Patients With Spina Bifida and Bladder Cancer: Atypical Presentation, Advanced Stage and Poor Survival

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Purpose: Patients with neurogenic bladder dysfunction due to spina bifida have been reported to be at increased risk for bladder cancer. Recent publications suggest that bladder augmentation is also a significant risk factor. We reviewed our experience with treating patients with spina bifida and bladder cancer.

Materials and Methods: Patients with spina bifida treated for bladder cancer between 1995 and 2005 were identified. Patient demographics, mode of bladder management, risk factors and presenting symptoms were recorded along with therapy, pathological findings and outcome. This patient cohort was combined with all prior known published studies for analysis.

Results: Eight patients with a median age of 41 years were treated. Only 1 patient (13%) had undergone bladder augmentation. Locally advanced stage (T3 or greater) or lymph node metastases were present in 88% of cases. Median survival was 6 months with only 1 patient alive with no evidence of recurrence at 20 months. A total of 11 prior published cases were identified and combined with this series. Transitional cell carcinoma was present in 58% of patients. Median survival was 6 months. Only 37% of patients had undergone bladder augmentation.

Conclusions: Patients with spina bifida and bladder cancer present at a young age with variable tumor histology and advanced stage, and they have poor survival. Presenting symptoms are often atypical and bladder cancer should be a consideration in this patient population, even in young adults. Due to poor survival further study is warranted in this population to determine whether screening would be beneficial for earlier detection and improved outcomes.

Key Words: bladder; spinal dysraphism; bladder neoplasms; urinary bladder, neurogenic

Although the incidence of spina bifida in North America has decreased in the last 15 years, it continues to affect 1/1,000 to 1/4,000 births.[1] Almost all patients with spina bifida have some degree of neurogenic bladder that requires consistent management. Currently no completely established guidelines regarding the method and timing of urinary tract evaluation for these patients exist. However, some investigators suggest that evaluation should include renal and bladder ultrasound, and urodynamics.[1,2] Improved treatment in patients with spina bifida has increased their life expectancy and expectation for urinary continence.[3,4]

Historically patients with spina bifida with severe neurogenic bladder dysfunction underwent ileal conduit diversion. Late complications, including upper tract deterioration, led to a shift in management to lower tract reconstruction.[4] Currently management for neurogenic bladder typically involves intermittent catheterization with or without the addition of anticholinergic drugs, eg oxybutynin.[2] Some patients require surgical intervention, such as augmentation cystoplasty.[2,4]

Patients with neurogenic bladder seem to be at increased risk for bladder cancer. Hypothesized etiological factors include chronic urinary tract infections, inflammation and indwelling catheters.[3] In spinal cord injured patients treated with chronic indwelling catheters for more than 10 years there is an almost 10% incidence of bladder cancer.[5] There are reports of bladder malignancy (transitional cell carcinoma and squamous cell carcinoma) developing in patients with spina bifida who undergo clean intermittent catherization.[6,7] Additionally, bladder cancer has been reported to develop in patients who have undergone augmentation cystoplasty.[4,8-10] We reviewed our experience with bladder cancer in patients with spina bifida treated at University of Iowa Hospitals and Clinics.

MATERIALS AND METHODS

Upon receiving Institutional Review Board approval we performed a retrospective chart review of all patients with spina bifida treated for bladder cancer. The billing database at our hospital was queried for patients with spina bifida and bladder cancer using International Classification of Diseases, 9th revision 741 (spina bifida) and 188 (malignant neoplasm of the bladder), and their subtypes to identify patients treated at our institution from 1995 to 2005. The records of all identified patients were reviewed. Patients with spina bifida occulta were excluded, as were patients without a histologically confirmed diagnosis of bladder cancer. We recorded patient demographics, mode of bladder management, risk factors such as smoking or chemical exposure and presenting symptoms. Treatment was noted, including surgery, chemotherapy and radiation. Pathologi-

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TABLE 1. *Demographics and presenting symptoms in patients with spina bifida and bladder cancer at University of Iowa Hospitals and Clinics from 1995 to 2005*

	No. Pts (%)
Median age at diagnosis (range)	41 (23–60)
No. sex:	
M	1 (13)
F	7 (87)
Augmentation	1 (13)
Presenting symptoms:	
Gross hematuria	5 (63)
Urosepsis	1 (13)
Renal failure	2 (25)
Difficult catheterizion	2 (25)
More frequent urinary tract infections	2 (25)
Sterile pyuria	1 (13)

TABLE 2. *Histopathological findings and treatment of patients with spina bifida and bladder cancer at University of Iowa Hospitals and Clinics from 1995 to 2005*

	No. Pts (%)
Histology:	
Transitional cell Ca	4 (50)
Squamous cell Ca	2 (25)
Adenoca	2 (25)
Stage:	
T2	2 (25)
T3	2 (25)
T4	4 (50)
Node pos	3 (38)
Treatment:	
Radical cystectomy	7 (88)
Radiation	2 (25)
Chemotherapy	2 (25)
Sigmoidectomy	1 (13)

cal data included the grade, stage and histological type of bladder cancer. Followup and survival were noted.

A PubMed™ search was performed to identify other publications of patients with spina bifida who had bladder cancer. Search terms included myelodysplasia, spina bifida, neurogenic bladder, bladder cancer and augmentation cystoplasty. Search terms were combined to identify prior published reports. Similar patient demographics, treatment and outcome were recorded when available. Statistical analysis was performed using SigmaStat™ 3.1.

RESULTS

We identified 1 male and 7 female patients diagnosed with spina bifida and bladder cancer during this period at our institution (table 1). Patients presented with gross hematuria (5 of 8 or 63%) and renal failure due to bilateral ureteral obstruction (2 of 8 or 25%). Three of the 5 patients who presented with gross hematuria had a history of hematuria. All 8 patients had a history of recurrent urinary tract infections. One of these 8 patients (13%) had a history of smoking (52 pack-years).

Bladder management included 2 patients with an artificial urinary sphincter, 4 on intermittent catheterization and only 1 with a permanent suprapubic tube. Only 1 female patient (13%) had undergone bladder augmentation surgery (ileum), which was performed 8 years before the bladder cancer diagnosis. Median patient age at diagnosis was 41 years (range 23 to 50). Five of the 8 patients (63%) were followed on a regular annual basis by urologists. Followup consisted of yearly visits with upper tract imaging or following serum creatinine and urinalysis. No patients underwent yearly cystoscopy or routine bladder imaging. Seven of the 8 patients (88%) had locally advanced tumor (T3) or lymph node metastases at presentation. Histologically 4 patients had transitional cell carcinoma, 2 had squamous cell carcinoma and 2 had adenocarcinoma.

Treatment included radical cystectomy in 7 patients and radiation therapy for unresectable tumor in 1. Neoadjuvant chemotherapy (cisplatin, methotrexate and vincristine) was given to a single patient before radical cystectomy with the goal of reducing the tumor burden. A single patient was treated with chemotherapy (gemcitabine and cisplatin) and radiation therapy after metastatic disease was detected. Only 1 patient was alive 20 months following surgery (stage pT2N0M0) with no evidence of disease. For all patients median survival time was 6 months (range 1 to 55, mean 20). Table 2 shows patient treatments and outcomes.

Review of prior published reports identified 11 additional patients with spina bifida who had bladder cancer (table

TABLE 3. *Prior published experience in patients with spina bifida and bladder cancer*

References	Pt Age—Sex	Bladder Augmentation (yrs postop)	Pathological Findings (stage)	Treatment	Survival (mos)
Qiu et al[11]	73—F	Gastric (13)	Transitional cell Ca (not available)	Radical cystectomy, sigmoidectomy	Not documented
Gaskill[3]	33—F	None	Transitional cell Ca (T4)	Radical cystectomy, chemotherapy	Not documented
Barrington et al[12]	33—M	Ileal undiversion (11)	Adenoca (T3)	Radical cystectomy, bilat nephroureterectomy	3 (dead of disease)
Baydar et al[13]	36—M	Gastric (14)	Adenoca in gastric remnant signet ring	Radical cystectomy	5 (no disease evidence)
Soergel et al[8]	44—M	Cecal (21)	Transitional cell Ca	Cystectomy	Not documented (dead of disease)
Soergel et al[8]	37—Not available	Ileocecal (17)	Transitional cell Ca	Radical cystectomy	8 (dead of disease)
Soergel et al[8]	29—F	Ileocecal (21)	Transitional cell Ca	Lymph node biopsy, urinary diversion	Not documented (dead of disease)
Koury and Freeman[6]	32—F	None	Transitional cell Ca (p'T4N0M0)	Radical cystectomy, sigmoidectomy	3 (no disease evidence)
Game et al[14]	53—M	None	Transitional cell Ca (pT3b)	Radical cystectomy	Not documented
Yaqoob et al[7]	45—F	None	Squamous cell Ca	Not reported	2 (dead of disease)
Yaqoob et al[7]	36—F	None	Squamous cell Ca	Not reported	Not documented (dead of disease)

3).[3,6–8,11–14] Only 5 patients had survival times published. Combining these 5 patients with the additional 8 in our series revealed a median survival of 6 months (range 1 to 55, mean 17). Only 3 patients were reportedly free of disease but followup was short (mean 9 months). Considering all 19 cases, median age at diagnosis was 37 years (range 23 to 73). Only 7 of 19 patients (37%) had undergone bladder augmentation with a median time from augmentation to cancer diagnosis of 14 years (range 8 to 21). The most common histology was transitional cell carcinoma in 58% of cases, followed by squamous cell carcinoma in 21%, adenocarcinoma in 16% and a signet ring carcinoma of gastrocystoplasty in 5%. Advanced stage or metastatic disease (T3 or greater, or lymph node positive) was present in 93% of patients (15 of 16) with staging data available. A single patient had T2 disease with negative lymph nodes. No patients presented with superficial or low grade transitional cell carcinoma.

DISCUSSION

To our knowledge we report the largest series to date of patients with spina bifida treated for bladder cancer. Prior publications consist mostly of case reports with a recent series of 3 patients by Soergel et al.[8] Analysis of our series and prior reported patients demonstrates common themes. Patients are younger than typical patients with bladder cancer and presenting symptoms may be atypical. Survival of these patients is poor since most have advanced disease and a subset has an aggressive variant, such as squamous cell cancer or adenocarcinoma.

The role of bladder augmentation as a risk factor for transitional cell carcinoma remains controversial. The estimated risk of carcinoma in patients with spina bifida who have bladder augmentation is between 1.2% and 3.8%, although this was only evaluated in patients with a history of bladder augmentation.[8] Although we cannot provide an estimate of the relative risk (incidence) of bladder cancer in our series, only 1 of 8 patients underwent prior bladder augmentation. This suggests that the risk of bladder cancer may be present in patients with spina bifida regardless of bladder augmentation. Additionally, only 37% of published cases had bladder augmentation. Filmer and Spencer reviewed publications regarding malignancy and bladder augmentation in 14 patients.[10] None of the patients cited had spina bifida and the majority had undergone augmentation for genitourinary tuberculosis, which may be a risk factor. Tumor histology is clearly different from that typically seen with bladder cancer with transitional cell carcinoma comprising only 58% of cases. Tumor histology in spinal cord injured patients was also reported to occur with an increased percent of squamous cell carcinoma and adenocarcinoma.[15]

Most of our understanding about the association of neurogenic bladder dysfunction and bladder cancer comes from prior studies in spinal cord injured patients, in whom the increased risk of bladder cancer is well established. For decades the strong association between squamous cell carcinoma of the bladder and a chronic indwelling catheter has been known. Mean time to cancer diagnosis from injury has been reported to be 23 to 34 years.[15,16] Pannek reported a longer latency time in patients with squamous cell vs transitional cell carcinoma (32 vs 20 years).[16] Statistically significant risk factors include an indwelling catheter for more than 8 years and bladder stones.[15] Chronic inflammation and urinary tract infections are thought to have a contributing role in carcinoma development. However, given that almost all patients with neurogenic bladder dysfunction have prior infections (100% of our patients), this is not a risk factor that can be used to identify those at risk.

Given the high mortality and percent of patients with advanced stage disease, screening patients with neurogenic dysfunction has been advocated. Although the value of surveillance cystoscopy, biopsies and cytology is controversial, several groups have recommended screening.[8,17-19] Recommendations for the protocol and timing vary. One study of spinal cord injured patients demonstrated a trend toward lower stage disease and better survival in those diagnosed by screening vs those presenting with symptoms.[19] Stonehill et al reported the use of cytology to follow a large population of spinal cord injured patients by evaluating 3 cytology samples per year.[17] With this approach cytology had 71% sensitivity and 97% specificity. They considered specimens positive when reported as suspicious, defined as atypical suspicious, suspicious for cancer, cancer, dysplasia or keratinizing squamous metaplasia, and they evaluated those patients further with cystoscopy.

The value of urinary cytology after bladder augmentation has not been well studied. Despite these findings cystoscopy with or without biopsy has not been found to be a valid screening test in spinal cord injured patients due to the low tumor incidence and excessive cost.[18,20] Recommendations recently published for patients with spina bifida were to perform yearly cystoscopy in all patients with a history of bladder augmentation starting 10 years after surgery.[8] It is important to note that there have been neither studies reporting screening in the spina bifida population nor data on whether it would improve outcome. More than half of our 8 patients were being followed regularly by urologists, and yet they still presented with advanced disease. Furthermore, screening this population of patients would significantly increase the number of costly studies and procedures performed on this complex population of patients. The cost, use of resources and possibility of morbidity associated with these procedures along with the lack of evidence for benefit make screening less appealing.

With improved health care patients with spina bifida are living longer into adulthood. Just how much longer these patients are living and whether bladder cancer will be an increasing prevalent problem in the future remains to be seen. Our experience suggests that this is a rare problem. The poor outcomes in these patients reinforces the need for lifelong urological followup. Additionally, it is paramount that we should educate these patients and their care providers to seek prompt attention if symptoms such as hematuria or other new problems arise. We must consider the possibility of bladder cancer when following these patients.

CONCLUSIONS

Patients with spina bifida and bladder cancer present at a young age with variable tumor histology and advanced stage, and they have poor survival. Presenting symptoms are often atypical and bladder cancer should be a consideration in this patient population, even in young adults. Due to poor survival further study is warranted in this population

to determine whether screening would be beneficial for earlier detection and improved outcomes.

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