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REVIEW

Schistosomiasis and Cancer in Egypt: Review

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ABSTRACT

Schistosomiasis is not known to be associated with any malignant disease other than bladder cancer. Bladder cancer is still the most common malignant tumor among males in Egypt and some African and Middle East countries. However, the frequency rate of bladder cancer has declined significantly during the last 25 years. This drop is mainly related to the control of Schistosomiasis. Many studies have elucidated the pathogenic events of Schistosomal-related bladder cancer with a suggested theory of pathogenesis. Furthermore, the disease presents with a distinct clinicopathologic profile that is quite different from bladder cancer elsewhere with younger age at presentation, more male predominance, more invasive stages, and occurrence of squamous cell carcinoma pathologic subtype. However, recent data suggest that this profile has been dramatically changed over the past 25 years leading to minimization of the differences between its features in Egypt and that in Western countries. Management of muscle-invasive localized disease is mainly surgery with 5-year survival rates of 30–50%. Although still a debatable issue, adjuvant and neoadjuvant chemotherapy and radiotherapy have improved treatment outcomes including survival and bladder preservation rates in most studies. This controversy emphasizes the need of individualized treatment options based on a prognostic index or other factors that can define the higher risk groups where more aggressive therapy is needed. The treatment for locally advanced and/or metastatic disease has passed through a series of clinical trials since 1970s. These phase II and III trials have included the use of single agent and combination of chemotherapy and radiotherapy regimens. The current standard of systemic chemotherapy of generally fit patients is now the gemcitabine–cisplatin combination. In conclusion, a changing pattern of bladder cancer in Egypt is clearly observed. This is mainly due to the success in the control of Schistosomiasis. It may also be due to increased exposure to other etiologic factors that include smoking, pesticides, and/or other causative agents. This change will ultimately affect disease management.

Introduction

It is estimated that over 20% of malignancies worldwide can be related to infectious agents [1]. *Schistosoma haematobium* is a blood fluke, which resides in the system venules and capillaries of the human bladder and other pelvic organs. It is endemic in Africa and the Middle East including Egypt. First identified by Theodor Bilharz in 1851, *S. haematobium* was

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initially implicated in bladder cancer induction by Fergusson in 1911 [2] and later confirmed in 1994 by the International Agency for Research on Cancer (IARC) to be carcinogenic [3]. Schistosomiasis has not known to be implicated in the etiology or pathogenesis of any malignant disease other than bladder cancer. So, this review will discuss different aspects of the association between this chronic infection and bladder cancer in Egypt.

Epidemiology, etiology and biologic aspects

Early reports from the Egyptian government in the 1920s indicated that *S. haematobium* infection rates were as high as 70–80%. Using tartar emetic at that time as treatment had reduced disease prevalence marginally to about 50% [4]. By 1980, a new effective compound (praziquantel) became available, and the ministry of health collaborated to design and implement the Schistosomal Research Project that suggested the National Schistosomiasis Control Program to begin mass treatment in schools and high-prevalence villages. With the success of this project, the prevalence dropped to 6.6% in 1993 and then to 1.9% in 2002 and 1.2% in 2006 [5,6]. This successful mass treatment was also accompanied by aggressive public awareness campaigns.

Recently, the 385-Mb genome of *S. haematobium* was entirely sequenced [7]. This was done using Illumina-based technology at 74-fold coverage and was also compared to sequences from related parasites. Genome annotation based on function, gene ontology, networking, and pathway mapping was also demonstrated. It is hoped that this unprecedented resource may benefit many fundamental research areas and help in the design of new disease interventions.

Likewise, and surely with the control of schistosomiasis, the frequency and incidence rates of bladder cancer consequently dropped. This drop started to occur with a lag period of 10–15 years. In late 1980s and early 1990s, bladder cancer accounted for approximately 25–27% of all cancers seen at the National Cancer Institute of Egypt, the largest and most comprehensive cancer center in the country. During the years 2001–2005, this percentage declined significantly to account for approximately 10–15% of all cancers seen at NCI, Egypt [8]. In more recent years, the data of the population based National Cancer registry that includes 5 governorates showed a frequency rate range of 6–9.2% and an incidence rate range of 11.6–15.6/100,000 normal population [9]. Thus, it is clear that changes in the epidemiology of schistosomiasis are reflected on the changing epidemiology of bladder cancer.

The mechanisms underlying this association, however, are largely unknown. Traditionally, it is believed that schistosomiasis may cause bladder cancer through bladder irritation, inflammation, and concurrent chronic bacterial infections [10–12]. The chronic inflammatory reaction due to the deposition of worms and eggs in the tissue consists of macrophages and neutrophils, which produce endogenous oxygen radicals. These radicals lead to the formation of carcinogenic N-nitrosamines [13]. Oxygen radicals are also responsible for various mutations [14], like sister chromatid exchanges [15], and DNA breaks [16]. Moreover, inflammatory cells may contribute to the activation of polycyclic hydrocarbons and aromatic amines that further produce specific carcinogenic metabolites [17].

Using normal epithelial cells *in vitro*, *S. haematobium* parasite extracts were able to induce cancer-like phenotypes such as loss of p27, increased expression of Bcl-2, proliferation, apoptosis, migration, invasion, and tumorigenesis [18]. The same authors also observed carcinogenic and mutagenic ability of the parasite extract when CD-1 mice normal bladders were exposed to it. After 40 weeks of intravesical instillation, 70% of these animals displayed urothelial dysplasia and low grade intravesical neoplasia. Twenty percent of the dysplastic bladders presented a mutation in codon 12 of exon 2 of Kras gene [19].

On the chromosomal level, several reports have elucidated the chromosomal alterations that characterize schistosomal bladder cancer cases [20,21]. Using fluorescence in situ hybridization to detect numerical chromosomal changes in subsequent series of cases with various stages of the disease, a theory of pathogenesis was proposed [22]. This suggested theory entails the occurrence of both chromosomes Y and 9 alterations for the carcinogenic event to start and then the development of two genetic pathways for the transition to invasive stages. The invasive tumors may then develop either from carcinoma in situ with deletions in the Y and 9 chromosomes, or from Ta cases having multiple alterations together including gain of chromosome 7 or deletions of chromosome 17 (Fig. 1).

Furthermore, studies at the molecular level [23–25] using different techniques have been done to assess markers of some oncogenes, tumor suppressor genes, cell cycle regulators, the tumor's ability to spread and metastasize, P-glycoprotein expression, and relation to some oncogenic viruses.

Activation of H-ras oncogene was found [24], and tumor expression of epidermal growth factor receptor, retinoblastoma, and p34 was positive in 64%, 58%, and 48% of the examined cases, respectively. The p53 profile was evaluated in urine, serum, and tumor tissue of the same samples. Mutant forms were found in 20% of urine, 59% of serum, and 40% of tumor tissue samples [25]. Moreover, the median values of the soluble adhesion molecules VCAM, ICAM, E-selection, and the microvessel counts expression angiogenesis were all significantly higher than normal control levels [25]. It was also observed that telomerase activity is increased in schistosomal bladder cancer (47%) although a lesser degree than that reported for transitional cell carcinoma in the western world [26].

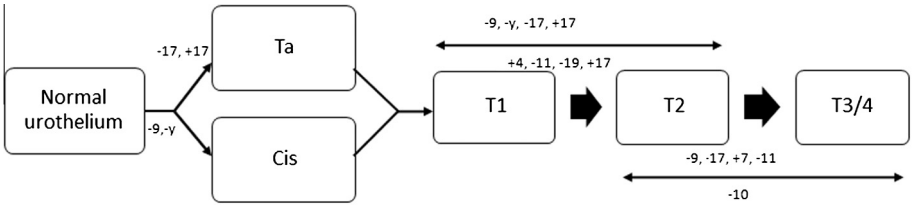

Fig. 1 A theory of Schistosomal Bladder Cancer Pathogenesis (chromosomal gains and/or deletions). Adapted from Khaled et al. [22].

Table 1 Randomized trials comparing preoperative radiotherapy with cystectomy alone. Adapted from Zaghloul [37].

Study (year)	Stage	Patients (n)		Dose (cGy)	Survival rates	
		Preop.	Cyst.		Preop.	Cyst.
Blackard et al. (1972)[a]	T2–T3	23	22	4500	39	36
Slack et al. (1977)	T2–T4	103	131	4500	44	32
Awwad et al. (1979)[b]	T3	36	17	4000–4080	53	19
Anderstorm et al. (1983)	T1–T3a	22	22	3200–5400	75	61
Ghoneim et al. (1985)	T1–T4	43	49	2000	39	32
Smith et al. (1997)	T2–T4	60	64	2000	53	43

Cyst: Cystectomy, Preop: preoperative radiotherapy.
[a] 3-Year overall survival.
[b] 2-Year overall survival.

The pattern and degree of aberrant methylation of multiple genes were also reported [27]. Twelve cancer-related genes (E-cadherin, DAP-Kinase, OMGMT, p14, p15, p16, FHIT, APC, RASSF 1A, GSTP1, RARB, and p73) were investigated. Schistosomal bladder cancer had more genes methylated than non-schistosomal tumors. While methylation of DAP-Kinase and RAR B was equally distributed between tumors with or without schistosomal association, methylation of FHIT, RASSF1 A, E-cadherin, P16, and MGMT tended to be more common in the parasite-associated tumors. Also, these tumors demonstrated high median methylation index (0.25) than non-schistosomal-associated cases. These results suggested that schistosomal involvement is associated with a greater degree of epigenetic changes in the bladder epithelium.

Finally, by using Mass ARRAY technology, all 27 schistosomal bladder cancer blood tested samples were associated with HPV-16 DNA. These findings have lead the authors [28] to suggest that clinical surveillance of serum and/or urine sediment indicated both analyzing subjects at high risk of developing schistosomal bladder cancer and monitoring the treatment for the disorder.

Lastly, with the anticipation that in the near future with the eradication of schistosomiasis, there will be a potential rise in the incidence of bladder cancer related to other risk factors, and a recent study has found that risk factors may include positive family history, exposure to pesticides, bladder stones, consanguinity, recent cystitis, and smoking. These factors seem to play now more important roles than schistosomiasis in the development of bladder cancer, especially in Upper Egypt [29].

Clinicopathologic characteristics

Schistosomal bladder cancer presents a distinctive clinicopathologic profile, quite different from that reported from Europe and North America. In Western countries, bladder cancer is three times more common in males than in females. Incidence peaks in the sixth, seventh, and eighth decades of life. Over 90% of the tumors are transitional cell carcinomas. Only about 25% of patients present with muscle-invasive disease, i.e., $\geqslant$T2 lesions [30].

Besides higher incidence rates of schistosomal bladder cancer compared to the urothelial cell bladder cancer seen in the West, there are other clinicopathologic differences. However, with the reduction in schistosomiasis due to control efforts over the past 40 years, these differences have been minimized. This is clearly shown by recent studies. In one of these studies [31], more than 9000 patients diagnosed and treated at the National Cancer Institute of Egypt between 1970 and 2007 have been retrospectively analyzed. A significant decline of the relative frequency was observed from 27.6% in the old series to 11.7% in the recent series. Likewise, schistosomal association dropped from 82.4% to 55.3% with obvious decrease in the degree of calcification and viability, the density of ova deposition, and the occurrence of less associated mucosal changes. The authors also described an increase in the median age at presentation from 47.4 years to 60.5 years. There was also a decrease in the male to female ratio from 5.4 to 3.3. A significant rise of transitional cell carcinoma from 16% to 65.8% with a decrease in squamous cell carcinoma from 75.9% to 28.4% was also reported.

In another study [32], data of 2778 patients seen at the NCI, Egypt, during six calendar years (1980–1983–1990–1994–2001 and 2005) showed also the same results, e.g., patients treated for bladder cancer in 2005 had a sixfold increased risk of transitional cell carcinoma vs. squamous cell carcinoma compared with patients treated in 1980.

A trend for more numbers of superficial (Pa-1) and less numbers of invasive tumors (P2-4) was also clear when comparing two central pathology registries that were studied for the years 2003–2004 vs. the years 1985–1989. Pa-P1 lesions increased from 7.8% to 35.1%, while P2-4 lesions dropped from 92.2% to 64.9% [33].

Management

Muscle-invasive and locally advanced disease

Treatment for muscle-invasive bladder cancer, which constitutes almost two-thirds of cases in Egypt, remains a challenge. This is because it aims at local disease control, elimination of micrometastases, and maintenance of the best possible quality of life without compromising survival.

Radical cystectomy is still the treatment of choice in most cases of muscle-invasive bladder cancer worldwide. It is associated with a 5-year disease-free survival rate of 30–50%. The independent prognostic factors that determine the outcome include tumor stage, grade, and pelvic nodal involvement [34,35]. Sophisticated techniques for urinary diversion after radical surgery have been developed and are under study to improve the quality of life and prognosis but even a continent and ideal diversion cannot substitute for the original bladder.

Table 2 Nonrandomized postoperative radiotherapy studies for bladder cancer. Adapted from Zaghloul [37].

Study year	Patients (*n*)	Tumor type	Radiation dose (cGy)	DFS	Local control	Distant metastasis
Cozzarini et al. (1999)	150	TCC	5000	44.6	88.4	NM
El Debawy (2000)	222	TCC, SCC, and adenocarcinomas	5000	75 ± 4	91 ± 2	17 ± 4
Zagloul et al. (2002)	89	TCC, SCC, and adenocarcinomas	5000	64 ± 10	88 ± 9	18 ± 7
Zagloul et al. (2006)	192	Adenocarcinomas	5000	56.7 ± 7.5	97.2 ± 2.8	25.3 ± 4.9
Zagloul et al. (2007)	216	Adenocarcinomas	5000	58 ± 6	94 ± 3	33 ± 6

DFS: Disease-free survival; NM: Not mentioned; SCC: Squamous cell carcinoma; TCC: Transitional cell carcinoma.

After radical surgery, local recurrence either alone or combined with systemic metastases has been shown to occur in 25–50% of such locally advanced cases [36]. While nonrandomized trials of preoperative radiotherapy have suggested improved survival rates, only one of the worldwide published six randomized preoperative radiotherapy trials (Table 1) shows survival benefit. On the contrary, most retrospective reports (Table 2) and the only published randomized trial that have used postoperative radiotherapy revealed a significant increase in disease-free survival rates [37].

However, postoperative radiotherapy remained unpopular because of the fear of late gastrointestinal complications. Most of these pre- and postoperative radiotherapy trials were performed in the 1970s to mid 1990s but with modern radiotherapy techniques now available, e.g., IMRT (Intensity Modulated Radiotherapy) and IGRT (Image Guided Radiotherapy), the possibility of minimizing morbidity and late complications as well as maximizing efficiency is surely expected.

In an effort to improve the unsatisfactory survival rates of radical surgery alone, and in order to avoid the possible late complications of radiotherapy, many adjuvant and neoadjuvant systemic chemotherapy trials have been conducted. The first trial was a phase III study randomized using single agent epidoxorubicin given pre- and postoperatively vs. radical cystectomy alone. One hundred and seventy patients were included in both arms, and a higher disease-free survival rate was observed for those patients who have completed their 6 cycles of chemotherapy [38]. Another study reported from Mansoura using cisplatin-based neoadjuvant chemotherapy in 194 patients, however, failed to show a survival benefit [39].

The promising results of using the gemcitabine–cisplatin combination and the known synergistic effects of gemcitabine with radiotherapy led to the initiation of subsequent randomized trials using both adjuvant and neoadjuvant combining chemo- and radiotherapy. In one study, 114 patients were randomized to either radical cystectomy alone, or to receive 3 cycles of gemcitabine–cisplatin regimen, and tumor response was then assessed. If a complete remission was achieved, 3 additional chemotherapy cycles were given followed by radical radiotherapy. Otherwise, surgery was performed. There was a trend toward increased survival of patients who have received neoadjuvant chemotherapy, but more importantly, bladder preservation was possible in 22% of patients [38].

In another study, the efficacy of adding adjuvant chemotherapy to postoperative radiotherapy was also evaluated in 142 high risk bladder cancer patients. A marginal difference of improved disease-free survival was observed for those who have received the combined modality treatment [40].

In addition, many studies have been done to avoid mutilating surgeries combining transurethral resection, radiation therapy, and systemic chemotherapy. However, no randomized trials have compared radical cystectomy vs. other approaches. In such approaches with different modalities, salvage cystectomy is being reserved for patients with incomplete response or local relapse.

So, the role of adjuvant and/or neoadjuvant chemotherapy, radiotherapy, or combined modality therapy in conjunction with local radical surgery is still a debatable issue in the treatment for muscle-invasive bladder cancer in general and of schistosomal bladder cancer in particular. Therefore, the need for developing a prognostic model to define high risk group that may benefit of additional therapy is highly indicated and may also explain the controversial date of such therapy. A prognostic index formed of the 3 known risk groups, namely P stage, tumor grade, and lymph node affection was evaluated in a group of 198 bladder cancer cases, and it may guide for more rationale choice of patients into future clinical trials [35].

Metastatic disease

In the absence of any data on tumor chemosensitivity profile of patients with schistosomal bladder cancer, and starting in 1970s, a series of phase II trials to screen single agent chemotherapeutic agents were conducted at the NCI, Egypt. Various drugs were tested in groups of 20–25 patients with advanced and/or metastatic disease [41]. About 5 agents gave moderate rates (30–60%). It was then logic to try to formulate combination(s) of the most active single agents. A combination of the epidoxorubicin–vincristine alternating with etoposide and ifosfamide thus tried with a response rate of 41% [42].

Table 3 Response rates of different combination chemotherapy regimens used for management of advanced schistosomal bladder cancer.

No. of patients	Evaluable	CR	PR	(CR + PR) (%)
Epidx–VCR alternating with VP16 – Ifos.	22	1	8	(41)
Gemcitabine–Cisplatin (Standard dose)	33	8	10	(54)
Gemcitabine–Cisplatin (Low dose – prolonged infusion)	54	5	27	(59)

This was followed by another phase II trial of the gemcitabine–cisplatin regimen [43]. Given to 37 patients with advanced disease, an overall response rate of 54% was achieved. In order to address the cost-benefit value of this rather expensive regimen, a trial of low dose prolonged infusion gemcitabine combined with cisplatin was applied on a group of 57 schistosomal bladder cancer cases. With an overall response rate of 50% and a median survival time of 11.5 months, the data were comparable to that obtained with the standard dose gemcitabine regimen but with much less costs [44]. A summary of the results on combination chemotherapy regimens in schistosomal bladder cancer is shown in Table 3.

While many targeted agents have been tried in urothelial cancer in many centers, the recent report of the expression of estradiol-like molecules by *S. haematobium* extract and its repressive role in inactivation of estrogen receptors in bladder epithelium [45] could have implications in designing targeted therapy of schistosomal-associated bladder cancer.

Future prospects

More insights into the pathobiology of schistosomal bladder cancer and its reflection on patients' management are clearly needed. Schistosomal bladder cancer in Egypt is a good example of a preventable malignant disease. Primary prevention should continue to eliminate the parasite nationwide. Early detection is also possible by selective scanning of the high risk groups, e.g., farmers >20 years of age, using urine cytology. Researchers should also be urged to the prospects of individualized treatment options based on new biologic prognostic markers and new targeted therapies. Finally, improving neoadjuvant and adjuvant measures will not only improve treatment results and quality of life but also avoid mutilating surgeries and increase rate of bladder preservation.

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