Morphological and Clinical Observations of Patients with Early Bladder Cancer Treated with Total Cystectomy

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Summary

In 21 cases, early bladder cancer was detected by urine cytology, although not by cystoscopy, and was treated by total cystectomy. The neoplasms, all transitional cell carcinomas of moderate to high degrees of anaplasia, were entirely in situ in 17 of the 21 patients; in 4, although mainly in situ, the tumors showed additional minimal microinvasion. Widespread mucosal involvement was demonstrated in every case by step-sectioning, and extension into the prostatic ducts occurred in 7 of the 19 male patients and into the mucosa of one or both distal ureters in 12 patients. Premalignant atypia of the mucosa was also widespread and direct intramucosal spread of cancer cells was a significant factor, particularly along the prostatic ducts and ureters. The duration of significant symptoms (follow-up for 9 years before cystectomy in several cases and for 8 years in 1 histologically proved case) suggests that the evolution of these tumors may be considerably longer than previously documented.

Since March 1970, a systematic application of urine cytology for the detection of malignant lesions in the urinary tract has been in use at the Mayo Clinic among outpatients chiefly from the urological service. Through August 1975, approximately 25,000 patients have undergone at least 33,500 urine cytological examinations, and close correlation with the cystoscopic findings showed that 89 of these patients without previous bladder neoplasm had urine cytological findings positive for urothelial cancer and, in each, the lesion was not identified at cystoscopy. (The lesion in 1 patient was first detected by urine cytology in 1967 at another institution.) In 33 of the 89 patients, the lesions have not yet been localized or proved, and follow-up is being continued. In the other 56 patients, localization and tissue proof of diagnosis have been established. Included among these are 2 patients with unilateral in situ carcinoma of the lower ureter, one with in situ carcinoma of the renal pelvis, and one with in situ carcinoma of the penile urethra. The lesions in the remaining 52 patients are all primary transitional cell carcinomas of the bladder. Of the 52 patients, 29 have been treated by local therapy and their condition is being closely followed. Twenty-three patients were subjected to total cystectomy, 2 at other institutions and 21 at our institution. This latter group will comprise this report.

Materials and Methods

All 21 patients (2 women, 19 men) were ambulatory and seen as outpatients in the Department of Urology. Freshly voided urine aliquots in amounts of 50 to 100 ml were obtained, processed immediately to a point of fixation through an 8-μm micropore filter, and stained by the Papanicolaou technique. Cystoscopic examinations were performed initially using local anesthesia and instruments with fiber-optic light source. When cytological results indicated cancer, repeat cystoscopic examination usually was performed in the hospital with the patient under general anesthesia; specimens for biopsy were obtained from any suspicious zones and from random regions of mucosa. Excretory urography, urinalysis, and standard urological investigation were performed on every patient.

Radical cystectomy was performed with each patient under general anesthesia. Resection included the prostate and the membranous urethra in males and the entire urethra in females. The pelvic segments of both ureters, generally 4 cm or more, were removed with the bladder, as well as the seminal vesicles in males. Total hysterectomy and partial vaginectomy were performed in females. Seven patients also had pelvic lymphadenectomy.

All specimens were preserved in 10% buffered formalin and were available for study. Most of the specimens had been fixed at the time of operation and pinned to corkboard in the distended state to facilitate anatomic orientation. These specimens were step-sectioned at 3-mm intervals from the distal resection margin of urethra throughout the entirety of the prostate and bladder and the lengths of both ureters. In 2 cases, neither ureter could be identified in the specimen, and in 4 cases only 1 ureter could be identified. On a diagrammatic drawing of the bladder, each block of tissue was located in its proper anatomic location and, after light microscopic examination of specimens, stained with hematoxylin and eosin; the lesions also were mapped and represented diagrammatically with respect to 4 categories of mucosa: (a) normal or near normal, (b) definitely altered atypia, (c) in situ carcinoma, and (d) microinvasive carcinoma.

Results

Gross Findings. No bladder showed evidence of grossly recognizable neoplasm. Examined in the fresh state imme-
diately after removal, mucosal vascular injection and a characteristic salmon-colored blush were usually apparent.

**Microscopic Findings.** All neoplasms were of transitional cell type, and all showed appreciable degrees of anaplasia (Grades 3 and 4). The neoplasms in 17 patients were entirely in situ. The morphological features were those of full-thickness alteration in the cytological characteristics of the mucosal cells with nuclear enlargement, increased nuclear-cytoplasmic ratio, irregularity of nuclear shape, increased nuclear staining density, and coarsened texture of nuclear chromatin. Abnormal mitoses were frequently present (Fig. 1). A characteristic feature was the loss of intercellular cohesiveness (Fig. 2) and also the loss of cohesiveness of the cells along the basilar zone to the basement membrane resulting in induced artifactual zones of totally denuded mucosa. Inflammation in the submucosa adjacent to in situ carcinoma was a constant and often severe finding, featuring an infiltrate of lymphocytes, plasma cells, and monocytes. Vascular endothelial proliferation and fibrosis in the submucosa also were frequently observed. In many bladders, Brunn’s epithelial nests were observed in the submucosa; frequently they were replaced by extension of the malignant cell population from the overlying surface (Fig. 3). In addition to extensive in situ malignant change, we noted microscopic zones of invasion into the submucosa in 4 patients, single foci in 3 patients, and multiple foci in 1 patient.

**Distribution of Mucosal Lesions.** In most bladders, in situ malignant change was extensive (Chart 1). In 15 of 21 patients, carcinoma involved more than one-third of the mucosa examined and, in 9 patients, involved 50 to 85% (Table 1). The trigone region and contiguous posterior wall of the bladder were particularly affected, being involved to some extent in 19 patients. The ureteral orifices, however, were not uniformly affected: both were affected in 9 patients, only the right in 3, and only the left in 6 being covered by malignant mucosa. In 7 patients, the mucosa in varying lengths of both distal ureters showed in situ carcinoma, as did the right ureter independently in 1 patient and the left ureter in 4 patients, a total of 12 patients with distal ureteral involvement. Severe mucosal atypia was present in the distal ends of 3 other patients. In every patient, mucosal findings in the distal ureters coexisted with identical changes on the bladder mucosa adjacent to that ureteral orifice. In no instance did in situ carcinoma of the ureteral mucosa exist independently of a concomitant change in the homolateral ureteral orifice and adjacent trigonal mucosa.

Twelve patients showed in situ carcinoma of the vesical neck and in 13, the urethra was involved. In no instance did the malignant change extend to the distal resection margin. Both female patients (Cases 5 and 17) showed involvement of the vesical neck and urethra. Seven of the 19 male patients showed extension of in situ carcinoma into the periurethral prostatic ducts. This was often extensive and invariably it was associated with in situ change in the adjacent urethral mucosa.

**The Nature of Epithelial Atypia.** Bladder mucosal atypia is recognized as varying degrees of alteration in the regularity of mucosal anatomy. The implication is one of a dynamic premalignant state with progressive loss of the normal polarity of the cell population, increased mitotic activity often in locations away from the normal basal germinative zones, and cytological alterations in the direction of malignancy (Fig. 4). Such atypia or premalignant change was widespread in the mucosa of every bladder and was often inti-
Table 1
Carcinoma in situ: clinical features

<table>
<thead>
<tr>
<th>Case</th>
<th>Duration of symptoms before cystectomy (mo)</th>
<th>Earliest cystoscopically detected findings</th>
<th>Findings on initial urinalysis</th>
<th>Other treatment</th>
<th>Date</th>
<th>% of Mucosal involvement</th>
<th>Postoperative course</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (64)*</td>
<td>60</td>
<td>Mucosal erythema</td>
<td>RBC 4-6</td>
<td>TUR prostate, 1968</td>
<td>1/15/70</td>
<td>60*</td>
<td>Living and well; no recurrence 66 mos.</td>
</tr>
<tr>
<td>2 (75)</td>
<td>18</td>
<td>Mucosal edema, erythema</td>
<td>RBC 5-8</td>
<td></td>
<td>2/9/70</td>
<td>30</td>
<td>Died MI*; no recurrence 16 mos.</td>
</tr>
<tr>
<td>4 (72)</td>
<td>60</td>
<td>Mucosal erythema</td>
<td>RBC 30-40</td>
<td>Biopsy bladder, 1968</td>
<td>11/13/70</td>
<td>70</td>
<td>Died PO, bowel perforation 6 days</td>
</tr>
<tr>
<td>5 (53)*</td>
<td>18</td>
<td>Reddened granular mucosa</td>
<td>Negative</td>
<td></td>
<td>12/30/70</td>
<td>35</td>
<td>Living and well; no recurrence 46 mos.</td>
</tr>
<tr>
<td>6 (64)</td>
<td>18</td>
<td>Reddened granular areas</td>
<td>RBC 1-10</td>
<td>AgNO₃ irrigation</td>
<td>6/9/71</td>
<td>35</td>
<td>Living and well; no recurrence 51 mos.</td>
</tr>
<tr>
<td>7 (64)</td>
<td>24</td>
<td>Diffuse erythema</td>
<td>RBC 20-30</td>
<td>TUR bladder, in situ, 1971</td>
<td>12/17/71</td>
<td>85</td>
<td>Died acute abdomen; no recurrence 24 mos.</td>
</tr>
<tr>
<td>8 (70)</td>
<td>48</td>
<td>Diffuse inflammation</td>
<td>WBC 20-30 RBC 30-40 RBC 4</td>
<td>TUR prostate, 1970</td>
<td>3/22/72</td>
<td>40</td>
<td>Living and well; no recurrence 38 mos.</td>
</tr>
<tr>
<td>9 (66)</td>
<td>106</td>
<td>Marked diffuse inflammation</td>
<td>RBC 6-8</td>
<td>TUR prostate, 1971</td>
<td>9/11/72</td>
<td>60</td>
<td>Living and well; no recurrence 26 mos.</td>
</tr>
<tr>
<td>10 (47)</td>
<td>26</td>
<td>Diffuse erythema</td>
<td>RBC 1-10</td>
<td>TUR prostate, 1971</td>
<td>10/17/72</td>
<td>25</td>
<td>Living and well; no recurrence 24 mos.</td>
</tr>
<tr>
<td>11 (51)</td>
<td>24</td>
<td>Diffuse granular erythema</td>
<td>Negative</td>
<td></td>
<td>12/7/72</td>
<td>40</td>
<td>Living and well; no recurrence 27 mos.</td>
</tr>
<tr>
<td>12 (62)</td>
<td>36</td>
<td>Irregular erythema</td>
<td>WBC 1-10 RBC 0 RBC 30-40</td>
<td>TUR prostate, 1973</td>
<td>8/22/73</td>
<td>30</td>
<td>Living and well; no recurrence 15 mos.</td>
</tr>
<tr>
<td>13 (65)</td>
<td>108</td>
<td>Granular areas, erythema</td>
<td>WBC 30-40 RBC 30-40</td>
<td>Segmental resection bladder, 1970 TUR prostate, 1966</td>
<td>8/29/73</td>
<td>50</td>
<td>Died MI, 4 days</td>
</tr>
<tr>
<td>14 (58)</td>
<td>48</td>
<td>Granular areas, erythema</td>
<td>RBC 5-12</td>
<td>Nephroureterectomy, ca ureter (in situ), 1970</td>
<td>5/7/74</td>
<td>65*</td>
<td>Living and well; no recurrence 18 mos.</td>
</tr>
<tr>
<td>15 (56)</td>
<td>48</td>
<td>Raised encrusted zones</td>
<td>WBC 1-4 RBC 10-15</td>
<td></td>
<td>8/30/74</td>
<td>40*</td>
<td>Living and well; no recurrence 12 mos.</td>
</tr>
<tr>
<td>16 (61)</td>
<td>96</td>
<td>Granular reddened mucosa</td>
<td>WBC 30-40 RBC occ.</td>
<td>Ro Rx 1974; TUR prostate, 1972, 1973</td>
<td>9/13/74</td>
<td>35</td>
<td>Living and well; no recurrence 10 mos.</td>
</tr>
<tr>
<td>17 (67)*</td>
<td>24</td>
<td>Granular erythematous zones</td>
<td>WBC 1-5 RBC 1-3</td>
<td>TUR prostate, 1969, 1973 bladder fulguration</td>
<td>12/5/74</td>
<td>20</td>
<td>Living and well; no recurrence 5 mos.</td>
</tr>
<tr>
<td>18 (72)</td>
<td>52</td>
<td>Erythematous mucosa</td>
<td>WBC 6 RBC 0</td>
<td></td>
<td>5/13/75</td>
<td>25</td>
<td>Living and well; no recurrence 4 mos.</td>
</tr>
<tr>
<td>20 (62)</td>
<td>34</td>
<td>Granular reddened areas</td>
<td>WBC 20-30 RBC 15-20 RBC 3</td>
<td>TUR prostate, 1973</td>
<td>8/7/75</td>
<td>75*</td>
<td>Living and well; no recurrence 1 mos.</td>
</tr>
<tr>
<td>21 (57)</td>
<td>42</td>
<td>Erythematous zones</td>
<td>WBC 3 RBC 10-15</td>
<td>TUR prostate, 1973, 1975</td>
<td>8/28/75</td>
<td>55</td>
<td>Living, immediately after operation</td>
</tr>
</tbody>
</table>

* Numbers in parentheses, age (years) at cystectomy.
* a Microinvasion also present.
* b MI, myocardial infarction; PO, postoperative; occ., occasional; Ro Rx, X-ray treatment.
* c Female.

Morphologically admixed with mucosa showing the full malignant change. The atypia was pronounced about the borders of in situ carcinoma, with frequent zones of continuous gradation of change (Fig. 5). This morphological appearance suggested a gradual extension of the borders of the neoplasm in the mucosa by a progressive process of evolution of premalignant atypia.

Intramucosal Spread of Carcinoma. In every patient, some more prominently than others, a unique histological mucosal phenomenon was observed at the junction of bev-
nign and malignant mucosa, demonstrating accrual of additional mucosa into the malignant process by direct intramucosal spread of malignant epithelial cells. Two related morphological forms were identified. For distances of 1 to 2 mm adjacent to malignant zones, carcinoma cells of the interior or basal layer of epithelium were observed to extend along the basement membrane beneath the adjacent intact benign mucosa, lifting this mucosa off its basal footings; on further proliferation, the malignant cells formed multiple cell layers and the benign epithelium appeared to slough and to be replaced by malignant cells (Fig. 6). A second form, a striking pagetoid type, spread into adjacent epithelium with 2 to 3 clusters of malignant cells noted as much as 4 mm from adjacent in situ carcinoma. This phenomenon was especially prominent at the advancing margin of carcinoma in situ in the prostatic ducts and the mucosa of the distal ureters (Fig. 7).

Clinical Features. All 21 patients presented with symptoms of an irritable bladder, such as dysuria, frequency, and nocturia. Only 1 patient (Case 20) noted gross hematuria, although 18 had some degree of microhematuria. One patient (Case 10) was incontinent. The cystoscopic findings (Table 1) were generally mucosal erythema often with some granularity. From the clinical record and from correspondence with home physicians, the date of onset of pertinent symptoms was estimated and the duration prior to date of cystectomy was calculated (Table 1). Most of the male patients had undergone some form of surgical intervention before establishment of the correct diagnosis; 11 had had a prostatic TUR. One patient had a left nephroureterectomy 4 years before cystectomy with the finding of an in situ transitional cell carcinoma of the lower ureter. Two patients had undergone segmental bladder resections 8 years and 3 years before cystectomy in an attempt to remove the in situ carcinoma. Only 1 patient received radiation therapy (5000 rads), completed 3 weeks before cystectomy. Follow-up data are current in every case. No patient has died of bladder cancer or has evidence of recurrence; 4 have died from unrelated causes.

Discussion

It is axiomatic that every carcinoma of an epithelial surface must first pass through an in situ stage before invasion and metastasis can occur. In discussing carcinoma of the bladder, it should be emphasized that there is a continuous spectrum of neoplasia covering a wide range of biological potential from the quasibenign transitional papilloma to the highly anaplastic carcinoma. We have no reason to believe that our outpatient population differs significantly from the broad general population at risk for bladder cancer in a way that would selectively favor an unusual distribution of bladder neoplasms. However, the screening technique, urine cytology, relying as it does on the presence of significant malignant morphological alteration, detects predominantly neoplasms in the more malignant zones of the biological spectrum. All carcinomas in this study were Grade 3 or 4, and our series of cases does not include examples of well-differentiated transitional cell neoplasms. Indeed, by cytological methods, these neoplasms are extremely difficult to detect when small; consequently, little or nothing is known of the early evolution of these lesions in humans. It is true, however, that almost all fatal bladder cancer is of the more anaplastic type and our data are valid with respect to early bladder cancer of this type.

In spite of a number of excellent reports on in situ carcinoma of the bladder, the natural history of the lesion is still not clear (4-6, 9, 11, 12). In most cases, the lesions have been detected in a symptomatic stage, and progressive and rapid evolution to invasive cancer has occurred (5, 11). Detailed historical data and long-term follow-up on asymptomatic patients with proved lesions treated conservatively, such as are abundantly available for in situ carcinoma of the cervix, have not been reported for bladder cancer, largely because of a lack of existence of organized screening programs. We believe that the proved and as yet unproved cases that we are currently following will be a useful source of such data; however, there is a definite suggestion from our present study that the natural evolution to invasive cancer may span a much longer period than was reported previously. Indeed 3 of our patients gave histories of symptoms for at least 9 years before cystectomy. One of these patients (Case 19) had tissue proof of in situ carcinoma in 1967, 8 years before total cystectomy was performed.

Total cystectomy in these 21 patients is a significant selection factor. Besides being deemed physically able to withstand this operation, all of these patients had severe, compelling symptoms. The unoperated patients were generally less symptomatic. On this basis we are justified in considering the neoplasms more advanced in cystectomized patients. In spite of this, it is remarkable that such wide expanses of bladder mucosa should be involved by in situ malignant change with only minimal microinvasion present in 4 cases. This finding implies that invasion occurs only after large areas of mucosa have already undergone malignant changes. We tried to relate the extent of mucosal change to the duration of symptoms as shown in Table 1. Our cases support the findings of Koss et al. (3) and of Skinner et al. (9) that invasive bladder cancer is associated with widespread in situ carcinoma and mucosal atypia.

In situ carcinoma has been well documented in the distal ureters of cystectomy specimens for advanced cancer (2), but the finding of distal ureteral involvement in over 50% of our patients is indicative of the widespread mucosal abnormality in this neoplasm. Likewise, the frequency of extension of the neoplasm into the prostatic ducts, first emphasized by Seemayer et al. (8) and by Thelmo et al. (10), has not been generally recognized. Over one-third of our male patients demonstrated this phenomenon.

Mucosal atypia and premalignant epithelial changes have been studied by Cooper et al. (1), by Schade (6), and by Schade and Swinney (7). They have emphasized the mode of development of carcinoma in abnormal, dysplastic epithelium. Our studies confirm these changes to be widespread in association with in situ carcinoma. Intramucosal extension of malignant cells into adjacent normal mucosa has not been emphasized previously, but in our study it appears to be the major mode of spread into the distal ureters and the prostatic ducts.
Morphological Studies of Early Bladder Cancer

References


Fig. 1. Transitional cell carcinoma in situ. There is disorganization of mucosal architecture, and individual cells show cytological features of cancer. H & E, x 640.

Fig. 2. Transitional cell carcinoma in situ. Intercellular attachments are defective with increased desquamation of malignant cells. H & E, x 400.

Fig. 3. Transitional cell carcinoma in situ with extension into Brunn's epithelial nest. H & E, x 250.

Fig. 4. Transitional epithelial atypia. The number of cell layers is increased and individual cells show cytological alterations short of malignancy. H & E, x 400.

Fig. 5. Transitional epithelial atypia with continuous gradation of change from mucosa in upper right to greatly altered borderline malignant mucosa in lower right. H & E, x 250.

Fig. 6. Extension along basilar layer of malignant cells beneath intact benign mucosa. H & E, x 400.

Fig. 7. Pagetoid spread of transitional carcinoma cells into intact mucosa. H & E, x 400.
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