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CARCINOMA IN SITU OF THE URINARY BLADDER
Report of a Case

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Cancer of the bladder is the most important of the malignant tumors of the urinary organs. In 1950, the Public Health Service reported that 177,464 persons in the United States died of malignant disease during 1945; of these, 5,410, or 3% of the total, died from bladder cancer. Per 100,000 population in 1945, the death rate from bladder cancer among persons 55 to 64 years of age was 10.5; among those 65 to 74 years old it was 26.2 and among persons 75 to 84 it has risen to 49.4. The ratio of male to female is 4 to 1.1

CASE HISTORY

A 62-year-old white male first presented to the Urology Clinic in 1961 with irritative bladder symptoms. He gave a history of having had a transurethral resection for benign prostatic hypertrophy elsewhere. The patient did not respond to anti-spasmodics; his urine was not infected. In January 1962 he was endoscoped and was found to have some residual anterior tissue. This was resected. He did well following this resection with no irritative symptoms and with good size and force to stream.

In May 1963 he again presented with irritative symptoms. A number 22F sound passed into the bladder with ease. The patient was placed on Levamine. His urine was uninfected.

In January 1964 he presented to the clinic with the history of having a few flecks of blood in his urine.

In March 1964 the patient was cystoscoped. A diffuse erythema was noted especially on the left of the trigone. Retrograde pyelograms were normal. A biopsy with a resectoscope was made and the pathology report was carcinoma in situ.

The patient was recystoscoped in June 1964. Some reddening of the entire left side of the trigone, and scarring from the previous biopsy were noted.

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In September 1964 the patient had another cystoscopic examination and was almost asymptomatic at this time. Again a slightly red heaped-up area on the left side of the trigone was noted. A transurethral resection of this area was performed. The pathology report was carcinoma in situ, and the resection was followed by four treatments with Thio-topa.

In January 1965 cystoscopy again showed a reddened elevated lesion on the trigone, spreading across the midline. This area was resected and the pathology report was again carcinoma in situ. Prior to this examination, the patient did not have any red blood cells in his urine.

In March 1965 a reddened area on the left side of the trigone was again noted with question of a cyst formation. Intravenous pyelograms were normal.

The patient was admitted to the hospital in April 1965 and had another transurethral resection of this area. The pathology report was transitional cell carcinoma with superficial invasion. Several reddened areas above the trigone were noted on this cystoscopy.

In June 1965 the patient had a cystectomy and ileac conduit. His postoperative course was uneventful and at present he is doing well with no evidence of metastatic or residual tumor.

Figure 1
Carcinoma in situ of the urinary bladder 175x.
Carcinoma in situ

Figure 2
Carcinoma in situ of the urinary bladder 840x.

Figure 3
Transitional cell carcinoma of the bladder showing superficial invasion 175x.
DISCUSSION

Because of their biologic characteristics, all papillary, fungating epithelial tumors should be called carcinoma, even those that appear histologically well-differentiated and apparently benign. Very well-differentiated forms recur, invade and have aggressiveness. These tumors provide a classic example of the necessity for a specific knowledge of the life history of all forms of neoplasia since in different locations essentially similar lesions may have totally dissimilar behavior.

The great majority of bladder tumors are epithelial. The term noninfiltrating implies that the basement membrane is intact beneath the tumor. When tumor cells break through this membrane the tumor becomes infiltrating. In the Brady Urological Institute, 33% of the epithelial tumors were found by Scott and McKay to be non-infiltrating when first seen. Most of these tumors were papillomas.

A noninvasive sessile carcinoma is called intraepithelial carcinoma or carcinoma in situ. The tumor has no pedicle, but its epithelium exhibits a variable degree of pleomorphism. Anaplasia, hyperchromatism, polynucleosis, disparity in size, shape, and staining quality of nuclei, increase in abnormal mitosis, and disorderly arrangement of the cells are frequently observed, but the basement membrane is intact. The multilayering of the epithelial cells, however, is not itself an indication of malignancy; pleomorphism, on the other hand, does indicate malignancy.
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In 1922 Broder attempted to relate prognosis of bladder tumors to differentiation of the cells from normal mature epithelium. However, in 1951 at Johns Hopkins Hospital it was demonstrated in a study of 95 cases that approximately 45% showed degrees of cellular differentiation in different parts of the same tumor.

In 1946, Jewett studied 107 autopsy cases of bladder carcinoma with regard to the incidence of metastases, e.g. regional and distal metastases, the number showing perivesical lymphatic or vascular invasion only, and the number with perivesical fixation of the mass. The percentage of cases without these evidences of tumor spread gives us our figure of potential curability:

Group A, submucosal infiltration, 100% potential curability.

Group B, muscular infiltration, 86.6% potential curability.

Group C, perivesical infiltration, 26% potential curability.

Powell showed that the lymphatics are larger and more numerous in the depths of the bladder wall, which may explain the higher incidence of metastases in Group C tumors.

The incidence of metastases and extravesical extension therefore varied directly with the depth to which the tumor had infiltrated the wall of the bladder.

Marshall studied 106 patients treated with excision and fulguration. The overall five-year survival rate was 69.8%. The stage and grade of tumor affected survival. Consequently, the five-year survival rate was 82% in patients with low stage, low grade tumor, 76% in patients with low stage, high grade tumor, 16.7% in patients with high stage, high grade tumor, 0% in (2) patients with high stage, low grade tumor.

Marshall concluded that the low grade and low stage carcinomas of the urinary bladder were reasonably well managed by local excision and fulguration, together with careful follow-up cystoscopic examinations. The operative risk was low; the morbidity was not great; continence was maintained; and most particularly the survival closely approximated the expectancy otherwise. In contrast, cancers of high grade malignancy, especially those in high stages were not satisfactorily controlled by local excision and fulguration.

Marshall and Whitmore made several conclusions from their study of bladder tumors. Some of those concerning low grade low stage tumors are as follows:

1. The most powerful influence on the patient’s course is the intrinsic nature of the neoplasm.

2. Initial treatment of choice, for patients with low grade carcinoma still in low stages, is local excision, fulguration and follow-up.
3. High grade carcinoma in low stages is also probably best managed by local excision, fulguration, and follow-up as the initial therapy. But close follow-up is required as a change of therapy will often be indicated.

As can be seen from the above, the survival rate from carcinoma of the bladder decreases as the stage increases. Carcinoma in situ is an entity by itself, that must be recognized, and a knowledge of its life history will determine the aggressiveness of the surgical approach.

Voutsa and Melamed in studying the cytology of in situ carcinoma of the urinary bladder followed 20 patients for six years. All patients had a past history of apparently successfully treated and eradicated benign papilloma or carcinoma. Cytological specimens were obtained in a follow-up period.

Papanicolaou stained smears of urinary sediment were studied — 350 specimens were examined in the 20 patients. In all cases, patients had specimens taken at the time when they had in situ carcinoma as well as could be determined clinically, cystoscopically, and pathologically.

Six cases showed progress from in situ to invasive carcinoma. In 6 patients who had a total cystectomy a diagnosis of in situ carcinoma without invasion could be confirmed by pathological study of the entire bladder. Of 8 patients remaining, 6 still have in situ carcinoma. Two died of unrelated disease without evidence of invasion.

The histological diagnosis of in situ carcinoma is based on apprasial of cytological alterations in sections of epithelium. Cytological diagnosis in smears rests on recognition of these same alterations in cells exfoliated from the epithelial surface.

The most consistent and most characteristic picture of the cytological presentation was a uniform pattern of malignant cells seldom seen in invasive carcinoma. Cells were found singly or in small clusters and could be numerous or few. Alterations within the cells were less bizarre and less obvious than in invasive carcinoma. In carcinoma in situ, cells were about the size of normal bladder epithelial cells or a little larger.

The nuclei were slightly enlarged, always hyperchromatic with coarse chromatic structure. The cytoplasm was usually thin and moderate in amount, and often showed a hazy opacity usually not seen in benign bladder epithelial cells.

The results of their study was that a cytological pattern does exist in carcinoma in situ which is different from that of invasive carcinoma.

Meicow in 1952 studied ten total cystectomy tumor-bearing and five control tumor-free bladders. Routine sections of the tumor and of pieces of normal looking mucosa were made.
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In two of the tumor-bearing bladders, areas of carcinoma in situ were found on section of the normal-appearing mucosa. Epithelial hyperplasia, cystitis cystica and glandularis were found on the other tumor-bearing bladders studied. In two of the bladders which showed hyperplasia, hyperchromatism was also noted. Of the five normal bladders studied, one with cystitis cystica was found.

The findings suggest that in any operation upon the bladder for the removal of a grossly obvious growth, there may already be present in that bladder, unseen with the naked eye, areas of hyperplasia or beginning anaplasia or both; these in time could result in gross new tumor formation. Many recurrences therefore are actually the coming of age symptomatically of a neoplastic process which may have been initiated before or after operation.

Melicow found that bladders which contained papillary tumors, single or multiple, showed a greater incidence of microscopic foci of epithelial activity than did solid solitary tumors. This conforms with the clinical observation that many of the papillary tumors may first spread in a horizontal plane while the indurated and ulcerative types penetrate earlier in a vertical plane into the muscularis. It has also been observed that papillary tumors are often multiple when initially seen.

Brunn’s nests in association with bladder tumors have been noted by many authors. Little attention has been given to the analogous association of other proliferative lesions.

Proliferative bladder lesions may be classified as:

1. Cystitis cystica.
2. Atypical hyperplasia.
3. Papillary hyperplasia.

Eisenberg made 171 consecutive bladder biopsies from bladders which contained overt tumors. The specimens were carefully examined for the occurrence of proliferative lesions of the type just described occurring in bladder mucosa distant from the immediate field of the overt tumors. He found that focal mucosal lesions of a proliferative nature with cellular atypism and abnormality of pattern frequently accompany overt bladder tumors, and demonstrated them in mucosa in approximately 30% of the infiltrating tumors studied. These focal lesions (such as in situ carcinoma) occur synchronously with the overt tumors, but the possibility remains that they might precede clinically manifest tumors.

Clinical correlations in a rigidly selected, fully followed group of 24 patients showed that in no case which progressed for five or more years in wholly satisfactory fashion were such lesions initially present. Whereas, in all cases with unsatisfactory
progress these lesions could be demonstrated. The suggestion is made that the presence or absence of these associated proliferative mucosal lesions is an ascertainable physical feature of bladder tumor formation which may have considerable prognostic significance.

L. N. Pyrah of Leeds University studied 365 cases of papilloma and 139 cases of papillary tumors showing carcinoma (carcinoma in situ) of the bladder. The sex ration male to female was 3.8 to 1 for carcinoma in situ. It was 2.9 to 1 for papilloma. The proportion of multiple to single tumors was higher in the carcinoma in situ group: 36% as compared to 25% in the papilloma group.

Most carcinoma in situ tumors were treated similarly to papillomas with fulgurative transurethral resection and suprapubic loop excision. Approximately 33%, however, were treated with more radical methods. Of patients with carcinoma in situ 36.4% underwent a second phase of treatment within the first year, compared with 20% in the papilloma group. In 7% of cases of papilloma an invasive cancer supervened, often after many years.

The death rate from invasive cancer in all cases originally diagnosed as papilloma is 6%. Death occurred at not less than five years and up to sixteen years following the initial diagnosis of papilloma.

The death rate from invasive cancer in all cases originally diagnosed as early carcinoma or carcinoma in situ is 7.9%, death frequently occurring in less than three years. Thus, it appears that death from invasive cancer occurs sooner in the early carcinoma group than in the papilloma group, although in other respects the two are similar.

Austin studied 12 total cystectomy bladders removed for tumor. Proliferative mucosal lesions of one variety or another were seen in all cases, confirming the findings of Melicow.

All 12 bladders showed diffuse atypical mucosal changes ranging through the entire pathologic spectrum. Four bladder specimens were found to contain grossly undetectable carcinoma in situ in the bladder far removed from the principal tumor. In two other cases, carcinoma in situ was discovered in the intramural distal end of a ureter and distant from the primary lesion.

In summary, it may be said that carcinoma in situ or intraepithelial carcinoma of the urinary bladder presents a perplexing problem to the urologist. When more tumors of this type are studied, definitive types of therapy may be determined.
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REFERENCES


