Original Contributions

Selective Expression of Cytokeratin Polypeptides in Various Epithelia of Human Brenner Tumor

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A human ovarian Brenner tumor presenting a wide spectrum of benign and malignant histologic features was studied for its patterns of intermediate filament expression. All epithelial elements of the tumor, regardless of their morphologic type, contained cytokeratins as their only intermediate filament component. Differences were detected, however, between tumor nests that displayed transitional epithelium and those with squamoid features. These differences were manifested by the presence of cytokeratin 18, in the former type only, and by the abundance of cytokeratins 10/11 in the latter. We also detected mixed epithelial nests in which both features were present, suggesting that the transitional epithelium transforms in polar fashion into squamous epithelium. Examination of cytokeratin patterns found in urothelium and in the surface epithelium of the ovary pointed to certain differences from the Brenner tumor epithelia. The significance of these latter findings with regard to cellular transformation and histogenesis of the Brenner tumor are discussed. HUM PATHOL 19:640–650. © 1988 by W.B. Saunders Company.

Since the first description of the ovarian Brenner tumor in 1907,[1] the histogenetic origin of this tumor has raised much discussion and speculation.[2–7] At present, this tumor is commonly considered to be an epithelial neoplasm originating from the ovarian surface epithelium which has undergone transitional-cell-type metaplasia.[8] Histologically, the Brenner tumor presents a wide spectrum of cellular patterns, ranging from benign tumors with nests of transitional-type epithelium embedded within a fibrous stroma, to malignant invasive neoplasms that frequently present squamous elements. In addition, other forms of the tumor recently have been reviewed and reclassified by Roth et al.[9,10] as metaplastic, proliferative, and of low malignant potential.

To study the cellular basis of the observed diversity of the various elements of Brenner tumor, we examined the expressions of various intermediate filament polypeptides in the tumor cells. This approach recently has been widely accepted as a most useful diagnostic tool in surgical pathology.[11,12] It has been well established that the five major classes of IFs are expressed in a cell-type-restricted fashion, enabling the distinction between epithelial, mesenchymal, myogenic, neuronal, and glial neoplasms.[13] Furthermore, characterization of the particular cytokeratin expression patterns in different epithelia enables distinction between different epithelial tumors and determination of their state of differentiation.[14]

In the present study, different monoclonal antibodies, including a battery of polypeptide-specific cytokeratin antibodies, were used to probe the state of differentiation of the various epithelia of the Brenner tumor. Our results indicate that the malignant and benign components of the tumor display similar cytokeratin polypeptides. Distinct differences were detected, however, between the transitional and squamous components. Moreover, using such antibodies, we were able to detect mixed nests containing both cell types, possibly representing the transformation of transitional into squamous epithelium.

REPORT OF A CASE

A 49-year-old white woman, gravida 2, para 0, was admitted for evaluation of lower abdominal pain and diarrhea of 6 weeks' duration. Physical examination revealed a large, nontender, partly mobile lower abdominal mass. On sonography, the mass was shown to be multilocular, reaching up to the umbilicus. The remaining physical findings and laboratory data were normal or within the normal range. Laparotomy revealed a large right ovarian tumor that was adherent to the pelvic wall and to the rectosigmoid. The peritoneal cavity contained about 1000 ml of clear fluid. A total hysterectomy with bilateral tuboophorectomy and omen-

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Keywords: Brenner tumor, cytokeratins, histogenesis, intermediate filaments, ovarian tumors.

0046-8177/88/1906-0002$5.00/0

tectomy was performed. Following the operation, the patient received chemotherapy. A second-look operation was performed about 3 months later, and no residual tumor was found.

PATHOLOGIC FINDINGS

Gross Findings

The uterus with both adnexae and omentum was received. The uterus weighed 250 g and showed an intramural leiomyoma. The left adnexa showed no abnormalities. The right ovary revealed a large encapsulated, predominantly cystic tumor 12 cm in diameter. The external surface was smooth with some lobulations. On cut surface, there was a predominant large cyst and many small cystic spaces in the surrounding tissue. The cysts contained a clear yellow to bloody fluid, and some showed papillary formations extruding into the lumen.

Microscopic Examination

For light microscopic examination, tumor tissue blocks from various regions of the tumor were fixed in 10% buffered formalin, embedded in paraffin, and stained with hematoxylin-eosin. Special stains used included periodic acid–Schiff with and without prior digestion with diastase, Masson's trichrome silver impregnation for reticulin, alcian blue, and mucicarmine.

On microscopic examination, there were areas of typical benign Brenner tumor, most of which displayed transitional-type epithelium with isolated nests of squamous cells. These squamous cells were mixed with a variety of other histologic patterns, such as proliferating Brenner tumor, foci of Brenner tumor "of low malignant potential," as well as many areas of malignant Brenner tumor showing predominantly squamous differentiation.[9,10] In other areas the malignant invasive foci were of an undifferentiated nature (fig. 1). In the present tumor we did not detect mucinous elements.

MATERIALS AND METHODS

Tissues

Fresh samples from the ovarian Brenner tumor, samples of normal urinary bladder mucosa, two urothelial carcinomas, and five normal ovaries were snap frozen in isopentane precooled in liquid nitrogen and stored at −70°C. All tissues, normal and neoplastic, were obtained from routine surgical operations performed at the Kaplan Hospital, Rehovot.

Immunochemical Reagents

The following antibodies were used in the present study:

KG 8.13. This broad-spectrum cytokeratin monoclonal antibody reacts with the cytokeratin filaments present in all cytokeratin-containing human epithelial cells tested. This antibody was raised against bovine muzzle cytokeratin and was found to react with a broad range of polypeptides including cytokeratins 1, 5, 6, 7, 8, 10, 11, and 18.[15] (The numbering of polypeptides is according to method of Moll et al.[16]).

KS 8.58. This cytokeratin-specific monoclonal antibody reacts with human polypeptides 13 and 16. These polypeptides are commonly present in nonkeratinizing squamous epithelium as well as in squamous carcinomas and squamous metaplasia.[17,18]

KM 4.62. This anti-cytokeratin monoclonal antibody was raised against the cytoskeletal components of cultured cell line (derived from human adenocarcinoma). In a previous study, we showed that this antibody reacts only with human cytokeratin polypeptide 19,[19] which is commonly present in simple epithelia.

KK 8.60. An anti-cytokeratin monoclonal antibody reactive with human cytokeratin polypeptide 10 and 11, this antibody is used as a marker of keratinization because it stains keratinizing squamous epithelia.[18]

K_s 18.18. This monoclonal anti-cytokeratin antibody reacts with human cytokeratin polypeptide 18, which is specific for nonsquamous epithelia.[20] This antibody was kindly supplied by W. W. Franke, of the German Cancer Research Center, Heidelberg, West Germany.

Desmoplakins. Antibodies to purified bovine desmoplakins I and II were raised in guinea pigs and reacted with human desmoplakins. These antibodies also were kindly supplied by W. W. Franke.[21]

Vim 13.2. This monoclonal anti-vimentin antibody was raised against human fibroblast vimentin (Bio-Makor, Rehovot, Israel).

Rabbit anti-vimentin antibody. This antibody was raised by multiple injections of vimentin isolated from cultured baby hamster kidney cell line.[22]

Desmin. A rabbit anti-desmin antibody was raised against purified chicken desmin. This antibody cross-reacted extensively with human desmin.[23]

Frozen sections of tissue blocks were cut at about −20°C in a Jung-Reichert cryostat (Frigocut 2800, FRG). The sections (4 to 5 μm thick) were collected on clean glass slides, air dried, acetone fixed, and immunolabeled as previously described.[24] Antibody-stained sections were dehydrated in absolute ethanol, mounted in Entellan (Merck FRG), and examined with a Zeiss Photomicroscope III equipped for epiflourescence observations with oil immersion, plan neofluar objectives (×25/0.8 or ×16/0.5).

RESULTS

Immunofluorescent Localization of Intermediate Filament Proteins in Brenner Tumor

Immunofluorescent labeling of Brenner tumor with antibodies to various intermediate filaments in

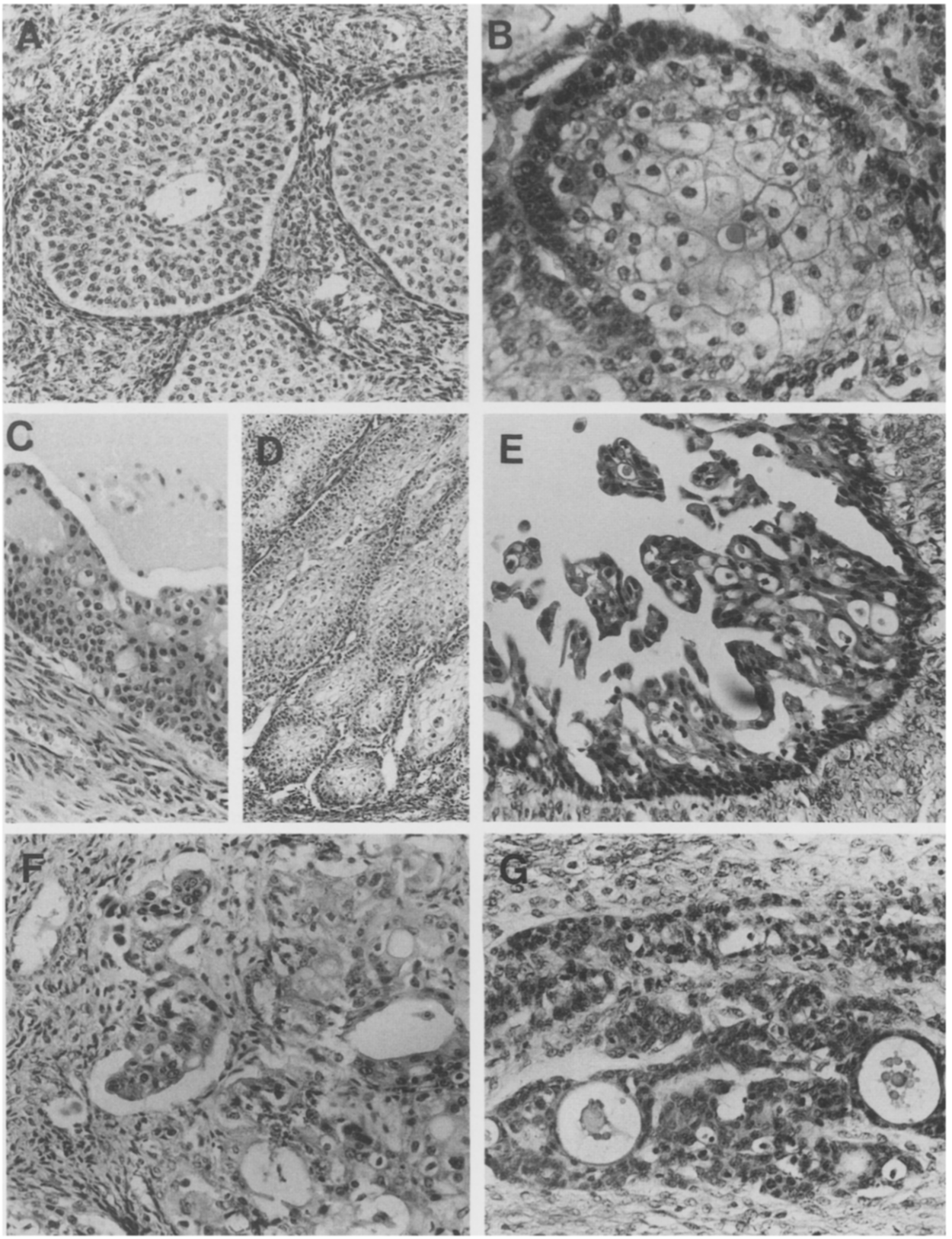

FIGURE 1. Histologic appearance of Brenner tumor, showing wide range of histologic features (*All* Hematoxylin-eosin stain). **A,** Typical benign Brenner tumor showing nest of transitional-type epithelium. (×150.) **B,** Squamous metaplasia of a nest of transitional epithelium. (×150.) **C,** Proliferating Brenner tumor of transitional epithelial type. (×90.) **D,** Proliferating tumor of squamous metaplastic type. (×60.) **E,** Brenner tumor of low malignant potential manifesting marked papillary growth. (×150.) **F,** Malignant Brenner tumor of the squamoid type. (×150.) **G,** Poorly differentiated malignant Brenner tumor. (×225.)

dicated that all the epithelial elements of the tumor contained cytokeratin (fig. 2A). Double immunofluorescent labeling for cytokeratin (using the broad-spectrum antibody KG 8.13) and vimentin clearly revealed the mesenchymal cells within the stroma and indicated that the tumor cells were keratin positive and contained essentially no vimentin (fig. 2B). Desmin-containing smooth muscle cells were often detected within the connective tissue (fig. 2C). These fibers, however, were discernible from the stromal fibroblasts as revealed by counterlabeling of the same sections for vimentin (fig. 2D).

To determine the cytokeratin polypeptide expression profile in the various histologic forms of the Brenner tumor, we labeled frozen sections with several polypeptide-specific cytokeratin antibodies. Examination of the transitional epithelial elements revealed positive staining throughout the tumor with antibodies KG 8.13 (fig. 3A), KM 4.62 (fig. 3B), and KS 8.58 (fig. 3C). Antibody K_s 18.18 gave largely positive staining of the transitional nests, with only individual cells remaining apparently negative (fig. 3F). Antibody KK 8.60, on the other hand, did not label most of the transitional nests, only occasionally showing positive labeling on individual cells or cell clusters within the tumor nests (figs. 3D and E). Labeling for desmosomes with anti-desmoplakin antibodies yielded punctate staining throughout the tumor (fig. 3G).

As shown in figure 1, extended regions through-

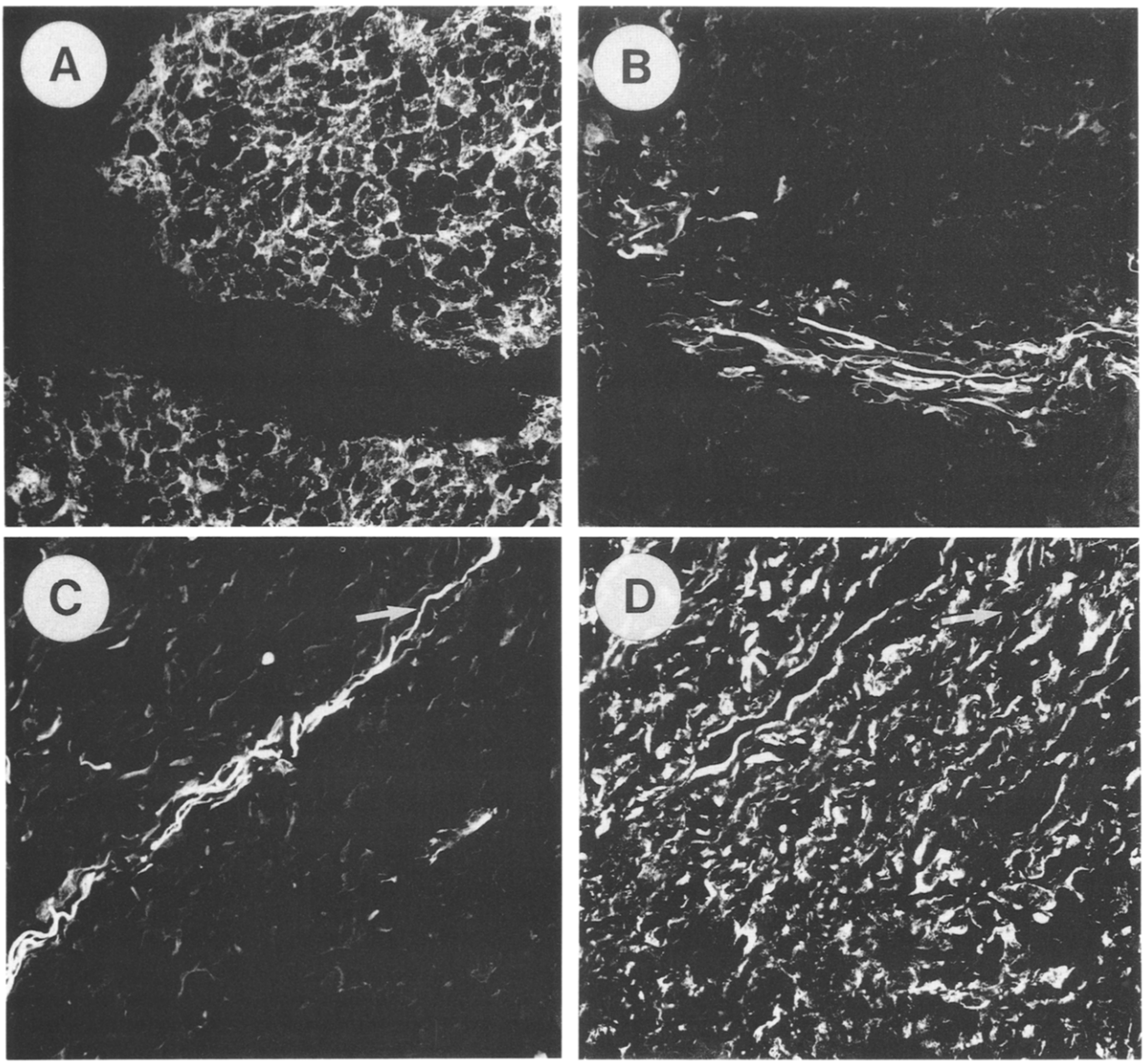

FIGURE 2. Double immunofluorescent labeling of the Brenner tumor for cytokeratin **(A)** and vimentin **(B)** and for desmin **(C)** and vimentin **(D).** *It is apparent that the tumor nests contain only intermediate filaments of the cytokeratin class and are devoid of vimentin. Moreover,* the desmin-positive muscle fibers are embedded in vimentin-rich stroma but are themselves apparently devoid of vimentin (matched arrows in **C** and **D**).

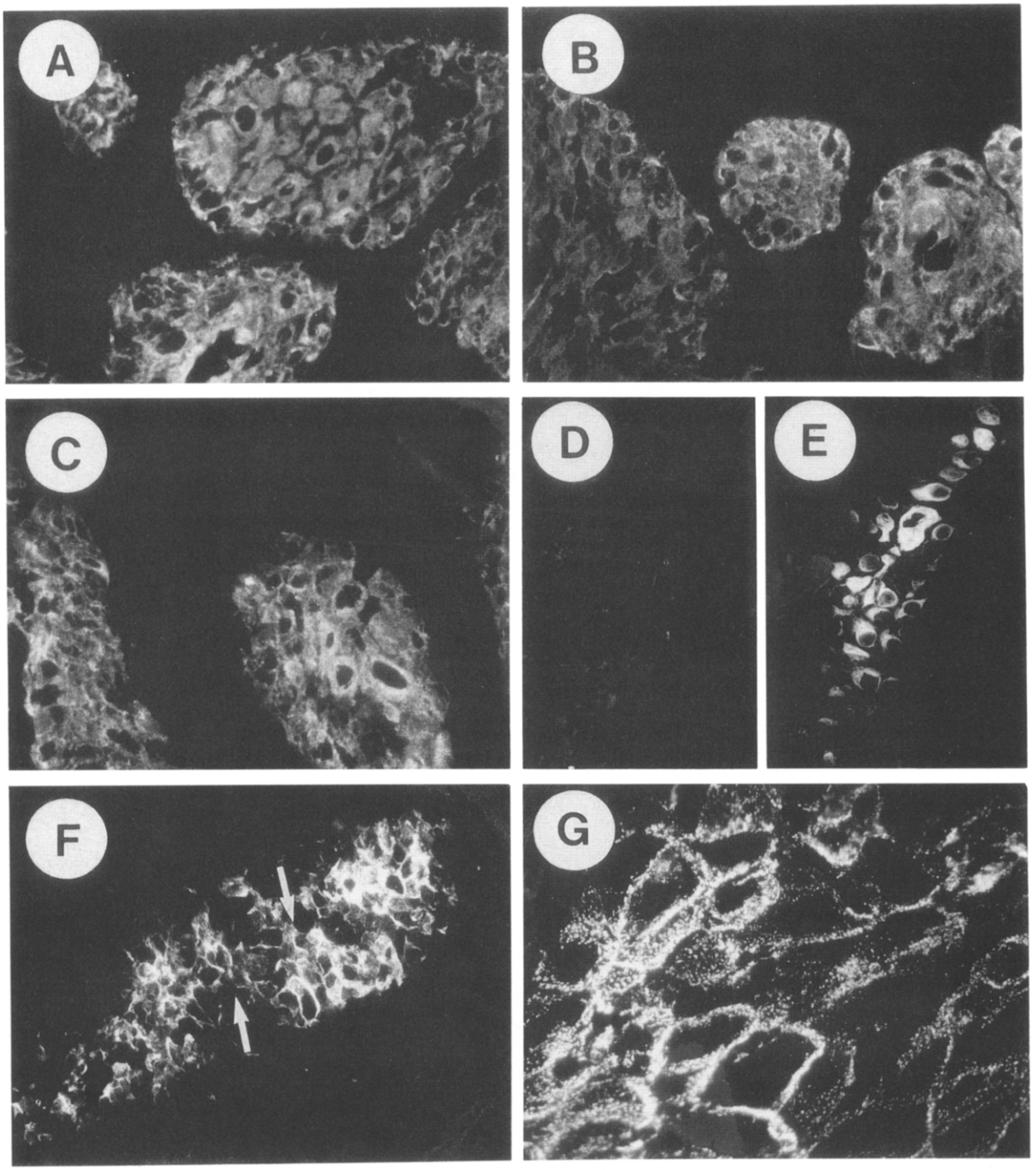

FIGURE 3. Transitional epithelial nests of the Brenner tumor labeled with various cytokeratin and desmosomal antibodies: **A,** KG 8.13; **B,** KM 4.62; **C,** KS 8.58; **D** and **E,** KK 8.60; **F,** K_s 18.18; **G,** anti-desmoplakin I and II. It is notable that the transitional nests are largely negative with KK 8.60 but occasionally display some postively labeled cells. Individual cells in the center of the nests were often devoid of labeling with K_s 18.18 (*arrows*).

out the tumor displayed squamous rather than transitional epithelial morphologic patterns. Those regions were uniformly labeled with the broad-spectrum antibody KG 8.13 (fig. 4A) as well as with antibodies KM 4.62 (fig. 4B) and KS 8.58 (fig. 4C). Staining for cytokeratins 10/11 with antibody KK 8.60 was largely positive, with only some isolated cells showing weak or even no detectable labeling (fig. 4D). The squamous regions were mostly negative for cytokeratin 18 (antibody K_s 18.18). However, at the periphery of the squamous epithelial nests, we have often observed one or few layers of cells displaying positive labeling with K_s 18.18 (fig. 4E). We propose that these tumor nests represent a transition state between the transitional and squamous epithelial forms of the tumor (*see* Discussion). Labeling with anti-desmoplakin revealed dense arrays of desmosomes at the periphery of essentially all the cells (fig. 4F).

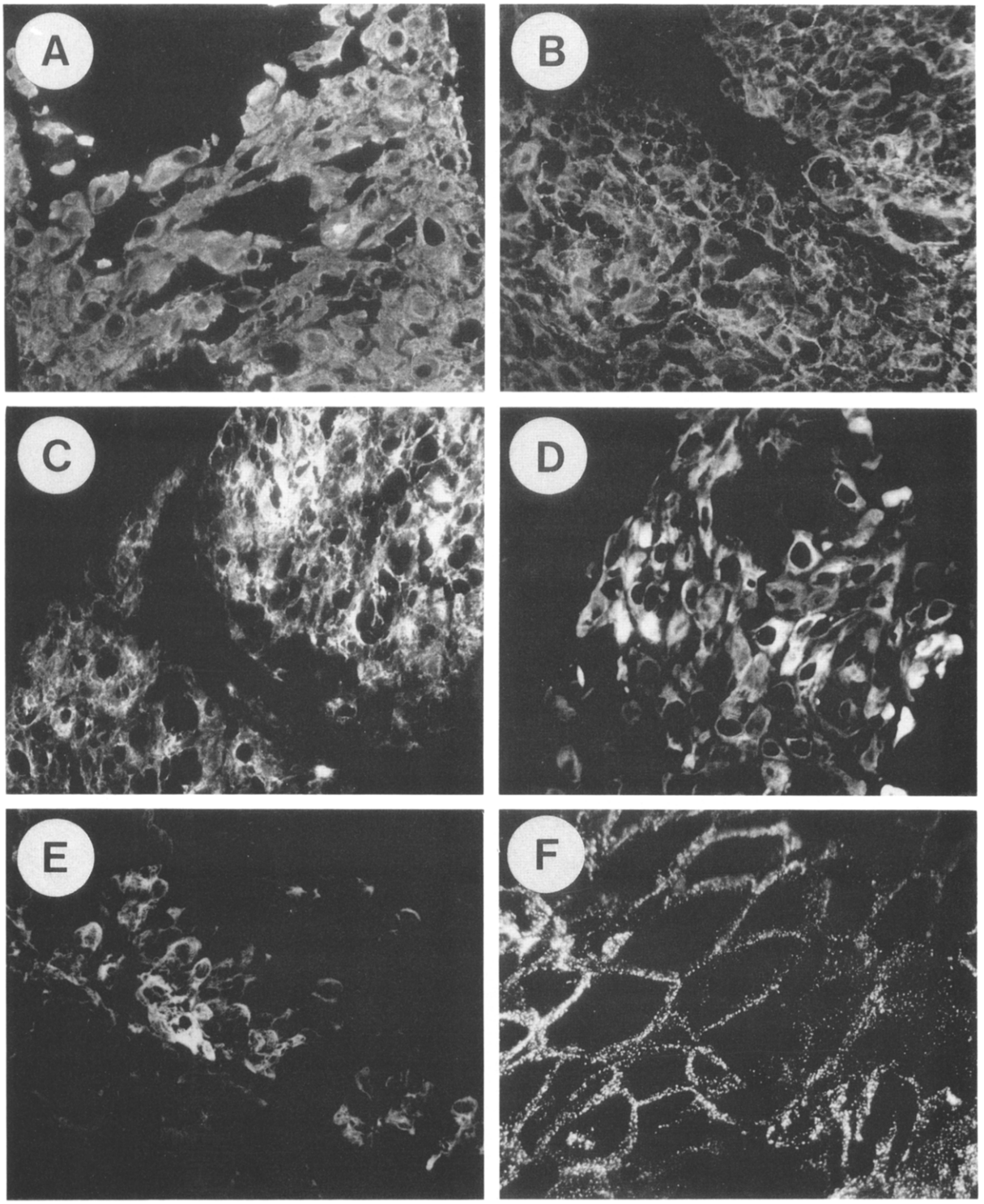

FIGURE 4. Squamous epithelial nests of the Brenner tumor labeled with various cytokeratin and desmosomal antibodies: **A,** KG 8.13; **B,** KM 4.62; **C,** KS 8.58; **D,** KK 8.60; **E,** K_s 18.18; **F,** anti-desmoplakin I and II. Note that only a few cells at the periphery of the squamous tumor nests are positively labeled with antibody K_s 18.18.

Immunofluorescent Labeling of Normal and Malignant Urothelium with Polypeptide-specific Anti-cytokeratin Antibodies

To study the interrelationship between the cytokeratin profiles of Brenner tumor and "typical" transitional epithelia, we examined the labeling patterns of normal urothelium (fig. 5) and urothelial carcinoma (fig. 6) with the various anti-cytokeratin antibodies. The staining of normal urinary blader was positive with the broad-spectrum anti-cytokeratin antibody KG 8.13 (fig. 5A) as well as with antibodies KM

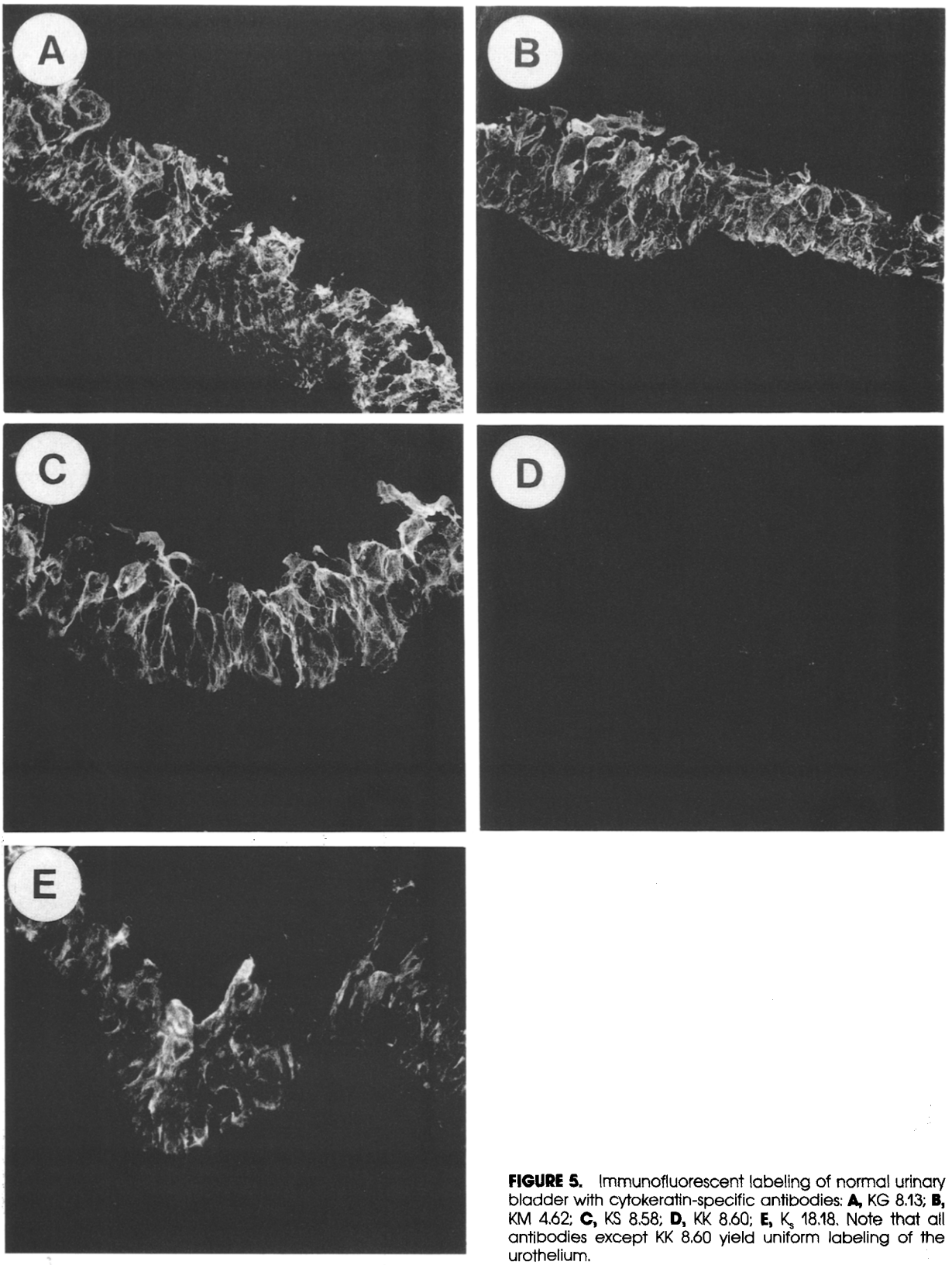

FIGURE 5. Immunofluorescent labeling of normal urinary bladder with cytokeratin-specific antibodies: **A,** KG 8.13; **B,** KM 4.62; **C,** KS 8.58; **D,** KK 8.60; **E,** K_s 18.18. Note that all antibodies except KK 8.60 yield uniform labeling of the urothelium.

4.62 (fig. 5B), KS 8.58 (fig. 5C), and K_s 18.18 (fig. 5E). No labeling was obtained with antibody KK 8.60 (fig. 5D).

Urothelial carcinoma of the urinary bladder was positively labeled with antibodies KG 8.13 (fig. 6A), KM 4.62 (fig. 6B), KS 8.58 (fig. 6C), and K_s 18.18 (fig. 6D). When antibody KK 8.60 was used, we obtained variations between the two tumors tested. One of

these tumors was essentially negative (fig. 6E), whereas the other appeared positive (fig. 6F).

Cytokeratin Expression in the Surface Epithelium of the Ovary

As pointed out earlier, the ovarium surface epithelium is commonly considered to represent the origin of Brenner tumor.[7–9] We therefore examined the staining patterns of the ovarian surface epithelium with the various anticytokeratin antibodies. As shown in figure 7, extensive labeling was obtained with the broad-spectrum anti-cytokeratin antibody KG 8.13 (fig. 7A), KM 4.62 (fig. 7B), and K_s 18.18 (fig. 7C). Antibodies KS 8.58 (fig. 7D) and KK 8.60 (fig. 7E) were both negative. Immunofluorescent labeling with anti-vimentin showed extensive labeling of stromal fibroblasts as well as labeling of the surface epithelium itself (fig. 7F), which is in line with the results of a previous report.[20] In addition, conspicuous arrays of desmosomes were detected on sections labeled with anti-desmoplakin (fig. 7G).

DISCUSSION

Our results indicate that all the epithelial elements of the Brenner tumor, regardless of their histologic appearance and grade of differentiation, react with the broad-spectrum cytokeratin antibody, indicating that all the cellular elements of the tumor retain epithelial characteristics. This finding is in line with those of previous reports on the distribution of the major intermediate filament subunits in this tumor.[25–27] However, in the present study, we went further by using a battery of monoclonal cytokeratin antibodies that selectively and specifically react with distinct cytokeratin polypeptides. This step has enabled us to investigate different patterns and pathways of epithelial differentiation that apparently occur within the Brenner tumor.

The localization of specific cytokeratin pointed to conspicuous differences between the Brenner tumor and its presumptive tissue of origin, i.e., the ovarian surface epithelium. The latter exhibited the acidic cytokeratins 18 and 19[20] and did not stain with antibodies to cytokeratin 10/11 and 13/16. These polypeptides were apparently present in the various elements of the Brenner tumor. Moreover, vimentin, which was present in the ovarian mesothelium, was absent from the tumor.

Changes in the cytokeratin profile continue to occur throughout the morphologic diversification of the tumor. Squamous differentiation in the various histologic types of Brenner tumor is well known.[9,10] Therefore, the focal presence of individual cells within the apparently nonsquamous, transitional-type tumor nests that show positive staining for cytokeratins 10 and 11 is of particular interest. These polypeptides are usually reliable markers for keratinization,[18] and their presence in cells in which keratinization is not evident by light microscopic examination may be indicative of an inherent potential for squamous differentiation. This notion was also corrobated in the study of squamous metaplasia of the uterine cervix,[28] where cytokeratins 10 and 11 appeared in metaplastic epithelium. The appearance of these cytokeratins suggest that following stratification, another step toward keratinization may take place.[29,30] It is thus not surprising that well-differentiated squamous nests in the Brenner tumor stained uniformly with antibodies KK 8.60 against cytokeratins 10 and 11, with the exception of a few isolated cells that may represent remnants of the original transitional epithelium. Futhermore, at the periphery of some squamous tumor nests, individual cells were found to be positively stained for cytokeratin 18, which is usually present in transitional-type epithelia, as well as in simple epithelial, and is absent from stratified epithelia. The presence of this polypeptide at the peripheral cells of the squamous nests, as well as the presence of cells containing the keratinization-specific polypeptides 10 and 11 in transitional nests, suggests that this may constitute evidence of transformation from transitional to squamous elements. This process appears to occur in a polar fashion, whereby cells at the center of transitional nests are the first to undergo squamoid transformation and the cells at the periphery are the last ones.

Further information on the relationship between the transitional epithelium of the Brenner tumor and "authentic" urothelium of the urinary bladder was obtained by immunofluorescent labeling of the latter with the various monoclonal cytokeratins. Although the staining patterns were largely similar, notable differences were detected between the two with respect to the labeling with antibody KK 8.60. This antibody, which reacts with cytokeratin polypeptides 10 and 11, exhibited positive labeling of individual cells and cell clusters within the transitional-type epithelium of the Brenner tumor, whereas no such labeling was detected with this antibody in normal bladder urothelium. In addition, normal urothelium also stained positively throughout with antibody K_s 18.18, whereas in the transitional nest of the Brenner tumor, individual cells apparently remained negative. In urothelial carcinoma, we have detected some variability, manifested by positive tumor labeling with antibody KK 8.60 in one case and no labeling in the other one tested. Otherwise, our results pertaining to urothelium were largely consistent with those of Achtstätter, et al.[31] Although cytokeratins 10 and 11, which were present in one of our cases, were not reported by Achtstätter and coworkers, this has been occasionally observed (Achstätter T, personal communication). The latter finding in bladder carcinoma may reflect the known squamous potential of urothelial carcinoma[32] and may also confirm the heterogeneity within this class of neoplasms.[31] It is also noteworthy that the presence of individual "keratinizing cells in the transitional epithelial nest of the Brenner tumor points to its tendency to undergo squamous metapla-

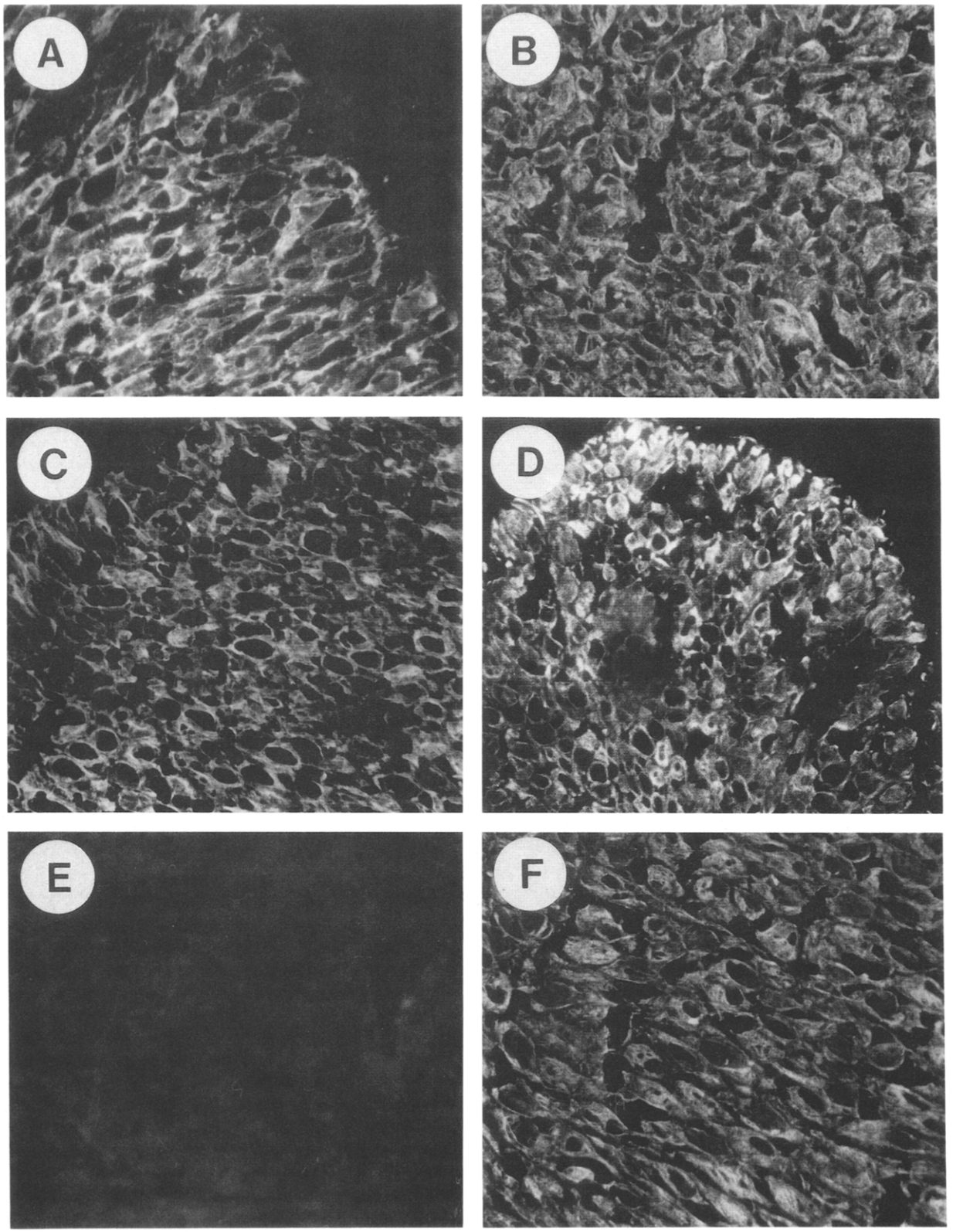

FIGURE 6. Immunofluorescent labeling of urothelial carcinomas of the urinary bladder with cytokeratin-specific antibodies: **A,** KG 8.13; **B,** KM 4.62; **C,** KS 8.58; **D,** K_s 18.18; **E** and **F,** two different cases labeled with antibody KK 8.60. Note that one tumor **(E)** is uniformly negative with antibody KK 8.60 but the other one **(F)** is uniformly positive.

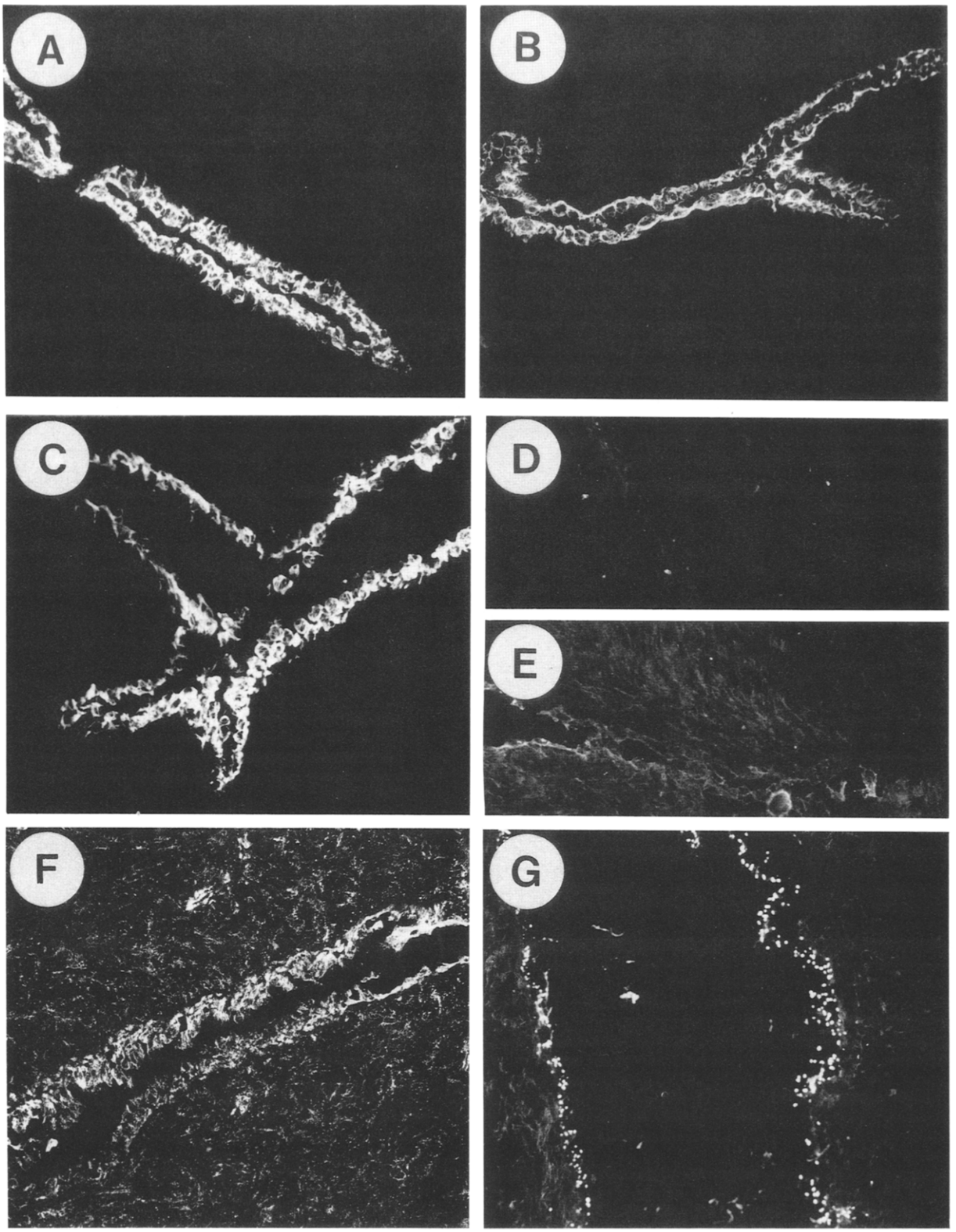

FIGURE 7. Immunofluorescent labeling of the ovarian surface epithelium with cytokeratin-specific antibodies: **A,** KG 8.13; **B,** KM 4.62; **C,** K_s 18.18; **D,** KS 8.58; **E,** KK 8.60; **F,** vim 13.2 (anti-vimentin); **G,** anti-desmoplakin I and II. Note that antibodies KS 8.58 and KK 8.60 yield only background staining and that both the surface epithelium and stromal fibroblasts are positively labeled for vimentin.

sia, ultimately leading to the generation of squamoid nests.

As pointed out earlier, vimentin could not be demonstrated in the epithelial elements of the Brenner tumor and is also absent in most ovarian epithelial tumors,[33,34] with the exception of rare serous tumors in which these filaments recently have been identified.[35] Desmin, presumably representing mus-

cle fibers in the stroma of the Brenner tumor, has been previously described in this neoplasm,[26] and was also present in the stroma of normal ovaries.[20]

In conclusion, this study establishes the pattern of expression in the various benign and malignant elements of a Brenner tumor. In addition, our results show some of the unique properties of the transitional-type epithelium of the Brenner tumor and its high potential for squamous metaplasia. The study also provides a unique look at the interrelationship and polarity of transformation from transitional to squamous epithelium in this neoplasm. It should also be pointed out that despite the close morphologic similarities between the transitional epithelium of Brenner tumor and that of urothelium, distinct differences exist with respect to their cytokeratin expression profiles, reflecting the differences in their tendency to form squamous epithelium. Finally, this study depicts a situation in which the neoplastic transformation of cells (ovarian mesothelium) is accompanied by a conspicuous alteration in their intermediate filament composition.

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