

Carcinoma In Situ of the Urinary Bladder with Transitional Cell Carcinoma of Prostate

—A Histopathologic Study and Mapping of the Urothelial Lesions—

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A 63-year-old male patient with extensive carcinoma in situ of the urinary bladder was found to have unsuspected transitional cell carcinoma of the prostate. Mapping of the totally embedded radical cystectomy specimen demonstrated diffuse, multifocal, epithelial abnormalities, ranging from mucosal atypia to the nonpapillary carcinoma in situ with extension to the urethra, prostatic ducts and glands, seminal vesicles and ureter, probably reflecting individual urothelial susceptibility in reaction to carcinogenic stimulus. The importance of prostatic assessment in the evaluation of the patient with carcinoma in situ of the urinary bladder is emphasized.

The natural history of carcinoma in situ of the bladder has been documented by Melamed and associates¹⁾. They have emphasized the sinister aspects of vesical carcinoma in situ and have advocated a radical operation in a variety of settings, including those cases difficult to control by endoscopic resection and those in which biopsies and/or urine cytology demonstrates a high grade tumor or progressively extensive bladder involvement.

Several cases of prostatic involvement in the absence of invasive carcinoma in the bladder has been documented in English literature²⁻⁴⁾. The purpose of this paper is to present a patients with carcinoma in situ of the urinary bladder without associated papillary carcinoma, who had in addition unsuspected extensive intraprostatic involvement.

CASE REPORT

A 63-year old Korean man underwent radical cystectomy with ileal conduit and urethrectomy in 1985, following a 8-month history of excessive urinary frequency, dysuria and noturia. There was occasional hematuria. He was smoker of 1 pack per day for 40 years. Because of persistence of symptoms cystoscopy was done and revealed nonspecific finding. There was no gross evidence of papillary or invasive tumor. Multiple mucosal biopsies revealed carcinoma in situ. Urine cytology results indicated cancer.

All specimens were preserved in 10% buffered formalin and were available for study. The specimen was fixed at the time of gross examination and pinned to woodboard in the distended state to facilitate anatomic orientation. The specimen was step-sectioned at 3 mm intervals from the distal resection

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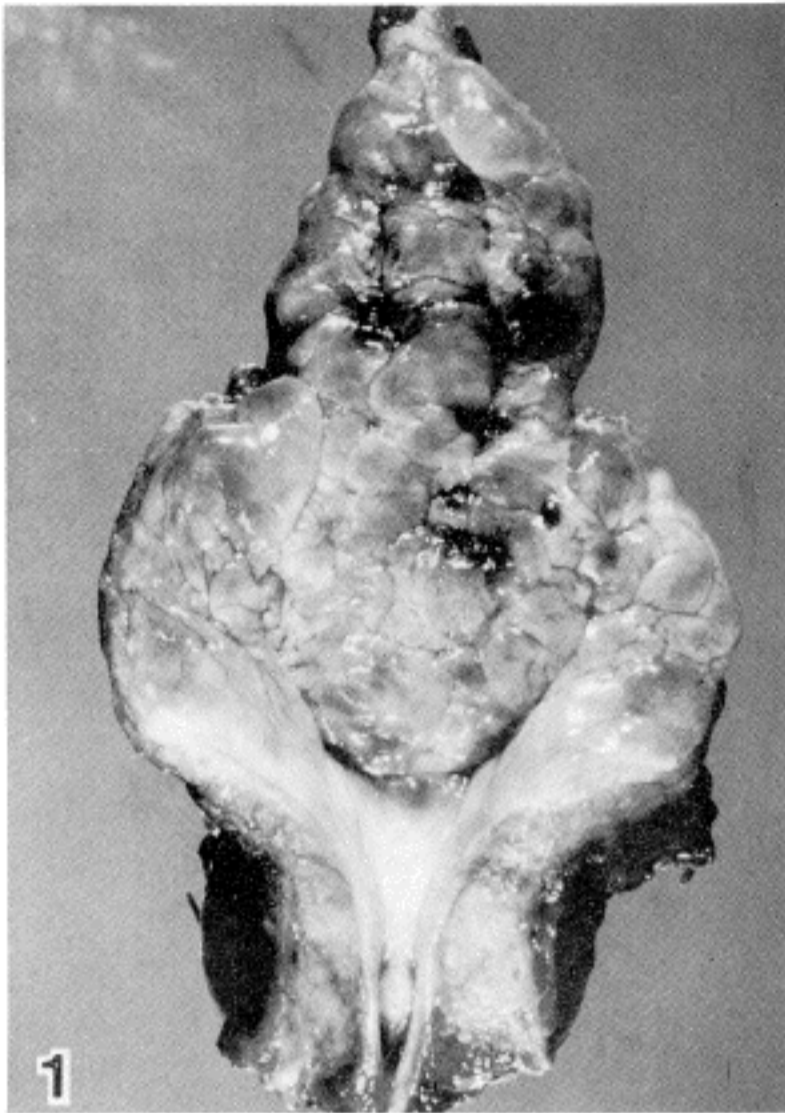


Fig. 1. Gross photograph of radical cystectomy specimen showing smooth edematous mucosa.

margin of urethra throughout the entirety of the prostate and bladder and the lengths of both ureters. 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 3 categories of mucosa: (a) normal or near normal, (b) definitely altered atypia, and (c) in situ carcinoma, according to the definition of Koss et al⁶⁾.

PATHOLOGIC FINDINGS

The specimen consisted of the bladder, prostate, seminal vesicles and ureter stumps. The mucosa of bladder is edematous and slightly hyperemic. There



Fig. 2. Map of bladder mucosal changes in cystectomy specimen.

was no evidence of grossly recognizable neoplasm. Several small fresh ulcers at the biopsy sites were found (Fig. 1). Mapping of the bladder revealed extensive carcinoma in situ of transitional cell type with appreciable degrees of anaplasia without evidence of invasion, of which the trigone region and contiguous posterior wall of the bladder were affected (Fig. 2).

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 (Fig. 3, 4). A characteristic feature was the loss of intercellular cohesiveness of the cells along the basilar zone to the basement membrane resulting in exfoliating

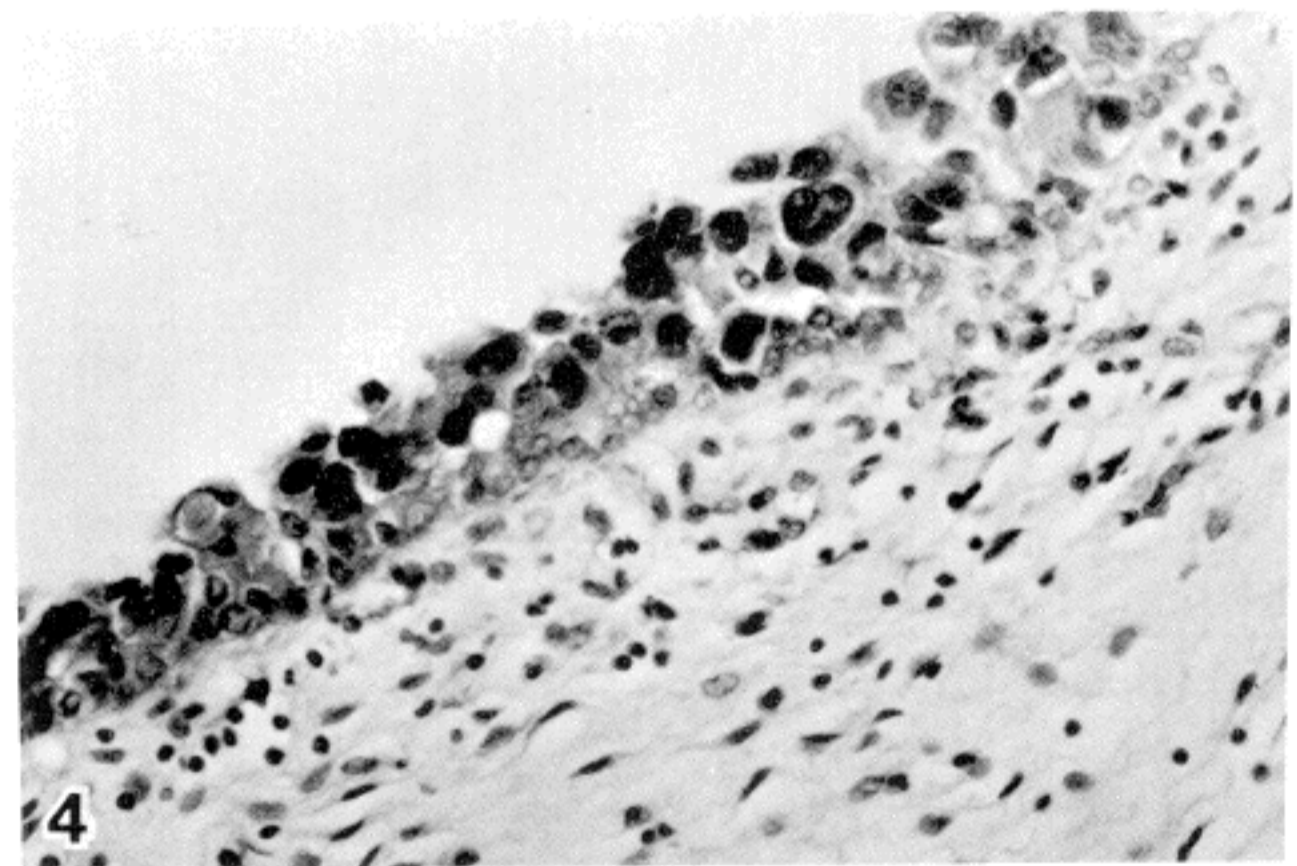
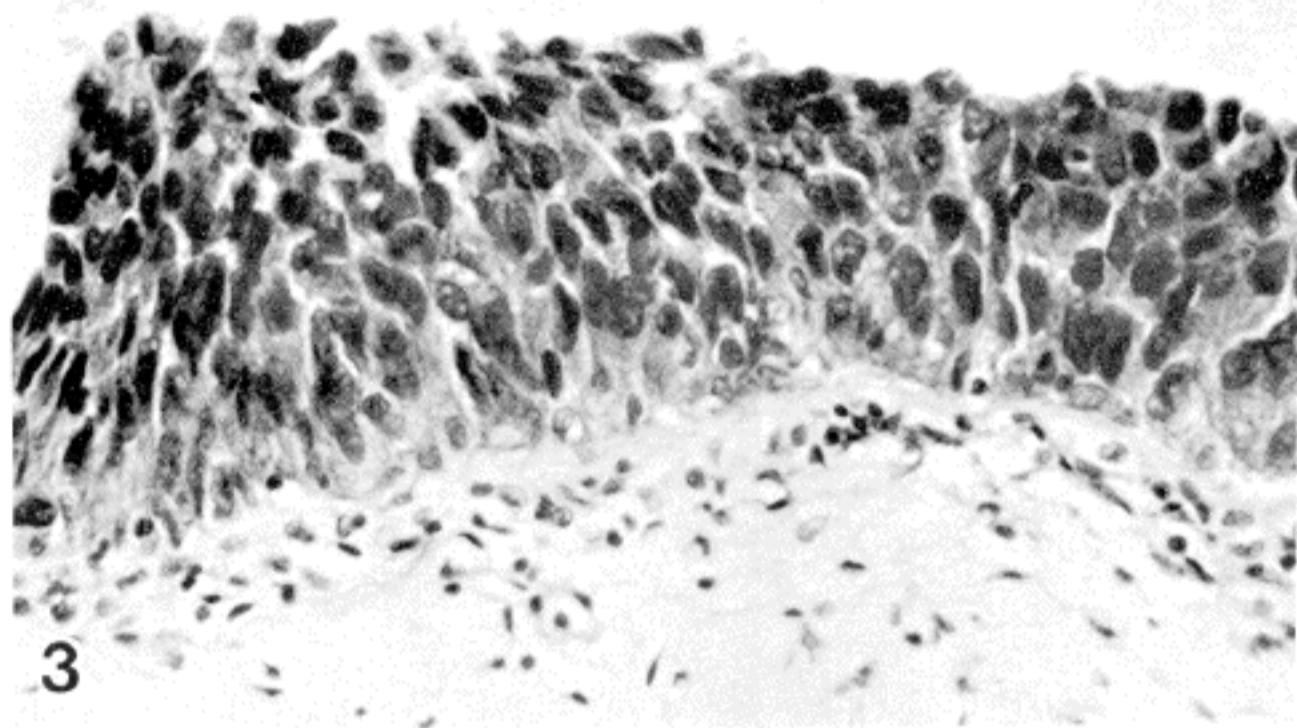


Fig. 3 and 4. In situ carcinoma of bladder showing large anaplastic cells with obvious nuclear abnormalities and a disorderly pattern of growth (hematoxylin & eosin, $\times 200$)

tumor cells into the lumen (Fig. 5). Bladder mucosal atypia is recognized as varying degrees of alteration in the regularity of mucosal anatomy 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 malig-

nancy (Fig. 6). Such atypia or malignant change was widespread in the mucosa of bladder and was often intimately 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. In this patient, a unique histological mucosal phenomenon

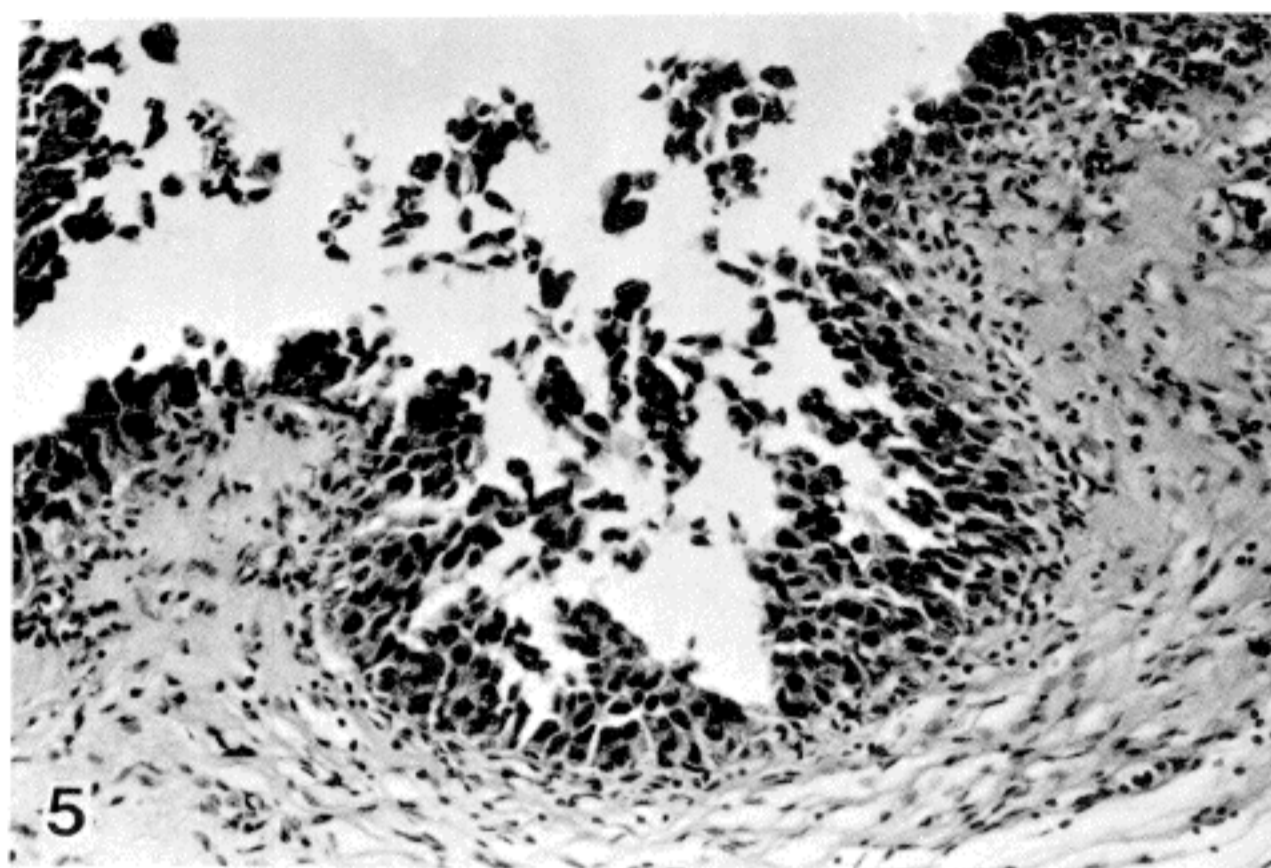


Fig. 5. Exfoliating tumor cells into the lumen due to loss of intercellular cohesiveness (hematoxylin & eosin, $\times 100$).

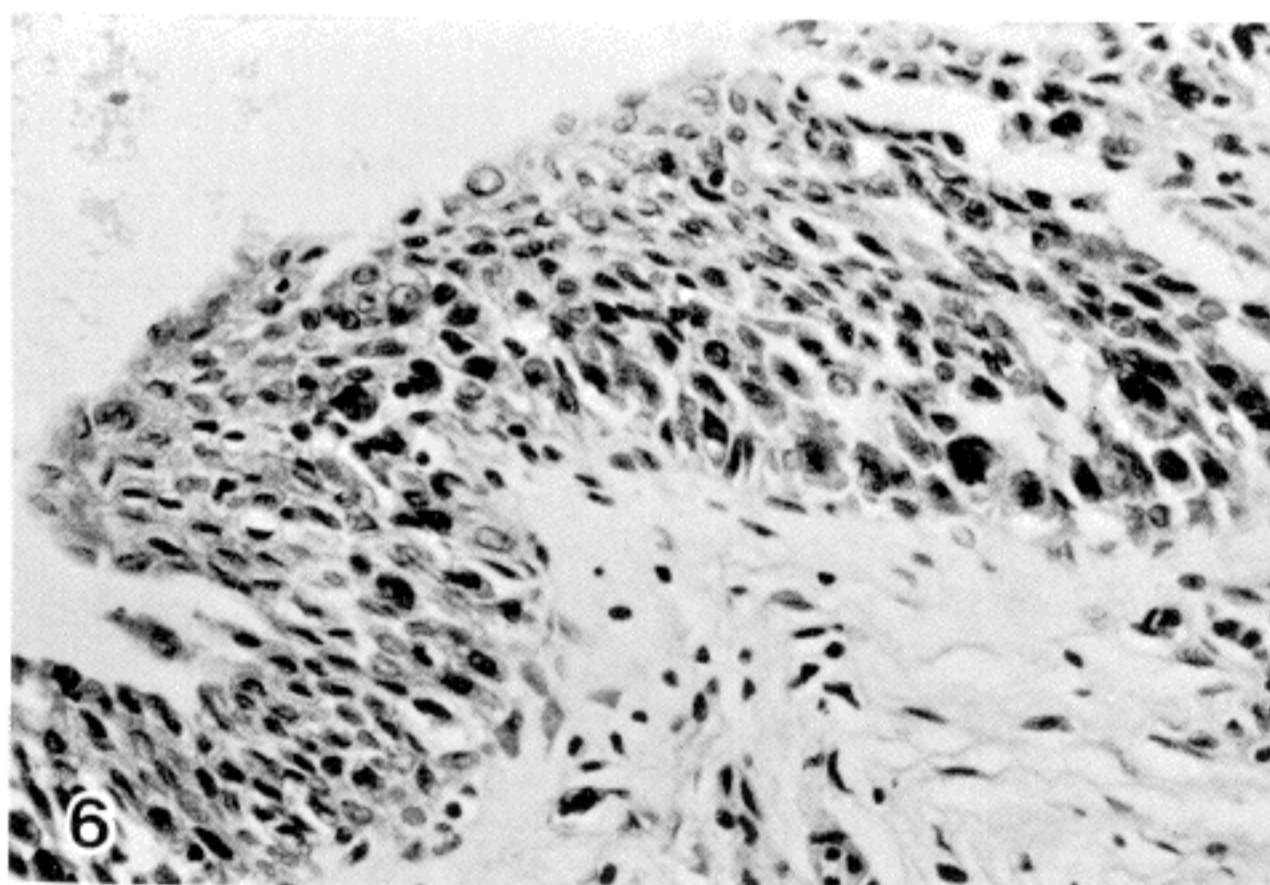


Fig. 6. Epithelial atypia of bladder, replaced by anaplastic cells in the lower portion of the bladder mucosa (hematoxylin & eosin, $\times 200$).

was observed at the junction of benign and malignant mucosa, demonstrating accrual of additional mucosa into the malignant process by direct intramucosal spread of malignant epithelial cells, lifting this mucosa off its basilar footings; a striking pagetoid type, spread into adjacent epithelium with 2 to 3 clusters of malignant cells (Fig. 7).

Inflammation in the submucosa, featuring an infiltrate of lymphocytes, plasma cells, and mononuclear cells. Vascular endothelial proliferation and fibrosis in the submucosa were frequently observed. Brun's epithelial nests were observed in the submucosa; frequently they were replaced by extension of the malignant cell population from the overlying surface

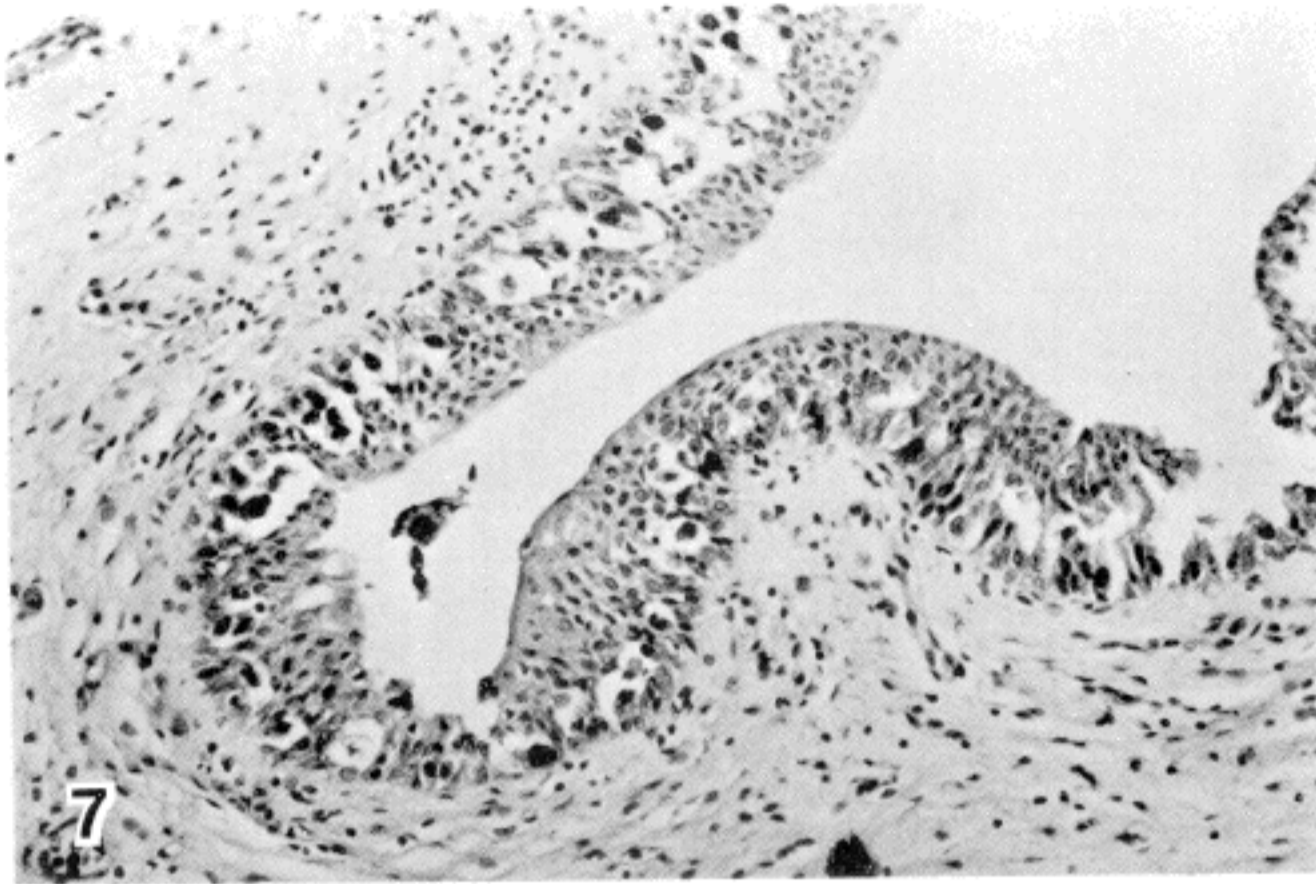


Fig. 7. Pagetoid spread of cancer cells into intact mucosa (hematoxylin & eosin, $\times 100$).

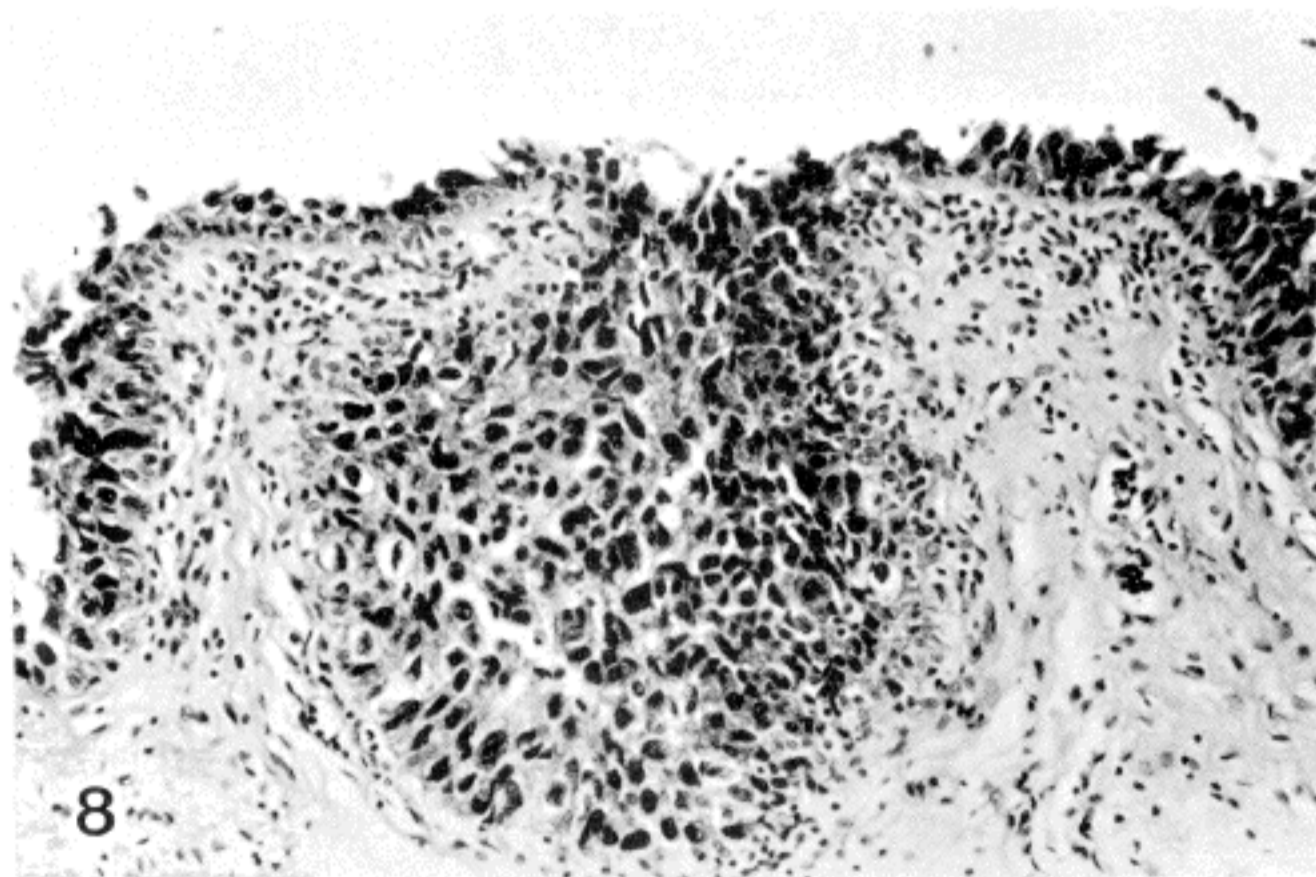


Fig. 8. Brunn's epithelial nest replaced by extension of anaplastic cells from the overlying surface (hematoxylin & eosin, $\times 100$).

(Fig. 8). The prostate disclosed extensive intraductal and intraacinar transitional cell carcinoma without stromal invasion (Fig. 9). No evidence of perineural invasion was found. The seminal vesicles, ureter and urethra were also involved by tumor extension. Except for carcinoma in situ in the bladder, most of the carcinoma was in the prostatic ducts and acini.

DISCUSSION

That carcinoma in situ may occur in association with infiltrating urothelial carcinoma has been well documented⁹⁾. Our present concern is with carcinoma in situ of urinary bladder occurring as an

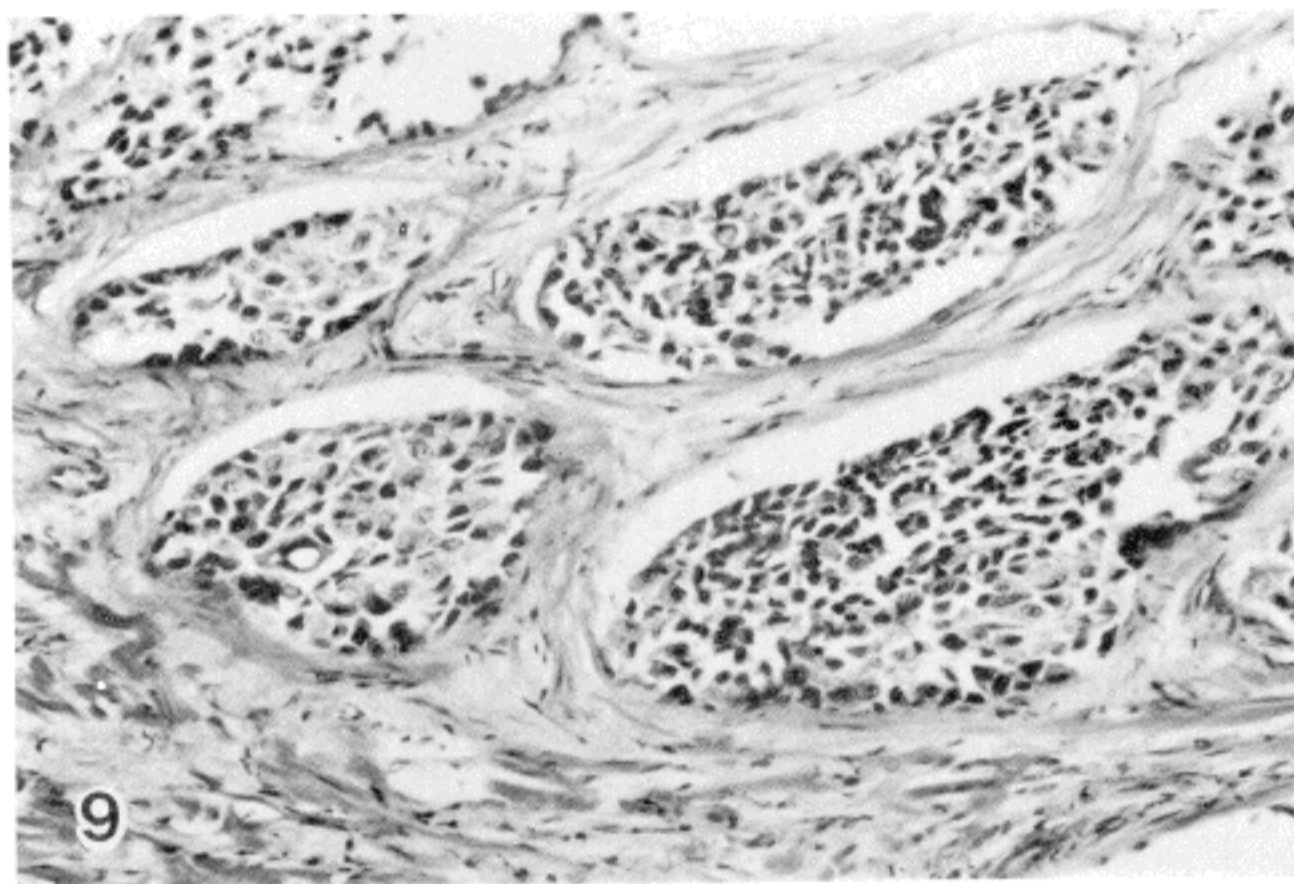


Fig. 9. In situ transitional cell carcinoma of prostatic glands (hematoxylin & eosin, $\times 200$)

isolated entity, in the absence of associated infiltrating carcinoma. Widespread mucosal involvement by premalignant atypia of the mucosa and direct intramucosal spread of cancer cells was a significant factor, particularly along the prostatic ducts and ureters. A multifocal theory of origin is generally accepted to explain multiple or asynchronous development of other transitional cell tumors⁶⁾.

However, to date, most cases have been attributed to direct extension from the malignant primary in the bladder. Prostatic involvement by transitional cell carcinoma of the bladder includes a spectrum of histologic patterns. Ductal only or ductal and acinar involvement occurs with or without stromal invasion. Non-invasive in situ prostatic patterns are usually associated with low stage bladder tumor. The contributions of Melamed¹⁾, Utz⁷⁾ have helped to clarify the natural history of this pattern of disease and have emphasized the variability of its course and its potential for escape from control by an endoscopic operation.

It is significant that spontaneous regression of carcinoma in situ did not occur despite clinical

remission of symptoms and reported cystoscopic absence of abnormalities in some instances. If untreated, this lesion will progress to an invasive neoplasm of the same histologic type in a significantly high percentage of cases. Utz⁷⁾ discussed in a later paper 62 patients with carcinoma in situ of the bladder, 37 of whom had invasive carcinoma and 24 of whom apparently died of the disease. The recurrence rate of carcinoma in situ was 82 per cent.

In situ carcinoma differs from the infiltrating form of the tumor not only in histologic stage but frequently in grade as seen in urine cytologic studies. By Farrow et al⁸⁾, all cases of early bladder cancer was detected by urine cytology, not by cystoscopy. Melamed¹⁾ has shown that cells from urothelial carcinoma in situ readily exfoliate in the urine not only because of active proliferation of the neoplasm compared to normal urothelium but also because of the loss of intercellular cohesion. Cytologic qualities of in situ carcinoma of the bladder are reflected principally by nuclear alterations. Malignant cells tend to be shed singly, are slightly larger than normal cells, have an increased nuclear-cytoplasmic

ratio and are hyperchromatic and pleomorphic. The cytologic background is usually quite clean, there being little evidence of inflammation. In the absence of such a urographic abnormality patients with positive cytologic examinations should be followed closely because the exfoliated cells usually are from poorly differentiated neoplasms.

The histology of carcinoma in situ of the bladder is variable. Usually there is an increase in the number of nuclei per given area, producing a crowded appearance. The nuclei are increased in size, hyperchromatic and contain prominent nucleoli and an overall striking loss of polarity is apparent. Mitoses, normal and abnormal, may be found in all layers of the bladder mucosa. Because of diminished intercellular cohesion and absence of stromal induction by tumor cells explain why the in situ carcinoma spreads superficially to form flat lesions, but fails to produce visible papillary tumors, the mucosal surface may be reduced to a single or only a few layers of epithelial cells and yet nuclear features are significant in most cases to permit a diagnosis of carcinoma in situ. The pagetoid cells appearing in the developing margins of the in situ carcinoma are unique; but the true nature of the pagetoid cells is obscure. Iwasaki et al⁹⁾ presume that pagetoid cells may represent transformed tumor cells showing differentiation toward the surface umbrella cells, or they are derived from Brunn's nests where the cells may gain potential to differentiate to glandular epithelium.

Mucosal atypia and premalignant epithelial changes have been emphasized as the mode of development of carcinoma in abnormal, dysplastic epithelium. Our study 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.

Complete mapping of epithelial lesions described

by Melamed et al¹⁾ and Koşş et al⁵⁾ is one of the most useful methods for studying the morphogenesis of bladder neoplasm. In the present study mapping was performed, disclosing the characteristic distribution of the epithelial lesions, in which carcinoma in situ occurred both in small isolated foci and in a single large geographic area separated by non-neoplastic mucosa and often intermingled with atypical epithelium. This finding seems to support the multicentric origin of carcinoma in situ and to indicate its intimate relationship to atypical epithelium.

The case presented herein differ in that in situ carcinoma of the bladder is seen in association with similar changes in the urothelium lining the urter, prostatic urethra. This association is not surprising in view of the recongnized propensity for urothelial carcinoma to occur multifocally. The significance of the observation lies rather in the fact that such prostatic involvement 1) is usually unsuspected, 2) is usually not looked for and 3) may lead to infiltrating involvement of an adjacent organ (stage A to D) simply by breaking through the basement membrane.

Transitional cell carcinoma of the prostate may be a manifestation of the multifocal malignant transformation of urothelium in response to a neoplastic stimulus^{10,11)}. The finding in some instances of distinctly separate bladder and prostatic tumors at cystoscopy and the documentation of transitional cell carcinoma of the prostate alone without antecedent or simultaneous vesical involvement support the concept that the urothelial lining of the prostatic urethra and ducts may give rise de novo to transitional cell carcinoma. The neoplasm may begin in the columnar or transitional cells that line the ducts or from the reserve basal cells lying on the basement membrane.

Other mechanisms to account for prostatic transitional cell involvement include cell implantation from more proximal tumors, direct extension from a bladder neoplasm with surface downgrowth into the

ductal orifices or direct invasion through the bladder neck muscle into the substances of the prostate. Finally, the association of transitional cell carcinoma of the prostate and bladder may result from de novo neoplasm of the prostatic ducts extending to the prostatic urethra and thence upward to the bladder.

It would appear that after diagnosis of carcinoma in situ of the bladder, consideration should be given to the possibility that the disease may be present in the intraductal system of the prostate. The present policy of close follow up, frequent cytology and multiple bladder biopsies have been unreliable. Transurethral prostatic sampling biopsy may be advisable in this setting. If prostatic extension is present, radical cystectomy should be considered. Therefore, it is reasonable to consider that radical cystoprostatourethrectomy is the treatment of choice for carcinoma in situ of the bladder.

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＝ 국문 초록 ＝

전립선의 이행상피암을 보이는 방광의 상피내암 1예

계명대학교 의과대학 병리학교실

홍 승 표 · 이 상 숙 · 정 재 홍

방광의 상피내암은 침윤성 이행상피암 주변에서 흔히 발견되나 단독으로 존재하는 경우는 드물다. 저자들은 63세 남자의 방광에 광범위하게 생긴 상피내암이 요도, 요관, 정낭과 전립선에 동시에 침범한 1예를 경험하여 이에 문헌 고찰과 함께 보고하는 바이다. 방광의 상피내암을 가진 환자에서 전립선 침범 여부를 미리 알므로써 더욱 적절한 치료를 할 수 있으리라 고 사료된다.