Bladder Cancer in Africa: Update

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Carcinoma of the bladder is the most prevalent cancer in Egypt and in most African countries. At the National Cancer Institute (NCI), Cairo, it constitutes 30.3% of all cancers. The median age at diagnosis is 46 years, with a male preponderance of 5:1. Whether in Egypt or other African countries such as Sudan, Kenya, Uganda, Gold Coast, and Senegal, it is mostly of the squamous cell type, and arises in a background of schistosomiasis or bilharziasis. Tumors are usually advanced at the time of presentation. Bladder carcinogenesis is probably related to bacterial and human papilloma virus (HPV) infections, usually associated with bilharzial infestation. Management is mainly surgery, with 5-year survival rates after radical cystectomy increasing from 35% in the 1970s to 48% in the 1990s. The addition of adjuvant and neoadjuvant radiotherapy and chemotherapy to surgery since 1976 significantly improved both disease-free and overall survival rates. Molecular genetic studies concerning potential prognostic markers, tumorigenesis, and tumor progression in bilharzial bladder cancer are limited. However, a comprehensive detailed analysis of these factors is underway. Bilharzial bladder cancer is a preventable malignant disease. Primary prevention could be possible if the parasite is eliminated nationwide. Chemoprevention using retinoids or cyclooxygenase 2 (COX-2) inhibitors is a possible alternative.

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CARCINOMA OF THE BLADDER is the foremost oncologic problem in Egypt. At the hospital of the National Cancer Institute (NCI), Cairo, it constitutes 30.3% of all cancers, 40.6% of male cancers, and 14.3% of female cancers. A lower overall frequency of 10.2% is reported by other Egyptian general hospitals. In a private pathology series, it contributed 20.6% of all cancers, 31.7% of male cancers, and 5% of female cancers.[1]

In Africa, a high frequency of bladder cancer has been reported in many countries. Along the river Nile in Africa, a high prevalence is reported in Sudan and in the countries around Lake Victoria (Kenya and Uganda). The disease extends to the west of the continent, with high rates reported in Gold Coast and Senegal. It is in these areas where cancers frequently arise in the bilharzial infected bladder.[2] The eastern side of the continent below the Equator also has a high frequency of the disease, as reported from Mozambique, Zambia, and New Guinea.

In Egypt, bladder carcinogenesis is probably related to bacterial and human papilloma virus (HPV) infections associated with bilharzial infestation, rather than the schistosoma parasite itself. Bacterial enzymes help liberate free carcinogens from their conjugated metabolites in urine, as well as produce carcinogenic nitrosamines from their precursors in urine. The frequency of HPV in tumors varies according to the method of study: 23% by polymerase chain reaction (PCR) and 46% by in situ hybridization (ISH).[3]

Egypt has the highest prevalence of schistosomiasis. The parasite was discovered by Theodore Bilharz in 1852. Ferguson presented the first evidence of the bilharzial cystitis problem in Egypt in 1911, and noted the association between bilharzial cystitis and bladder cancer.[4]

The ancient Egyptians, settling and cultivating the Nile Valley, were among the first to contact schistosomiasis in an endemic manner. Thus, it was mentioned in medical papyri and in engravings[5] on the walls of the temples as early as the sixth century BC. This was later confirmed by paleopathologic studies that directly demonstrated the eggs of the parasite in Egyptian mummies from the 20th dynasty. However, the historical evidence is not conclusive as to whether the ancient Egyptians knew about bladder cancer and its relation to schistosomiasis.

PATHOLOGY

In Egypt, bladder cancer has a clinicopathologic pattern that differs in some important aspects from that seen in Europe and North America. The peak age of diagnosis is usually 50 ± 5 years, with a male to female ratio of 5:1. Most tumors present as bulky fungating nodular masses with deep infiltration into the bladder wall (P_3, 73%; P_4, 16%), whereas papillary types are rare (7%). The carcinoma usually arises from the upper vesical hemisphere (56%), while the trigone is a rare site of

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tumor development (8.5%). Tumor multicentricity is not uncommon, occurring in 6% to 22% of cases.

The majority of tumors are of the squamous cell variety, which represents 59% to 81% of cases in different reports. However, a recent trend toward a relative increase in the frequency of the transitional cell variety has been reported.[1,7] In Western populations, the incidence of nonbilharzial squamous cell carcinoma is between 3% and 6.7% of all bladder cancers.[8]

The carcinoma is associated with a variety of atypical epithelial changes in bladder mucosa, including metaplasia, dysplasia, and carcinoma in situ. The majority of patients (86% to 91%) present with advanced-stage disease (T3 and T4) and the frequency of lymph node metastases is about 18%.[9,10]

OTHER BIOLOGIC ASPECTS

Detailed molecular genetic studies of transitional cell carcinoma of the bladder have led to a working hypothesis of tumorigenesis and progression,[11] and to the use of some of these markers as determinants of prognosis and predictors of the ultimate clinical outcome. Similar studies in bilharzial-related bladder cancer are limited. In one study, point mutations of *H-ras* were observed in three of 12 (16%) bilharzial bladder cancer cases.[12] Data on the presence of tumor *p53* mutations conflict, ranging from 20% to 86% of cases studied. Deletions affecting p16/INK4A and other abnormalities on chromosome 9 have also been reported.[13-15]

At the NCI, Cairo University, we have undertaken a collaborative effort to characterize the cytogenetic and molecular events associated with bilharzial-related bladder cancer in relation to other clinicopathologic characteristics. This was the main goal of a research grant provided by the Schistosomal Research Project (SRP) of the US American International Development Program (US-AID) and Ministry of Health in Egypt.

Using the fluorescence in situ hybridization (FISH) technique, the most common numerical chromosomal abnormalities detected were loss of chromosome 9 in 48% of cases studied, numerical alteration in chromosome 17 in 19.4%, gain of chromosome 7 in 10%, and characteristic loss of the Y chromosome in 36%.[16,17] At the molecular level, different techniques have been used to assess markers expressing the tumor's ability to spread and metastasize (soluble adhesion molecules, tissue nm23 expression, and microvessel counts reflecting tumor angiogenesis), tumor-suppressor and cell-cycle regulatory genes (*p53*, *Rb*, *p34*, and *EGFR*), P-glycoprotein expression, and relation to some oncogenic viruses (HPV and Epstein-Barr virus [EBV]).

The median values of the soluble adhesion molecules, vascular cellular adhesion molecule (VCAM), intercellular adhesion molecule (ICAM), and E-selectin, and of angiogenic levels measured by enzyme-linked immunosorbent assay (ELISA) for 67 cases (2,290, 348, 33, and 400 ng/mL, respectively), were all significantly higher than normal control levels. Using a monoclonal antibody against Factor VIII, microvessel counts per 100 × hpf were evaluated for 60 cases. Fifty percent had counts below 65, 37% had counts between 65 and 100, and 13% had counts above 100 per 100 × hpf. Tumor tissue nm23 expression, evaluated by immunohistochemistry (IH) for 42 cases, was not found in 14 (33%), weekly positive in 14 (33%), moderately positive in 10 (24%), and strongly positive in four (10%).

Tumor expression of epidermal growth factor receptor, retinoblastoma, and p34 (assessed in 40, 47, and 46 cases) was positive in 25 (63.5%), 27 (57.5%), and 22 (48%) of the examined samples, respectively. The *p53* profile was evaluated in urine, serum, and tumor tissue using both IH and DNA sequence analysis. Mutant forms were found in nine of 46 (20%) urine samples and in 34 of 58 (59%) serum samples, and in tumor tissue by IH in 34 of 93 (37%) and by DNA sequence analysis in 10 of 25 (40%) of the cases studied.

IH evaluation of the multidrug resistance (*MDR*) gene expression was performed for 73 cases and was positive in 29 samples (40%). On evaluating *p53* and *MDR* expression simultaneously for the same samples, most of the cases (54 of 73 [74%]) showed one of the two markers positive, while the second was negative. Twenty-two percent of patients (n = 16) showed both markers negative. Only three cases were positive for both markers. HPV detection was done by ISH for 50 cases. A positive signal was found in 24 (48%) cases. None of the 40 cases studied had EBV genome (using generated primers). Correlation between all of the above parameters to the different

clinicopathologic characteristics and to final treatment outcome is under evaluation.

CLINICAL PICTURE

Two distinctly different bladder cancers exist in Egypt, namely, the bilharzial and nonbilharzial types. The less common nonbilharzial type is observed among urban populations, affects elderly patients who usually present with superficial tumors, and the histopathology is invariably of the transitional cell type.

The bilharzial type is prevalent in rural areas. With the exception of necroturia, the symptoms of frequent urination, pelvic pain, hematuria, dysuria, and pyuria differ little from the symptoms associated with chronic or recurrent bilharziasis. Thus, by the time the patient arrives at a large medical center, the disease is usually relatively advanced.

The diagnostic work-up is normally straightforward. Rectal or vaginal examination reveals a hard mass in the pelvis. Weakness of foot adduction implies obturator nerve involvement. Edema of the inner thigh without whole-leg edema implies obstruction of the obturator vein. Whole-leg edema is not unusual and is caused by iliac vein obstruction or iliac node infiltration. Intravenous urogram, transrectal ultrasound, or computed tomographic scans are useful adjuncts in the evaluation. Hydronephrosis and hydroureter are common due to long-standing obstruction. The bladder and even the lower ureters are frequently calcified by bilharziasis. Laboratory investigations usually reveal a mild anemia.

Leukocytosis is common because of the chronic urinary tract infection. Serum creatinine and blood urea are usually normal, except in advanced cases. As with other cancers, the diagnosis should be confirmed microscopically. Urine cytology is most useful in diagnosing squamous carcinoma. Its specificity is lower in transitional and adenocarcinoma. However, cystoscopic examination and evaluation of the mass under anesthesia is mandatory in most cases, and cytoscopic biopsy must confirm the diagnosis.

TREATMENT

Surgery

Few patients are eligible for segmental resection. Only 19 of 190 resectable bladder cancers were found suitable for this procedure. The limited indications for such a procedure were cited as small size permitting excision with a safe margin, solitary tumors away from the trigone, absence of associated precancerous lesions, and adequate residual bladder capacity. However, the majority of the 19 patients needed augmentation cystoplasty and their reported 5-year survival rate was only 27%.[18]

Radical cystectomy with urinary diversion is generally considered the most feasible procedure for most resectable tumors and is the only curative modality so far available, with survival rates between 27% to 39%.[10] Ghoneim et al[19] recently reported on 1,026 cases of bladder cancer collected between 1969 and 1990. There were 764 males and 262 females, with an average age of 43 ± 8 years, subjected to radical cystectomy and urinary diversion. Follow-up ranged from 0 to 24.2 years, with a median 4.05 years. The postoperative mortality rate was 4% and most patients had advanced-stage tumors. Squamous cell carcinoma accounted for 59% of cases, transitional cell carcinoma for 22%, and adenocarcinoma for 11%. The 5-year survival rate was 48%. Tumor stage, tumor grade, and lymph node status had a significant impact on survival; the 5-year disease-free survival rate was 23% for node-positive cases versus 53% for node-negative cases.

Adjuvant Therapy

Since 1976, a series of phase II clinical trials for screening of various chemotherapeutic agents in advanced and late cases of bilharzial bladder cancer has been conducted at the NCI, Cairo. Different drugs were screened, one by one, in groups of 20 to 25 patients with inoperable, metastatic, or recurrent disease.

Ten drugs induced overall response rates between 18% and 60%: epidoxorubicin (60%), vindesine (41%), vincristine (44%), ifosfamide (40%), hexamethylmelamine (38%), etopside (36%), pentamethylmelamine (32%), cyclophosphamide (19%), and dibromodulcitol (18%)[20] (Table 1). Chemotherapy appeared to be more efficacious in metastatic than in local lesions. Based on these data, a combination regimen of the most active agents yielded a response rate of 46%.[21] Another trial, still ongoing, is showing promising results using the combination of gemcitabine and cisplatin, with a preliminary overall response rate of 50%.[22]

Table 1. Chemotherapy in Bilharzial Squamous Cell Carcinoma of the Bladder

Drug	No. of Patients						
	Evaluable	CR	PR	CR + PR	MR	SD	PD
Bleomycin	21	0	0	0 (0%)	2	6	13
Doxorubicin	27	0	0	0 (0%)	2	4	21
Tenoposide	26	0	1	1 (4%)	2	6	17
Fluorouracil	32	0	2	2 (6%)	3	17	10
Methotrexate	14	0	1	1 (7%)	0	2	11
Cisplatin	18	1	2	3 (16%)	0	3	12
Dibromodulcitol	22	1	3	4 (18%)	0	6	12
Cyclophosphamide	21	1	3	4 (19%)	2	9	6
Pentamethylmelamine	25	1	7	8 (32%)	2	9	6
Etoposide	19	0	7	7 (36%)	3	5	4
Mexamethylmelamine	26	0		10 (38%)	12	0	4
Ifosfamide	20	0		8 (40%)	2	2	8
Vincristine	25	2		9 (44%)	0	8	6
Vindesine	32	3		10 (41%)	0	9	10
Epidoxorubicin							
Every wk	18	0	9	9 (50%)	0	7	2
Every 3 wk	18	0	11	11 (60%)	0	7	0
Neoadjuvant	21		20	20 (95%)*			

Abbreviations: CR, complete response; PR, partial response; MR, minor response; PD, progressive disease; SD, stable disease.

* Twenty of 21 patients with squamous cell carcinoma treated neoadjuvantly and adjuvantly had a grade 1 to 3 "chemotherapeutic" effect.

These results have encouraged the use of neoadjuvant and adjuvant chemotherapy in bladder cancer. A study evaluating neoadjuvant epirubicin in patients with T2-T3 disease randomized patients to receive either two courses of epirubicin (120 mg/m^2 every 21 days) preoperatively and four additional courses after radical cystectomy, or radical cystectomy alone. In the neoadjuvant arm, necrosis was found in 95% of patients with squamous cell carcinoma and in 57% of those with transitional cell carcinoma. The estimated disease-free survival rates for epirubicin-treated versus cystectomy-alone patients were 74% and 38%, respectively.[23] Adjuvant therapy was tried in another randomized trial, with epirubicin given as 120 mg/m^2 for four courses every 3 weeks versus observation alone after cystectomy. Results will be published soon.

In addition to local recurrence, which accounts for approximately 60% to 70% of treatment failures and low survival figures, other causes include early postoperative complications, and early or late hepatic and/or renal failure. Distant metastases are not a significant cause of patient death from bilharzial bladder cancer, although an increase in the frequency of distant metastases has been reported recently.[24] This high incidence of local tumor recurrence highlights the necessity of using local adjuvant therapy to improve final treatment outcome. This adjuvant treatment may be in the form of preoperative or postoperative radiotherapy, or both. However, in a large series from the NCI, Cairo, among 147 patients treated with concentrated preoperative radiotherapy (200 cGy over 1 week), there were eight inoperable cases (5.4%) compared with 13.1% among 837 patients treated with radical cystectomy alone.[25] However, the improvement in survival was not significant with the addition of preoperative radiotherapy (36% and 38% for cystectomy alone or with preoperative radiotherapy, respectively).

In a randomized clinical trial, Zaghloul et al[26] compared cystectomy alone to two different fractionated postoperative radiotherapy schedules in 236 bilharzial bladder patients. There was marked improvement of 5-year local control rates of the two postoperative radiotherapy regimens (87% and 93%) over the cystectomy-alone rate (50%). This improvement of local control resulted in a better 5-year disease-free survival (49% and 44%) for postoperative multiple daily fractionation or

conventional radiotherapy than for cystectomy alone (25%).

FUTURE DIRECTIONS

Bilharzial bladder cancer in Egypt is a good example of a preventable malignant disease. Primary prevention could be possible if the parasite is eliminated nationwide. The current strategy involves a combination of snail control and mass therapy of the infested rural population by the proven efficacious antibilharzial drugs. These efforts have recently significantly reduced the prevalence of bilharziasis in Egypt. Chemoprevention by the administration of retinoids to revert to normal, precancerous atypical squamous metaplastic lesions is another feasible approach. The increased expression of cyclooxygenase 2 (COX-2) observed in a recent study suggests that inhibitors of this enzyme may be useful for chemoprevention of bilharzial bladder cancer.[27] Secondary prevention is also possible by early detection of the disease in rural population using urine cytology. Selective scanning of the high-risk group (farmers aged $\geq$ 20 years) proved to be effective for the early detection of bladder cancer, with a yield of two per 1,000 individual screened.[28]

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