Virchows Arch [Pathol Anat] (1985) 407:25–32

Virchows Archiv A

Inverted papilloma: observation with scanning and transmission electron microscopy

Nobuo Moriyama[1], Hideyuki Akaza[1], Toru Suzuki[1]*, Kazuki Kawabe[2], and Tadao Niijima[1]

[1]Department of Urology, Faculty of Medicine, The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113
[2]Department of Urology, Branch Hospital, Faculty of Medicine, The University of Tokyo, Mejirodai, Bunkyo-ku, Tokyo 112, Japan

Summary. Three cases of inverted papilloma of the urinary bladder were studied by transmission electron microscopy. Scanning electron microscopic observation was made in one of these. The surfaces of the outermost tumour cells were covered with short stubby microvilli. Multiple bud like proliferations of the tumour cells were compatible with a trabecular type of inverted papilloma. The tumour cells of the trabeculum mimicked the intermediate and basal cells of the epithelium which covered the surface. Microcysts are believed to be formed by epithelial migration into pits, creating an epithelial inversion, and do not represent central necrosis. Ultrastructure suggests that inverted papilloma is a very well differentiated tumour.

Key words: Human bladder tumour – Inverted papilloma – Ultrastructure

Introduction

Inverted papilloma of the human urinary bladder is rare. The first case report was published by Potts and Hirst (1963). Since then, cases have accumulated in the literature and clinicopathological features have been proposed (DeMeester et al. 1975; Caro and Tessler 1978; Kunze et al. 1983). Inverted papilloma is generally a non-recurring solitary tumour of the trigone, bladder neck, or posterior urethra with a non-papillary smooth surface. It is histopathologically characterized by endophytic growth covered with normal, atrophic, or hyperplastic urothelium. Although the electron microscopic appearance has been reported (Moriyama and Ito 1979; Alroy et al. 1980; Iwata et al. 1982), the topographic features have not been detailed precisely. Scanning and transmission electron microscopic studies provide information about the nature and biological potential of this bladder tumour.

* *Current address:* Department of Urology, Dokkyo University School of Medicine, Mibu, Tochigi 321-02, Japan

Offprint requests to: N. Moriyama at the above address

Cases

Case 1. A 37 year old male presented with bladder outlet obstruction. A characteristic solitary lesion was discovered at the bladder neck on cystoscopy. This was completely resected. This patient has been followed for seven years, without evidence of recurrence.

Case 2. A 66 year old male underwent transurethral resection of the prostate for symptoms of outlet obstruction. At the time of surgery, a solitary smooth surfaced lesion was discovered at the bladder neck. There has been no recurrence at six years.

Case 3. A 35 year old male underwent cystoscopy in the evaluation of haematuria. A solitary bladder neck lesion was completely resected. Cystoscopy is negative at one year.

Materials and methods

Biopsy specimens were immediately hemi-sectioned for light and electron microscopic studies. For light microscopic evaluation, the tissues were fixed in 10% formalin, embedded in paraffin, and then stained in the usual fashion. For transmission electron microscopic (TEM) study, the tissues were cut into small pieces and fixed overnight in aldehyde solution (1% paraformaldehyde and 2% glutaraldehyde in 0.1 M cacodylate buffer, pH 7.4). They were postfixed in 2% osmium tetroxide solution for 1 h, then dehydrated with ascending series of ethanol and embedded in Epon 812. Sections were cut by a glass or a diamond knife equipped on a LKB 8800 ultratome. After staining with uranyl acetate and lead citrate, they were examined in a Hitachi 12-A TEM. For scanning electron microscopic (SEM) study, only case 3 was available. Specimens were similarly fixed, dehydrated, then transferred into isoamyl acetate and finally dried in a critical point drying apparatus using liquid carbon dioxide. After mounting on the aluminium stubs, specimens were sputter-coated with gold and examined in a Hitachi S-430 at 15–25 KV.

Results

1. Light microscopic findings

Tumours were covered with normal, atrophic and hyperplastic transitional epithelial with a maximum of 7 layers. At least 2 layers of transitional cells were observed in atrophic areas. Inner areas showed epithelial cords with irregular and dendroid patterns. The basement membranes of epithelial cords demonstrated intact margins. Connective tissue and capillaries were also noted in the interstitium. Gland formations (microcysts) were observed in some areas. Periodic acid Schiff positive materials were found in the lumen of the microcysts. The epithelium of the tumour surface exhibited bud like proliferations with deep pits, connected with the inverted epithelial cords. The cells of epithelial cords were uniform and resembled the intermediate and basal cells of the surface epithelia (Fig. 1).

2. SEM findings

The tumour surface was smooth and slightly lobulated at low magnification, and several pits were recognized (Fig. 2). Outermost cells of the tumour were polygonal, forming a pavement-like surface. These cells consisted of two types (Fig. 3). The luminal surfaces of the first type demonstrated densely packed microvilli, which microvilli were short, stubby and sometimes

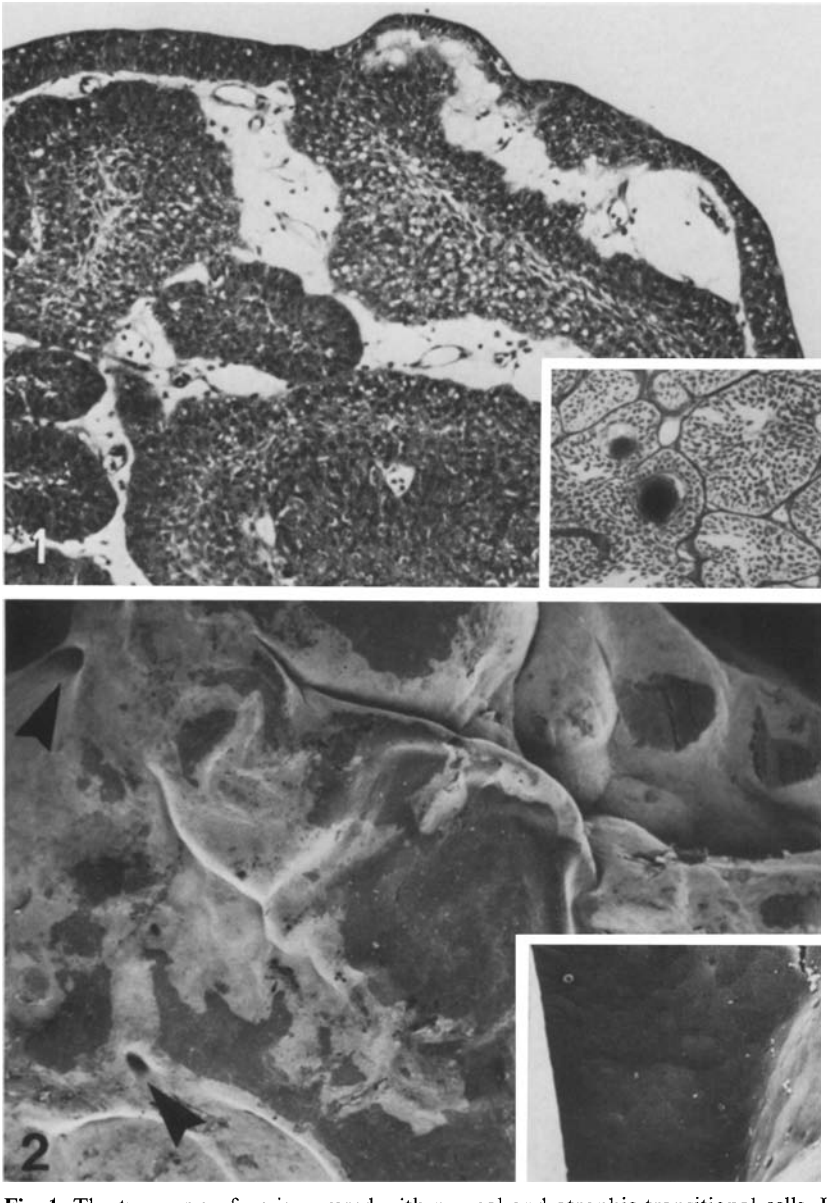

Fig. 1. The tumour surface is covered with normal and atrophic transitional cells. Inner layer shows epithelial cords with irregular patterns (H.E. stain). Case 3. Insert. Microcysts are recognized in the epithelial cords. (Silver stain). Case 1

Fig. 2. The tumour surface is smooth, and slightly lobulated. Arrows indicate pits. ×70. Case 3. SEM. Insert. The wall of a pit is covered with polygonal surface cells. ×280. Case 3

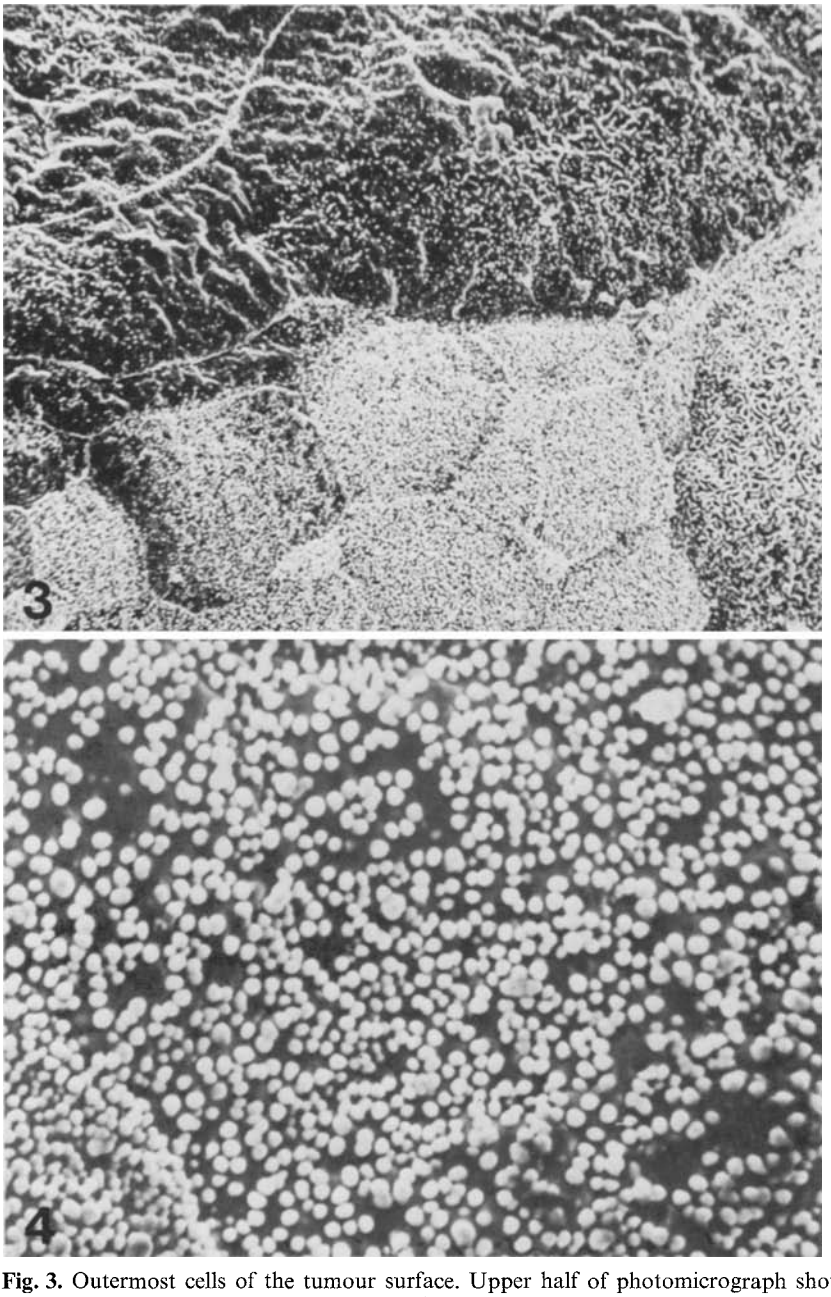

Fig. 3. Outermost cells of the tumour surface. Upper half of photomicrograph shows sparse microvilli. Lower half reveals dense microvilli. × 2,200. Case 3. SEM

Fig. 4. Microvilli of the outermost cells of the surface are short, stubby and dense. × 7,000. Case 3. SEM

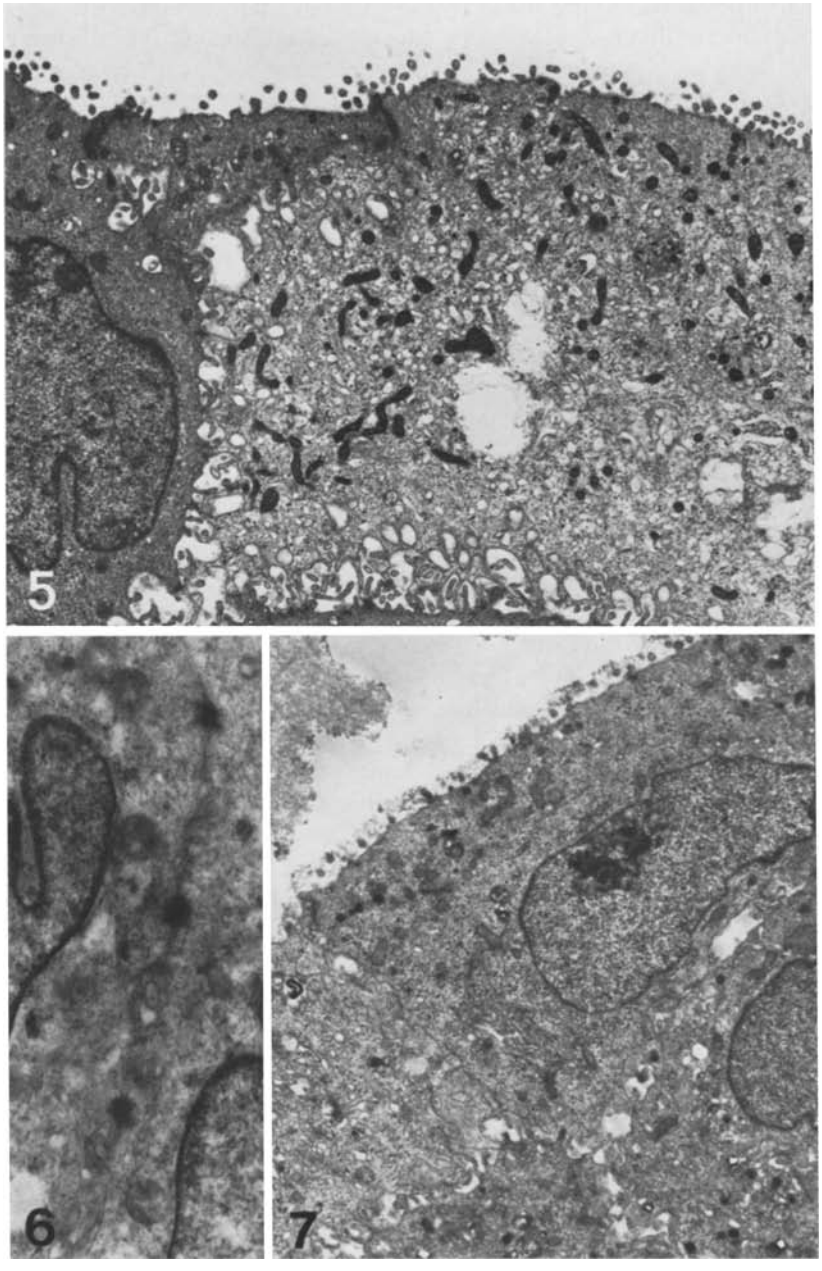

Fig. 5. Outermost cells of the tumour surface demonstrate the cuboidal cell with microvilli on the luminal surface and round vesicles beneath the surface. ×4,800. Case 3. TEM

Fig. 6. Desmosome are recognized in the tumour cells of the epithelial cords. ×9,600. Case 1. TEM

Fig. 7. Microvilli are observed on the surface cells of the microcyst. ×3,600. Case 2. TEM

branching in appearance. Cell borders were distinct and exhibited 3 or 4 rows of short microvilli (Fig. 4). Outermost cells of the second type showed irregular surfaces with sparse microvilli. The irregular surfaces are considered to represent degenerated microridges. The outermost cells with microplicae were scattered within the tumour surface (Fig. 3). The cut surfaces of the tumour revealed pits forming long holes like ants nests, the walls of which were covered with polygonal surface cells with distinct cell borders (Fig. 2 Insert). The surfaces of these cells were diffusely covered with densely packed stubby microvilli, and these cells were almost identical to those covering most of the tumour surface. Pleomorphic microvilli were not seen anywhere within the tumour.

3. TEM findings

Outermost, intermediate and basal cells were clearly recognized within the epithelium of the surface. The outermost cells were flat or cuboidal in type, these cells had short microvilli, some of which were branching. Asymmetrical cytoplasmic membranes were not recognized. The cytoplasm beneath luminal membranes contained several round vesicles and no discoid vesicles, lysosomes were also demonstrated and rough endoplasmic reticulum was prominent. The Golgi apparatus was well developed. Some nuclei were oval with slight notching (Fig. 5). Cells with sparse microvilli occasionally exhibited electron lucent cytoplasm and scanty organelles, and therefore were considered to be degenerative. Tight junctions were recognized between adjacent outermost cells. The surface cells facing pits were cylindrical in shape and their cytoplasmic features were the same as those of the outermost cells covering the tumour surface. Intermediate and basal cells showed similar findings. These cells and nuclei were perpendicular to the basement membranes, and contained several lysosomes. Mitochondria were scattered around the nuclei. The outstanding findings of these cells were deep nuclear notches or clefts. Nucleoli were not so conspicuous. Neighboring cells were joined with well developed desmosones, basement membranes were relatively thick and collagen fibers were scattered in an interlacing pattern.

Epithelial cords were composed of the cells which resembled intermediate and basal cells of the tumour surface. However, lysosomes were not so numerous. Desmosomes were abundant (Fig. 6). Microcysts were lined with cuboidal or flat cells with short microvilli (Fig. 7). Surface cells resembled the outermost cells of the tumour surface, although they had few lysosomes. They had no asymmetric unit membranes on their luminal surfaces. Tight junctions were also recognized between the adjacent surface cells. The luminal surfaces of these cells were covered with dense fuzzy material in all cases. The lumen of microcysts contained mainly monotonous dense materials and small amount of cell debris.

Discussion

Inverted papilloma is generally considered to be benign (DeMeester et al. 1975; Tannenbaum 1976; Caro and Tessler 1978), but there have been

some reports of its malignant transformation (Lazarevic and Garret 1978; Whitesel 1982; Altaffer et al. 1982). Kunze et al. (1983) distinguished two basic histological types of inverted papilloma: trabecular and glandular. The trabecular type develops with a proliferation of basal cells of the transitional cell epithelium. The presence of multiple bud like basal cell proliferations of the urothelium covering this tumour, and the close resemblance of the trabecular cells to normal basal cells are two remarkable characteristics. The genesis of the glandular type is considered to represent von Brunn's cell nests. Our three cases were similar to the trabecular type of their (Kunze et al. 1983) category.

In case 3, SEM observation showed short stubby microvilli on luminal surfaces of outermost cells. From the TEM findings, the other two cases would be expected to demonstrate similar appearances. Pleomorphic microvilli which are prominent in bladder cancer (Kjoergaard et al. 1977; Jacobs et al. 1981; Suzuki 1982) were not observed in inverted papilloma of the urinary bladder. Alroy et al. (1980) also reported that the luminal surfaces of outermost cells, and what he calls "neoplastic cells forming glands" have short microvilli. Short, regular or stubby microvilli were reported on the outermost cells of benign urothelial lesions (Kjoergaard et al. 1977; Jacobs et al. 1981; Suzuki 1982). Considering the type of microvilli present in our cases, the outermost cells of inverted papilloma probably represent well differentiated tumour cells.

Iwata et al. (1982) reported that inverted papilloma had small pits on its surface. The cut surface observations in our series demonstrate surface cells of pits resembling outermost cells with abundant short stubby microvilli. This finding was confirmed in TEM observations. Such pits have not been observed in papillary bladder tumours (Kjoergaard et al. 1977; Jacobs et al. 1981; Suzuki 1982) and seem to be characteristic of inverted papilloma. This feature supports epithelial inversion as the genesis of inverted papilloma of the trabecular type.

Asymmetric unit membranes which are characteristic of normal superficial cells (Haynes et al. 1975; Jacob et al. 1978; Suzuki 1982) are not observed in our cases. Round vesicles were recognized on the outermost cells of inverted papilloma. These vesicles have been found in well differentiated bladder tumours and normal urothelium (Fulker et al. 1971; Suzuki 1982). Secondary lysosomes were numerous. These lysosomes are also present in normal urothelium and well differentiated bladder tumours (Fulker et al. 1971; Hoyes et al. 1972; Hynes et al. 1975; Jacob et al. 1978). Desmosomes were relatively abundant in our cases. Alroy et al. (1980) also reported inverted papilloma had large numbers of desmosomes that reflecting the benign nature of this neoplasm, similar to the non invasive papillary transitional carcinoma.

Kunze et al. (1983) proposed that microcysts were most likely to be the result of cellular necrosis within the cord of the trabeculum. However, Alroy et al. (1980) reported tight junctions at the apical pole of the luminal surface cells, thus suggesting glandular formation, or true epithelial structures. Degenerated and desquamated cells were also disclosed in the lumen.

This study likewise demonstrates that luminal surface cells of microcysts possess tight junctions and microvilli and resemble the outermost cells of the tumour. The material contained in the microcysts is homogeneous. Microcysts are therefore thought to be caused by the inversion of the epithelial cells of the tumour surface.

Ultrastructurally, inverted papilloma reveal the characteristics of both normal urothelium and well differentiated bladder tumours. Consequently, inverted papilloma is probably a very well differentiated urothelial tumor.

Case 1 and 2 were briefly reported elsewhere (Moriyama and Ito 1979).

References

Alroy J, Miller AW, Coon JS, James KK, Gould VE (1980) Inverted papilloma of the urinary bladder. Ultrastructural and immunologic studies. Cancer 46:64–70

Altaffer LF, Wilkerson SY, Jordan GH, Lynch DF (1982) Malignant inverted papilloma and carcinoma in situ of the bladder. J Urol 127:816–818

Caro DJ, Tessler A (1978) Inverted papilloma of the bladder. Cancer 42:708–713

DeMeester LJ, Farrow GM, Utz DC (1975) Inverted papillomas of the urinary bladder. Cancer 36:505–513

Fulker MJ, Cooper EH, Tanaka T (1971) Proliferation and ultrastructure of papillary transitional cell carcinoma of the human bladder. Cancer 27:71–82

Haynes M, Troff PA, Islam AKMS, Hirst AG (1975) An ultrastructural study of the urinary bladder in children correlated with histological bacteriological and chemical findings. J Clin Pathol 28:176–188

Hoyes AD, Ramus NI, Martin BGH (1972) Fine structure of the epithelium of the human fetal bladder. J Anat 111:414–425

Iwata H, Bekku T, Yokoyama M, Ochi K, Morita M, Takeuchi M (1982) Inverted papilloma of urinary bladder. Scanning and transmission electron microscopic observation. Urology 19:322–324

Jacob J, Ludgate CM, Forde J, Tulloch WS (1978) Recent observations of the ultrastructure of human bladder. 1. Normal bladder of elderly subjects. Cell Tiss Res 193:543–560

Jacobs JB, Cohen SM, Farrow GM, Friedell GH (1981) Scanning electron microscopic features of human urinary bladder cancer. Cancer 48:1399–1409

Kjoergaard J, Starklint H, Bierring F, Thybo E (1977) Surface topography of the healthy and diseased transitional cell epithelium of the human urinary bladder. Urol Int 32:34–48

Kunze E, Schauer A, Schnitt M (1983) Histology and histogenesis of two different types of inverted urothelial papillomas. Cancer 51:348–358

Lazarevic B, Garret R (1978) Inverted papilloma and papillary transitional cell carcinoma of urinary bladder. Cancer 42:1904–1911

Moriyama N, Ito K (1979) Electron microscopic observations of the inverted papilloma of the urinary bladder. J Clin Electron Microscopy 12:145–156 (Jap)

Potts I, Hirst E (1963) Inverted papilloma of the bladder. J Urol 90:175–179

Suzuki T (1982) A scanning and transmission electron microscopic study on the human normal urinary bladder and bladder tumors. Jpn J Urol 73:469–487 (Jap)

Tannenbaum M (1976) Inverted papilloma: Urotehelial tumor of benign biological potential. Urology 7:76–79

Whitesel JA (1982) Inverted papilloma of the urinary tract. Malingant potential. J Urol 127:539–540

Accepted March 22, 1985