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Immunohistochemical Diagnosis of Renal Pelvis Transitional Cell Carcinoma in a Dog

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Abstract : A 9-year-old, male, Doberman pinscher dog with 5-month history of intermittent hematuria, vomiting and glucosuria was referred to local animal hospital. Abdominal ultrasonography showed an irregular and hyperechoic mass in the renal medulla of the enlarged left kidney. Grossly atrophied renal cortex and medulla and marked hydronephrosis were observed on the cut surface of kidney. A single, numerous papillary projected, pedunculated mass 4~5.5 cm in diameter was occupied in renal pelvis, and extended from pelvis to the inlet of ureter. Histopathologically, the mass had numerous papillary structures with arboriform pattern. These papillae were consisted of fibro-vascular stalks that were lined by multiple layers of neoplastic urothelium (transitional epithelium) with marked cellular atypia. Immnohistochemical (IHC) staining demonstrated that the neoplastic cells showed strong positive reactions for cytokeratin (CK) 7, CK 19, CK clone MNF116 and CK high molecular weight, but negative signals for CK 8 low molecular weight. Based on the gross findings, histopathology and CKs profile using IHC staining, this mass was diagnosed as renal pelvis transitional cell carcinoma in a dog.

Key words **:** cytokeratin, dog, IHC, renal pelvis, transitional cell carcinoma.

Introduction

Primary renal neoplasms are uncommon in the dog and account for 0.3~1.7% of all canine tumors (10). According to survey using archival materials, there were twice as many secondary tumors (68%) than primary tumors (32%) in canine renal tumor (9). Approximately 85% of primary renal tumors in dogs are of epithelial origin, and about 90% of the epithelial tumors are classified as malignant (8,9). The combined data of total 464 canine primary renal tumors from four sources indicated 65% of which were renal cell carcinoma (RCC), 8% nephroblastoma, 6% undifferentiated sarcoma, 5% transitional cell carcinoma (TCC), and others (9). In dogs with primary renal tumors the most common clinical sign are hematuria (32%), inappetance (27%), lethargy (26%), weight loss (20%), vomiting (13%), polydipsia or polyuria (10%), pain (7%), and behavior changes (5%) (1).

Several cases of RCCs were reported in some dog species such as Pekingese, Yorkshire terrier, and Poodle in Korea (2). TCC were also reported in Yorkshire terrier and Maltese-dog (4,7). But all reported TCC cases were arose from urinary bladder. In this paper, we report a case of TCC of renal pelvis and cytokeratins (CKs) profile of TCC in a dog. To the author's knowledge, this is the first pathological study for renal pelvis TCC of dog in Korea.

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Case

A 9-year-old, male, Doberman pinscher dog with 5-month history of intermittent hematuria, vomiting and glucosuria was referred to local animal hospital. Abdominal ultrasonography showed an irregular and hyperechoic mass in the renal medulla of the enlarged left kidney. After performing nephrectomy and partial ureterectomy, whole left kidney with renal mass was removed and submitted for histopathologic examination.

The kidney with renal mass was fixed 10% neutral buffered formalin, processed in a routine method, and stained with hematoxylin and eosin (H&E) and periodic acid-Schiff (PAS) for light microscopic examination. Additional paraffin-embedded sections were used for immunohistochemistry (IHC). After mounting on silane coated glass slides, each section was stained by a labeled streptavidin-biotin peroxidase method. To clarify the neoplastic epithelial cells, primary antibodies specific to CK markers such as monoclonal mouse anti-human CK 7 (Dako, Denmark), CK 19 (Dako, Denmark), CK clone MNF116 (Dako, Denmark), CK 8 low molecular weight (CK 8 LMW, Dako, Denmark) and CK high molecular weight (CK HMW, Dako, Denmark) were used.

Grossly, the left kidney was larger than normal. On the cut surface of kidney, renal cortex and medulla were atrophied, and marked hydronephrosis was observed due to severe dila-

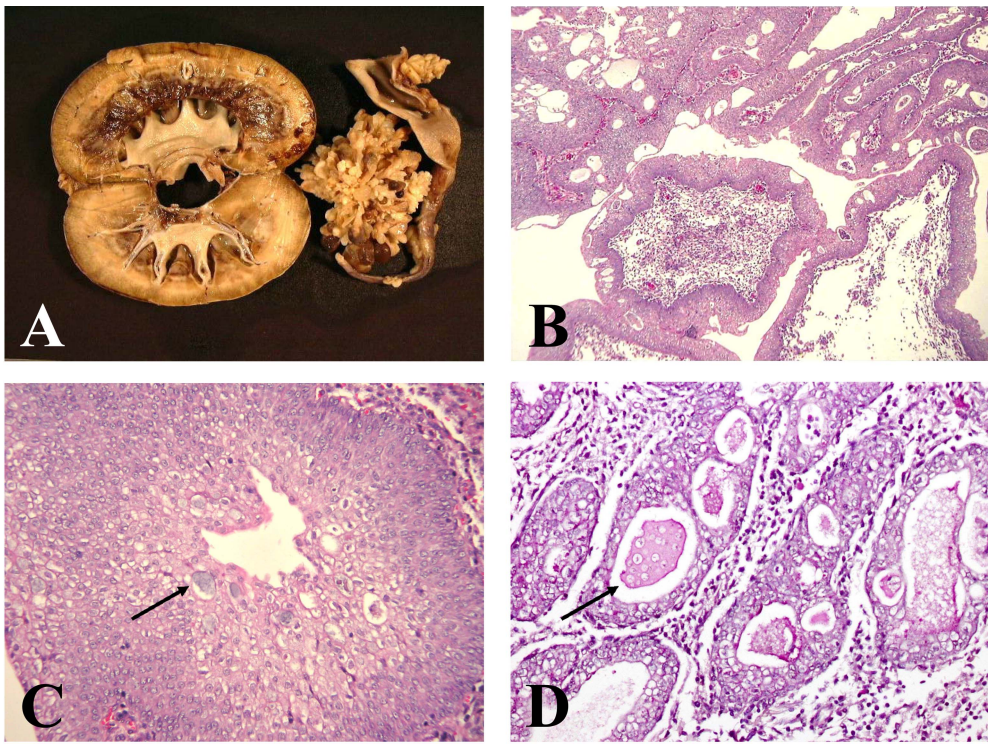

Fig 1. Gross and histopathologic findings of renal pelvis transitional cell carcinoma in a dog. Note hydronephrosis in left kidney and a single, numerous papillary projected, pedunculated mass 4~5.5 cm in diameter from pelvis to the inlet of ureter (A). Papillary structures were composed of fibrovascular stalks and lined by neoplastic transitional epithelium. H&E, × 40 (B). Cytoplasms of neoplastic cells had various sized vacuoles, and microcysts containing mucinous materials (arrow). H&E, × 200 (C). There were also cystic spaces containing amorphous PAS-positive materials (arrow) in urothelial layers. PAS, × 200 (D).

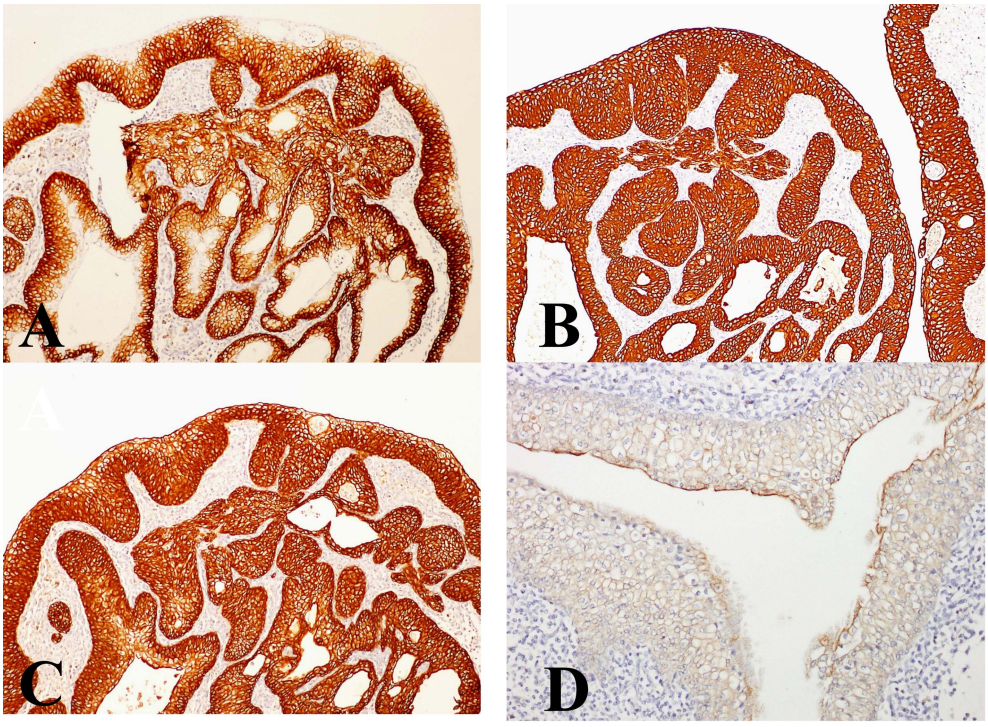

Fig 2. Cytokeratins profile using Immunohistochemical staining of renal pelvis transitional cell carcinoma. Neoplastic transitional cells express positive reactions for CK 7 (A), CK 19 (B), CK MNF 116 (C), but negative for CK 8 LMW (D). IHC, × 200.

tation of the renal pelvis. A single, numerous papillary projected, pedunculated mass 4~5.5 cm in diameter was occupied in renal pelvis, and extended from pelvis to the inlet of ureter (Fig 1A). Therefore proximal part of ureter was severely distended and obstructed due to pelvic mass.

Histopathologically, the mass had numerous papillary structures with arboriform pattern. These papillae were consisted of fibro-vascular stalks that were lined by multiple layers of neoplastic urothelium (transitional epithelium) with marked cellular atypia (Fig 1B). Many neoplastic cells infiltrated into the stalk or submucosa, and then formed variable sized nests, looks-like Brunn's nests in bladder. Neoplastic cells showed characteristic palisading arrangement of cuboidal to polyhedral cells, and perpendicularly distributed to the basement membrane. The cells had pale basophilic cytoplasm, oval nucleus and one or more nucleoli, and indistinct cellular border. Some cytoplasms of neoplastic cells had various sized vacuoles, and microcysts containing PAS-positive mucinous materials (Fig 1C). There were also cystic spaces of various sizes, containing degenerated cellular debris and amorphous PAS-positive eosinophilic proteineous materials in urothelial layers (Fig 1D). Many mitotic figures and abnormal mitoses were observed in high power field. Severe multifocal accumulation of mononuclear inflammatory cells such as lymphocytes and macrophages with/without cholesterol clefts and hemorrhage were scattered throughout the submucosa of mass.

Multifocal confluent pyelonephritis with necrotic foci and hemorrhage were presented in renal parenchyma. According to IHC, the neoplastic cells demonstrated strong positive reactions for CK 7, CK 19, CK clone MNF116 and CK high molecular weight (Fig 2A, B, C). However the neoplastic cells showed negative signals for CK 8 low molecular weight (Fig 2D). Based on the gross findings, histopathology and CKs profile using IHC, this mass was diagnosed as TCC of renal pelvis in a dog.

Discussion

TCCs may originate in the renal pelvis, ureters, urinary bladder, or urethra of the dog (12). Although malignant tumor in urinary bladder is uncommon in the dog, TCC is the most common neoplasm affecting the bladder of dogs (11). Most TCC cases arise from transitional epithelium of the urinary bladder and may extend into the urethra, or, less commonly, originated from urethral epithelium and locally invaded the bladder wall (15). It has been suggested that the greater incidence of primary neoplasms in the bladder is closely associated with retention of urine that allows increased contact time of carcinogenic agents with the bladder epithelium (12). Although the etiology of canine TCC is multifactorial, risk factors associated with bladder cancer in dogs include exposure to topical insecticides for flea and tick control, marshes sprayed with chemicals for mosquito control, female gender, obesity, and breed such as Scottish terrier (9,11). Several carcinogens including intermediate metabolites of tryptophan, cyclophosphamide, and nitrosamine family have been associated with morphologic changes and TCC of the bladder in dogs.

Tumors of the renal pelvis and ureter are rare in animals (8,9). Previous reports included TCCs, papilloma, and leiomyosarcoma in dogs, and hemangiomas in cattle with enzootic hematuria (9). TCC of the renal pelvis is very rare tumors, which occur in the dog, cow, pig, and horse (8). When TCC is located in renal pelvis, it is likely to cause hydronephrosis because of partial or complete obstruction of urinary passage. And also stasis of urine is an important predisposing factor in the pathogenesis of cystitis and pyelonephritis (8). Secondary lesions such as hydronephrosis and subsequent multifocal pyelonephritis closely associated with primary renal pelvis TCC were nicely demonstrated in this case.

CKs, the intermediated filament proteins characteristically found in epithelium and epithelial tumors, comprise a family of at least 20 different polypeptides (5). IHC using antibodies specific to CK is a useful tool for the identification of normal and neoplastic cells of epithelial origin. Determination of the CK profile of a particular carcinoma is very useful in the differential diagnosis of carcinomas. Hence we applied IHC staining using several antibodies against CKs to confirm the epithelial origin in this case. According to manufacturer's explanations, CK 7 antibody labels distal convoluted tubules, collecting ducts of kidney, and all cell layers of urothelium (transitional epithelium). CK 19 typically expressed in simple epithelium, transitional epithelium and renal tubules of the kidney, but not in stratified squamous epithelia. CK clone MNF116 antibody labels non-squamous stratified epithelium, transitional epithelium, and proximal and distal convoluted renal tubules. CK HMW antibody labels squamous cell and ductal or transitional carcinomas. CK 8 LMW antibody labels tubular epithelia in kidney and renal cell carcinoma. In this case of renal pelvis TCC, neoplastic cells demonstrated strong positivities for CK 7, CK 19, CK clone MNF116, and CK HMW, but negative signals for CK 8 LMW. Therefore we successfully ruled out squamous cell carcinoma of renal pelvis origin and RCC. According to two previous literatures, 3 (50%) of 6 TCC and 53 (98.1%) of 54 TCC in dogs were positive for CK 7, respectively (5,14). And the only TCC negative for CK 7 was the anaplastic cell type (14). However 3 RCCs and one squamous cell carcinoma showed negative results against CK 7.

The most common clinical signs in dog with renal pelvic TCCs is hematuria, as observed in this case; other nonspecific signs include anorexia, weight loss, abdominal pain and prostration (10,13). Hypertrophic osteopathy, a kind of paraneoplastic syndrome, was reported in a 6-year-old male dog with renal pelvis TCC (6). Metastases of renal pelvis tumors are rare and sometimes occur as an extension of the renal capsule to the intestinal serosa and wall (3). It is believed that unilateral nephrectomy and ureterectomy were important treatment options in unilateral primary renal neoplasm (6,10). But in the case of bilateral renal involvement, neither surgical nor medical therapy is effective (3). According to previous report, uni-

lateral nephrectomy, ureterectomy and chemotherapy with carboplatin were performed to renal pelvis TCC case in a dog (13). There was no evidence of metastasis observed in the radiographic examination of the thoracic region, abdominal ultrasonography, and laparotomy at the time of nephrectomy. However five months after nephrectomy, renal pelvis tumor metastases were observed in organs within the thorax and abdominal cavities (13). Therefore to increase the survival time and the patient's quality, more detail studies on the response of renal pelvis tumor to the combined therapy of surgical complete excision and adjuvant chemotherapy should be warranted.

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개의 신우 이행상피암종의 면역조직화학적 진단

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요 약 : 9세령의 수컷 도베르만견이 5개월간 간헐적인 혈뇨, 구토 및 당뇨증상을 보여 동물병원에 내원하였다. 초음파상에서 종대된 좌측 신장의 수질부위에 종괴가 발견되었다. 육안적으로 좌측 신장의 피질 및 수질부는 현저하게 위축되어 있었으며 신우 부위는 종괴로 인하여 확장된 수신증을 나타내었다. 크기 4~5.5 cm의 유두상으로 돌출된 꽃자루와 같은 단일종괴가 신우 부위에 있으며, 요관으로 뻗어 있었다. 병리조직학적으로 종괴는 나뭇가지 모양으로 무수히 돌출된 유두상의 돌기들로 구성되어 있었다. 이 돌기들은 섬유혈관성 중심부와 뚜렷한 이형태성을 가지는 여러 층의 종양화된 이행상피들로 피복되어 있었다. 면역조직화학염색을 실시한 결과 종양세포들은 사이토케라틴(cytokeratin: CK) 7, 19, CK clone MNF116 및 CK HMW에 대해서 양성을 보였으나 CK 8 LMW에서는 음성 반응을 나타내었다. 육안적인 특징, 병리조직학적 소견 및 면역조직화학염색에 의한 사이토케라틴의 반응성을 토대로 이 종괴는 개의 신우에서 발생한 이행상피암종으로 진단되었다.

주요어 : 개, 면역조직화학염색, 사이토케라틴, 신우, 이행상피암종