Stereotypes of Structural Modification of the Urothelium in Various Diseases of the Urinary Bladder and Prostate

G. I. Nepomnyashchikh, S. V. Aidagulova, D. L. Nepomnyashchikh, M. M. Boboev, V. I. Isaenko, N. A. Abdullaev, O. I. Ivaninskii, and I. S. Kunin

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Structural modification of the urothelium was studied in various diseases of the urinary bladder and prostate, including urinary bladder cancer, vibration cystopathy, chronic prostatitis, benign prostate hyperplasia, and chronic cystitis. The general phenomena of changes in urinary bladder epithelium were atrophy, squamous metaplasia, and instability of the urothelium (focal atrophy, dysplasia, hyperplasia, and metaplasia). This phenomenon can be interpreted as a morphological marker for cancer risk.

Key Words: *urinary bladder cancer; chronic cystitis; chronic prostatitis; vibration cystopathy; urothelium*

The state of epithelial structures during chronic exposure to unfavorable factors is manifested in general biological and general pathological phenomena that have a morphological phenotype of degeneration, metaplasia, dysplasia, hyperplasia, and atrophy. These changes not only reflect epithelial damage, but also result from regenerative processes under the influence of pathogenic factors [1,4].

Stereotypic reactions of the epithelium under various physiological and pathological conditions include hyperplasia, dysplasia, and metaplasia. These states should be considered together. They represent various stages of the same process of physiological and reparative regeneration, which sometimes results in the transformation of normal epithelium to neoplastic epithelium. Reparation and malignant transformation of the epithelium are a multistage process. Various stages of regeneration and malignant transformation (acanthosis, hyperplasia of cells, dysplasia, or carcinoma *in situ*) are often revealed during examination of the sample.

Much recent attention is paid to comorbid diseases in men. Chronic prostatitis is often transformed into hyperplasia and adenoma of the prostate gland (PG) and usually accompanied by interstitial cystitis. Both processes have similar symptoms and are difficult for differential diagnostics and therapy. Moreover, they are characterized by high risk of tumor development [3,7-11].

Here we compared urothelial transformation in various diseases of the urinary bladder (UB) and PG to identify structural markers of anaplasia.

MATERIALS AND METHODS

A clinical, endoscopic, and pathomorphological study involved 242 patients with tumor or non-tumor diseases of UB.

Group 1 consisted of 68 patients (62 men and 6 women, 46-83 years) with various types of UB cancer (biopsy specimens and surgical specimens), including tumor tissue fragments and apparently normal mucous membrane (MM) of the extra-tumor origin. Exophytic, endophytic, and mixed tumors

Institute of Regional Pathology and Pathomorphology, Siberian Division of the Russian Academy of Medical Sciences, Novosibirsk, Russia. ***Address for correspondence:*** pathol@soramn.ru. G. I. Nepomnyashchikh

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were found in 38, 20, and 10 patients, respectively. Pathomorphological study of tumor fragments showed that 52 patients have transitional cell carcinoma of UB of different differentiation. Squamous cell keratinizing carcinoma and adenocarcinoma were diagnosed in 9 and 7 patients, respectively.

Group 2 consisted of 64 patients with vibration disease from local vibration (58 men and 6 women, 38-65 years). Complex clinical and endoscopic study showed that the majority of patients with vibration disease have UB disorders (oligakisuria and hypotonia).

Group 3 consisted of 35 men (28-63 years) with chronic prostatitis (30 biopsy specimens) and benign prostate hyperplasia (5 biopsy specimens).

Group 4 (reference group) consisted of 52 patients with chronic cystitis (7 men and 45 women, 17-70 years). Biopsy specimens of MM were taken from the cervix and right lateral wall of UB.

Light microscopy and electron microscopy were performed with fragments of UB MM. Paraffin sections were stained with hematoxylin and eosin in combination with Perls staining. Van Gieson's staining was also used. Elastic fibers were stained with Weigert's resorcin-fuchsin. PAS reaction was conducted. For electron microscopy, the samples were fixed in 4% paraformaldehyde. The tissue was subjected to standard treatment and embedded into a mixture of Epon and araldite. Semithin sections were stained with Schiff reagent and azure II. Ultrathin sections were contrasted with uranyl acetate and lead citrate and examined under a JEM-1010 electron microscope.

RESULTS

Various diseases were accompanied by the following structural modifications in UB MM: atrophy, hyperplasia, squamous metaplasia, dysplasia, and mosaic epithelial layer (similarly to the previously described phenomenon of bronchial epithelium instability) [5].

Atrophic modification of the urothelium was most pronounced in vibration disease. Diffuse atrophy of UB MM was revealed in cystoscopy. The transitional urothelium was thinned and had no surface umbrella-like cells (Fig. 1, *a*). Desquamation of several regions was related to severe degeneration of epitheliocytes and loosening of intercellular junctions. These structural modifications can be interpreted as vibration cystopathy.

Diffuse atrophy of the urothelium was accompanied by focal squamous metaplasia (33% specimens; Fig. 1, *b*) and, more rarely, by glandular metaplasia. Squamous metaplasia was characterized by the formation of multilayer epithelium, which consisted of numerous layers of polygonal cells. These cells became flattened with the transition to the epithelial surface. They were connected by well-developed desmosomes. Lght microscopy of semithin sections showed that these desmosomes look like intercellular bridges. Considerable amounts of the PAS-positive substrate were often found in the cytoplasm of metaplastic epitheliocytes.

Similarly to vibration disease, chronic prostatitis was characterized by urothelial atrophy in UB MM. Our results are consistent with published data on cystopathy [6]. Transitional epithelium of UB was atrophic along the length of MM. The number of layers decreased to 3-5, which was accompanied by flattening or absence of umbrella-like urothelial cells. The number of epithelial layers remained unchanged in MM folds (7-15). However, the outer layer was desquamated (Fig. 1, *c*). In other regions, atrophy of transitional epithelium was accompanied by total desquamation of the epithelial layer in MM. The basal membrane had individual cells with acidophilic cytoplasm. Focal squamous metaplasia of the urothelium was rarely found in chronic prostatitis. This state was manifested in a small number of epithelial layers and low content of glycogen in epitheliocytes.

As differentiated from vibration cystopathy and chronic prostatitis-associated cystopathy, chronic cystitis was characterized by the preservation of transitional urothelium (Fig. 1, *d*) and focal proliferation of the urothelium. It was often related to focal infiltration with inflammatory cells, high structural density of plethoric microvessels, and perivascular edema.

Focal urothelial dysplasia was rarely found in benign prostate hyperplasia. UB tumors were often accompanied by urothelial dysplasia in the perifocal area. This state differed from hyperplasia. Elongated dark cells were localized not only in the basal area, but also in the middle region of the epithelial layer. These changes in epitheliocytes are characterized by high risk of *in situ* transformation into carcinoma.

Light microscopy revealed the presence of perifocal tumors in 25% specimens from patients with UB tumors. These tumors were histologically similar to the "primary" tumor (microscopically verified tumor site). Otherwise, they were similar to individual cells and keratinous pearls in squamous cell carcinoma. Moreover, tumor cells were found in the lumen of small vessels.

The wall of UB was sampled at various distances from the macroscopic boundary of neoplasm.

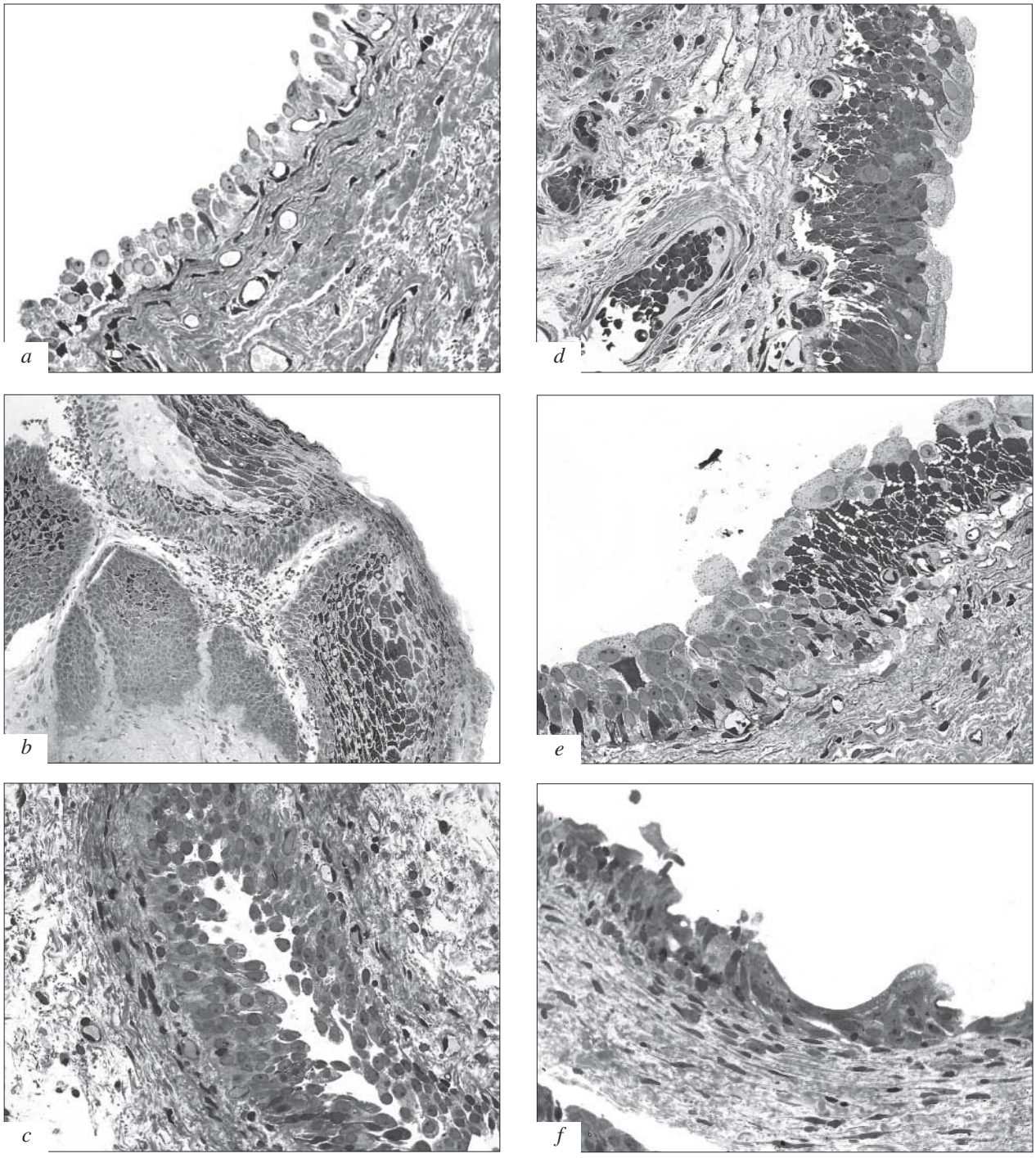

Fig. 1. Stereotypic structural changes in the urothelium in biopsy specimens from UB. Vibration cystopathy (*a*, *b*); chronic prostatitis (*c*); chronic cystitis (*d*); benign prostate hyperplasia (*e*); and transitional cell carcinoma of UB (perifocal area, *f*). Semithin sections, staining with Schiff reagent and azure II. Urothelial atrophy (×500, *a*); squamous metaplasia (×200, *b*); degeneration and desquamation of the urothelium (×400, *c*); transitional urothelium and plethora of subepithelial microvessels (×400, *d*); polymorphism of the epithelial layer (*e*); and abnormal modification of the urothelium (×400, *f*).

Transitional cell carcinoma was characterized by degeneration of transitional epithelium and signs of dysplasia. Squamous cell carcinoma of UB was manifested in squamous metaplasia, keratinization, and acanthosis of the epithelium. These changes were accompanied by polymorphocellular infiltration of the stroma with lymphocytes (arranged into follicles) and small number of neutrophils. MM sclerosis was found in the majority of specimens. The severity of sclerosis depended on the age of

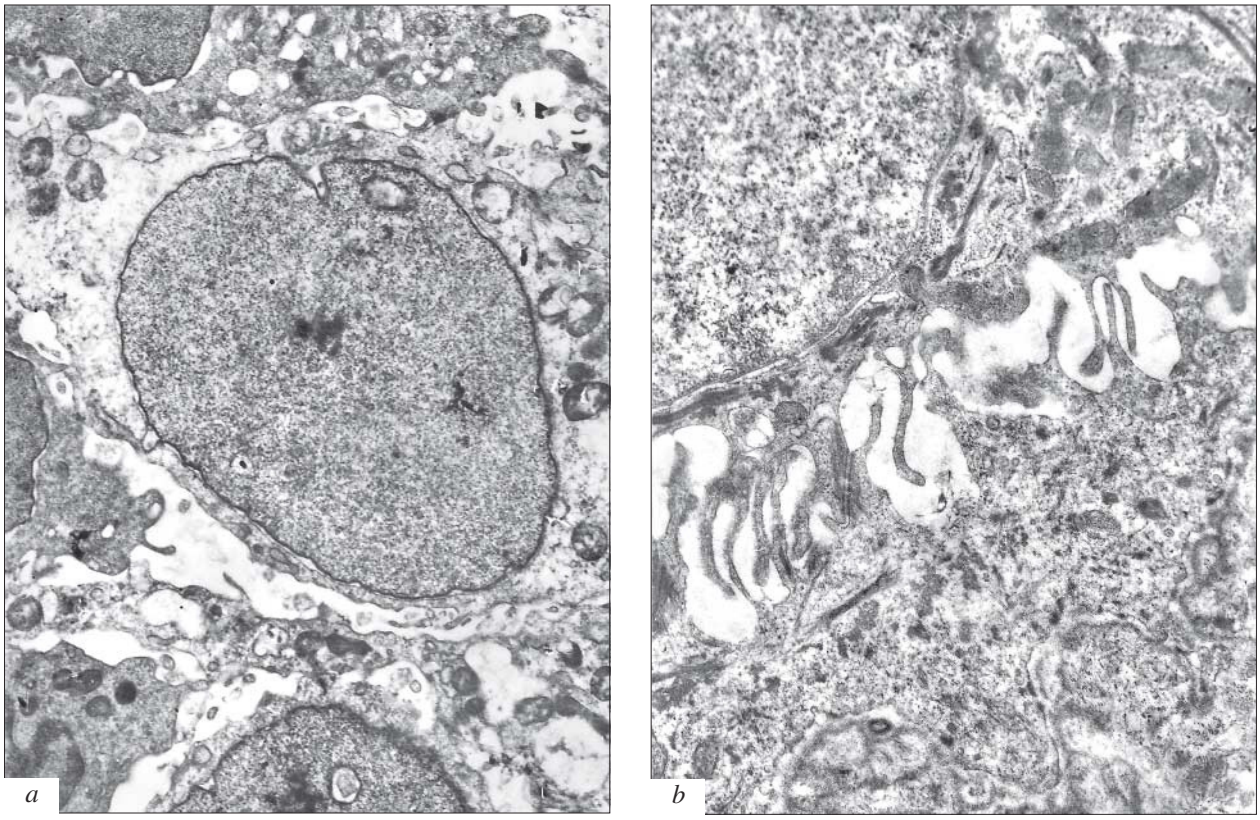

Fig. 2. Stereotypic structural changes in urothelial cells in biopsy specimens from UB. Vibration cystopathy (*a*) and benign prostate hyperplasia (*b*). Electron-diffraction patterns. Destruction of mitochondria and loosening of the cytoplasm (×4000, *a*); and fragments of dendritic cells and destruction of desmosomes (×10,000, *b*).

patients and duration of pathological changes in UB and/or PG.

Our results indicate that malignant transformation of MM in patients with UB cancer involves not only primary tumor or adjacent regions, but also distant area (luminescence study) [2].

Chronic diseases of UB that occur individually or in combination with prostate disorders are characterized by epithelial layer mosaicism of different degree (Fig. 1, *e*, *f*). This state is manifested in the presence of alternate regions of atrophy, hyperplasia, metaplasia, and dysplasia. The phenomenon of instability was described in bronchopathy [5] and serves as the marker of cancer risk. High incidence of this phenomenon probably underlies the multifocal tumor growth in UB MM. These data are of considerable importance. Despite the existence of various clinical, morphological, immunohistochemical, and other parameters, there is no general prognostic criterion for the development and prognosis of tumor process.

Ultrastructural characteristics of the urothelium were stereotypic in all groups of patients. They were determined by epitheliocyte location in the site of structural changes (atrophy, squamous metaplasia, or degeneration of transitional epithelium). Atrophic cells were strongly polymorphic due to differences in the electron density of nuclei and cytoplasmic matrix. The decrease in the number and destruction of mitochondria, as well as the reduction of protein-synthesizing organelles contribute to depletion of epitheliocytes (Fig. 2, *a*).

At the site of squamous metaplasia, urothelial cells were of polygonal shape and had numerous processes and electron-dense cytoplasm with small glycogen inclusions (chronic prostatitis) or considerable amounts of glycogen (vibration disease and chronic cystitis). Metaplastic epitheliocytes had the minimum amount of membrane cytoplasmic organelles and different number of tonofilaments that play a role in the formation of desmosomes. Widening of the intercellular space was related to edema of several regions (Fig. 2, *b*).

The phenotype of transitional epithelium was preserved. The cells of normal ultrastructure were shown to alternate with abnormal urothelial cells (signs of focal and total alteration in cytoplasmic organelles). Groups of cells with large electron-transparent vacuoles and lipid drops were revealed in the epithelial layer.

Epithelial atrophy of different location and metaplasia are of frequent occurrence [4,6]. Atrophic epitheliocytes are characterized by stereotypic morphological signs (*e.g.*, presence of flattened cells, 1-2 layers of cells on the basal membrane, and tendency to desquamation). However, these cells can undergo unusual structural modifications. Endothelium-like transformation of cells is often observed and probably serves as the compensatory mechanism [4]. Little is known about atrophy as a general pathological process. Atrophic changes are usually described in macroscopic or microscopic examination. Ultrastructural signs of cells in various types of atrophy received little attention. Atrophy has a particular role in lung carcinogenesis. Atrophy also contributes to neoplastic transformation. Atrophy, dysplasia, and apoptosis are mediated by the same pathogenetic mechanisms and involve a variety of cellular oncogenes and p53 suppressor gene.

The phenomenon of metaplasia was well described by I. V. Davydovskii. Independently on the nature of metaplasia, this process is physiologically determined. Metaplasia plays an adaptive role. However, metaplasia often has poor prognosis in clinical practice. The adverse effect of metaplasia is associated with the fact that metaplastic tissues develop due to incomplete or atypical regeneration and, therefore, can undergo neoplastic transformation. Hence, the problem of tumor growth is closely related to metaplasia. Moreover, metaplastic process is considered as precancer.

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