancer biomarkers in invasive bilharzial squamous bladder cancers. Poster Presentation. In: 94th Annual Meeting American Urologic Association, Dallas, USA, May 1999. (This paper studies some important markers implicated in the diagnosis and prognosis of bladder cancer)

Gonzalez-Zulueta M, Shibata A, Ohnseit P.F. et al. High frequency of chromosome 9p allelic loss and CDKN2 tumor suppressor gene alterations in squamous cell carcinoma of the bladder. *JNCI*, (1995) 87: 1383-1391. (This article is a pioneer work on chromosomal changes in Egyptian bladder cancer)

Pycha A, Mian C, Posch B, et al. Numeric aberrations of chromosomes 7, 9, and 17 in squamous cell and transitional cell cancer of the bladder: A comparative study performed by fluorescence in situ hybridization. *J.Urol* (1998) 160:737-740. (This article describes different chromosomal aberrations in the multistep carcinogenesis of bladder cancer)

Aly M.S. and Khaled H.M. Chromosomal aberrations in bilharzial bladder cancer as detected by fluorescence in situ hybridization. *Cancer Genet Cytogenet* (1999) 144:62-67. (This article studies different chromosomal changes by FISH method)

Khaled H.M., Aly M.S. and Magrath I.T. Loss of Y chromosome in bilharzial bladder cancer. *Cancer Genet Cytogenet* (2000) 117:32-36. (This paper discovers a new chromosomal pattern in bladder cancer in Egypt)

Aly M.S. and Khaled H.M. Chromosomal aberrations in early-stage bilharzial bladder cancer. *Cancer Genet Cytogenet* (2002) 132:41-45. (This paper deals with P0 and P1 early bladder lesions)

Khaled H, Aly M, Mokhtar N. Chromosomal aberrations in Cis and Ta bilharzial bladder cancer: A theory of

pathogenesis. In press. (This recent paper studies carcinoma-in situ and papillary tumors of bladder in terms of chromosomal changes)

Fadl-Elmula I, Kytola S, Leithy M, et al. Chromosomal aberrations in benign and malignant bilharzia-associated bladder lesions analyzed by comparative genomic hybridization. *BMC Cancer* (2002) 2:5-11. (This study compares benign versus malignant chromosomal changes in bladder lesions)

El-Rifai W, Kamel D, Larramendy M, et al. DNA copy number changes in schistosoma-associated and non-schistosoma-associated bladder cancer. *Am J Pathol* (2000) 156:871-878. (This work studies DNA amplification in bilharzial and non-bilharzial bladder cancer)

Muscheck M, Abol-Enein H, Chew K, et al. Comparison of genetic changes in schistosome-related transitional and squamous bladder cancers using genomic hybridization. *Carcinogenesis* (2000) 21:1721-1726. (The work compares the different pathologic types in terms of some oncogenes)

Weintraub M, Khaled H, Zekri A, et al. p53 mutations in Egyptian bladder cancer. *Int J Oncol* (1995) 7:1269-1274. (The article studies p53 tumor suppressor gene as a causative factor in bladder carcinogenesis)

Osman I, Scher H, Zhang Z, et al. Alterations affecting the p53 control pathway in bilharzial-related bladder cancer. *Clin Cancer Res* (1997) 3:531-536. (The work describes different pathways involving tumor suppressor genes in cancer bladder)

Khaled H, Bahnasi A, Zekri A, Aboul Kassem H, Mokhtar N. Correlation between p53 mutations and HPV in bilharzial bladder cancer. *Urologic Oncol* (2003) 21 in press. (This work studies the viral role of human papilloma virus in Egyptian bladder cancer)

Warren W, Biggs P, El-Baz M, Ghoneim M, et al. Mutations in the p53 gene in schistosomal bladder cancer: a study of 92 tumors from Egyptian patients and a comparison between mutational spectra from schistosomal and non-schistosomal urothelial tumors. *Carcinogenesis* (1995) 16:1181-1189. (This important paper deals with carcinogenic pathways in bladder cancer associated with schistosomiasis)

Habuchi T, Takahashi R, Yamada H, et al. Influence of cigarette smoking and schistosomiasis on p53 gene mutation in urothelial cancer. *Cancer Res* (1993) 53:3794-3795. (This paper highlights the positive impact of smoking in bladder carcinogenesis)

Osman I, Scher H, Zhang Z, et al. Expression of cyclin D1, but not cyclins E, and A, is related to progression in bilharzial bladder cancer. *Clin Cancer Res* (1997) 3: 2247-2251. (The paper studies the expression of different cell cycle regulatory proteins as prognostic markers in bladder cancer)

Fujita J, Nakayama H, Onoue H, et al. Frequency of active oncogenes in human bladder cancers associated with schistosomiasis. *J Cancer Res* (1987) 78:915-920. (This work describes oncogenic mutational changes in bladder cancer)

Gad El-Mawla N, El-Bolkainy N, Khaled H. Bladder cancer in Africa: update. *Seminars Oncol* (2001) 28:174-178. (This review article collects all available data on bladder cancer in Africa)

Abdel-Salam I, Khaled H, Gaballah H, et al. Telomerase activity in bilharzial bladder cancer: Prognostic implications. *Urologic Oncol* (2001) 6:149-153. (This paper estimates serum telomerase level as a sensitive prognostic tool)

Khaled H, Raafat A, Mokhtar N, Zekri A, Gaballah H. Human papilloma virus infection and overexpression of p53 protein in bilharzial bladder cancer. *Tumori* (2001) 87:256-261. (This pioneer work deals with implicating human papilloma virus in Egyptian bladder cancer)

Lopez-Beltan A, Escudero A, Carrasco-Aznar J, Visioso-Recio L. Human papilloma virus infection and transitional cell carcinoma of the bladder. *Path Res Pract* (1996) 192:154-159. (This work confirms that HPV is associated with transitional carcinoma in Egypt)

Biographical Sketches

Dr. Nadia Mokhtar is Chairman of the Dept. of Pathology NCI, Cairo University since August 2001. She is a physician/ pathologist/ cytologist with more than thirty years experience in the field of surgical pathology, cytology, oncology, immunopathology and molecular pathology. As a professor of pathology at the National Cancer Institute of Cairo University, she had a long academic career and offered technical expertise to a

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